Biomedical & Pharmacology Journal, December 2023. Vol. **16**(4), p. 2241-2250

Protective Effect of Ethanolic Extract of *Syzygium Campanulatum* leaf in *Wistar Albino* Rats Against Triton and Atherogenic Diet-Induced Hyperlipidemia

Nadira Noushida[1], Roopa P Nayak[1]*, Manodeep Chakraborty[2], Thriveni Raunak Salian[3] and Mohammed Gulzar Ahmed[3]

[1]Pharmacology Department, Yenepoya Medical College, Mangalore, Karnataka, India.
[2]Pharmacology Department, Himalayan Pharmacy Institute, Sikkim, India.
[3]Pharmaceutics Department, Yenepoya Pharmacy College and Research Centre, Mangalore, Karnataka, India.
*Corresponding Author E-mail: roopapnayak@yenepoya.edu.in

https://dx.doi.org/10.13005/bpj/2800

(Received: 04 October 2022; accepted: 27 March 2023)

Hyperlipidemia is characterized by an abnormal elevation in the major circulatory lipids and lipoproteins; this adversely affects the pathways of cholesterol transport. Syzygium campanulatum Korth is an evergreen shrub in the kingdom of Myrtaceae. Leaves are popular for their hepatoprotective, antiangiogenesis, and anticancer properties. The purpose of this research was to assess the antihyperlipidemic effect of ethanolic leaf extract of S. campanulatum in experimental rats against atherogenic diet-induced hyperlipidemia. During the 20 days, rats were fed an atherogenic diet mixed with standard pellets. The treatment of S. campanulatum (250/500 mg/kg) was given for 14 days. After 48 h blood samples from rats were collected, serum was collected for evaluation of lipoproteins (high-density lipoprotein, low-density lipoprotein, total cholesterol, triglycerides), and liver tissue was separated for evaluation of tissue antioxidants (superoxide dismutase, catalase, thiobarbituric acid reactive species, and glutathione). The results showed that when compared to rats on a normal diet, an atherogenic diet generated a substantial ($p < 0.001$) decrease in serum HDL-C and a substantial ($p < 0.001$) rise in blood TC, TG, and LDL-C. The hyperlipidaemic groups that received S.Campanulatum 250/500 mg/kg and Atorvastatin 10 mg/kg showed a substantial ($p < 0.001$) decrease in serum levels of TC, TG, LDL-C, and significant ($p < 0.001$) increase in HDL-C respectively, compared to rats with hyperlipidemia control. The study indicates that the ethanolic extract of S.Campanulatum has substantial antihyperlipidemic action, indicating that it might be a potential natural medicine used in addition to currently prescribed hyperlipidemia treatments.

Keywords: Atherogenic diet; Atorvastatin; Hyperlipidemia; Syzygium Campanulatum.

Syzygium campanulatum Korth (S. Campanulatum) is an evergreen bush in the kingdom of Myrtaceae. In Malaysia and Singapore, it's also known as "kelat paya," and it's commonly grown as a hedge. It is a typical decorative tree that is grown in public spaces like parks and roadways. When crushed, its leaves emit a cinnamon-like odor. Some of its regional names are pokok kelat paya, red lip, Chinese red-wood (Chinese name), Australian brush cherry, wild cinnamon, Ubah Laut (East Malaysia), and kelat oil. Despite its traditional use as a stomachic, no

pharmacognostic or phytochemical profiling of *S. campanulatum* has been reported to date, except for the isolation of betulinic acid. The fruits, which resemble blackberries, are visible from December to January and April to May. The shades of the juvenile leaves and flowers distinguish the two kinds of *S. campanulatum:* one has yellow foliage and white-creamy flowers, while the other has red foliage and red blossoms. It contains different phytoconstituents such as flavonoids, phenolics, antioxidants, and betulinic acid. Leaves are known for hepatoprotective, antiangiogenesis, and anticancer properties.[1,2]

Hyperlipidemia is characterized as an elevation in the blood's TG, TC, and LDL-C concentrations.[3,4] It is a severe risk factor for cardiovascular illnesses, in particular atherosclerosis, coronary heart disease, and hypertension, according to various studies.[5] Hyperlipidemia is characterized by an abnormal elevation in the major circulatory lipids and lipoproteins; this adversely affects the pathways of cholesterol transport.[6,7] Increased formation of free radicals/reactive oxygen species in hyperlipidemic conditions is known to participate in cardiac dysfunction, CVD progression, cardiac apoptosis, and necrosis.[7,8] The constancy of hyperlipidemia is influenced by a variety of causes, including ethnicity, genetic background, lifestyle factors such as poor dietary and exercise habits, poorly controlled diabetes, excessive alcohol consumption, and stress are all examples of risk factors. These diseases are caused by an increase in the consumption of a high-fat diet, which harms human health and life.[9]

Several classical hypolipidemic medicines are commonly used in clinical practice to treat this illness, including fibrates, nicotinic acid, its derivatives, bile acid sequestrants, and HMG-CoA reductase inhibitors. However, these medications can cause skeletal muscle toxicity, cutaneous flushing, decreased renal function, liver toxicity, and gastrointestinal discomfort in patients. As a result, new effective hypolipidemic medications with fewer (or no) side effects are urgently needed.[10] Elevated blood triglyceride and cholesterol levels are the key risk factor for atherosclerosis, according to the American Heart Association. As a result, therapists consider hyperlipidemia therapy to be one of the most important strategies for slowing the atherogenic process.[11,12] Because of their low toxicity and health benefits, phytomedicines are becoming more popular, and they are suitable for long-term use as a dietary functional food. Flavonoids may help prevent and treatment of overweight, dyslipidemia, diabetes, and atherosclerosis, according to findings from preclinical pharmacologic tests and epidemiological investigations.[13-16] Phytomedicines might thus play a crucial part in the establishment of innovative treatment techniques. Therefore, the current study investigates the anti-hyperlipidemic action of the polyphenol-rich ethanolic leaf extract of *S.Campanulatum* against triton and atherogenic diet-induced hyperlipidemia in experimental rats.

