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Therapeutic Effects of Ipomoea batatas L. Extract-Containing Capsule and Simvastatin Combination versus Simvastatin in Dyslipidemic Patients

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Purple sweet potato extract (PSPE) have been shown to exhibit antidyslipidemic effect, but the clinical effects of PSPE and statin combination has not been investigated. This study was aimed to reveal the effect of PSPE and statin combination on lipid profile, malondialdehyde (MDA) and superoxide dismutase (SOD) level in mild and moderate dyslipidemia cases. The study design was a limited clinical trial with a randomized pre and posttest control group design. Subjects were divided into simvastatin (control) group and simvastatin + PSPE capsules group (10 individuals per group). Both groups received simvastatin 20 mg daily (4 weeks), with the administration of PSPE capsules for the second group 400 mg/day, BID, 4 weeks). The aforementioned variables were subsequently analyzed using paired t-test and t-test, when appropriate. Better lipid profile improvements, lower MDA levels, and higher SOD level ($p<0.05$) were revealed in patients treated with simvastatin + PSPE compared to simvastatin alone. It can be inferred that combination of PSPE and simvastatin exhibits a clinically better effect as antidyslipidemic agent and antioxidant in dyslipidemic patients than simvastatin alone.

Keywords: Dyslipidemia; Lipid Profile; Oxidative Stress; Purple Sweet Potato Capsules; Simvastatin.

The use of conventional drugs to treat metabolic disorders is currently quite satisfying, specifically in terms of overcoming dyslipidemia. However, disorders that require a long treatment, such as dyslipidemia, often cause boredom for patients to take conventional medicines, so that most patients tend to use various natural medicines or herbal medicines.1 Simvastatin is a drug that belongs to the class of statins commonly used to treat dyslipidemia, with the mechanism of action is inhibit the action of the enzyme HMG-CoA reductase which is a precursor of cholesterol synthesis. Simvastatin or other statin classes are still recommended to treat dyslipidemia, but because they have to take the drug for a long time, patients often look for other alternative drugs that are considered safe. Herbal medicines is often combined with simvastatin. The combination of herbal medicines with conventional drugs is not totally safe, with difficult-to-predict (if not impossible) outcomes.1,2

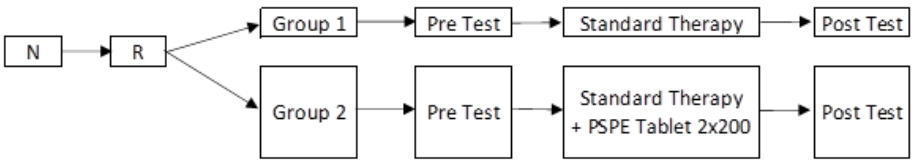
Research on purple sweet potato extract (PSPE) has been widely carried out in several countries including Indonesia. PSPE in Bali has

been studied since 2008 until now. Anthocyanin fraction (AF) from purple sweet potato can inhibits hepatic lipid accumulation through the activation of adenosine monophosphate–activated protein kinase (AMPK) signaling pathways.3 In 10 years of research conducted in Bali, it has been shown that PSPE exerts antioxidant effects and prevents dyslipidemia in animals and humans.4–8 In order to be administered for humans, hypolipidemic and antioxidant properties of PSPE and simvastatin combination versus simvastatin therapy alone is essential to be evaluated in dyslipidemic patients. This study was aimed to reveal the effect of PSPE and statin combination on lipid profile, MDA and SOD level in mild and moderate dyslipidemia cases.

MATERIAL AND METHODS

This study is a limited clinical trial (phase 1) with a randomized pre and post-test control group design (Figure 1). The sample size in this study was 20 people based on the requirements of the phase 1 clinical trial. The studies using patient blood for laboratory testing were approved by The Research Ethics Committees of Faculty of Medicine/Sanglah General Hospital, Denpasar, Bali, Indonesia (Ethical Clearance Letter No. 2455/UN14.2.2.VII.14/LP/2019). Written informed consents were obtained from patients for their participations in this study.

