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Research Article
Synergistic Effects of Turmeric, Strawberry and Broccoli in Improving Lipid Profile in Adult Patients with Hypercholesterolemia

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Abstract
Background and Objective: Turmeric, strawberries and broccoli are popular in the community for their beneficial effects in improving lipid profile, but poor bioavailability and absorption of their phytochemical compounds might reduce their effects while given separately. Therefore, their combination might provide a synergistic enhancement of their property as hypolipidemic agents. This study aims to examine the effects of turmeric, strawberry and broccoli in improving lipid profile in adult patients with hypercholesterolemia. **Materials and Methods:** Twenty hypercholesterolemic adult patients from Unggul Karsa Medika Hospital in Bandung, Indonesia were recruited for the study, they were given 600 mg/day of turmeric/curcuminoid, 100 g of fresh strawberry and 100 g of boiled broccoli for 30 days. The measurement of the patient's characteristics (body weight, height, BMI) and biochemical parameters in the blood (total cholesterol, triglyceride, LDL-C, HDL-C, SGOT, SGPT, urea and creatinine) were conducted before and after the treatment. **Results:** The mean age of the patients was 49.15$\pm$1.9 years old, with mean height 1.56$\pm$0.014 m, weight 61.43$\pm$1.96 kg and mean body mass index 25.25$\pm$0.87 kg/m^2. Lipid profile before the treatment: Total cholesterol 239.75$\pm$6.56 mg/dL, LDL-C 172.9$\pm$6.53 mg/dL, HDL-C 66.55$\pm$3.37 mg/dL and triglyceride 193.7$\pm$18.45 mg/dL; after the treatment: Total cholesterol 220.7$\pm$9.39 mg/dL, LDL-C 153.95$\pm$9.98 mg/dL, HDL-C 59.2$\pm$2.45 mg/dL and triglyceride 145$\pm$16.55 mg/dL. The result showed a significant reduction of total cholesterol ($p = 0.014$), LDL-C ($p = 0.036$), HDL-C ($p = 0.001$) and triglyceride ($p = 0.015$) after the treatment. Other biochemical parameters (SGOT, SGPT, urea and creatinine) showed normal levels before and after the treatment. **Conclusion:** In summary, supplementation of turmeric, strawberry and broccoli improves lipid profile in adult patients with hypercholesterolemia.

Key words: Broccoli, strawberry, turmeric, lipid profile, hypercholesterolemia

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

As the most prevalent non-communicable disease in the world, Cardiovascular Disease (CVD) is the leading cause of global mortality and economic burden, including in Indonesia[1]. The main risk factor for CVD is dyslipidemia, characterized by increased levels of total cholesterol (TC), LDL Cholesterol (LDL-C), triglyceride (TG) and decreased levels of HDL Cholesterol (HDL-C)[2]. Hypercholesterolemia is defined as an increase of total cholesterol in the blood ($\geq$200 mg/dL), while hypertriglyceridemia is defined as an increase of triglycerides in the blood ($\geq$150 mg/dL)[3]. To prevent CVD occurrence, dyslipidemia must be managed through a safe, cost-effective, low-side-effects strategy as its pharmacology and non-pharmacology intervention.

Indonesian people frequently use traditional drugs for pharmacology intervention of chronic diseases, such as dyslipidemia and CVD[4]. Turmeric is a traditionally popular drug with numerous benefits for health, facilitated by its properties as an antioxidant, anti-inflammatory, antimicrobial, cardioprotective, antiobesity and hypolipidemic[5,6]. Curcumin, a polyphenol derived from turmeric, is dispersed in ethanol and possesses lipid-modifying activity, especially triglycerides and HDL-C while total cholesterol and LDL-C were unaltered[7]. However, the therapeutic effect of curcumin is affected by its low solubility in water and poor absorption in the gut[8]. Therefore, a non-pharmacology intervention must also be considered to potentiate the hypolipidemic effect of turmeric.

