FiberCreme as a Functional Food Ingredient Reduces Hyperlipidemia and Risk of Cardiovascular Diseases in Subjects with Hyperlipidemia

Sunarti¹, Hasanah Mumpuni², Nadia Yasmine³, Yustinus Marsono⁴, Dwi Larasatie Nur Fibri⁵, and Agnes Murdiati⁶

¹Department of Biochemistry, Faculty of Medicine, Public Health, and Nursing, Gadjah Mada University, Yogyakarta 55281, Indonesia
²Department of Cardiology and Vascular Medicine, Faculty of Medicine, Public Health, and Nursing, Dr. Sardjito General Hospital, Gadjah Mada University, Yogyakarta 55281, Indonesia
³Faculty of Medicine, Public Health, and Nursing, Gadjah Mada University, Yogyakarta 55281, Indonesia
⁴Department of Food and Agricultural Product Technology, Faculty of Agricultural Technology, Gadjah Mada University, Yogyakarta 55281, Indonesia

ABSTRACT: FiberCreme is a commercial nondairy creamer made with isomalto-oligosaccharides (IMO) that is a source of dietary fiber. A study showed that IMO could decrease cholesterol (CH) and triglycerides, which are factors related to the risk of cardiovascular diseases and insulin resistance. This study evaluated FiberCreme’s ability as a functional food ingredient to reduce CH and the risk of cardiovascular diseases in subjects with hyperlipidemic. This controlled clinical study trial involved 53 (23 ∼ 57 years old) subjects with borderline high CH (>190 mg/dL) or triglycerides (>150 mg/dL) or both, who were divided into FiberCreme and control groups. The participant received 86 g of cookies daily for 4 weeks. The FiberCreme and control groups consumed FiberCreme-containing cookies and cookies with coconut cream with 5.78% and 4.69% fibers, respectively. Lipid profile, anthropometry, body composition, and food intake were also measured. Data analysis was performed using SPSS v.25. This study suggests that FiberCreme cookies can significantly reduce CH, triglycerides, and cardiac risk ratio scores.

Keywords: cardiac risk ratio scores, cholesterol, FiberCreme, isomalto-oligosaccharides, triglyceride

INTRODUCTION

Many animal and human studies have reported that dietary fiber (DF) promotes health and prevents diseases, even cardiovascular diseases. However, DF is resistant to enzymatic digestion in the human gastrointestinal tract (GIT). Thus, the intestinal cells do not absorb it; nonetheless, colonic bacteria ferment it partially or wholly to produce short-chain fatty acids (SCFAs). FiberCreme is a healthy commercial nondairy creamer that uses a combination of fiber from various oligosaccharides and fully hydrogenated coconut oil to replace the glucose in conventional creamer. Isomalto-oligosaccharides (IMO) are DFs in the form of oligosaccharides that improve lipid profiles (Wang et al., 2001; Marsono et al., 2020) and are components of FiberCreme. Many animal and human studies showed that IMO can improve lipid profiles. For example, replacing cellulose with IMO in the diet of rats reduced total plasma lipids, cholesterol (CH), and triglycerides compared with the control group (Marsono et al., 2020). Supplementation with 10 g of IMO daily for 4 weeks was effective in reducing total plasma CH and low-density lipoprotein-CH (LDL-C) (Yen et al., 2011). Additionally, patients receiving hemodialysis taking 30 g of IMO for 4 weeks had lower total CH and triglyceride levels and higher high-density lipoprotein-CH (HDL-C) levels than the baseline (Wang et al., 2001). FiberCreme has also been reported to improve blood lipid profiles in rats fed a high-CH diet (Marsono et al., 2020).

CH can be used to determine the atherogenic index, which helps predict cardiometabolic risk, e.g., the cardio-
risk ratio (CRR), calculated from the CH/HDL-C formula (Lafta, 2014). Blood CH levels are determined by endogenous synthesis and absorption of dietary CH and reabsorption of bile salts that influence bile synthesis.

Many pathways have been proposed to explain the effect of DF in lowering CH. DF deconjugates bile acids, leading to decreased reabsorption and increased excretion of bile acids in feces and stimulating the liver to synthesize bile from circulating CH. Han et al. (2019) reported that cereal fiber reduces the absorption and increases intestinal CH efflux and clearance in rats fed a high-CH diet. This occurs by modulating peroxisome proliferator-activated receptor (PPAR)α, liver X receptor (LXR)α, and sterol-regulatory element binding proteins (SREBPs) signaling pathways, which are involved in CH metabolism to lower CH levels.

