Unity in Diversity and the Standardisation of Clinical Pharmacy Services

Editors: Elida Zairina, Junaidi Khotib, Chrismawan Ardianto, Syed Azhar Syed Sulaiman, Charles D. Sands III and Timothy E. Welty
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Ethanol extract of *Annona squamosa* L. improves the lipid profile in hyperlipidemia rats

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**ABSTRACT:** Dyslipidemia is an important factor of cardiovascular disease. Sugar apple (*Annona squamosa* L.) fruit is empirically used to decrease the blood lipid. The aim of this study was to investigate the effect of the ethanol extract from sugar apple peel on lipid profile. Sprague–Dawley rats were given high-cholesterol food for 14 days. A total of 30 rats were divided into six groups, namely normal (I), negative (II) and positive/simvastatin control (III), and test groups, including extract doses of 125 (IV), 250 (V), and 500 mg/kg (VI). After 2 weeks, total cholesterol and triglyceride levels were decreased by 14.43%, 38.26%, 48.95%, 28.10%, 57.12%, and 65.22%, whereas HDL cholesterol levels were increased by 21.19%, 36.57%, and 40.30% in groups IV, V, and VI, respectively. There was no significant difference in total cholesterol and HDL cholesterol parameters between groups III and VI. The study showed that sugar apple peel can improve the lipid profile by lowering total cholesterol and triglyceride levels and increasing HDL cholesterol levels.

**1 INTRODUCTION**

Cardiovascular disease (CVD), which is initiated by atherosclerosis of the arterial vessel wall to the occurrence of further atherothrombotic, has become the most significant cause of morbidity and mortality in many countries, including Indonesia. Coronary artery disease (CAD), ischemic stroke, and peripheral arterial disease (PAD) are the most common manifestations of this group of disease. This disease involves very high direct and indirect healthcare costs (Reiner et al. 2011).

CVD is caused by many factors. Some factors such as age and male gender cannot be changed, while elevated blood pressure, type 2 diabetes mellitus, dys-lipidemias, inflammation, and oxidative stress are categorized as modifiable risk factors. Nowadays, modifiable factors relate to lifestyle changes such as tobacco smoking, lack of physical activity, and dietary habits and are known to contribute to the disease significantly (Reiner et al. 2011).

Dyslipidemia is a major risk factor for atherosclerotic CVD and it occurs before all other risk factors. Hypercholesterolemia and atherosclerosis increase the risk of ischemic cerebrovascular events. High cholesterol levels are associated with high levels of triglycerides and low-density lipoprotein cholesterol (LDL-C) and low levels of high-density lipoprotein cholesterol (HDL-C). Abnormalities of blood lipid levels also play a role in metabolic disease (Jellinger et al. 2017).

The result of basic health research in 2013 showed a 2% prevalence of coronary heart disease (CHD), 35.9% of abnormal cholesterol, 24.9% of non-optimal (high and very high) limits, 22.9% of low HDL-C levels, and 15.9% of high and very high LDL-C levels. The US Preventive Services Task Force (USPSTF) proves that lipid profile measurement can identify persons at risk of CHD but without presenting any clinical symptoms, and lipid-lowering drugs for them are recommended to lower the risk of CHD incidence without posing other significant risks (Badan Penelitian dan Pengembangan Kesehatan 2013).

Research and the use of lipid-lowering drugs have significantly improved recently, due to the increase of high-CVD cases. There are several synthetic lipid-lowering drugs that clinicians and patients can choose appropriately for specific cases. With regard to side effects and high cost of synthetic drugs, the use of herbal medicines has attracted the attention as alternative medicine. Empirical effectiveness, minimal side effects in clinical experience, and relatively low cost have increased the used of herbal medicine. Herbal drugs are used widely in Indonesia, even when the biologically active compounds are still unknown. The use of natural drugs for different diseases was approved by the World Health Organization (WHO). Therefore, it is necessary to know the efficacy, dosage, and mechanism of action and other aspects of herbal drugs (Panda et al. 2013).
Sugar apple fruit (*Annona squamosa* L) is widely consumed by Indonesians because of its good taste and benefits to the body. Almost all part of the plant, namely leaves, fruits, seeds, barks, and roots, have been used empirically as traditional medicine (Saha 2011).