MATERIALS AND METHODOLOGY

Drugs, reagents, and chemicals

Experimental hyperlipidemic diet

Triton WR-1339 was obtained from Sigma-Aldrich, Experimental feed containing a well-powdered mixture of cholesterol (2%) was Procured from Loba Chemie Pvt. Ltd., cholic acid (1%) and peanut oil (10%) from Sisco Research Laboratories Pvt. Ltd., sucrose (40%) from Merck Life Science Pvt. Ltd., and normal laboratory diet (47%) (figure 3a). Atorvastatin was obtained from a local pharmacy. Total cholesterol, HDL, LDL, and Triglyceride kits were procured from Agappe diagnostics Ltd (Kerala, India).

Collection of Plant Materials

Syzygium campanulatum fresh leaves were collected from Udupi Manjunath Melkaje medicinal garden. The leaves were authenticated by DR H.S Shenoy, Principal scientist and Head of the division, Pilikula nisargadhama, Mangalore. Voucher specimen (9489/*Syzygium campanulatum Korth*.)

Preparation of ethanol extract

After collecting the leaves, they were placed in a clean tray and dried in the shade. By utilizing a dry grinder, the dried leaves were reduced in size to a coarse powder and then sieved (20 Mesh). The powdered sample was extracted by using Soxhlet Apparatus with ethanol.

Experimental animals

The male adult Wistar albino rats with body weights 170-220 g was used as experimental animals. Rats were procured from CPCSEA-

approved breeders and maintained at CPCSEA approved institute animal house of Yenepoya University. The study protocol was approved by the Institutional Animal Ethical Committee Yenepoya medical college (YU /IAEC /8/2020) and the study was initiated only after the approval of the institutional animal ethics committee. The rats used in the experiment were categorized into five groups, consisting of six rats each (60 Numbers).

Tritron induce hyperlipidemia model (n=6)

Group 1: Normal control pre-treatment with vehicle
Group 2: Disease control (Triton WR-1339 (400 mg/kg))
Group 3: Standard drug Atorvastatin 10 mg/kg
Group 4: Low dose of *S. Campanulatum* 250 mg/kg
Group 5: High dose of *S. Campanulatum* 500 mg/kg

After fasting 24hrs rats were treated with triton at a dose of 400 mg/kg i.p, the hyperlipidemia was induced with triton WR-1339 for all groups except the normal control group. The treatment of *S. Campanulatum* 250/500 mg/ml, was administered immediately following the triton injection, and the second dose of extracts was given 20 hours later.

Atherogenic diet-induced hyperlipidemia model (n=6)

Group 1: Normal control pre-treatment with vehicle
Group 2: Disease control (atherogenic diet)
Group 3: Standard drug (Atorvastatin (dose of 10 *mg/kg*)) + atherogenic diet). [17]
Group 4: Low dose of *S. Campanulatum* (250 mg/kg) + atherogenic diet
Group 5: High dose of *S. Campanulatum* (500 mg/kg) + atherogenic diet

For the 20 days of the period, an atherogenic diet was mixed with a standard pellet and given to rats. The treatments were started on the 7th day of the atherogenic diet and continued till the 20th day, a total of 14 days of treatment of *S. Campanulatum* extracts (250/500 mg/kg) was given.

Blood collection and biochemical parameter analysis and estimation of liver enzymes

In triton induced hyperlipidemia model 4 hours after the second dosage, blood samples were drawn, and serum was separated from the blood for evaluation of lipoproteins. The hyperlipidemia was induced with an atherogenic diet model 48 h after the last dose blood samples were collected via cardiac puncture technique and centrifuged at 2500rpm for 10 minutes and the blood serum was collected and utilized to analyze biochemical parameters and estimation of liver enzymes and the standard diagnostic kits and semi autoanalyzer instrument was used for evaluation of lipoproteins (HDL, triglycerides, LDL, total cholesterol), liver enzymes (SGOT, SGPT, ALP, and LDH) and tissue antioxidants (superoxide dismutase, catalase, thiobarbituric acid reactive species, and glutathione).[18]

In vivo antioxidant enzymes assay and histological Analysis

Immediately following sacrifice, a tiny part of the liver tissues from each rat group was removed and with ice-cold phosphate buffer it was homogenized for estimation of tissue antioxidants was performed using a UV spectrophotometer (SHIMADZU 1900), and other parts of the liver tissues of each group were fixed for histopathology study in 10% formalin were prepared with pH of 7.4 phosphate buffer kept at room temperature for 24 hours. Before being examined under a light microscope, tissue-fixed slides were stained with hematoxylin and eosin.

Statistical analysis

The data were presented as mean±SEM and were analyzed using one-way ANOVA followed by Tukey-Kramer multiple comparison tests, with $P<0.05$ considered statistically significant. The statistical program used for data analysis was GraphPad Prism 6.01.