The DF fraction of Pleurotus ostreatus (PDF) induces mRNA expression of CH-associated genes [e.g., diacylglycerol acyltransferase 1 (DGAT1), farnesyl-diphosphate farnesyltransferase 1 (FDFT1), sterol-O-acyltransferase 1 (SOAT1), and SREBF1] which can exhibit CH-lowering effects in Caco-2 cell cultures (Caz et al., 2015). Furthermore, Hu et al. (2020) showed that a dextrin resistance intervention (5 g/kg body weight) for 10 weeks decreased CH and lipid deposition in the liver and increased insulin resistance in rats induced by a high-fat and high-fructose diet. Therefore, DF is recommended to lower blood CH levels and statins (Soliman, 2019). This study evaluated the benefits of the high IMO content in FiberCreme as a functional food ingredient to reduce hyperlipidemia and the risk of cardiovascular diseases.

MATERIALS AND METHODS

Study participants and settings

This controlled clinical study trial involved 53 (23 ~ 57 years old) hyperlipidemic participants who were divided into FiberCreme (n=27) and control (n=26) groups. Participant’s criteria were borderline high CH (>190 mg/dL) or triglycerides (>150 mg/dL) or both. The participants were excluded if they had a severe hyperlipidemia-related illness, pregnancy, or lactation. The recruitment of participants was conducted by distributing videos to target subjects containing explanations related to the aims and objectives of the study and possible side effects. This study started after obtaining ethical approval from the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia (REF no. KE/FK/0404/EC/2021). All protocols followed the guidelines endorsed in the Declaration of Helsinki. Informed consent forms were completed and signed by the participants before study participation.

Data collection

The sample size was determined based on the results of changes in total CH levels of 18% (0.18) from a study by Mohamed et al. (2015). The minimum sample size (n=20) was determined for each group following the formula by Kadam and Bhalerao (2010), with a research power and a significance level of 80% and 0.05, respectively. The sample size was increased by 50% to anticipate dropouts (31 participants per group) because this study was conducted during the COVID-19 pandemic.

This study involved hyperlipidemic participants; therefore, the formulation of cookies was developed to obtain a low-fat but sufficient fiber content. The compositions of both cookies were similar except for the intervention cookies, which contained 1) FiberCreme, while the control cookies 2) contained coconut cream in a similar amount. Both cookies were packed in similar packages and divided between participants every 2 weeks. An investigator not involved in the cookies’ preparation performed the intervention blinding, and the statistician was blinded to the study until the analysis ended. The nutritional facts of both cookies are presented in Table 1.

Based on previous studies, foods containing 2.5 ~ 4.9 g per serving are good fiber sources (Home & Garden Information Center, 2021). FiberCreme cookies, for example, contain 5.78% fiber (Table 1), and each participant received 86 g of cookies daily, containing 4.9 g of fiber, for 4 weeks. However, in the end, the average consumption of cookies was 80 g daily (93%), containing 4.62 g of fiber, because some participants contracted COVID-19 during the intervention and could not consume all cookies daily. The distribution of cookies to participants every 2 weeks and consumption of cookies were monitored and ensured by WhatsApp (WhatsApp LLC., Menlo Park, CA, USA). Additionally, participants were asked to consume their usual diet and perform regular physical activities during the intervention.

The primary outcomes were lipid profile and CRR. In contrast, the secondary outcomes were anthropometry, body age, body fat, visceral fat, blood pressure, and dietary intake related to energy, carbohydrates, protein, total

| Table 1. Nutritional composition in 100 g of FiberCreme and coconut cookies |
|-----------------|-----------------|-----------------|
| Composition     | FiberCreme cookies | Coconut cookies |
| Energy (kcal)   | 409.00           | 393.80          |
| Lipid (%)       | 11.45            | 11.98           |
| Carbohydrate1 (%) | 71.89           | 69.82           |
| Protein (%)     | 5.04             | 4.83            |
| Water (%)       | 4.73             | 7.31            |
| Ash (%)         | 1.11             | 1.37            |
| Fiber (%)       | 5.78             | 4.69            |

1Carbohydrate content calculated by difference.
fat, and DF. All variables were assessed at the start and end of the intervention.