*Annona squamosa* L, belonging to the family of Annonaceae was identified to have various pharmacological activities such as antidiabetic, antiinflammation, analgesic, antimalarial, antioxidant, antimicrobial, and cytotoxic. Rofida & Firdiansyah (2015) showed that ethanol extract of the leaves can reduce the LDL-C level of hyperlipidemia rat at dose 0.25 mg/g BW. Thus, the aim of this study was to determine the effect of sugar apple peel ethanol extract on lipid profile, based on total cholesterol, triglyceride, and HDL-C parameters.

2 METHOD

2.1 Materials

The study materials were sugar apple fruits obtained from Balai Penelitian Tanaman Rempah dan Obat (BALITRO), simvastatin tablet (Kalbe Farma, Jakarta, Indonesia) 0.18 mg/kg BW, and high-cholesterol foods that induce hyperlipidemia, consisting of 80% egg yolk, 15% sucrose solution, and 5% animal fat. Sprague–Dawley rats (2–3 months old) weighing 180–200 g were obtained from Faculty of Animal, Bogor Agricultural Institute. Reagent kit used for the examination of total cholesterol (Ref # 80106), triglycerides (Ref # 80019), and HDL-C (Ref # 90206) was obtained from Biolabo. Other reagents include Stiasny, Meyer, Dragendorff, Lieberman Burchard, ether, petroleum ether, ferric chloride 1%, amyl alcohol, ethanol 70%, and EDTA.

Tools used were glasses, mesh 4/18, rotary evaporators, water baths, analytical scales (AND GR 200), oral zonde, animal scales, syringes, microcentrifuge tubes, micropipettes, microcentrifuges (PLC-03), and Microlab L300 chemistry analyzer.

Sugar apple fruit was determined by Herbarium Bogoriense LIPI. Peel powder (500 g) was passed through mesh numbers 4 and 18 and then weighed. A total of 1250 g of peel powder was extracted by kinetic maceration using 35% of 70% ethanol, soaked for 6 h while stirring, and kept for 18 h before filtered. Remaceration was conducted until the macerate showed no color. The filtrate was concentrated by using a rotary evaporator (Kementrian Kesehatan RI 2011). Measurement of drug extraction ratio (DER), yield, and phytochemical screening were performed on viscous extract.

Phytochemical screening of Farnsworth (1966) includes the identification of parameters of alkaloids, flavonoids, saponins, tannins, quinones, steroids and triterpenoids, essential oils, and cou-marins on powder and sugar apple peel extract.

2.2 Testing method

Acclimation of 30 rats was performed for 1 week before randomizing the animals into the following six groups: group I (normal control), group II (negative control), group III (positive control), group IV (dose I), group V (dose II), and group VI (dose III). All groups except group I were given 20 g/kg BW hyperlipidemia inducing food for 14 days. Subsequent treatments were standard feeding for groups I and II, standard feeding as well as simvastatin 0.18 mg/kg BW and sugar apple peel extracts of doses of 125, 250, and 500 mg/kg BW for groups III, IV, V, and VI for 14 days.

2.3 Lipid profile analysis

Total cholesterol, triglyceride, and HDL-C are the test parameters in this study. Levels of total cholesterol and triglyceride were determined using CHOD-PAP and GPO-PAP enzymatic methods. HDL-C measurements used a specific detergent that would precipitate lipoproteins other than HDL; then, the cholesterol content of HDL in the supernatant was measured. The measurement was performed using Microlab 300 at a wavelength of 546 nm.

Plasma EDTA was used as sample. The specimens were taken from the orbital sinuses on days 0, 7, 14, 21, 28, and 35. Before sampling, the animals were weighed to obtain weight data.

3 RESULTS AND DISCUSSION

3.1 Sugar apple peel extract and phytochemical screening

The result of the determination of sugar apple powder used for extraction showed that 100% of powder can pass through mesh number 4 and 20.9% of powder can pass through mesh number 18, calculated against 100 g of peel powder. This result meets the quality requirement that is 100% can pass through mesh number 4 and not more than 40% can pass through mesh number 18 (Departemen Kesehatan RI 1995). The fine degree of the peel powder aims to enlarge the contact surface area between powder particles and solvent so that extraction of secondary metabolite could be optimal while not complicating the filtration process.

