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Original Research Article

Effect of *Morinda citrifolia* Fruit Extract Capsule on Total Cholesterol Levels in Patients with Hypercholesterolemia

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Abstract

Purpose: *To investigate the reducing effect of Morinda citrifolia capsules (MCC) on total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in hypercholesterolemia patients.*
Methods: *This study was a randomized double-blind placebo-controlled clinical trial, with 60 subjects placed in two groups, viz, experimental (MCC group) and placebo (P group). The first group received two capsules of MCC (each capsule contains 500 mg extract) while the second group received two capsules of placebo (comprised of 500 mg fillers) 3 times daily, for 14 days for both groups. Overnight fasting cubiti venous blood (3 mL) was taken from each subject each time measurements were carried out. TC and LDL-C were measured by spectrophotometric assay using an automated analyzer.*
Results: *The results show that there was significant decrease in TC and LDL-C on day 14, compared to control (P group). Reduction in TC and LDL-C was 13.8 and 15.5 %, respectively. Decrease in TC and LDL-C levels was influenced by factors, such as age, BMI, exercise, diet, and smoking habits. In MCC group, the capsules significantly decreased TC levels ($p < 0.05$).*
Conclusion: *The results suggest that 1 g MCC, given orally thrice daily, significantly reduces TC and LDL-C levels in patients with hypercholesterolemia.*

Keywords: *Hypercholesterolemia, Cholesterol levels, Morinda citrifolia*

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INTRODUCTION

Hypercholesterolemia is characterized by increase in serum cholesterol level above the normal values (> 200 mg/dL). It is often associated with the elevated of serum low-density lipoprotein cholesterol (LDL-C) concentration because it carried 65-75 % of total cholesterol (TC) [1,2]. The incidence of hypercholesterolemia will continue to grow unanimously as the unhealthy lifestyle such as smoking, obesity, lack of exercise and the consumption of high-fat meals. The increase of TC and LDL-C can be modified by non-pharmacology therapy, such as changes in life style and habits (e.g., inclulging in exercise, diet and no smoking) and pharmacotherapy (medication use) [3]; thus, the process of atherosclerosis can be prevented as early as possible [4-7].

Morinda citrifolia (MC) is commonly known as "Noni" [8,9]. MC fruit has been used as a traditional medicine for about 2000 years. It has many effects and activities, such as antibacterial, antiviral, anti-diabetes, antihypertensive, immunostimulatory, and anticancer [10]. MC fruit contains polysaccharides, fatty acid, glycosides, iridoids, anthraquinones, coumarins, flavonoids, lignans, phytosterols, and carotenoids [9]. MC

has a wide safety range, its LD_{50} more than 15.000 mg/kg [11,12] and can be tolerated up to 10 g/day with no side effects [13]. MC is one of many plants with fruit that could decrease the TC and LDL-C and has been studied in mice [14]. Series of clinical studies in America proved that MC fruit juice could decrease the TC and LDL-C significantly in hypercholesterolemia patients with smoking habits [15-17]. The clinical usage of MC fruit in hypercholesterolemia patients as reported warrants further evaluation in more subjects. In this study, we evaluated the effect of oral administration of MCC in 60 subjects with hypercholesterolemia.

EXPERIMENTAL

Materials

Each 500 mg *Morinda citrifolia* capsule (MCC) containing 90 % dry extract of MC fruits and 10 % filler and was registered for sale in Indonesia.

Design

This study was conducted between April and October 2012, and was a double-blind design, randomized controlled clinical trial, conducted in patients at a clinic in South Jakarta, Indonesia.

METHODS

Subjects were randomly assigned into two groups: MCC group and the P group. Each subjects received a material study and they were monitored every Monday and Thursday to evaluate the outcome for 14 days. The age, sex, body mass index, and compliance of all the subjects with the standard diet regimen (low fat diet), exercise, and smoking behavior was assessed using a questionnaire, based on cross-sectional study, at the end of study. Blood samples were collected twice a week to determine the TC and LDL-C values in the laboratory during the study. The values of TC and LDL-C were determined from fasting blood cholesterol. They were measured at baseline, day 3, 7, 10 and 14 of study period. Overnight fasting venous blood (3 mL) was taken from each subject each time the measurements were done. The TC and LDL-C were measured using enzymatic methods by spectrophotometric assays on automated chemistry analyzer. The blood was taken at the laboratory of Biomedika, South Jakarta, Indonesia and analyzed using a reagent kit (Roche Diagnostics, GmBH, Manheim, Germany)