The subjects of this study were adult patients with mild to moderate dyslipidemia. The inclusion criteria were 30-70 years old, suffering from dyslipidemia as indicated by laboratory tests with total cholesterol levels above 200 mg / dl or other lipid profile abnormalities, such as LDL levels above 100 mg / dl or triglycerides above 150 g / dl, even though total cholesterol was below 200 mg / dl for both men and women. The exclusion criteria were patients who showed symptoms of certain diseases, known to use continuous medication such as hypertension, diabetes mellitus, psychiatric disorders, alcohol drinkers, or patients who showed analysis of high SGPT / SGOT levels or abnormal kidney function. Patients who met the inclusion criteria were divided into 2 groups constitutively according to arrival to the study center, namely as the combination (PSPE+statin) group (group 1) or as the simvastatin group (group 2). Group 1 was given combination capsules of PSPE at a dose of 2 times 400 mg / day with simvastatin 20 mg / day at night. Group 2 was only given simvastatin at a dose of 20 mg / day. The duration of treatment was 4 weeks. After 4 weeks of treatment, laboratory examinations were carried out to evaluate the lipid profile, MDA and SOD levels. From the definition of operational variable, lipid profiles which define as dyslipidemic conditions are laboratory tests with total cholesterol levels above 200 mg/dl or other lipid profile abnormalities, such as LDL levels above 100 mg/dl or triglycerides above 150 g/dl, even though total cholesterol was below 200 mg/dl for both men and women. MDA level (mmol/l), is the level measured in plasma using the TBARS method in the Biomolecular laboratory of Faculty of Medicine of Universitas Udayana, Bali or Nutrition laboratory, Center for Food Studies of Universitas Gadjah Mada, Yogyakarta. SOD is the concentration of SOD enzymes in plasma (u/



N	= Patients with Dyslipidemia
R	= Randomization
Group 1	= Dyslipidemic patients who met the inclusion criteria were given standard therapy for 4 weeks, consisting of 10 people, as controls.
Group 2	= Dyslipidemic patients who met the inclusion criteria were given standard therapy and purple sweet potato extract tablets 2 times 400 mg/day for 4 weeks, consisting of 10 people, as trials.

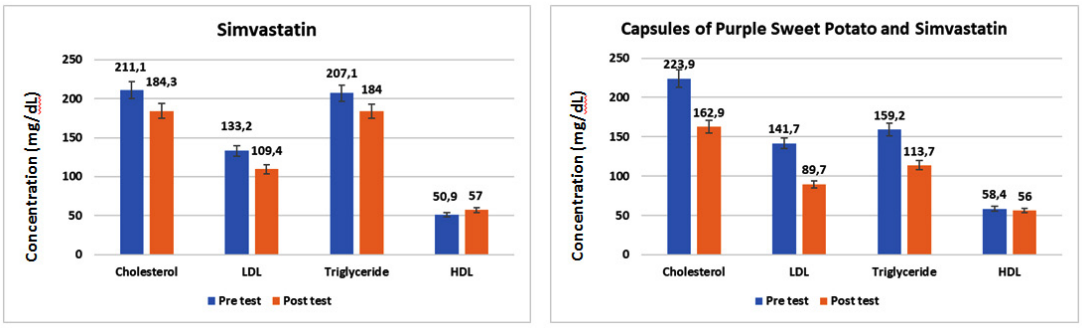
Fig. 1. Study Design

gHb) as measured by the RENDOK system in the Biomolecular laboratory of Faculty of Medicine of Universitas Udayana, Bali or Nutrition laboratory, Center for Food Studies of Universitas Gadjah Mada, Yogyakarta. The data were analyzed by paired t-test and t-test, when appropriate, with a significance level of 95%.