Viscous extract (108.6 g) was obtained from the extraction of 1.25 kg of sugar apple peel powder, with yield of 8.66% and DER of 11.55. Phytochemical screening indicates alkaloids, flavonoids,
saponins, quinones, tannins, steroids, and triter-penoids compounds in the extract of sugar apple peel.

3.2 Total cholesterol parameter

Total cholesterol was measured to determine the total cholesterol level at baseline, after hyperlipidemia food induction, and after treatment.

Table 1 shows that the average range of total cholesterol levels at baseline was 46.3–49.1 mg/dL. Kolmogorov–Smirnov and Levene test results showed normal distributed and homogeneous data. ANOVA test showed no significant difference (p > 0.05), which means that the baseline of total cholesterol in all the study groups was the same. Total cholesterol levels increased on day 7 (for groups II–VI) with a range of 79.0–87.7 mg/dL. The hyperlipidemia induction was continued until day 14 and obtained a range of 95.8–107.1 mg/dL. The results showed that induction for 14 days was more optimal in increasing total cholesterol levels.

On day 21, total cholesterol reduction occurred in all treatment groups, ranging from 70.9 to 97.8 mg/dL. Simvastatin decreased total cholesterol by 31.6%, dose I by 9.4%, dose II by 14.0%, and dose III by 25.8%. While on day 28, simvastatin lowered total cholesterol by 54.8%, dose I by 14.4%, dose II by 38.2%, and dose III by 48.9%. On the basis of these data, it can be proved that the antihypercholesterolemia effect strengthened after treatment for 14 days.

Results on day 35 showed a slight increase in cholesterol levels in all the treatment groups compared to day 28, but not significantly different (p > 0.05). This suggests that administration of simvastatin and ethanol extract of sugar apple peel for 2 weeks still gives effect even though the treatment has been stopped. Figure 1 shows the mean cholesterol levels during the study.

The post hoc LSD test result on day 21 found a significant difference between group II and groups III (p = 0.000) and VI (p = 0.000). This showed that simvastatin and dose III treatment for 7 days were able to significantly reduce the total cholesterol level. Meanwhile, the significant difference between groups II and V was obtained in the day 28 of analysis, which showed that a longer time was needed to obtain the antihyperlipidemia effect from the extract with a lower dose.

3.3 Triglyceride parameter

Triglyceride level was measured to determine the total triglyceride level at baseline, after hyperlipidemia food induction, and after treatment. Table 2 shows that the average range of triglyceride levels on day 0 was 35.3–38.2 mg/dL. ANOVA test showed no significant difference (p > 0.05) between the groups, which indicates the same baseline of triglyceride level in all the study groups, within normal limits.

Sucrose content on additional food was able to increase triglyceride levels on day 7 (for groups II–VI) with a range of 87.5–93.3 mg/dL. The hyperlipidemia induction was continued until day 14 and obtained a range of 151.0–173.2 mg/dL. The results showed that induction for 14 days was more optimal in increasing triglyceride levels.

![Figure 1. Total cholesterol levels during the study.](https://bookshef.vitalsource.com/#/books/9781351622974/cfl/6/126/l4/116/4@0:86.1)
### Cholesterol level (mg/dL)

<table>
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<tr>
<th>Days/group</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>47.9 ± 2.36</td>
<td>46.3 ± 216</td>
<td>46.6 ± 2.14</td>
<td>49.1 ± 3.14</td>
<td>47.6 ± 2.95</td>
<td>47.3 ± 1.98</td>
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<tr>
<td>7</td>
<td>50.9 ± 1.98</td>
<td>80.0 ± 4.88</td>
<td>79.0 ± 6.84</td>
<td>87.5 ± 5.85</td>
<td>87.7 ± 4.27</td>
<td>85.3 ± 3.46</td>
</tr>
<tr>
<td>14</td>
<td>55.0 ± 2.94</td>
<td>95.8 ± 5.49</td>
<td>103.7 ± 6.63</td>
<td>107.1 ± 8.88</td>
<td>104.1 ± 5.22</td>
<td>101.4 ± 5.40</td>
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<td>21</td>
<td>56.6 ± 3.68</td>
<td>95.8 ± 4.79</td>
<td>70.9 ± 3.23*</td>
<td>97.0 ± 7.58</td>
<td>89.5 ± 8.35</td>
<td>75.2 ± 4.82*</td>
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<tr>
<td>28</td>
<td>57.4 ± 3.29</td>
<td>97.2 ± 4.53</td>
<td>46.9 ± 1.84*</td>
<td>91.7 ± 5.83</td>
<td>64.3 ± 5.51*</td>
<td>51.8 ± 2.23*</td>
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<tr>
<td>35</td>
<td>59.5 ± 3.42</td>
<td>90.7 ± 5.33</td>
<td>48.7 ± 2.93</td>
<td>92.7 ± 6.13</td>
<td>67.0 ± 4.85</td>
<td>54.3 ± 2.00</td>
</tr>
</tbody>
</table>

