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The Effect of *Syzygiumpolyanthum* Extract in Lipid Profile of Hypercholesterolemic Animal Model

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Abstract: Syzygiumpolyanthum (Sp) extract has the potential as an antioxidant, anti-inflammatory, and antidiabetic activity due to the presence of flavonoids. This study aimed to explore the anti hypercholesterolemia potential of Sp leaves extract in rats. Thirty male Wistar rats, ranging from 200-250 grams body weight, were randomly divided into five groups (group 1: normal group; group 2: hypercholesterol rats without treatment; group 3: hypercholesterol rats with simvastatin treatment; group 4: hypercholesterol rat with Sp extract 100 mg/kg BW; group 5: hypercholesterol rats with Sp extract 200mg/kg BW). The induction of hypercholesterolemia rats was done by giving high cholesterol diet (HCD). This study showed that Sp extract and simvastatin treatment have improved HDL levels and normalized the elevated levels of cholesterol and LDL. The antioxidant components were decreased in all hyperlipidemic groups compared to group 1. Sp extract was proven to improve SOD level and catalase as an indication of improvement in antioxidant potential. Sp extract treatment has improved the levels of SOD and catalase as an indication of improvement in the antioxidant potential. In conclusion, our results show that Sp extract can improve the hypercholesterolemic condition through ameliorating dyslipidemia, reducing HMG-CoA content, binding of bile acids, and improving the antioxidant status.

Keywords: antioxidants, hypercholesterolemia, catalase, Syzygium, hyperlipidemias.

蒲公英提取物对高胆固醇血症动物模型血脂谱的影响

摘要:

由于黄酮类化合物的存在，蒲公英(斯普)提取物具有作为抗氧化、抗炎和抗糖尿病活性的潜力。本研究旨在探讨斯普叶提取物在大鼠体内的抗高胆固醇血症潜力。30只雄性威斯塔大鼠，体重200-

250克，随机分为5组（第1组：正常组；第2组：未治疗的高胆固醇大鼠；第3组：辛伐他汀治疗的高胆固醇大鼠；第4斯普提取物100毫克/公斤体重；第5组：斯普提取物200毫克/公斤体重的高胆固醇大鼠）。通过给予高胆固醇饮食（硬质合金）来诱导高胆固醇血症大鼠。该研究表明，斯普提取物和辛伐他汀治疗改善了高密度脂蛋白水平，并使升高的胆固醇和低密度脂蛋白水平正常化。与第1组相比，所有高脂血症组的抗氧化成分均有所降低。证明斯普提取物可提高草皮水平和过氧化氢酶，作为抗氧化潜力提高的指标。斯普提取物处理提高了草皮和过氧化氢酶的水平，作为抗氧化潜力提高的指标。总之，我们的结果表明，斯普提取物可以通过改善血脂异常、降低HMG-

辅酶一种含量、结合胆汁酸和改善抗氧化状态来改善高胆固醇血症。

关键词: 抗氧化剂，高胆固醇血症，过氧化氢酶，合子，高脂血症。

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1. Introduction

Hypercholesterolemia is a metabolic disease characterized by increased cholesterol and lipoproteins in the blood plasma [1]. These conditions can lead to various metabolic disorders such as cardiovascular disease and diabetes, which are major socio-economic problems resulting from a combination of modern lifestyle and dietary habits [2]. In hypercholesterolemia conditions, increased levels of low-density lipoprotein (LDL) in the subendothelial area of the arteries will cause inflammation and plaque formation, which ultimately results in hypertension, decreased potential function of metabolic organs (liver and kidney), and diabetes [3]. Clinical trials conducted on hypercholesterolemia have shown that drugs that reduce lipid levels significantly reduce morbidity and mortality [4]. Elevated LDL cholesterol levels increase atherosclerosis risk and promote cardiovascular disease development [5]. Dyslipidemia is a condition associated with uncontrolled type II DM [6].

Syzygiumpolyanthum is a medicinal plant that has been used from generation to generation as a kitchen spice or used to treat various health problems [7, 8]. This herb has been studied to explore various pharmacological effects [8, 9]. Several studies extensively demonstrated its phytochemical composition, antioxidant potential, and antidiabetic potential in vitro and in vivo [9, 10]. Previous studies have shown the potential of *S. polyanthum* in a diabetic animal model showing the ability to lower glucose. In contrast, the potency of *S. polyanthum* on blood glucose can lower blood cholesterol [11]. This study is the first study to explore the antioxidant mechanism of S.polyanthum in lowering blood cholesterol levels. This study aimed to explore the role of *S. polyanthum* extract on the lipid profile of hypercholesterolemic rats.

2. Methods/Material

2.1. Ethical Approval

Our animal experiments were conducted with the permission of the Institutional Animal Care and Use Committee, Faculty of Medicine of Universitas Sriwijaya (No. 299/kptfkunsri-rsmh/2020). All experimental procedures in this study were performed according to PREPARE: guidelines for planning animal research and testing [12].