RESULTS AND DISCUSSION

Ethanolic extraction and Phytochemical screening

In the current study, the percentage yield was obtained at 18% and Aisha FA *et al.,* (2013) performed a study on *S.Campanulatum* methanolic extract was obtained with a percentage yield (16.4 percent, w/w) compared to this study in the present study percentage yield was higher i.e. in the percentage yield is high in ethanolic extracts than methanolic extract. The qualitative phytochemical results showed the existence of alkaloids, flavonoids, steroids and triterpenoids, cardiac glycosides, carbohydrates, phenol, saponin, and tannins.

Effect of extracts on serum lipid level

The increased blood lipid concentration

is a significant modifiable dangerous factor for developing atherosclerosis and cardiovascular disease. It is a class of metabolic diseases characterized by a rise in blood lipid levels. Cholesterol, cholesterol esters, phospholipids, and triglycerides are examples of lipids. LDL cholesterol levels that are elevated are linked to the development of atherosclerosis.

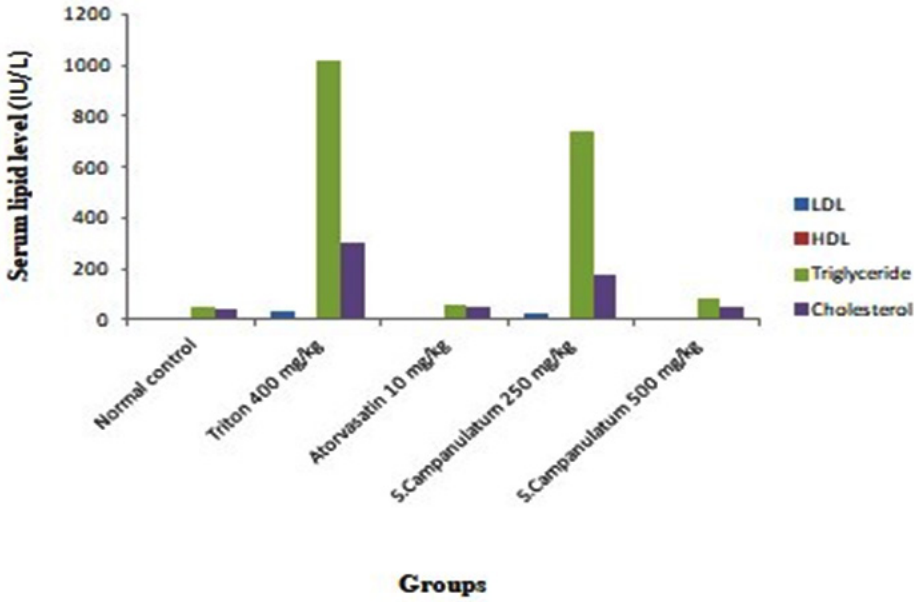

Fig. 1. Effect of *S.Campanulatum* on triton-induced hyperlipidemic rat's serum triglycerides, total cholesterol, LDL, and HDL level

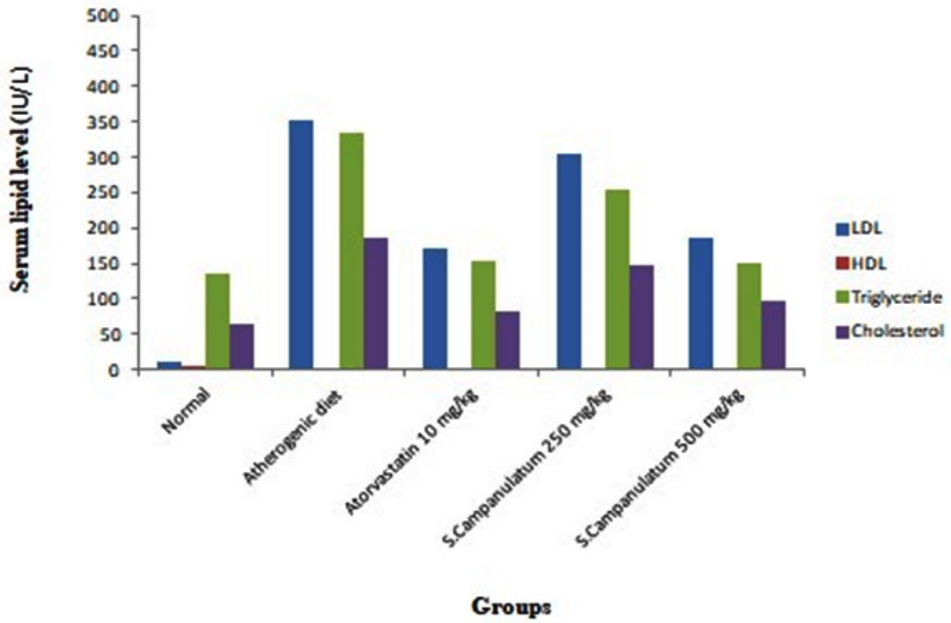

Fig. 2. Effect of *S.Campanulatum* on atherogenic diet-induced hyperlipidemic rat's serum total cholesterol, triglycerides, and phospholipids level