Subjects

The Ethics Committee of the Faculty of Medicine, University of Indonesia - Cipto Mangunkusumo Hospital, Central Jakarta, Indonesia reviewed the research protocol used and approved it (Reg. no. 127/PT02.FK/ETIK/2012); followed the guidelines of World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects [18]. The 60 subjects were selected for the study using the following criteria. The inclusion criteria for this study are diagnosis of hypercholesterolemia with an increased TC > 200 mg/dL and LDL-C > 130 mg/dL, in males and females, aged over 30 years and willing to give informed consent. Exclusion criteria were the use of supplement or drugs that will interfere with cholesterol metabolism, pregnant and breast feeding women, women with hormone replacement therapy, and patients with chronic disease. Reasons for dropping out of the study include non-compliance to protocol agreed upon at the beginning of the study, change in the type of drug that has been established at the beginning of the study, patient experiencing side effects of MCC and refusal to continue the research.

Statistical analysis

The data was analyzed by descriptive and analytical method using Students' t- and Chi square tests. Significance level was set at $p < 0.05$ and all data were analyzed using a statistical software package (SPSS, version 17.0).

RESULTS

Characteristics of subjects

The results showed that patients who had serum total cholesterol > 200 mg/dL and LDL cholesterol > 130 mg/dL were mainly those whose age were < 40 years old (53.3 %). Overweight patients (BMI > 25 kg/m^2) were 55 %. Also, 28.3 % of patients do not engage in regular exercise. Patients on low fat diet constituted 60 % while others were not. Most of the patients were non-smokers (73.3 %).

Effect of MCC in hypercholesterolemic patients

This study also showed a significant reduction of total and LDL cholesterol in experimental group compared to control group (Figures 1 and 2).

Table 1: Demographic profile of subjects

Variable	N (%)	Control (%)	Total (%)
Age			
≤ 40 years	19 (63.3)	13 (43.3)	32 (53.3)
> 40 years	11 (36.7)	17 (56.7)	28 (46.7)
Sex			
Male	16 (53.3)	18 (60.0)	34 (56.7)
Female	14 (46.7)	12 (40.0)	26 (43.3)
Body Mass Index			
≥ 25 kg/m^2	11 (36.7)	16 (53.3)	27 (45.0)
< 25 kg/m^2	19 (63.3)	14 (46.7)	33 (55.0)
Exercise			
Not regular	7 (23.3)	10 (33.3)	17 (28.3)
Regular	23 (76.7)	20 (66.7)	43 (71.7)
Diet			
Not compliant	8 (26.7)	16 (53.3)	24 (40.0)
Compliant	22 (73.3)	14 (46.7)	36 (60.0)
Smoking habit			
Smoking	7 (23.3)	9 (30.0)	16 (26.7)
Non-smoking	23 (76.7)	21 (70.0)	44 (73.3)