As a non-pharmacology intervention, a healthy diet is an important part of a healthy lifestyle that people worldwide become more aware of. The definition of a healthy diet requires knowledge about the effects of foods, nutrients and food components on health and disease[9]. The dietary approaches to stop hypertension (DASH) and Mediterranean diets are proven to be effective in dyslipidemia prevention[10-12]. These diets contain more plant-based food, such as fresh fruits, vegetables, whole grains, legumes, seeds and nuts[9]. Fresh fruits and vegetables provide a satiety feeling, improve gastrointestinal function and contain bioactive compounds that deliver beneficial effects on lipid profile[13,14].

Strawberries and broccoli are fruits and vegetables frequently used in combination for a healthy diet. Strawberries contain high polyphenols and dietary fibers, contributing to their effects in reducing CVD risk factors, including dyslipidemia[15]. Polyphenols from strawberries interact with gut microbiota by affecting microbiota and by being metabolized by it[9]. High concentrations of polyphenols, glucosinolates, sulforaphane and selenium in broccoli made this vegetable known for possessing health-promoting properties[16]. Recent studies have proven the positive effects of turmeric, strawberries and broccoli on improving dyslipidemia, nevertheless, their combination might generate a synergistic effect in modifying the lipid profile in the blood. This study aims to investigate whether the combination of turmeric, strawberry and broccoli might enhance their capability to improve lipid profile in adult patients with hypercholesterolemia.

MATERIALS AND METHODS

Participant recruitment: Twenty adult patients with hypercholesterolemia were recruited from Unggul Karsa Medika Hospital (Bandung, Indonesia). The study was carried out from July, 2022 until February, 2023. The participants were assessed for eligibility with inclusion criteria: Healthy adults between 18-60 years old and fasting plasma total cholesterol >200 mg/dL. The exclusion criteria were history of cardiovascular disease, diabetes mellitus, Infectious disease, gastrointestinal absorption disorder, neurological disease, kidney/liver dysfunction, hypertension, allergy/intolerance to broccoli/strawberry/turmeric used in the study, taking lipid-lowering or anti-inflammatory medication, consuming other supplements, smoking, pregnant or lactating.

Ethical consideration: The study protocol was approved by the Research Ethics Committee, Unggul Karsa Medika Hospital (ethics number: 005/KEP-LIT/VIII/2022) and was conducted following the 1975 Declaration of Helsinki as revised in 1983. Informed consent was signed by all participants before the beginning of the study.

Study design: This study used a pre-test and post-test design. All subjects participated in 30 days of treatment with 600 mg curcuminoid (Sari Kunyit/Turmeric, Sidomuncul, from Ungaran, Semarang, Indonesia), 100 g of fresh strawberry and 100 g of fresh broccoli from Lembang, Bandung, Indonesia. Compliance was monitored by evaluating the daily log for dietary records and consumption of broccoli, strawberry and turmeric.

Clinical assessment, anthropometry and lipid profile analysis: The participants visited Unggul Karsa Medika Hospital before and after treatment in an 8 hrs fast state. Anthropometric (height, weight, BMI), medical history, dietary intake and fasting blood samples (total cholesterol, triglyceride, LDL-C, HDL-C, SGOT, SGPT, urea and creatinine) were examined in this study. For anthropometry data, height and weight measurements were taken using Seca Mechanical Column Scale-Seca 755 and Measuring Rod-Seca 224 (SECA, China).

Statistical analysis: Statistical analysis was conducted using SPSS 26, all data were presented as Means±SEM (Standard Error of the Mean) and a 0.05 significance level was set. A paired sample t-test or Wilcoxon was used to compare the changes in lipid profile levels before and after the treatment.

RESULTS

Participant characteristics: In this study, 20 participants were recruited from December, 2022 to February, 2023. The characteristics of the participants were: Mean age 49.15±1.9 years old, height 1.56±0.014 m, weight 61.43±1.96 kg and BMI 25.25±0.87 kg/m^2. The data was presented in Table 1.