Effect of extracts on triton-induced hyperlipidemia

The hyperlipidemia induced by triton is via several mechanisms, primarily by inhibiting lipoprotein lipase activity, preventing their uptake from circulation through extrahepatic tissues, resulting in an increased level of circulating lipoproteins, which can result in the blockage of TG-rich lipoprotein clearance. A single dose of triton in experimental animals increased serum lipid levels.[19,20] which was compared to our study the experimental animals were injected with alone triton WR-1339 400 mg/kg led to the elevation of serum triglyceride 1021.455±3.986, cholesterol 304.892±3.825, LDL-C 32.931±4.003 level, and decreased HDL-C 0.139±0.031 values in rats when compared with normal control rats triglyceride 48.749±1.524, cholesterol 41.181±0.998, LDL-C 0.903±0.209 and HDL-C 2.178±0.264. At this time, in the rats treated with *S.Campanulatum* 250 and *S.Campanulatum* 500 mg /kg and standard drug atorvastatin10 mg/kg significant serum lipid-lowering effect was observed triglyceride 738.359±3.348, 80.505±3.840 59.900±0.649, cholesterol 171.823±1.821, 48.141±2.905, 49.758±0.918, LDL-C 20.798±2.570, 6.697±2.041, 10.758±1.825 when compared to triton 400 mg/kg and increased level of HDL-C 0.831±0.050, 1.822±0.154 and 1.136±0.092 was also observed. *S. Campanulatum* hypolipidemic activity could,

Table 1. Effect of *S.Campanulatum* on SGOT, SGPT, ALP, and LDH in atherogenic diet-induced hyperlipidemia in Rats

Treatment	SGPT (IU/L)	SGOT (IU/L)	ALP (IU/L)	LDH (IU/L)
N.Control	64.547±1.141	114.385±1.264	166.513±0.949	293.246±1.011
Atherogenic diet	131.946±2.692***	229.769±0.657***	690.201±4.735***	769.417±4.140***
S. Campanulatum 250 mg/kg	113.970±0.982^{abc}	180.804±0.855 ^{abc}	465.081±4.761^{abc}	513.496±0.816^{abc}
S. Campanulatum 500 mg/kg	68.530±2.014^{abc}	144.776±3.022 ^{abc}	249.081±1.866^{abc}	338.236±0.776^{abc}
Atorvastatin 10 mg/kg	96.072±0.791^{abc}	120.802±0.924 ^{abc}	179.966±0.794^{abc}	394.781±0.813^{abc}

The results were reported as mean±SEM and analyzed using one-way ANOVA followed by Tukey-Karmer multiple comparison tests. Values were considered statistically significant when $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ as compared to the normal group and $^{a}P<0.05$, $^{ab}P<0.01$, $^{abc}P<0.001$ compared to the atherogenic diet group (n=6). SGPT- Serum Glutamic Pyruvic Transaminase, SGOT- Serum Glutamic Oxaloacetic Transaminase, ALP- Alkaline phosphatase, LDH- Lactate dehydrogenase.

Table 2. Effect of *S.Campanulatum* on *in vivo* antioxidant enzymes in diet hyperlipidemic rat model

Treatment	Glutathione (µg/mg protein)	LPO (µg/mg protein)	Catalase (µg/mg protein)	SOD (µg/mg protein)
N.Control	77.213±0.803	6.535±0.603	95.390±1.557	24.873±0.156
Atherogenic diet	2.121±0.382***	26.101±0.826***	21.053±0.725***	4.308±0.362***
S. Campanulatum 250 mg/kg	22.926±0.513^{abc}	14.550±0.377^{abc}	49.691±1.375^{abc}	9.685±0.763^{abc}
S. Campanulatum 500 mg/kg	57.308±0.550^{abc}	7.065±0.374^{abc}	78.726±2.807^{abc}	19.201±0.710^{abc}
Atorvastatin 10 mg/kg	65.668±1.533^{abc}	6.830±0.626^{abc}	89.180±1.611^{abc}	23.240±0.291^{abc}

The results were reported as mean±SEM and analyzed using one-way ANOVA followed by Tukey-Karmer multiple comparison tests. Values were considered statistically significant when $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ as compared to the normal group and $^{a}P<0.05$, $^{ab}P<0.01$, $^{abc}P<0.001$ compare atherogenic diet group (n=6). LPO-Malondialdehyde, (Lipid peroxidation), SOD-Superoxide dismutase.

therefore, either increase the activity of lipolytic enzymes or stimulate fecal bile acid excretion, resulting in lower circulating lipoprotein levels. [21,22]

S. Campanulatum appears to have no negative effects in normal rats based on its effects on organ function markers and other biochemical indices, and it is pharmacologically effective and independent of negative side effects in hyperlipidemic rats with impaired cardiac, hepatic, and renal functions. increased serum creatinine levels as a defense against kidney damage.[23,24] The histopathological investigation of the liver segment of the normal control rats (Fig. 4a) revealed normal hepatic cell arrangements with no changes. Histopathological investigation of the liver section of rats treated with triton 400 mg/kg treated group (Fig. 4b) revealed that different degrees of pathological changes such as the nucleus