**Obey in order to follow the instrument at low fat diet*

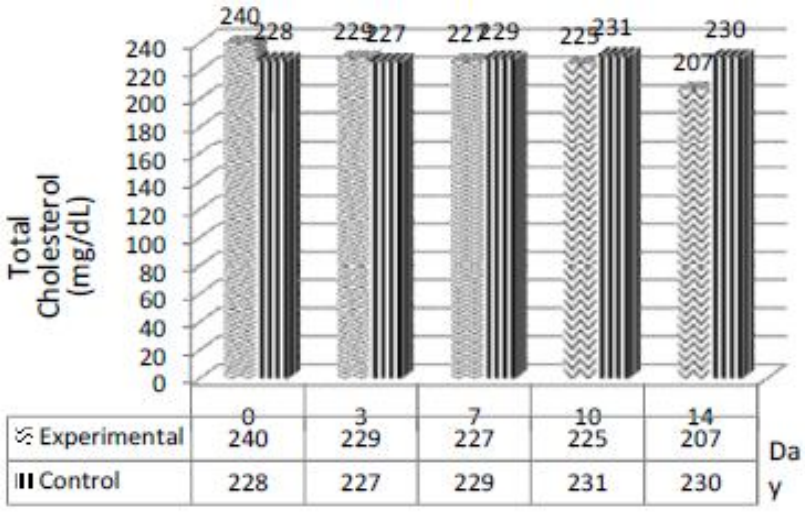

Fig 1: Effect of extract on TC levels in subjects

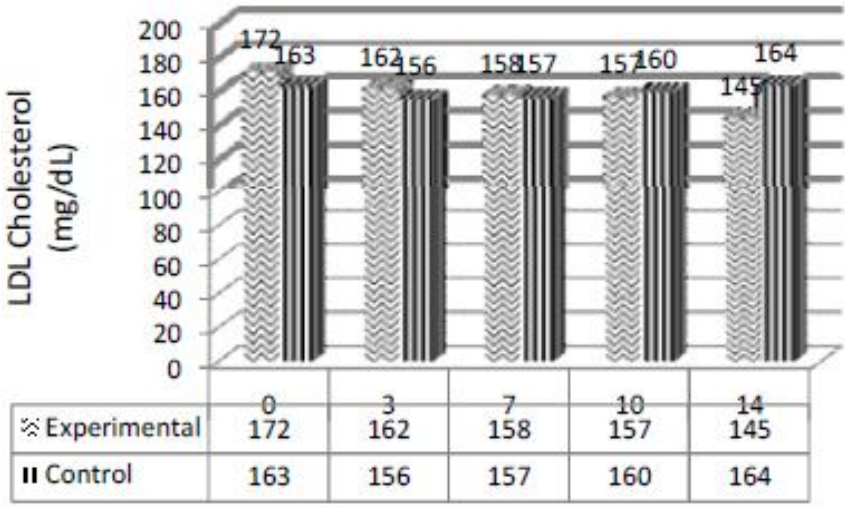

Fig 2: Effect of extract on LDL-C levels in subjects

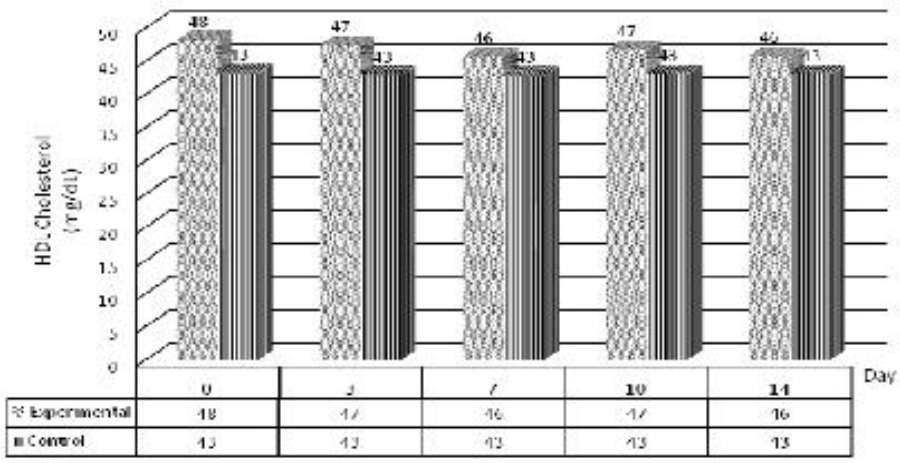

Fig 3: Effect of extract on HDL-C levels in subjects

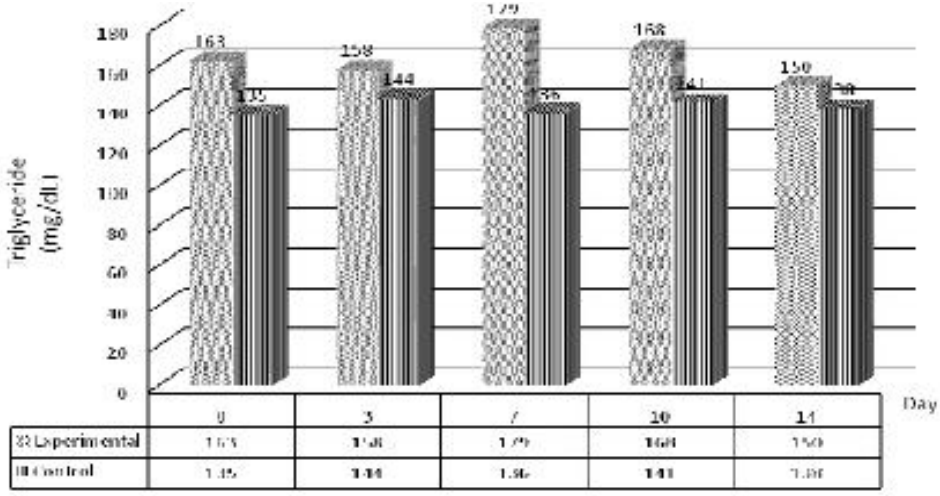

Fig 4: Effect of extract on triglyceride levels in subjects

Table 2: Profile of lipids level (mg/dL, mean ± SD) before and after the intervention