2.2. *Syzygiumpolianthum* Extract (SPE) Preparation

Leaves of *Syzygiumpolyanthum*, obtained from the Department of Botany, Institute Pertanian Bogor (Bogor Institute of Agriculture), Indonesia, were finely powdered with an electric grinder. The water extract (WE), similar to that traditionally used to make tea, was made by boiling 20 g of the dry plant material in 500 ml of water, followed by filtration and lyophilization. The ethanol-water extract (EWE) was processed by adding 20 g of the simplicia to 800 ml of an ethanol-water mixture (50:50). The extract was then warmed at 40◦C for 4 hours; after that, it was filtered three times, followed by evaporation in a Büchi rotary evaporator.

2.3. Animals

Thirty male Wistar rats (*Rattus novergicus)* were obtained from Eureka Laboratory and Experimental Animal Breeding Co., Ltd (Palembang, Indonesia), ranging from 200-250 grams body weight. After acclimatization for seven days, these rats were randomly divided into five equal groups. All rats were housed under a 12 h light/dark cycle with ad libitum access to water and food.

One control group kept only routine feed; the rest of the groups were also fed a high cholesterol diet (HCD). The induction of hypercholesterolemia rats was done by giving HCD with the following composition: wheat flour 60 g/100 g, Soy flour 17.75 g/100 g, peanut oil 10 g/100 g, sugar 7 g/100 g, salt mixture 2 g/100 g, vitamin mix 1 g/100 g, cholesterol 2 g/100 g, cholic acid 0.25 g/100 g. HCD administration was carried out for four weeks.

Simvastatin tablet (20 mg, Dexamedica, Palembang, Indonesia) was used as a cholesterol-lowering synthetic drug. The drugs and S. polyanthum extract were intubated orally with a ball-tipped intubation tube to individual experimental rats in the morning at least one hour before the normal routine feeding. The feeding and drug administration schedule has been presented in Table 1.

Next, blood was drawn from the veins in the rats to measure cholesterol levels. Rats with cholesterol levels of more than 120 mg/dL were selected to be included in the study. Furthermore, the animals were fasted overnight and were euthanized by intraperitoneal injection of 10% chloral hydrate (0.3 ml / 100 g) and beheaded at 10 pm to compensate for the circadian rhythm of lipid synthesis. The blood was collected in procoagulant-coated tubes via cardiac puncture methods. The blood was allowed to clot by keeping the tubes undisturbed for 2 hours. The blood coagulation was centrifuged at 2500 ×g for 20 minutes for serum separation. The serum was stored at -20^{o}C until used.

Total protein, total lipid, bile acids, lipid peroxides, and glutathione were analyzed using diagnostic kits (Agappe Diagnostics, Cham, Switzerland). The VLDL was calculated using the relation VLDL cholesterol = TG/5. AST, ALT, and ALP activities were determined using standard kits (Agappe Diagnostics, Cham, Switzerland). Antioxidant enzyme activities (SOD and catalase) were assessed by analysis kit (Sigma Aldrich, Singapore). All chemical compounds and reagents used in the study were of analytical grade.

Liver, kidney, brain, and heart were excised shortly after decapitation, washed with phosphate-buffered saline blotted using blotting sheet, and weighed. The activity of HMG-CoA reductase was assessed in the

liver. For homogenization of the liver, kidney, and brain, the measured amount of the organs was taken in phosphate-buffered saline (1:5 weight/volume) and homogenized in ice-cold temperature. The homogenates were centrifuged at 2500 ×g for 5 minutes to precipitate the unhomogenized components and connective tissue. The supernatant was used to evaluate total protein, glutathione, and TBARS by previously described methods [13, 14].

2.4. Phytochemical Analysis of SPE

Phytochemical analysis of the plant was performed by extracting 60 g using a Soxhlet extractor with n-hexane (HE), then followed by methanol. The dry methanol extract was partitioned with butanol and water at a 1:1 ratio. The butanolic phase was then dried (BE), followed by evaporation of all of the extracts in a rotary Büchi evaporator. All of the extracts were kept at −4◦C until use [15].

2.5. Data Analysis

All experiments were performed in triplicates. The values for any experiment were the mean of the triplicate values. Values are expressed in the mean of triplicate experiments with standard deviation. Data were analyzed using SPSS 25.0 (SPSS, Inc., Armonk, NY, United States) by one-way analysis of variance (ANOVA) followed by post hoc analysis to assess the difference in mean expression levels of each protein. All data were expressed mean + standard deviation (SD), and a p-value of 0.05 was considered statistically significant.