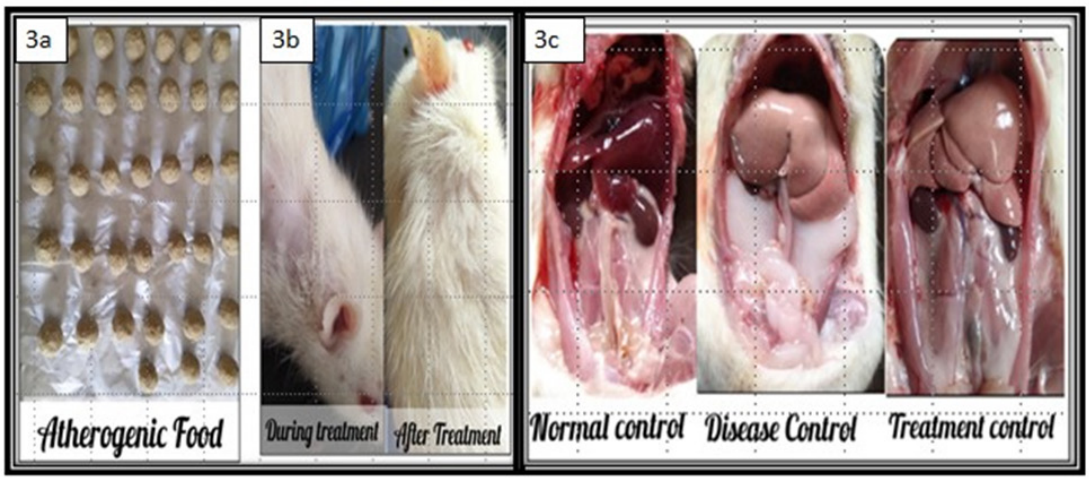

Fig. 3. (3a) Atherogenic diet (3b) Hair loss during treatment and changes after treatment (3c) Difference between the pathology of liver of normal control, hyperlipidemic rats and rats treated with extracts

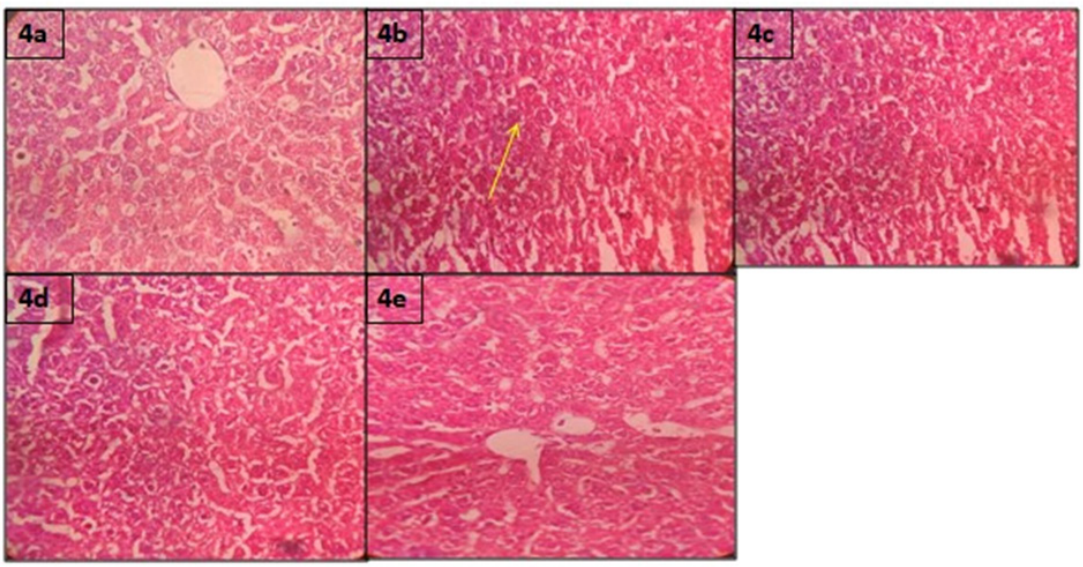

Fig. 4. Effect of *S.Campanulatum* on the morphology of liver in Triton 400 mg/kg diet-induced hyperlipidemia in rats (magnification 40x) 4(a) Normal Control, 4(b) Triton 400 mg/kg, 4(c) *S.Campanulatum* 250 mg/kg, 4(d) *S.Campanulatum* 500 mg/kg, 4(e) Atorvastatin 10 mg/kg. The yellow arrow represents the necrosis of hepatic cells and the absence of a nucleus.

was absent, there is degeneration of fat in the center lobules, hepatic cell necrosis, and cloudy swelling. The microscopic examination revealed that in rats treated with *S.Campanulatum* 250 mg/kg (Fig.4c), there is moderate damage in liver cells some nucleus are absent but there was the recovery of the damaged cells to normal. The liver section of rats treated with *S.Campanulatum* 500 mg/kg and atorvastatin 10 mg/kg (Fig. 4d, 4e,) revealed that near normal arrangement hepatic cells and central vein were present, the results are related to the normal control group.

Effect of extracts on diet-induced hyperlipidemia

Induction of hyperlipidemia with atherogenic diet rats showed hair fall (Figure 3b) and the presence of extended adipose tissue in their intra-abdominal space and fatty liver were seen in the rats treated with atherogenic diet as compared to normal control rats where abdominal space consist of normal fats and normal liver organ and the rats treated with extracts recover from the hair fall and intra-abdominal fat was reduced as compared to atherogenic diet groups (Figure 3c). Jayant S *et al.,* (2012) noticed that providing all the animals with repeated administration of cholesterol and cholic acid (dissolved in ground nut oil) for 28 days elevated the main lipid profile parameters, including LDL-C, TG, VLDL-C, cholesterol, and decreased HDL-C.[17] The atherogenic diet used in this study was also containing a mixture of cholesterol and cholic acid dissolved in peanut oil. The data shown in Table 1 represent that feeding rats with an atherogenic diet caused a substantial ($p < 0.001$) rise in serum triglyceride 335.036±2.764, LDL-C 351.296±2.187, total cholesterol 186.203±1.328, and a significant ($p < 0.001$) reduction in serum HDL-C 0.245±0.029 when compared to the control group. When compared to the atherogenic diet group, oral administration of atorvastatin to rats resulted in a substantial ($p < 0.001$) decrease in blood levels of triglyceride 154.120±4.606, LDL-C 172.128±1.649, and, total cholesterol 83.207±3.818 as well as a significant ($p < 0.001$) rise in HDL-C 2.563±0.032 levels. The hyperlipidaemic rats that received *S.Campanulatum* 250/500 mg/kg showed a significant ($p < 0.001$) decline in serum levels of triglyceride 254.940±4.279, 148.804±2.655, total cholesterol 145.739±1.352, 98.074±2.681, LDL-C