Values are given as mean ± SD (six animals per group). Mean values were statistically significant at *p > 0.05. Treatment rats were compared with negative control rats.

Table 2. Triglyceride levels during the study.

### Triglyceride level (mg/dL)

<table>
<thead>
<tr>
<th>Day/group</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>36.6 ± 4.83</td>
<td>35.3 ± 6.48</td>
<td>35.3 ± 2.65</td>
<td>36.8 ± 6.83</td>
<td>37.2 ± 6.98</td>
<td>38.2 ± 5.61</td>
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<tr>
<td>7</td>
<td>44.3 ± 3.28</td>
<td>89.5 ± 6.92</td>
<td>87.5 ± 9.95</td>
<td>90.6 ± 7.11</td>
<td>91.7 ± 6.98</td>
<td>93.3 ± 6.64</td>
</tr>
<tr>
<td>14</td>
<td>47.5 ± 2.92</td>
<td>155.3 ± 18.46</td>
<td>151.0 ± 13.08</td>
<td>170.0 ± 7.41</td>
<td>173.2 ± 5.47</td>
<td>156.4 ± 24.90</td>
</tr>
<tr>
<td>21</td>
<td>49.2 ± 2.48</td>
<td>137.0 ± 7.97</td>
<td>77.1 ± 12.04*</td>
<td>154.3 ± 5.52*</td>
<td>90.3 ± 8.38*</td>
<td>90.0 ± 7.82*</td>
</tr>
<tr>
<td>28</td>
<td>50.2 ± 1.28</td>
<td>138.9 ± 3.43</td>
<td>28.7 ± 0.80*</td>
<td>122.0 ± 5.14*</td>
<td>74.3 ± 2.83*</td>
<td>54.4 ± 2.07*</td>
</tr>
<tr>
<td>35</td>
<td>52.0 ± 2.91</td>
<td>147.3 ± 8.30</td>
<td>32.1 ± 2.47</td>
<td>124.8 ± 11.52</td>
<td>76.9 ± 5.85</td>
<td>37.5 ± 4.40</td>
</tr>
</tbody>
</table>

Values are given as mean ± SD (six animals per group). Mean values were statistically significant at *p < 0.05. Treatment rats were compared with negative control rats.

Figure 2. Triglyceride levels during the study.

Triglycerides test result on day 21 showed a decrease in triglyceride levels in the range of 77.1–154.3 mg/dL. Triglyceride levels were decreased by 48.9%, 9.2%, 42.7%, and 36.7% for groups III, IV, V, and VI, respectively. On day 28, the effect increased by 91.0%, 28.2%, 57.1%, and 65.2% for groups III, IV, V, and VI, respectively.

Post hoc LSD test result on day 21 and Mann–Whitney U test on day 28 and day 35 showed significant difference (p < 0.05) between group II and groups III, IV, V, and VI. This suggests that treatment starting at 7 days can significantly reduce triglyceride levels, and this effect persists even though the treatment has been discontinued for 7 days. There was no significant difference (p > 0.05) between groups I and VI on day 28, which showed that dose III can lower triglyceride levels to normal limits.

#### 3.4 High-density lipoprotein cholesterol parameter

The results showed an average range of HDL-C level between 36.7 and 38.5 mg/dL (normal) and no significant difference (p > 0.05) for all the groups at baseline. Table 3 shows a decrease in average HDL-C level on day 7 in the range of 29.1–31.0 mg/dL. The decline continued until day 14, on which HDL-C levels reached 20.8–23.1 mg/dL for groups II–VI.

Figure 3 shows an elevated HDL-C level after 7 days treatment with a range of 22.6–30.4 mg/dL. Groups III, IV, V, and VI showed an increase of 30.3%, 8.7%, 40.7%, and 28.9%, respectively. On day 28, the corresponding effects of increased HDL-C levels by the group became stronger by 67.1%, 26.9%, 57.9%, and 67.0%.