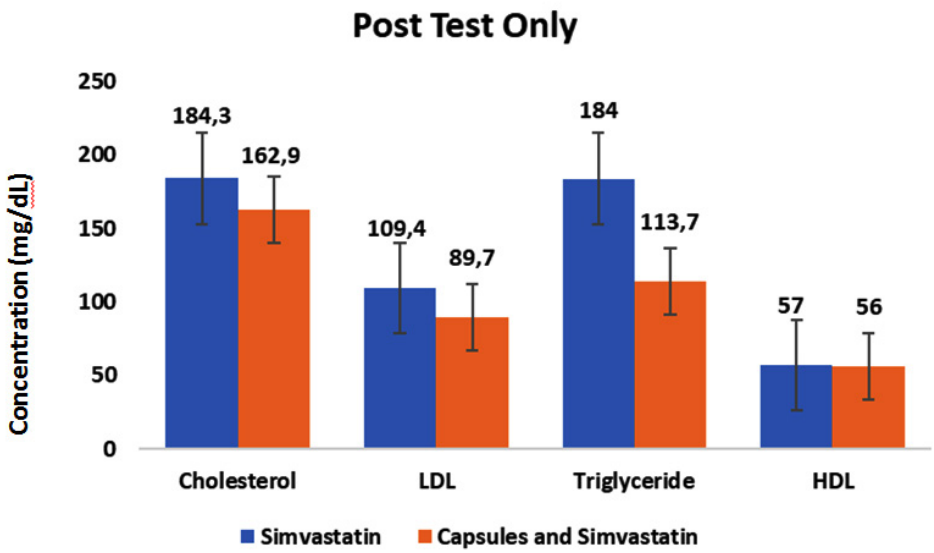
The purple sweet potato tuber extract capsules were made by the following procedure. Thick purple sweet potato tuber extract was mixed with lactosum in a blender with a ratio of 2 parts extract to 1 part lactosum. The addition of the lactosum was done gradually until a solid dry mixture obtained. The solid dry mixture was cut according to the designed capsule dosage. This study designed 400mg capsules, which were made with 40 grams of thick extract plus 20 grams of lactosum mixed until they were solid and then cut into 100 parts. One part of the cut was put into capsule No. 0, so that it can accommodate the dry extract containing a mixture of extract and lactosum weighing 400mg / capsule. The finished capsules were weighed again to make sure they weigh the same.

RESULTS

The result of lipid profile in the patients that were given simvastatin only shown improvement in lipid profile and significantly different compared to before the treatment ($p<0.05$). In the group of patients that were given combination of purple sweet potato extract capsules and simvastatin, those findings were more significant compared



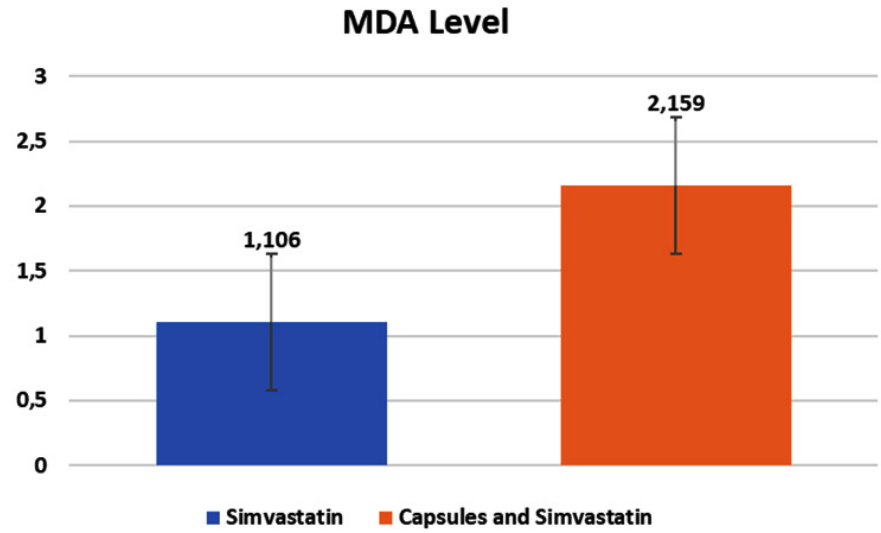
Graph 1. The pre- and post-test result of lipid profile among groups.