Effect of turmeric, strawberry and broccoli on plasma lipid profile: After 30 days of treatment with turmeric, fresh strawberries and boiled broccoli, the plasma lipid profiles were significantly reduced. Total cholesterol, LDL-C, HDL-C and triglyceride before the treatment were: 239.75±6.56, 172.9±6.53, 66.55±3.37 and 193.7±18.45 mg/dL, respectively, while after the treatments were: 220.7±9.39, 153.95±9.98, 59.2±2.45 and 145±16.55 mg/dL, respectively. The difference between after and before the treatment for total cholesterol, LDL-C, HDL-C and triglyceride were: -19.05±6.61 mg/dL ($p = 0.014$), -18.95±8.41 mg/dL ($p = 0.036$), -7.35±1.98 mg/dL ($p = 0.001$) and -48.7±16.53 mg/dL ($p = 0.015$), as shown in Table 2.

Effect of turmeric, strawberry and broccoli on other biochemical parameters in the blood: After 30 days of treatment with turmeric, fresh strawberries and boiled broccoli, the other biochemical parameters in the blood: SGOT, SGPT and creatinine were not significantly affected, while we found a significant decrease in urea levels in the blood, but the level is still categorized as normal level. The SGOT, SGPT, urea and creatinine before the treatment were: 24.4±2.66 and 31.6±5.29 IU/L, 24.5±2.28 and 0.721±0.03 mg/dL, respectively, while after the treatments were: 24.35±2.08 and 29.6±5.43 IU/L, 18.9±1.63 and 0.6985±0.03 mg/dL, respectively. The differences between after and before the treatment for SGOT, SGPT, urea and creatinine were: -0.05±1.54 IU/L ($p = 0.931$), -2±3.82 IU/L ($p = 0.111$), -5.6±2.22 mg/dL ($p = 0.016$) and -0.0225±0.02 mg/dL ($p = 0.374$), as shown in Table 3.

DISCUSSION

This study found improvement in the lipid profile of hypercholesterolemic patients after 30 days of treatment with turmeric, combined with fresh strawberries and boiled broccoli consumed every morning at 10 am. Total cholesterol,

Table 1: Participant characteristics at baseline

Characteristics	Total (%) or Mean±SEM
Sex, n (%)	
Male	2 (10%)
Female	18 (90%)
Age (y)	49.15±1.9 mg/dL
Height (m)	1.56±0.014 mg/dL
Weight (kg)	61.43±1.96 mg/dL
BMI (kg/m^2)	25.25±0.87 mg/dL

BMI: Body mass index

Table 2: Change in plasma lipid profile before and after treatment

Plasma lipid profile	Mean±SEM (mg/dL)
Total cholesterol	
Before	239.75±6.56
After	220.7±9.39
Δ (mg/dL)	-19.05±6.61*
LDL-C	
Before	172.9±6.53
After	153.95±9.98
Δ (mg/dL)	-18.95±8.41*
HDL-C	
Before	66.55±3.37
After	59.2±2.45
Δ (mg/dL)	-7.35±1.98**
TG	
Before	193.7±18.45
After	145±16.55
Δ (mg/dL)	-48.7±16.53*

*Means statistically significant ($p<0.05$) and **Means statistically very significant ($p<0.01$)

Table 3: Change in other biochemical parameters in the blood before and after treatment

Other biochemical parameter	Mean±SEM (IU/L or mg/dL)
SGOT	
Before	24.4±2.66
After	24.35±2.08
Δ (IU/L)	-0.05±1.54
SGPT	
Before	31.6±5.29
After	29.6±5.43
Δ (IU/L)	-2±3.82
Urea	
Before	24.5±2.28
After	18.9±1.63
Δ (mg/dL)	-5.6±2.22*
Creatinine	
Before	0.721±0.03
After	0.6985±0.03
Δ (mg/dL)	-0.0225±0.02

*Means statistically significant ($p<0.05$)

