

Jamu formula could reduce plasma cholesterol patients with mild Hypercholesterolemia

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Abstrak

Latar belakang: Pengobatan hiperkolesterolemia sering berlangsung seumur hidup sehingga menyebabkan penderita meninggalkan obat kimia dan memilih obat herbal. Penelitian ini merupakan uji klinik yang bertujuan untuk mengetahui khasiat dari formula jamu antikolesterol yang terdiri dari daun jati belanda, daun jati cina, daun tempuyung, daun teh hijau, rimpang temulawak, rimpang kunyit dan herba meniran dalam menurunkan kadar kolesterol darah sebagai bagian dari program Sainifikasi Jamu.

Metode: Penelitian ini menggunakan metode kuasi eksperimental dengan desain pre dan post. Jumlah subjek 50 pasien dengan hiperkolesterolemia ringan yang memenuhi kriteria inklusi. Penelitian dilakukan di Rumah Riset Jamu (RRJ) Hortus Medicus Tawangmangu pada bulan September sampai Desember 2014. Uji statistik yang digunakan adalah uji t berpasangan dengan bantuan program SPSS 16.

Hasil: Formula jamu antihiperkolesterol yang diminum setiap hari selama 28 hari mampu menurunkan rata-rata kadar kolesterol plasma subjek dari 212.42 mg / dl menjadi 196.6 mg / dl. Uji t test berpasangan didapatkan hasil $p < 0,05$ yang berarti ada perbedaan rerata kadar kolesterol sebelum dan sesudah pemberian jamu.

Kesimpulan: Formula jamu antihiperkolesterol mampu menurunkan kadar kolesterol plasma pasien dengan hiperkolesterolemia ringan pada pemberian selama 28 hari. (*Health Science Journal of Indonesia 2018;9(2):87-92*)

Kata kunci: hiperkolesterolemia, jamu, Sainifikasi jamu

Abstract

Background: Treatment of hypercholesterolemia often lasts a lifetime, therefore patients leave chemical drugs and choose herbal medicines. The aim of this clinical study is to evaluate the efficacy of antihypercholesterol jamu formula consists of Guazuma ulmifolia leaves, Cassia senna leaves, Sonchus arvensis leaves, Camellia sinensis leaves, Curcuma xanthorrhiza rhizomes, Curcuma longa rhizomes and Phyllanthus niruri herbs to lowering cholesterol plasma level as part of Sainifikasi Jamu program.

Methods: This study was a quasi-experimental with pre and post test design. The total subjects were 50 patients with mild hypercholesterolemia who met the inclusion criteria. The research took place at RRJ 'Hortus Medicus' Tawangmangu between September to December 2014. The data were analyzed using a paired t-test with SPSS 16 software.

Results: Results showed jamu anticholesterol formula which is taken every day for 28 days lowered the mean of cholesterol plasma level of 212.42 mg / dl to 196.6 mg / dl. Paired t test at 95% confidence level acquired p value < 0.05 , showed that there is significant differences in the mean cholesterol level subjects before and after the study.

Conclusion: The administration of jamu antihypercholesterol formula for 28 days could reduce plasma cholesterol level in subjects with mild hypercholesterolemia. (*Health Science Journal of Indonesia 2018;9(2):87-92*)

Keywords: hypercholesterolemia, Jamu, Sainifikasi Jamu

Hypercholesterolemia is a medical condition characterized by increased of cholesterol level in the blood exceeds the normal limit.¹ Cholesterol has a soft structure, such as a candle, consisting of fat that can be produced by the body or derived from food.² Cholesterol is produced in the liver, and has a function to build cell walls as well as a precursor of steroid hormones.³ Normally cholesterol plasma level is below 200 mg/dL, while the cholesterol level more than or equal to 200 mg/dL indicates hiperkolesterolemia (Table 1).¹

Table 1. Classification of Plasma Cholesterol Level.¹

Total Cholesterol (mg/dl)	Classification
<200	Normal
200-239	Borderline high
≥240	High

Hypercholesterolemia increases the risk of coronary heart diseases, cardiovascular diseases, and stroke through atherosclerosis process.^{1,2} The high blood cholesterol levels are giving rise to a low-grade systemic inflammatory response in multiple vascular beds. Inflammation increases Reactive Oxygen Species (ROS) production that may damage cellular defence mechanisms leading to atherogenesis, protein damage and enzyme inactivation, with the final result of vascular dysfunction.^{4,5}