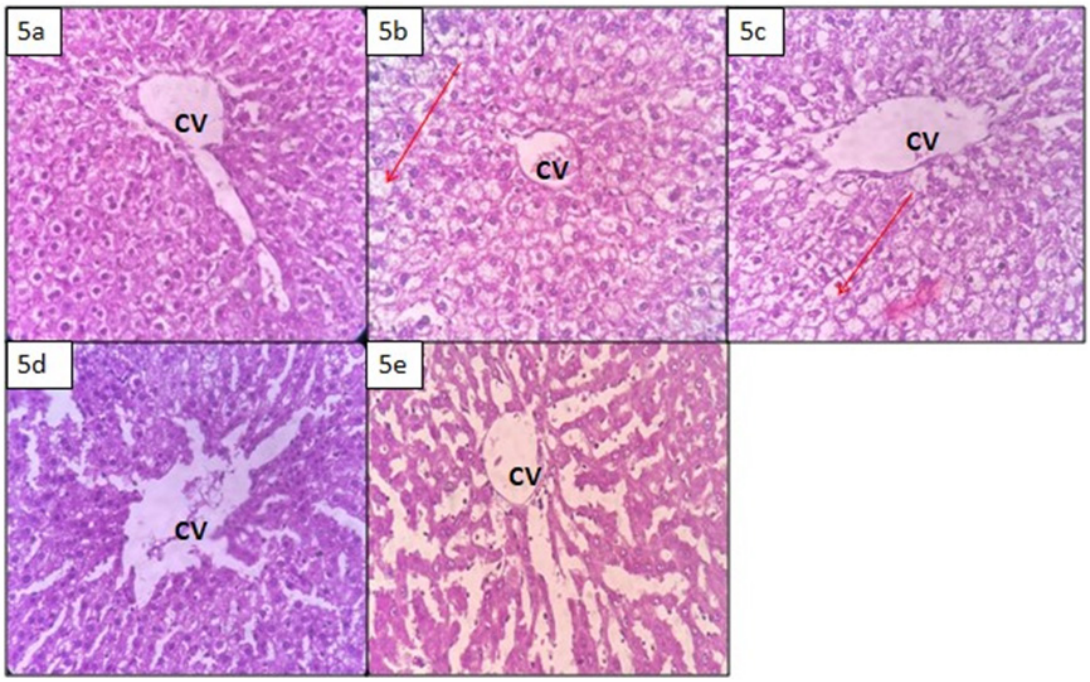

Fig. 5. Effect of *S.Campanulatum* on the morphology of liver in atherogenic diet-induced hyperlipidemia in rats (magnification 40x) 5(a) Normal Control, 5(b) Atherogenic Diet Control, 5(c) *S.Campanulatum* 250 mg/kg, 5(d) *S.Campanulatum* 500 mg/kg, 5(e) Atorvastatin 10 mg/kg. The red arrow indicates the fat deposited in the cytoplasm, CV- central vein.

304.591±2.661, 184.932±4.768 and substantial ($p < 0.001$) increase in HDL-C 1.556±0.045, 2.4±0.028 respectively, compared to rats on a high-fat diet. Significant ($p< 0.01$) differences were identified between doses of both plant extracts, indicating that this lipid-lowering action was dose-dependent.[25] However, the lipid-lowering impact of conventional medicine (atorvastatin) was still greater than that of *s.campanulatum* leaf extracts. A possible mechanism of action for S. campanulatum extracts is an increase in HDL-C, which is linked to the mobilization of cholesterol from peripheral cells to the liver by the activity of Lecithin Cholesterol O-acyltransferase (LCAT).[26] The LCAT enzyme is involved in the processes of HDL maturation, cholesterol flux from cell membranes into HDL, and cholesterol transesterification. Diet-induced hyperlipidemia tends to result in a decrease in enzyme activity. [27]

Effects of extracts on liver function enzymes in an atherogenic diet-induced hyperlipidemic rat model

A chronic disease called nonalcoholic fatty liver disease has a strong correlation with obesity. Additionally, the emergence of a fatty liver is one of the most typical symptoms of those with hyperlipidemia. Various studies have shown that high-fat feeding caused laboratory animals to have decreased HDL-C levels and increased TC, TG, LDL-C, and Atherogenic index levels in their serum.[28] Thus, we also investigated *S.Campanulatum's* impact on liver lipids. The liver function enzymatic activities were evaluated in the control group, atherogenic diet group, and atherogenic diet rats were given the standard drug atorvastatin or extracts at two different doses for comparison (Table 1). When the disease group was compared to the normal control, there was a significant ($p<0.001$) increase in liver function enzymatic activities (SGOT, SGPT, ALP, LDH) in the atherogenic diet-induced hyperlipidemic rat group. The hyperlipidaemic rats receiving *S.Campanulatum* 250/500 mg/kg revealed a substantial ($p < 0.001$) decline in serum levels of SGOT, SGPT, ALP, and LDH compared to rats of atherogenic diet control.[29] Furthermore, atorvastatin treatment improved the levels of SGOT, SGPT, ALP, and LDH in rats with atherogenic diet-induced hyperlipidemia.