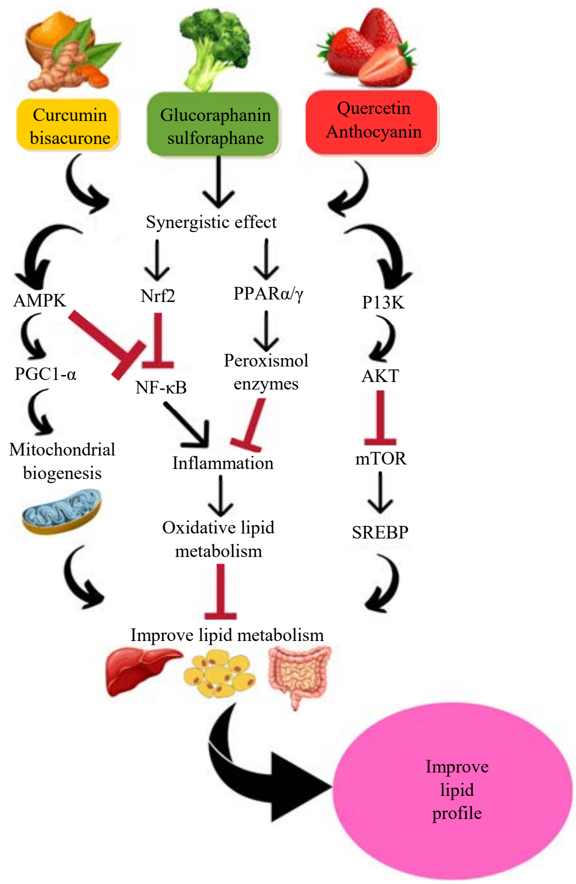

Fig. 1: Proposed mechanisms of synergistic effects of turmeric, strawberry and broccoli in improving lipid profile

LDL-C, HDL-C and triglyceride levels were decreased significantly, as shown in Table 2. This finding was similar to another study which also found a decrease in total cholesterol, LDL-C and triglyceride after 30 days of treatment with curcumin or turmeric in overweight hyperlipidemic patients[17]. Other studies showed changes only in total cholesterol, LDL-C and triglyceride levels after treatment with curcumin, strawberry or broccoli[18-21].

Interestingly, this study found a significant decrease in HDL-C (Table 2). Decades ago, HDL-C levels were known to have a linear inverse correlation with CVD events, but recently, this paradigm has changed after other studies found a nonlinear correlation between HDL-C and CVD events[22-25]. Recent studies have concluded that low to moderate HDL-C levels are inversely correlated with CVD risks, but extremely high levels of HDL-C ($\geq$90 mg/dL) are correlated with high CVD risks and mortality, creating a U-shaped association[23-25]. Therefore, the decrease of HDL-C in this study might indicate a positive impact on CVD risks, considering the mean of the HDL-C levels before and after the treatments are still categorized as normal levels (Table 2). The results of other biochemical parameters in the blood showed normal levels of SGOT, SGPT, urea and creatinine before and after the treatments, indicating that the treatment did not induce changes in the liver and kidney function (Table 3).

Studies have proven that turmeric, strawberries and broccoli have potential roles in reducing CVD risk factors by modulating lipid levels[5,15,20,26]. Several mechanisms were proposed for this curcuminoid action, such as induction of PPARα/γ, scavenging free radical and signal transduction modification (Akt, AMPK, Nrf2, FOXO, SREBP1/2) correlated with lipid homeostasis genes[7,27]. As the major constituent in turmeric, curcuminoid decreased triglycerides and increased HDL-C, while total cholesterol and LDL-C were found unaltered[7]. Nevertheless, the poor bioavailability of curcumin might reduce its effectiveness when given orally in patients with hypercholesterolemia[28]. Therefore, other nutraceutical components might be combined with turmeric to enhance its effects on lipid profile.