The cardiovascular disease (CVD) is the number one killer in the world especially in developing country.⁶ World Health Organization reported about 1,7 million people died each year from CVD's. It is estimated 31% of all deaths world wide and more than 75% of CVD deaths occur in low income and middle income countries.⁷ Along with advancement of technology and change in modern lifestyles, an estimated number of patients with hypercholesterolemia will increase. According to Riset Kesehatan Dasar (RISKESDAS) in 2013 the prevalence of hypercholesterolemia in the Indonesian population aged 15 years and over was 35,9%.⁸ Hypercholesterolemia treatment becomes very important in order to reduce the risk of complications. The priority treatment for mild/ borderline high of hypercholesterolemia (cholesterol values 200-239 mg/dl) is the lifestyle changes such as regular exercise, reducing intake of fatty foods, and last step is using drugs/ herbs that can lower cholesterol plasma level.^{2,9}

Hypercholesterolemia is a matabolic disorder that often require lifelong treatment. These conditions often make patients leave conventional treatment and chose herbal treatment.¹⁰ Based on data from

the Rumah Riset Jamu 'Hortus Medicus' there are about 500 new cases of hypercholesterolemia during 2013. Indonesia has some Jamu formulas that have empirically been used to lower blood cholesterol level.

The potential of Jamu anticholesterol formula consists of *Guazuma ulmifolia*, *Cassia senna*, *Sonchus arvensis*, *Camellia sinensis*, *Curcuma xanthorrhiza* (*C. xanthorrhiza*), *Curcuma longa* (*C. longa*) and *Phyllanthus niruri* as alternative medicine that should be investigated. Preclinical study regarding this formula had been conducted by Saryanto et al in 2014 with the result administration of jamu anticholesterol formula infusion at dose 270 mg / 200 gram body weight, 540 mg / 200 gram body weight and 1080 mg / 200 gram body weight in rats, previously given high-fat feed for 30 days causing a decrease in cholesterol respectively of 57 mg / dl , 120 mg / dl and 121 mg / dl were lower than positive controls with the administration of simvastatin which decreased by 99 mg / dl and higher than negative control. The oral single dose of jamu formula used in this study does not cause toxic effects, with an LD50 value greater than 5000 mg / Kgb, categorized as Practical Non Toxic (PNT) or including non-toxic materials. Sub-chronic toxicity test showed that administration of jamu formula for 3 months did not resulting toxic effect or death in the rats. Neither of damage was found on the organ examination, so the jamu formula in the safe category were used.^{11,12}

The aim of this study is to evaluate the efficacy of the jamu anticholesterol formula in lowering cholesterol plasma level, in term of Saintifikasi Jamu program.

METHODS

Plants Materials

The anticholesterol jamu were prepared and packaged by post harvest division of Medicinal Plant and Traditional Medicine Research and Development Center. One packaged for daily dosage contains 6 gram *Guazuma ulmifolia* dried leaves, 1 gram *Cassia sennae* dried leaves, 6 gram *Sonchus arvensis* dried leaves , 5 gram *Camellia sinensis* dried leaves, 5 gram *C. xanthorrhiza* dried rhizomes, 4 gram *C. longa* dried rhizomes and 3 gram *Phyllanthus niruri* dried herbs. Raw materials used in this study had passed the quality control stages before packaged : determination of simplicia species, sortation to ensure simplicia is free from contaminants and several tests to ensure water level was less than 10%, total plate count, mold and yeast less than 10, no microbial pathogens found

in the simplicia and the aflatoxin count was not more than 30 parts per million.

Inclusion and Exclusion Criteria

Inclusion criteria were: 1. Women or men aged 25-60 years, old or new patients with mild/borderline hypercholesterolemia (total cholesterol 200-239 mg/dl), 2. The patient's condition is stable evidenced by clinical examination, laboratory and ECG, 3. Patients were willing to follow the study/ follow-up schedule by signing the informed consent

Exclusion criteria were: 1. Pregnant or breastfeeding women (based recognition), 2. Patients taking the drug or other herbal ingredients which had an indication for lowering cholesterol and blood-thinning medications such as warfarin, digoxin 3. Patients with severe disease complications and gastrointestinal conditions (eg advanced cancer / terminal, 2,3,4 NYHA heart failure, severe diabetes, severe hypertension, gastritis, ulcer pepticum, Crohn's disease and colitis.), 4. Patients have an allergies/hypersensitivities to any component of test material.

Study Design

This research was a quasi experimental with pre-post test design. Total sample were 50 patients with mild hypercholesterolemia who met the inclusion criteria at the Rumah Riset jamu (RRJ) 'Hortus Medicus' Medicinal Plant and Traditional Medicine Research and Development Center, Tawangmangu. The research was carried out between September to December 2014 with the ethical approval by The Ethic Commission of Health Research and Development Department, Health Ministry Republic of Indonesia (LB 02.01/5.2/KE 364/2014).

Sample size was determined using the following formula :¹³

$$n = \frac{Z^2 P(1-P)}{d}$$

n is the sample size, Z is the level of confidence (75%), P is expected prevalence (30%) and d is presicion (5%)

Sample size was 47,25 with an estimated 5% dropout, the total sample was 50 subjects.