Parameter	Control		Experimental	
	Day 0	Day 14	Day 0	Day 14
Total Cholesterol	228.2 ± 18.7	230.2 ± 19.8	240.0 ± 26.8	207.0 ± 24.7
LDL Cholesterol	163.0 ± 17.5	164.0 ± 18.6	171.5 ± 22.2	144.9 ± 21.9
HDL Cholesterol	43.1 ± 10.7	42.9 ± 9.5	48.1 ± 12.2	45.7 ± 11.9
Triglyceride (TG)	135.5 ± 48.5	138.4 ± 48.5	162.6 ± 86.6	150.0 ± 73.8

As Table 2 shows, there were differences in TC and LDL-C levels in the two groups ($p < 0.05$). There was no significant difference in TC and LDL-C levels from baseline level to day 14 in the control group but there was a significant decrease in TC and LDL-C levels in the experimental group at day 14. The reductions in TC and LDL-C were 13.8 % (33.0 mg/dL) and 15.5 % (26.6 mg/dL), respectively, using control group as the baseline. But, MCC could not increase HDL-C or decrease TG because the result showed that there are no significant differences ($p > 0.05$).

Bivariate analysis

The correlation between TC and factors that could influence the concentration of TC, such as age, sex, BMI, exercise, diet and smoking habits at the experimental group were analyzed but that between LDL-C level and the factors was not because LDL-C is the major component of TC [1]. When TC increases, the LDL-C will automatically increase too. Therefore, it would be more accurate to analyze correlation between TC and all of factors.

Table 3 shows the results of correlation analysis between average TC reduction and factors that influence the concentration of TC in experimental group. Age was found to be associated with TC level reduction (OR = 2.8; p = 0.042). The TC reduction was also influenced by changes in BMI (OR = 6.2; p = 0.0001), exercise (OR = 14; p = 0.001), diet (OR = 16.3; p = 0.0001) and smoking habits (OR = 14; p = 0.001). The highest odd ratio (OR) was showed by dietary factor (16.3). The result shows that there were significant differences in average TC level reduction in relation to differences in age, BMI, exercise, diet and smoking habits ($p < 0.05$) while for the sex factor, there was no significant different in TC reduction ($p > 0.05$).

DISCUSSION

Morinda citrifolia (MC) is one of the traditional medicines used to treat cardiovascular diseases such as hyperlipidemia. As MC is reported to be rich in flavonoids, a polyphenol substance, which could inhibit lipid biosynthesis [19] especially by inhibiting the HMG Co-A reductase [20]. Various studies, both in humans and animals, have shown similar results in reducing effect to TC and LDL-C. Mandukhail [14] conducted a research in rats that injected high dose of lipids and the results showed that MC extract inhibited biosynthesis, absorption and secretion of lipids on day 10. Besides that, Subramanian and Rao [21] gave a result that MC might act as an anti-diabetic, anti-hyperlipidemia and anti-oxidant in diabetic rats. In humans, Wang *et al* [15] found that 68 smoking volunteers who were given MC two times a day for 30 days showed reduced levels of TC and LDL-C. All the studies mentioned above produced similar results with this study. In this study, MCC reduced serum TC and LDL-C level because there were significant decreases in TC and LDL-C level ($p < 0.05$).

There are other factors that could influence TC level in human. They are age, sex, BMI, exercise, diet and smoking habits. The first factor was age (OR = 2.8; p = 0.042). Serum TC level starts to increase at 20 years old and continues until 60-65 years old [5]. Devroey *et al* [22] observed that increase in TC and LDL-C levels correlates with increase in age. However, in other studies by Raitakari *et al* [23], dyslipidemia was found in children and adolescents. Indonesian Health Household Survey in 2004 [24] stated that hypercholesterolemic patients had been shifted from the usual age. They showed that hypercholesterolemic patients whose ages range between 25 - 34 years old was 9.3 %. In this study, subjects under 40 years old showed greater reduction lipid levels following consumption of MC fruit extract capsule.