Effect of extracts on *in vivo* antioxidant enzymes in atherogenic diet hyperlipidemic rat model

It is known that high-fat diets cause more oxidative stress across different tissues, which may lead to some physically degenerative diseases. Although the activities of glutathione peroxidase (GPx) and superoxide dismutase (SOD) were assessed as indicators of serum or liver antioxidant capacities, the contents of malondialdehyde (MDA) in the serum or liver served as a marker to ascertain the lipid peroxidation levels in the serum and liver, respectively.[28] In this study Administration of an atherogenic diet for 3 weeks lowered the liver GSH level and at the same time increased the LPO. Treatment with extracts *S.Campanulatum* 250/500 mg/kg replenished GSH levels and caused a decrease in LPO levels caused by the treatment of an atherogenic diet. The activities of the antioxidant enzyme SOD were decreased in atherogenic diet group administration compared to induced liver damage (Table 2). Treatment of the extracts counteracted the observed decrease in the activity of the enzyme.

Histopathological observation

Microscopical analysis of a liver segment from the normal control group (Fig. 5a) revealed normal hepatic cell organization. Microscopical examination of the atherogenic diet-treated group's liver segment (Fig. 5b) revealed varying degrees of pathological alterations, including severe fatty degeneration, cloudy swelling, and hepatic cell necrosis, Boobalan Raja found comparable fatty changes in the hepatic tissue of hypercholesterolemic rats.[30] Histopathological study of rats treated with *S.Campanulatum* 250 mg/kg (Fig. 5c) showed less severe fatty changes compared to disease control. Some damaged hepatic cells were seen. Microscopical examination of *S.Campanulatum* 500 mg/kg treated group's liver section (Fig. 5d) revealed mild fatty changes and recovery of damaged hepatic cells to normal. Rats given the standard drug (Fig. 5e) had normal hepatic cells and central veins, which were comparable to the normal control group.

CONCLUSION

The present study concluded that this is the first study of the antihyperlipidemic activity of

S.Campanulatum ethanolic leaf extract. Ethanolic extract at a high dose (500 mg/kg) has an effective reduction of hyperlipidemia in a triton and high atherogenic diet model, with comparable effects when compared to the Atorvastatin-treated group. The protective effect of plant extract is also revealed by histopathological studies. The active component in the plant may be able to reverse the lipid metabolic abnormalities seen in hyperlipidemia, however further research is needed to find out the active elements responsible for the activity and mechanisms of these benefits. As a result, it can be used as a therapeutic antihyperlipidemic drug or as an adjuvant to current hyperlipidemia treatment.

ACKNOWLEDGMENT

The authors are thankful to the management of Yenepoya (Deemed to be University), Mangalore

Conflict of Interest

There are no conflicts of interest regarding the publication of this article

REFERENCES

1. Aisha AFA, Ismail Z, Abu-Salah KM, Siddiqui JM, Gafar G, Majid AMSA. Syzygium campanulatum Korth methanolic extract inhibits angiogenesis and tumor growth in nude mice. BMC Complement Altern Med. 2013;13(1):168-79.
2. Memon AH, Ismail Z, Aisha AF, Al-Suede FS, Hamil MS, Hashim S, Saeed MA, Laghari M, Abdul Majid AM. Isolation, characterization, crystal structure elucidation, and anticancer study of dimethyl cardamonin, isolated from Syzygium campanulatum Korth. Evidence-Based Complementary and Alternative Medicine. 2014 Jan 1;2014.
3. Hmidani, Abdelbasset, et al. Effect of phoenix dactylifera seeds (dates) extract in triton WR-1339 and high fat diet-induced hyperlipidemia in rats: a comparison with simvastatin. J Ethnopharmacol, 2020, 259: 112961.
4. Nie, Chaohong, et al. Determination of quality markers of Xuezhiling tablet for hyperlipidemia treatment. Phytomedicine, 2018, 44: 231-238.
5. Cicero, Arrigo FG; Colletti, Alessandro. Combinations of phytomedicines with different lipid-lowering activity for dyslipidemia management: the available clinical data. Phytomedicine, 2016, 23.11: 1113-1118.
6. Zafari AM, Yang EH. Myocardial infarction. Practice essentials 2018.
7. Durkar AM, Patil RR, Naik SR. Hypolipidemic and antioxidant activity of ethanolic extract of Symploccus racemosa Roxb. In hyperlipidemic rats: An evidence of participation of oxidative stress in hyperlipidemia. Indian J Exp Biol. 2013; 52:36-45.
8. Kaliora AC, Dedoussis GV, Schmidt H. Dietary antioxidants in preventing atherogenesis. Atherosclerosis. 2006;187(1):1-7.
9. WU, Pin-Hsin; HAN, Samuel Chieng-Haw; WU, Meng-Hsiu. Beneficial effects of hydroalcoholic extract from Rosa roxburghii Tratt fruit on hyperlipidemia in high-fat-fed rats. Acta Cardiologica Sinica, 2020, 36.2: 148.
10. HE, Dongye, et al. Hypolipidemic Activity of Camellia euphlebia Flower Extract in High–fat-fed Mice. Plant Foods for Human Nutrition, 2017, 72.4: 372-379.
11. EL-TANTAWY, Walid Hamdy, et al. The anti-hyperlipidemic activity of an extract from roots and rhizomes of Panicum repens L. on high cholesterol diet-induced hyperlipidemia in rats. Zeitschrift für Naturforschung C, 2015, 70.5-6: 139-144.
12. Moss JN, Dajani E. Antihyperlipidemic agents. In: Turner RA, Hebborn P, editors. Screening methods in toxicology. New York: Academic Press, Vol. 2, 1971:121
13. Lee K, Bode A, Dong Z. Molecular targets of phytochemicals for cancer prevention. Nat Rev Cancer 2011;11:211-8.
14. Zhao S, Wang Y, Zhang X, et al. Melatonin protects against hypoxia/reoxygenation-induced dysfunction of human umbilical vein endothelial cells by inhibiting reactive oxygen species generation. Acta Cardiol Sin 2018;34:424-31.
15. Cimen B, Uz A, Cetin I, et al. Melatonin supplementation ameliorates energy charge and oxidative stress induced by acute exercise in rat heart tissue. Acta Cardiol Sin 2017;33:5308.
16. Leyva-Soto A, Chavez-Santoscoy R, Lara-Jacobo L, et al. Daily consumption of chocolate rich in flavonoids decreases cellular genotoxicity and improves biochemical parameters of lipid and glucose metabolism. Molecules 2018;23:2220
17. Bidkar JS, Ghanwat DD, Bhujbal MD, Dama GY. The anti-hyperlipidemic activity of Cucumis melo fruit peel extracts in high cholesterol diet induced hyperlipidemia in rats. Journal of Complementary and IntegrativeMedicine.2012Sep4;9(1).
18. Sikarwar MS, Patil MB. Antihyperlipidemic activity of Salacia chinensis root extracts in triton-induced and atherogenic diet-induced hyperlipidemic rats. Indian J Pharmacol. 2012;44(1):88-92.