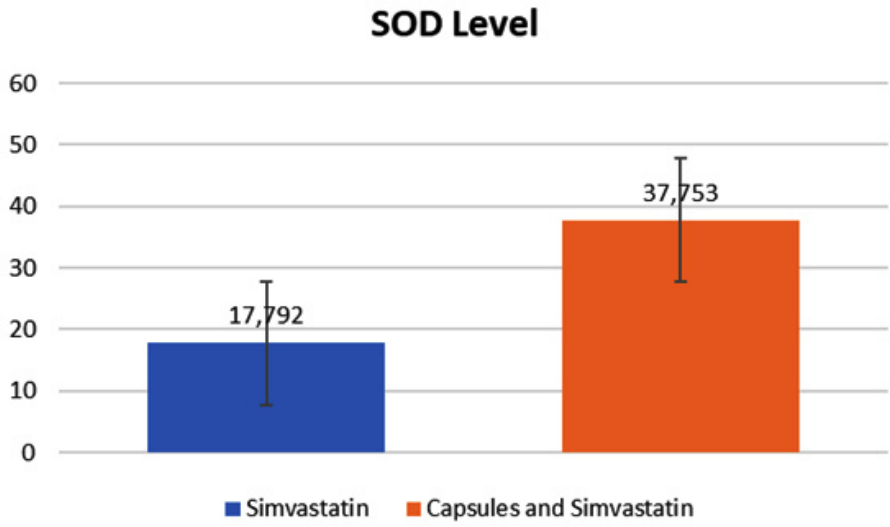
Graph. 2. Comparison of the lipid profile improvements between groups

to simvastatin alone. The complete result of lipid profiles pre and posttest among the group is shown in Graph 1. In simvastatin only group, the cholesterol and LDL level were significantly different, however triglyceride and HDL level were not changed significantly. Different results were found among the group that was given combination of purple sweet potato extract capsules and simvastatin, in this group the HDL level the only parameter that was not changed significantly.

In graph 2, we can see that the decreasing of cholesterol, LDL, and triglyceride levels are greater in patients that were given combination of 2 x 400 mg purple sweet potato extract capsules daily and 20 mg simvastatin daily that simvastatin only group. However, the HDL level between the two groups was not changed significantly. Statistic test shown that the decreasing of triglyceride level between the two groups was significantly different ($p<0.05$), but the decreasing of cholesterol and



Graph 3. Comparison of decreasing MDA level between Simvastatin only group with Combination of Purple Sweet potato Extract Capsules and Simvastatin group



Graph 4. Comparison of increasing SOD level between Simvastatin only group with Combination of Purple Sweet potato Extract Capsules and Simvastatin group

Table 1. Paired T-Test Analysis of MDA and SOD Level in Both Groups

Variables	Group	Mean ± SD	p-value*
MDA Level	Simvastatin only	1.106±0.302	0.000
	Simvastatin + PSPE	2.159±0.152	
SOD Level	Simvastatin only	17.792±6.880	0.000
	Simvastatin + PSPE	37.753±11.697	

*p-value<0.05 is statistically significant

LDL were not significantly different (p>0.05). The result of this study shown that the giving of combination of purple sweet potato extract capsules and simvastatin is better in improving lipid profile compared to simvastatin only group.

The evaluation of blood MDA level and blood SOD activity level in the dyslipidemia patients that were given standard treatment with 20 mg simvastatin daily shown decreasing of blood MDA level and increasing blood SOD level. Those findings were significantly different compared to the pretest results (p<0.05). In the group that was given combination of 2 x 400 mg purple sweet potato extract capsules daily and 20 mg simvastatin daily, the decreasing MDA level and increasing SOD activity were significantly different compared to pretest result (p<0.05). Comparison of decreasing MDA level and increasing SOD activity among the two groups were shown in graph 3 and graph 4.

As shown in the graph, we can see that giving combination purple sweet potato extract capsules and simvastatin could decrease MDA level greater than simvastatin only group and this finding is significantly different (p<0.05).