The primary end point of this study was the decrease of average plasma cholesterol level below 200mg / dl and the secondary end point which expected was a reduced risk of atherosclerosis.

All subjects were examined on plasma cholesterol. After diagnosis of hypercholesterolemia was confirmed, each subject was given 7 packs of jamu anticholesterol formula for 7 days. Subjects should return once a week and drank jamu for 28 days. At the end of day 28, all subjects had a plasma cholesterol examined again.

Jamu Formula

All subjects were instructed to boil 1L of water every morning for 28 days, one pack of jamu formula was put into boiling water, wait 15 minutes and stop the boiling process. Filtered the water after it is cooling down, and take it each a glass two times a day after breakfast and dinner.

Statistical analysis

Data were analyzed using paired t test with the Statistical Product and Service Solutions (SPSS) program for window version 16.

RESULTS

All fifty subjects completed the research for 28 days. More than 50% subjects are women, aged between 41-60 and overweight. (table 2). Education and Age had correlations with cholesterol level ($p < 0,05$) while gender, occupation, hypercholesterolemia history, Body Mass Index (BMI) and smoke habit had no correlation.

There are significant differences in reduction mean of subjects plasma cholesterol level before and after the study ($p < 0.05$) (tabel 3).

A total of 35 subjects experienced a decrease in plasma cholesterol level, whereas 13 subjects experienced an increase in plasma cholesterol level, and 2 subjects of study experience no change in plasma cholesterol level. The increase in the level of cholesterol at the end of the study can be caused by several factors: heredity, high-fat diet and lack of exercise. Hereditary factors play an important role in the occurrence of hypercholesterolemia. The hereditary hypercholesterolemia is more difficult to treat than lifestyle hypercholesterolemia. In this study there were no restrictions on diet for the subjects, only suggestion to reduce high fatty foods, so that the increase in the level of cholesterol in 13 study subjects may occur due to excessive intake of fatty foods.¹⁴ In addition, lack of physical activity can also lead to increased cholesterol level of 13 study subjects.¹⁵

Table 2. The characteristics of Subjects

Variables	Number of Subjects (n=50)	P
<u>Gender</u>		
Men	17 (34%)	0,119*
Women	33 (66%)	
<u>Education</u>		
Elementary basic (Elementary and Junor High School)	1 (2%)	0,000*
Middle (Senior High School)	27 (54%)	
High (Bachelor)	22 (44%)	
<u>Occupation</u>		
House wifeves	16 (32%)	0,390*
Civil servants	21 (42%)	
Enterpreuners	10 (20%)	
Private employeers	3 (6%)	
<u>Hypercholesterolemia history</u>		
No history	7 (14%)	0,651*
< 1 year	32 (64%)	
1-5 year	11 (22%)	
<u>Age</u>		
31-40 y.o	12 (24%)	0,036*
41-50 y.o	25 (50%)	
51-60 y.o	13 (26%)	
<u>Smoke habits</u>		
Yes	2 (4%)	0,640*
No	48 (96%)	
<u>Body Mass Index (BMI)</u>		
Underweight	0 (0%)	0,526*
Normal	22 (44%)	
Overweight	12 (24%)	
Obese	16 (32%)	

*Chi Square test at the confidence level 95%

Table 3. The averages of plasma cholesterol levels before and after

Variable	D-0	D-28	P
Average of plasma cholesterol level (mg/dl)	212,42	196,6	0,000*

*: paired t test with the level of confidence 95%

Cholesterol plasma level of 28 subjects at the end of the 4th week became normal (<200 mg/dl), while 22 subjects still had cholesterol level above 200 mg/dl. There were 9 subjects that although experience decrease in cholesterol level but still above the normal level, the limited 28 days intervention could become the reason.

Administration of antikolesterol jamu formula for 28 consecutive days was relatively safe for the liver and kidneys of the subjects, indicated by the absence of significant changes in the levels of Serum Glutamic Piruvic Transaminase (SGPT), Serum Glutamic Oxaloacetic Transaminase, Ureum and Creatinine. A

full report on the safety of this jamu formula will be written in another article.

DISCUSSIONS

The prevalence of hypercholesterolemia in Indonesia is indeed higher in women, namely 14.5% while in men 8.6%.^{14,16} Subject ages were in the range of 30-60 years, none of subjects under 30 years old. This is consistent with the theory that increasing age is one of the risk factors for hypercholesterolemia.¹⁷ The majority of subject education is secondary and high education. This plays a role in treatment behavior. Higher education encourages a person to be more curious about his health condition. Usually mild hypercholesterolemia is asymptomatic and often be found incidentally on routine health checks. The BMI 28 subjects were in the category of overweight and obese. As we all know being overweight is a predisposing factor for hypercholesterolemia.¹⁷

According to our knowledge, there are no similar study to this clinical study ever published. However, the scientific articles related to the safety and efficacy of each constituent plant in lowering plasma cholesterol invivo have been widely found.