19. Akinmoladun AC, Adegbamigbe AD, Okafor NR, Josiah SS, Olaleye MT. Toxicological and pharmacological assessment of a multiherbal phytopharmaceutical on Triton X 1339 induced hyperlipidemia and allied biochemical dysfunctions. Journal of Food Biochemistry. 2021 Mar;45(3):e13238.
20. Ramchoun M, Khouya T, Harnafi H, Amrani S, Alem C, Benlyas M, Kasbi Chadli F, Nazih EH, Nguyen P, Ouguerram K. Effect of aqueous extract and polyphenol fraction derived from Thymus atlanticus leaves on acute hyperlipidemia in the Syrian Golden Hamsters. Evidence-Based Complementary and Alternative Medicine. 2020 Mar 28;2020.
21. Manuwa TR, Akinmoladun AC, Crown OO, Komolafe K, Olaleye MT. Toxicological assessment and ameliorative effects of Parinari curatellifolia alkaloids on triton-induced hyperlipidemia and atherogenicity in rats. Proceedings of the National Academy of Sciences, India Section B: Biological Sciences. 2017 Jun;87(2):611-23.
22. Patil RH, Prakash K, Maheshwari VL. Hypolipidemic effect of Celastrus paniculatus in experimentally induced hypercholesterolemic Wistar rats. Indian journal of clinical biochemistry. 2010 Oct;25(4):405-10.
23. El-Demerdash FM, Nasr HM. Antioxidant effect of selenium on lipid peroxidation, hyperlipidemia, and biochemical parameters in rats exposed to diazinon. Journal of Trace Elements in Medicine and Biology. 2014 Jan 1;28(1):89-93.
24. LEE, Se-Eun, et al. Effect of Ephedrae Herba methanol extract on high-fat diet-induced hyperlipidaemic mice. Pharmaceutical biology, 2019, 57.1: 676-683.
25. Yaribeygi H, Simental Mendía LE, Butler AE, Sahebkar A. Protective effects of plant derived natural products on renal complications. Journal of cellular physiology. 2019 Aug;234(8):12161-72.
26. Khanna AK, Rizvi F, Chander R. Lipid lowering activity of Phyllanthus niruri in hyperlipidemic rats. Journal of Ethnopharmacology. 2002 Sep 1;82(1):19-22.
27. Zulet MA, Barber A, Garcin H, Higueret P, Martinez JA. Alterations in carbohydrate and lipid metabolism induced by a diet rich in coconut oil and cholesterol in a rat model. Journal of the American College of Nutrition. 1999 Feb 1;18(1):36-42.
28. Zhu Z, Lin Z, Jiang H, Jiang Y, Zhao M, Liu X. Hypolipidemic effect of Youcha in hyperlipidemia rats induced by a high-fat diet. Food & function. 2017;8(4):1680-7.
29. Alqarni, Mohamed MM, et al. Antioxidant and antihyperlipidemic effects of Ajwa date (Phoenix dactylifera L.) extracts in rats fed a cholesterol rich diet. Journal of food biochemistry, 2019, 43.8: e12933.
30. Raja B, Saravanakumar M, Sathya G. Veratric acid ameliorates hyperlipidemia and oxidative stress in Wistar rats fed an atherogenic diet. Molecular and cellular biochemistry. 2012 Jul;366(1):21-30.