The similar result also found in SOD activity. The giving of combination purple sweet potato extract capsules and simvastatin could increase SOD activity greater than simvastatin only group (p<0.05). The result analysis with paired T-test of MDA and SOD level in both groups can be seen in Table 1.

DISCUSSION

The decrease in lipid profile in patients who were given a combination of capsules of purple sweet potato extract with simvastatin was greater than in patients given simvastatin alone. Statistically this difference was very significant, especially the decrease in triglycerides and LDL (p <0.05). Simvastatin is a drug used to improve the lipid profile of dyslipidemic patients with a mechanism of action as 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (HMG CO A reductase inhibitor) through its inhibition in the formation of L- Mevalonate. Which is competitive so that it is reversible.9 The results of this study indicate that the administration of simvastatin decreased cholesterol and LDL. The decrease in LDL due to simvastatin administration is due to an increase in LDL receptors on hepatocyte cells, resulting in an increase in LDL uptake in the blood which causes a decrease in blood LDL.9 In this study, simvastatin 20mg / day reduced cholesterol and LDL but did not increase HDL and did not affect triglyceride levels.

The combination of capsules of purple sweet potato extract and simvastatin in this study showed a reduction in cholesterol and LDL was greater than single simvastatin. Triglyceride reduction was even significantly different from patients who were given only simvastatin (p<0.05). Purple sweet potato tuber extract contains quite high flavonoids,10 which has been shown that flavonoids from certain plants can improve lipid profiles in mice through inhibition of fatty acid synthase (FAS), thereby improving lipid profiles.11,12 Although the types of flavonoids from purple sweet potato tuber extract are not necessarily the same, they may have similar effects. The results showed that the mechanism of flavonoids improving lipid profile varied widely. It is suspected that some flavonoids affect the transcription factor SREBP-2 which plays a role in increasing LDL receptor expression and regulating 3-hydroxy-3-methylglutaryl-CoA reductase, so that flavonoids will affect lipid profiles.13 Flavonoids

from some plants can also improve lipid profiles through the activation of PPARa, which is a transcription factor against several enzymes that regulate lipid metabolism in the liver and muscles, resulting in improvements in lipid profiles, especially a decrease in LDL.13

The results of this study indicate that the combination of simvastatin with capsules of purple sweet potato extract further increases the effect of simvastatin, especially in decreasing total cholesterol and LDL. Capsules containing purple sweet potato extract will increase the inhibitory effect of simvastatin against HMG-Co-A reductase enzymes so that the effect of reducing total cholesterol is more pronounced. The effect of reducing LDL was also greater in the combination of simvastatin with purple sweet potato tuber extract capsules because there was a potentiating effect in increasing LDL receptors so that the clearing effect of LDL was increased, which led to a more pronounced decrease in LDL.

The results of MDA and SOD examinations showed a greater decrease in MDA and an increase in SOD in patients who were given a combination of capsules of purple sweet potato extract with simvastatin. This happened due to the fact that flavonoids contained in the extract are antioxidants with various mechanisms15-19 so that the decrease in MDA and the increase in SOD activity was more significant.

A study also revealed that serum level of LDL cholesterol has positive correlation with hyperuricemia in dyslipidemic Korean adults.20 Milanesi et al. revealed that uric acid is a renotoxic agent, partially due to its effect in upregulating the expression of pro-oxidant Nox4 in human tubular cells.21 Recently, Balinese purple sweet potato extract had been shown to exhibit tendency in attenuating renal expression of Nox4 protein in a murine model of hyperuricemia.22 Since dyslipidemia is linked to hyperuricemia, these findings can be regarded as signs that purple sweet potato is a promising antidyslipidemic pharma food with potential additional effect as renoprotector. Further studies are very important to be conducted in order to elucidate the exact role of purple sweet potato in dyslipidemia and related diseases.

CONCLUSION

The combination of purple sweet potato extract (PSPE) capsules with simvastatin is better than simvastatin alone in improving the lipid profile and mitigating oxidative stress in patients with mild-to-moderate dyslipidemia.

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Conflict of Interest

The authors declare no conflict of interest.

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