From this study, sex did not give a significant decrease in TC level. Theoretically, before the age of 50, TC in males might be higher than in females at the same age. But, after the age of 50 the reverse is the case. It is caused by hormonal effect in females after menopause. After menopause (natural or surgical) TC would rise so

Table 3: Correlation analysis results between average TC reduction and factors that influence TC reduction in experimental group (n =30)

Variable	Reduction		OR	*p**
	Mild	Good		
Age				
≤ 40 years	3 (33.3 %)	16 (76.2 %)	2.8	0.042
> 40 years	6 (66.7 %)	5 (23.8 %)		
Sex				
Male	6 (66.7 %)	10 (47.6 %)	-	0.440
Female	3 (33.3 %)	11 (52.4 %)		
Body mass index				
≥ 25 kg/m^2	8 (88.9 %)	3 (14.3 %)	6.2	0.0001
< 25 kg/m^2	1 (11.1%)	18 (85.7 %)		
Exercise				
No regular	6 (66.7 %)	1 (4.8 %)	14	0.001
Regular	3 (33.3 %)	20 (95.2 %)		
Diet				
Not compliant	7 (77.8 %)	1 (4.8 %)	16.3	0.0001
Compliant	2 (22.2 %)	20 (95.2 %)		
Smoking habit				
Smoking	6 (66.7 %)	1 (4.8 %)	14	0.001
Non-smoking	3 (33.3 %)	20 (95.2 %)		

**Significant at p < 0.05; cut off point was 33 mg/dL, i.e., it was good if the reduction ≥ 33 mg/dL*

LDL-C rises too [5]. However, there were some studies which showed that sex did not affect the TC reduction. John *et al* [25] in his research stated that control of dyslipidemia did not vary significantly across ethnic-sex group and prevalence of dyslipidemia did not differ significantly between women and men. Cooke and Hammerash [26] also reported the same. They showed that there were no significant sex differences in potency groups to manage dyslipidemia. Another study by Syed *et al* [27] showed that there were no significant reductions in serum TC and LDC-C levels in both male and female patients ($p > 0.05$).

Another factor was BMI. In this study BMI gave OR = 6.2 and $p = 0.0001$. This result shows that there was a significant correlation between BMI and TC reduction. Freeman and Junge [5] stated that high BMI or body weight increases the risk of a higher TC level. Denke [28] explained that there was a relationship between body weight changes and serum TC level among people between adults and middle age.

Exercising regularly could lower the levels of TC, LDL-C, and triglycerides in humans [29]. This study shows a significant difference between patients who exercised regularly and those who did not (OR = 14; $p = 0.001$). Kuriyan *et al* [30] produced same results with this study. They explained that physical activity reduces most of the artherosclerotic risk factors and regular exercise has been shown to reduce LDL-C and triglycerides.

Lifestyle modification to normalize body weight and having healthy patterns of dietary intake might give a significant result in serum TC reduction. Individualized dietary intake for reducing TC level in blood have shown to be modestly effective. Diets low in saturated fat and cholesterol could lower LDL-C [30]. Our study showed that diet could decrease TC level. A comparison between patients with a good diet and those without showed significant differences in TC reduction (OR = 16.3; $p = 0.0001$).

One other factor that influenced the reduction of TC level was smoking habits (OR = 14; $p = 0.001$). A cigarette contains many toxins such as tar, nicotine and carbon monoxide. Smoking can decrease the oxygen serum level and lead to elevation in heart rate, reduction in high density lipids (HDL) and damage of endothelium [31]. Jacobson [32] stated that there was a correlation between smoking and TC level while Schultemaker [33] explained that there was a significant difference in the TC levels of patients who smoked and those who do not. Shi-Dou Lin *et al* [34] also found that TC level is related to smoking habits. Thus, the findings are buttressed those of the cited above, especially with regard to correlation between smoking habit and reduction in TC level.

No serious adverse effects were reported during the present study. Adverse events were just limited to mild gastrointestinal symptoms such as flatulence and abdominal distention after the first few doses but the symptoms subsided within a week in all subjects.

CONCLUSION

The results indicate that 1 g extract, when given orally three times a day, significantly reduces TC and LDL-C levels. It seems that consumption of MCC when combined with suitable control of some factors such as age, BMI, diet, exercise and smoking habit significantly reduces TC levels in patients. The results from this study justify the medicinal use of *Morinda citrifolia* in hypercholesterolemia and may also be of relevance in the treatment of cardiovascular diseases.

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