Post hoc LSD test result on day 21 showed a significant difference between group II and groups III, IV, V, and VI, which showed that simvastatin and apple sugar peel extract of doses II and III can increase HDL cholesterol levels. Dose I showed
the effect after 2 weeks of treatment. The effect does not change during the recovery period. On day 28, there was no significant difference between groups III and VI suggesting that dose III could increase HDL-C as well as positive control, exceeding normal-group HDL-C levels.

Increased blood lipid levels can have adverse health effects. Hypercholesterolemia, especially high LDL-C levels with low levels of HDL and increased free radicals, accelerates the process of atherosclerosis. In this study, we used ethanol extract of sugar apple peel, which is suspected to have antihyperlipidemia effect. Phytochemical screening of the extracts showed flavonoid content.

Flavonoids reduce cholesterol synthesis by inhibiting 3-hydroxy 3-methyl-glutaryl-CoA (HMG-CoA) reductase, decreasing the activity of Acyl-CoA cholesterol acyl transferase (ACAT) enzyme, and decreasing the absorption of fat in the gastrointestinal tract, which affects the decrease of blood cholesterol (Rumanti 2011, Akanji et al. 2009). Flavonoids are cofactors of cholesterol esterase enzymes that activate p-450 enzymes that lead to increased excretion of bile resin and decreased blood cholesterol levels. Flavonoids increase lipoprotein lipase activity that hydrolyzes triglycerides in the chylomicron molecule. Flavonoids also reduce blood viscosity so as to reduce the occurrence of fatty deposits in blood vessels (Sharma et al. 2013). Flavonoids found in plants protect the body from cardiovascular disease and some other chronic diseases, in which flavonoids can improve endothelial function of blood vessels. Flavonoids are also known to be natural antioxidants, thereby reducing the sensitivity of LDL cholesterol. In addition to flavonoid content, the extract of sugar apple peel contains alkaloids that inhibit lipase enzyme activity. Thus, it may inhibit the breakdown of fat into smaller fat molecules. This results in a reduction in the amount of fat absorbed by the body (Novianti et al. 2015).

Table 3. HDL-C levels during the study.

<table>
<thead>
<tr>
<th>Day/group</th>
<th>HDL-C level (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>0</td>
<td>37.3 ± 1.17</td>
</tr>
<tr>
<td>7</td>
<td>36.3 ± 1.10</td>
</tr>
<tr>
<td>14</td>
<td>35.8 ± 0.78</td>
</tr>
<tr>
<td>21</td>
<td>34.7 ± 0.70</td>
</tr>
<tr>
<td>28</td>
<td>33.4 ± 1.71</td>
</tr>
<tr>
<td>35</td>
<td>31.8 ± 1.75</td>
</tr>
</tbody>
</table>

Values are given as mean ± SD (six animals per group). Mean values were statistically significant at *p < 0.05. Treatment rats were compared with negative control rats.

Figure 3. HDL-C levels during the study.

Ethanol extract sugar apple peel also contains saponins that bind to the bile salts, which are necessary for the cholesterol absorption process. Saponin activates the cell surface and inhibits cholesterol reabsorption after removal from the bile, thus increasing bile acids and neutral sterols in the feces. Low concentrations of free bile salts can lower the absorption of triglycerides in the intestine (Novianti et al. 2015). Saponins bind to bile acids and decrease the enterohepatic circulation of bile acids and increase cholesterol excretion. Saponins and cholesterol target the same receptor causing them to be competitively bound to cholesterol receptors on cells. In addition, saponins may affect cholesterol biosynthesis in the liver (Ratnawati & Widowati 2011).

4 CONCLUSIONS

This study showed that total cholesterol and triglyceride levels were decreased by 14.43%, 38.26%, 48.95% and 28.10%, 57.12%, and 65.22%. HDL-C was increased by 21.19%, 36.57%, and 40.30% in groups IV, V, and VI, respectively, after treatment for 2 weeks. The effect of the highest dose of the test group was not significantly different from that of the positive control, meaning that it demonstrates the same effectiveness in improving the lipid profile by lowering total cholesterol and triglyceride levels and increasing HDL-C levels.
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REFERENCES