2.6. Research Hypothesis

The hypothesis in this study is *that Syzygiumpolyanthum* extract can improve the hypercholesterolemic condition by ameliorating dyslipidemia, reducing HMG-CoA content, binding bile acids, and improving the antioxidant status.

3. Results

The body weights of experimental groups are described in Fig. 1. It was observed that the escalation in body weight was more significant in the experimental groups fed with high cholesterol diet than the normal control group fed with normal rodent feed. *S. polyanthum* extract treatment has reduced the increase in body weight when compared to group 2 and simvastatin groups.

The serum lipid profile of the experimental groups is displayed in Fig. 1 and 2. There was an elevated level of total cholesterol and LDL, whereas there were depleted HDL levels in group 2 compared to group 1. *S. polyanthum* extract and simvastatin treatment have improved HDL levels and normalized the elevated levels of cholesterol and LDL. HMG-CoA enzyme activity was measured by assessing the amount of CoA released (Table 3). The enzyme activity was highest in group 2 compared to simvastatin, *S. polyanthum* extract, and group 1. The activity was lowest in *S. polyanthum* extract-treated group, and the values were similar to the simvastatin group but higher than group 1. The antioxidant components were lessened in all hyperlipidemic groups compared to group 1. S. *polyanthum* extract treatment has ameliorated SOD and catalase level as an indicator of betterment in the antioxidant potential. Bile acid was also decreased with *S. polyanthum* extract treatment; thus, the *S. polyanthum* extract treatment has improved the antioxidant defense, reduced the activity of HMG-CoA, and reduced the contents of bile acid in the serum.

Serum biochemical parameters in the experimental groups are displayed in Table 2. It was observed that there were no considerable changes in serum protein, and albumin was observed between the hypercholesterolemic and normal control groups. However, there was a reduction in urea and creatinine levels between the hypercholesterolemic and normal control groups. Treatment with *S. polyanthum* extract has improved urea and creatinine levels towards normal compared to group 2, and the effect is dose-dependent.

Table 1 Feeding and drugs administration schedule in rats during the experimental period

Experimental group	Treatments
Untreated control and normal routine feed	Normal routine feed 0 to 56 days + aquadest ad libitum
Untreated control on high cholesterol diet	High cholesterol diet 0 to 28 days, normal routine feed 29 to 56 days, aquadest ad libitum
Treated group on simvastatin tablet	High cholesterol diet 0 to 28 days, normal routine feed + simvastatin tablet 29 to 56 days
Treated group on *S. polyanthum*extract100 mg/kg BW	High cholesterol diet 0 to 28 days, normal routine feed + *S. polyanthum* extract 100 mg/kg BW 29 to 56 days
Treated group on *S. polyanthum* extract 200 mg/kg BW	High cholesterol diet 0 to 28 days, normal routine feed + *S. polyanthum* extract 200 mg/kg BW 29 to 56 days

Table 2 Comparison of total protein, albumin, urea and creatinine levels between groups

Group	Total protein	Albumin	Urea	Creatinine
1	$6.42^{a} \pm 0.63$	$4.34^{a} \pm 0.38$	$48.34^{b} \pm 7.38$	$0.64^{a} \pm 0.18$
2	$6.92^{a} \pm 0.36$	$3.68^{a} \pm 0.19$	$40.12^{a} \pm 2.19$	$0.74^{a} \pm 0.19$
3	$6.88^{a} \pm 0.43$	$4.41^{a} \pm 0.24$	$41.34^{b} \pm 2.24$	$0.75^{a} \pm 0.24$
4	$6.67^{a} \pm 0.44$	$4.34^{a} \pm 0.38$	$43.34^{b} \pm 2.38$	$0.71^{a} \pm 0.38$

5	$6.52^{a} \pm 0.23$	$4.34^{a} \pm 0.38$	$42.34^{b} \pm 2.38$	$0.69^{a} \pm 0.38$

[a] p<0.05 VS group 2
[b] p>0,05 VS group 2; ANOVA pos hoc Bonferroni

Table 3 Comparison of HMG CoA reductase, bile acid, SOD and catalase levels between groups

Group	HMG CoA-reductase (nM/mg Pro)	Bile acid (μM/dL)	SOD (IU/mg Pro)	Catalase (IU/mg Pro)
1	$80.42^{b} \pm 4.63$	$0.44^{a} \pm 0.18$	$5.34^{a} \pm 1.38$	$18.34^{a} \pm 4.38$
2	$120.92^{a} \pm 6.36$	$0.68^{a} \pm 0.19$	$8.12^{a} \pm 2.19$	$18.12^{a} \pm 5.19$
3	$62.88^{b} \pm 3.43$	$0.51^{a} \pm 0.24$	$5.34^{a} \pm 2.24$	$25.34^{a} \pm 4.24$
4	$61.67^{b} \pm 4.44$	$0.39^{a} \pm 0.38$	$4.84^{a} \pm 2.38$	$19.84^{a} \pm 4.38$
5	$60.52^{b} \pm 4.23$	$0.31^{a} \pm 0.38$	$4.24^{a} \pm 2.38$	$18.24^{a} \pm 4.38$