Aqueous extract of *Guazuma ulmifolia* leaves contains tannin, flavonoids and saponin.¹⁸ Aqueous extract at a dose of 50 mg/kg bw can lower total cholesterol and Low Density Lipid (LDL) level significantly compared control.¹⁹ Mucilage in Jati belanda can swell in the stomach so that pressing appetite. Alkaloids in Jati belanda has the activity in inhibiting pancreatic lipase enzyme that hydrolyze fat.¹⁰ Dried extract of Jati belanda leaves doses of 2, 4, and 8 g/kgbw that administered in male mice once a day for 3 months did not increase the level of creatine and plasma urea and an average diameter size of the rat kidney glomerulus.^{18,19} This suggests that long-term administration Jati belanda leaves does not disturb the function of kidney.^{20,21}

Cassia senna is a medicinal plant that has been known throughout the world. Society of India and the Middle East since long ago use *Cassia senna* to treat hemorrhoids, as a laxative, colon cleansing, helps get rid of all the toxins in the body, and to reduce body weight.²² In Indonesia *Cassia senna* leaves commercially sold in the form of tea bags or dried leaves with claims of efficacy to reduce body weight, laxative and lowering plasma cholesterol. *Cassia sennae* leaves contain hydroxyanthracene glycosides, with the derivate are

sennosides (BO-linked glycosides) has the effect of laxative. Sennosides are not absorbed in the upper intestine, and will be changed by bacteria in the large intestine becomes metabolically active rheinanthrone. Rheinanthrone would increase the motility of the colon, so shortening the transit time of food in the colon.²³ Cassia sennae leaves also contain flavonoids that can inhibit pancreatic lipase enzyme.²² Dose of sennosides up to 500mg/kgbw given to dogs for 4 weeks showed no toxic effects, as well as the dose to 100 mg/kg in rats during administration of 6 months.²³

Camellia sinensis leaves contain polyphenols (catechins and flavonoids), alkaloids, volatile oil, polysaccharides and amino acid.^{24,25} Catechins in tea can lowering total cholesterol and Low Density Lipid level in blood plasma. This is associated with the increasing of body metabolism. Epigallocatechin-3-gallate (EGCG) in green tea stimulate thermogenesis and fat oxidation which has implications for body weight loss EGCG inhibits the activity of acetyl CoA carboxylase in fatty acid biosynthesis cycle, hence reducing the accumulation of triacylglycerol (triglycerides) in fat tissue.^{24,26,27}

Sonchus arvensis leaves contain kaempferol, quercetin, orientin, rutin, catechin and miristisin.²⁸ Indonesia community since long ago have been using tempuyung to treat kidney stones and lowering plasma cholesterol.²⁹ It is rich in polyphenols, which have antioksidan activity.²⁸ Empirically tempuyung leaf infusion has used to lower plasma cholesterol level.²¹ Studies in mice, showed the ethanol extract of *Sonchus arvensis* leaves with doses up to 1.000 mg/kg proved to be safe and efficacious to lowering plasma cholesterol.³⁰

Curcuma xanthorrhiza rhizomes well known as temulawak and *Curcuma longa* rhizomes or turmeric or kunyit in bahasa has been used by local community in Indonesia as traditional remedy since centuries. Temulawak contains curcuminoid fraction which had been proven can reduce cholesterol in hypercholesterol rats through inhibition of 4 gene related oxidative stress expression CD44, ICAM-1, iNOS, and LOX-1.³¹ Based on the invivo study, supplementation of turmeric extract in rats fed with high-cholesterol diet significantly increased the expression of cholesterol 7 α -hydroxylase, hemeoxygenase 1, and low-density lipoprotein receptors as well as decreased in 3-hydroxy-3-methylglutarylCoA reductase level when compared with rats fed a normal or high-cholesterol diet, showing that turmeric could prevents hypercholesterolemia

and fatty liver formation by the modulation of expressions of enzymes that are important to cholesterol metabolism.³²

Hydro-alcoholic extract of leaves of *Phyllanthus niruri* in India known as *Phyllanthus amarus* Schumach possessed significant hypolipidemic activity at doses 300 and 500 mg/kg in cholesterol diet induced hyperlipidemia rats. The extract contain of alkaloids, flavonoids, saponins and tannins. Saponin was known to elicit serum cholesterol lowering activity.³³

In conclusion, administration of antikolesterol Jamu formula for 28 days significantly lowered plasma cholesterol levels in study subjects with mild hypercholesterolemia.

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