**Anthropometric measurements and body composition**
All variables were measured twice, before and after the intervention. First, anthropometry and body composition were determined by bioimpedance analysis and height according to the midline. Meanwhile, body weight (kg) divided by the square of height (m²) was used to determine body mass index (BMI). A Semiquantitative Food Frequency Questionnaire was used to evaluate food intake. The questionnaire results were analyzed using Nutrisurvey 2007 (SEAMEO TROPED RCCN-University of Indonesia, Jakarta, Indonesia).

**Biochemical measurements**
Total CH, triglycerides, HDL-C, and LDL-C levels were measured before and after the intervention. To obtain ethylenediaminetetraacetic acid (EDTA) plasma, 10 mL of venous blood was transferred into a vacutainer tube containing EDTA (Wuhan Desheng Chemical Technology Co., Ltd., Wuhan, China) and then centrifuged at 3,000 rpm for 10 min at room temperature. Total CH, triglycerides, HDL-C, and LDL-C were measured by enzymatic colorimetric methods using the Roche diagnostic kit (F. Hoffmann-La Roche Ltd., Basel, Switzerland).

**Statistical analysis**
Data analysis was performed using SPSS version 25 (IBM Corp., Armonk, NY, USA). Participants' characteristics were analyzed by Levene's tests for equality of variance and independent sample t-tests to compare scores between groups. Data in tables were presented as mean and standard deviation (SD), meanwhile data in figure was presented as mean and standard error (SE) with a 95% confidence interval, and differences were significant at P<0.05. Anthropometric scores and dietary intakes are presented as mean±SD. The mean change of scores within each group was analyzed by paired samples t-test. The effects of the cookies’ intervention on changes in lipid profile and the CRR value within and between groups were compared by analysis of variance.

**RESULTS**

**Subjects**
This study enrolled 81 volunteers as study participants and 19 were excluded. Based on age criteria, 62 participants were assigned to the FiberCreme group (n=31 receiving the FiberCreme cookies) and the control group (n=31 receiving the coconut cookies). Nine participants did not provide posttest data because they were infected with the COVID-19 virus; thus, the FiberCreme and the control groups had 27 and 26 participants, respectively. Participants’ baseline characteristics did not significantly differ between the two groups except for BMI and body fat (Table 2).

**Anthropometry and food intake data**
The consumption of total energy, carbohydrates, and fiber significantly increased after 4 weeks of intervention, but no significant changes were noted in body weight and BMI in the FiberCreme and control groups (P>0.05; paired Student’s t-test; Table 3).

**Lipid profile and CRR data**
Triglycerides, total CH, HDL-C, LDL-C, and CRR levels were not statistically significantly different between the FiberCreme and control groups before the intervention. However, triglycerides, CH, and CRR levels were statistically significantly decreased in the FiberCreme group after the intervention but not in the control group. Changes in the mean CRR were also significantly different between the FiberCreme and control groups (Table 4). Comparisons of changes in lipid profile and CRR in the FiberCreme and control groups are shown in Fig. 1.

| Characteristic                  | FiberCreme group | Control group | P (95% confidence interval) |
|--------------------------------|------------------|---------------|-----------------------------|
| Age (yr)                       | 42.59±9.99       | 46.61±9.86    | 0.147 (−9.900 to 1.455)     |
| Weight (kg)                    | 70.59±14.13      | 68.20±8.90    | 0.465 (−4.142 to 8.943)     |
| Height (cm)                    | 157.07±11.67     | 162.08±7.28   | 0.068 (−9.499 to 1.453)     |
| Body mass index (kg/m²)        | 28.44±4.09       | 25.90±2.19    | 0.007* (0.725 to 4.362)     |
| Waist/hip ratio                | 0.91±0.09        | 0.92±0.07     | 0.833 (−0.484 to 0.039)     |
| Body age (yr)                  | 55.96±8.47       | 51.35±8.59    | 0.054 (0.090 to 9.323)      |
| Body fat (%)                   | 35.74±6.12       | 29.51±4.10    | <0.001* (3.345 to 9.114)    |
| Visceral fat (%)               | 11.44±4.13       | 9.39±4.19     | 0.077 (−0.235 to 4.354)     |
| Systolic blood pressure (mm Hg)| 122.96±13.25     | 125.00±8.60   | 0.512 (−8.223 to 4.149)     |
| Diastolic blood pressure (mm Hg)| 80.00±12.09    | 84.62±7.61    | 0.104 (−10.210 to 0.979)    |