Broccoli (*Brassica oleracea var Italica*) has edible (florets, sprouts) and non-edible parts (stalks, leaves, seeds)[29,30]. Compared to other parts, broccoli florets have higher levels of amino acids, neoglucobrassicin, glucoraphanin, water-soluble phenolic compounds and vitamin C[29,30]. Glucoraphanin is a form of glucosinolate that has been proven to reduce LDL-C via Nrf2 inducer sulforaphane and correlated with mitochondrial fatty acid oxidation and lipid synthesis modulation via PI3K-AMPK signaling[21,26,31]. The combination of sulforaphane and curcumin has been studied for their synergistic anti-inflammation effects in macrophage cells (RAW 264.7 cells); antioxidant and antiproliferative properties in human colon cancer cells (HT-29) and as future chemotherapy agents[32-35].

Besides sulforaphane, polyphenols and anthocyanin might also enhance a synergistic effect with curcumin and broccoli. Strawberry contains polyphenols (anthocyanin, proanthocyanidins, ellagitannins), minerals, vitamins, flavonoids (quercetin, catechin, kaempferol) and dietary fibers, making it a functional food with a potential role in reducing cholesterol levels[15,20]. Several studies have combined curcumin and quercetin or anthocyanin to prove their anti-inflammatory, anti-microbial, antioxidant, wound wound-healing properties and for the prevention of diabetes and obesity[36-38].

The proposed synergistic effects of turmeric, broccoli and strawberries were summarized in Fig. 1. Curcumin and bisacurone in turmeric; glucoraphanin and sulforaphane from broccoli; quercetin and anthocyanin from strawberries are phytochemicals frequently studied in research because of their properties as anti-inflammatory, hypolipidemic and cardioprotective agents. Molecular mechanisms for those properties involved AMPK, PPARα/γ, PI3K-Akt-mTOR and Nrf2-NF-κB signaling pathways[5,7,8,27,39]. The AMPK increased ACC which then increased mitochondrial biogenesis, improving mitochondrial dysfunction correlated with disruption of lipid metabolism found in dyslipidemia[40-42]. The induction of PPARα increased beta-oxidation of free fatty acids thus preventing lipid accumulation in the liver, while induction of PPARγ increased FAT/CD36, removing lipid peroxides and oxidized LDL in systemic circulation[41-44]. Pathway signaling of PI3K-Akt-mTOR might also be activated, reducing oxidative stress and lipid accumulation in the liver[41,43,45]. The last proposed mechanism was the Nrf2-NF-κB pathway, indicating the role of Nrf2 as the regulator of antioxidant enzymes and inhibitor of NF-κB, reducing oxidative lipid metabolism, thus improving dyslipidemia[39-41]. Further studies with a larger number of male and female hypercholesterolemic patients and *in vitro* and animal studies to prove the proposed mechanism for the synergistic enhancement of turmeric, broccoli and strawberry would be required to confirm the results obtained in this study.

CONCLUSION

A combination of traditional drugs and a healthy diet might result in beneficial effects for preventing cardiovascular disease by eliminating risk factors such as dyslipidemia. Turmeric, strawberry and broccoli are known as hypolipidemic agents by affecting lipid metabolism through several molecular mechanisms. This study found a significant decrease in total cholesterol, LDL-C, HDL-C and triglyceride after treatment, with normal levels of liver enzymes, urea and creatinine. In summary, combining those three ingredients provides a synergistic enhancement for achieving lipid profile improvement in adult hypercholesterolemic patients.

SIGNIFICANCE STATEMENT

The purpose of this study is to explore the synergistic effect of combining turmeric, strawberry and broccoli in improving lipid profile in patients with hypercholesterolemia. The combination of turmeric as a traditional drug and fresh strawberries and broccoli for a healthy diet was given to twenty hypercholesterolemic patients for 30 days. The result showed a significant decrease in total cholesterol, LDL-C, HDL-C and triglyceride without change of SGOT, SGPT, urea and creatinine in the blood. In conclusion, the combination of turmeric, strawberry and broccoli enhanced the hypolipidemic effects on hypercholesterolemic patients. This finding supported the concept of combining traditional herbs and a healthy diet for improving lipid profile.

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