[a] p<0.05 VS group 2
[b] p>0,05 VS group 2; ANOVA pos hoc Bonferroni

Table 4 Phytochemical test of SPE

Extract	Alkaloid	Triterpenoid	Flavonoid
SPE	+	+	+++

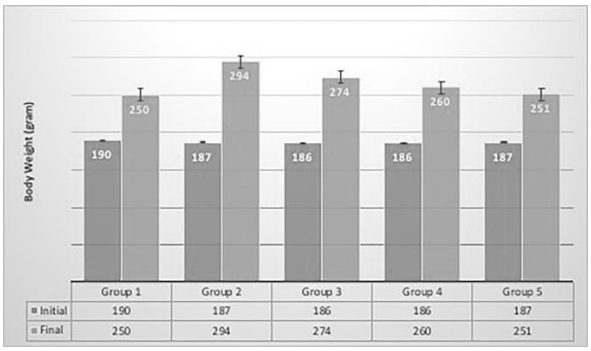

Fig. 1 The comparison of body weight of rats between treatment groups

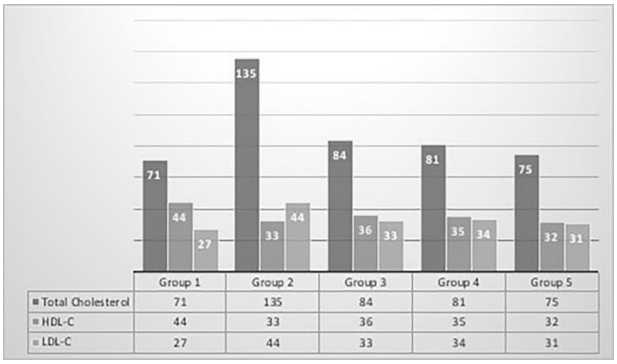

Fig. 2 Comparison chart of total cholesterol, HDL-C, and LDL-C between treatment groups

4. Discussion

Feeding rats with a diet containing high cholesterol content induces hypercholesterolemic conditions with damaged lipid profile and antioxidant defense. Oxidative stress, defined as a disturbance of the balance between oxidative and antioxidative processes, plays an essential role in atherosclerosis's pathogenesis [16]. Animal studies and human clinical trials have established a relationship between hypercholesterolemia and lipid peroxidation [4, 17]. The mechanism of initiation of atherogenesis results from the aggrandizement of oxidized lipids inside the artery wall. High cholesterol levels and LDL in plasma are prominent risk factors for atherosclerosis and cardiovascular diseases [2].

Herbal plants and their derivatives are promisingly gaining wide usage worldwide as they are a potential source of bioactive agents used as pharmaceuticals [7-9]. The phytochemical analysis test in this study shows that each SPE is rich in flavonoids. Flavonoids are the main secondary metabolites and are believed to play a role in inhibiting inflammation and oxidants associated with hyperglycemia [11].

Syzygiumpolyanthum has wide usage as a pharmaceutical agent in treating diabetes and has anti-inflammatory, antimutagenicity, and antitumor activities [8, 11]. There was an inflated level of total cholesterol and LDL in our study, whereas decreased HDL and antioxidant enzymes in the group hypercholesterolemic without treatment were observed. *S. polyanthum* treatment has improved the antioxidant enzyme levels, reduced the cholesterol content, improved the HDL levels, and reduced the serum's LDL content, promoting the lipid profile and the antioxidant status to a near-normal range. The widespread phenomenon may be attributed to HMG-CoA reductase's inhibition, a regulatory enzyme for cholesterol synthesis from the precursors. Statins, a group of anti hyperlipidemia drugs, act by inhibiting the HMG-CoA reductase enzyme [18]. Inhibition of cholesterol synthesis will decrease circulating LDL-C because reduced cholesterol levels in the hepatocyte cause it to upregulate the expression of the LDL-C receptors. In our study, the HMG-CoA activity in *S. polyanthum* group; activity was lower than the simvastatin group; the effect may be due to *S. polyanthum* extract on the enzyme synthesis rather than inhibiting its activity. The limitation of this study is that it was conducted in an animal model of diabetic nephropathy (in vivo), and the exact dose and safety have not been tested in humans.

5. Conclusion

In conclusion, our results show that *Syzygiumpolyanthum* extract can improve the hypercholesterolemic condition by ameliorating dyslipidemia, reducing HMG-CoA content, binding bile acids, and improving the antioxidant status. The use of *Syzygiumpolyanthum* extract in clinical situations requires further research and clinical trials of its proper dosage and safety in humans.

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