Values are presented as mean±standard deviation or number (range). Significant difference at *P<0.05.
### Table 3. Anthropometric and dietary intake cores before and after the intervention

| Variables          | FiberCreme group (n=27) | Control group (n=26) |  
|--------------------|--------------------------|----------------------|  
|                    | Mean±SD                  | P (95% CI)           | Mean±SD                  | P (95% CI)           |  
| **Anthropometric** |                          |                      |                          |                      |  
| Weight (kg) Before | 70.60±14.13              | 0.340 (−0.247 to 0.692) | 67.81±9.405              | 0.589 (−0.383 to 0.659) |  
| Weight (kg) After  | 70.37±14.27              |                      | 67.67±9.647              |                      |  
| BMI (kg/m²) Before | 28.44±4.09               | 0.231 (−0.075 to 0.298) | 25.90±2.19               | 0.324 (−0.209 to 0.608) |  
| BMI (kg/m²) After  | 28.32±3.94               |                      | 25.70±2.61               |                      |  
| **Dietary intake**|                          |                      |                          |                      |  
| Energy (kcal/d) Before | 2,192.30±982.70         | <0.001* (−450.144 to 208.395) | 1,981.41±703.90         | <0.001* (−418.230 to −215.015) |  
| Energy (kcal/d) After  | 2,521.56±1,022.86        |                      | 2,298.03±772.24          |                      |  
| Carbohydrate (g/d) Before | 236.35±128.97           | <0.001* (−74.509 to 44.320) | 224.19±93.41            | <0.001* (−75.923 to −43.178) |  
| Carbohydrate (g/d) After  | 295.76±126.28           |                      | 283.74±103.88           |                      |  
| Protein (g/d) Before | 74.81±35.59              | 0.295 (−9.880 to 3.121) | 70.64±34.66              | 0.338 (−8.941 to 3.186) |  
| Protein (g/d) After  | 78.19±37.28              |                      | 73.51±33.78              |                      |  
| Total fat (g/d) Before | 114.69±56.96             | 0.091 (−15.054 to 1.189) | 101.57±38.16            | 0.090 (−14.127 to 1.083) |  
| Total fat (g/d) After  | 121.63±61.06             |                      | 108.10±38.97            |                      |  
| Dietary fiber (g/d) Before | 21.02±11.71             | <0.001* (−5.548 to −2.080) | 22.53±11.60            | 0.028* (−0.219 to −2.327) |  
| Dietary fiber (g/d) After  | 24.83±11.41              |                      | 24.44±12.12              |                      |  

The mean score changes in the groups were analyzed by paired t-test. Significant difference at *P<0.05.

SD, standard deviation; CI, confidence interval; BMI, body mass index.

### Table 4. Lipid profile and cardio-risk ratio of participants before and after intervention

| Variable          | Period       | FiberCreme group (n=27) | Control group (n=6) | MD between group | 95% CI     |
|-------------------|--------------|-------------------------|---------------------|------------------|------------|
| Triglycerides (mg/dL) | Before (mean±SD) | 146.8±67.44            | 156.48±67.36        | −9.61            | −26.04 to 71.15 |
|                   | After (mean±SD) | 131.32±50.14           | 165.37±65.99        | −34.05           | −2.90 to 74.38 |
|                   | MD within groups | −15.55                  |                      | 8.89             | −35.28 to 17.90 |
|                   | 95% CI         | 0.33 to 30.77           | −35.28 to 17.90     |                  | −18.12 to 3.53 |
| Total cholesterol (mg/dL) | Before (mean±SD) | 214.68±22.61           | 212.96±39.90        | 1.72             | −13.41 to 26.14 |
|                   | After (mean±SD) | 192.84±22.26           | 199.65±53.66        | −6.80            | −18.12 to 3.53 |
|                   | MD within groups | −21.84                  |                      | −13.32           | −13.41 to 26.14 |
|                   | 95% CI         | 13.40 to 30.28          | −3.90 to 30.53      |                  | 0.18 to 1.50  |
| LDL-C (mg/dL)      | Before (mean±SD) | 128.70±19.56           | 138.70±33.56        | −10              | −6.36 to 26.94 |
|                   | After (mean±SD) | 128.94±21.73           | 137.05±33.14        | −8.10            | −8.32 to 24.96 |
|                   | MD within groups | 0.24                    |                      | −1.65            |                  |
|                   | 95% CI         | −5.41 to 4.92           | −3.33 to 6.63       |                  | −14.96 to −2.72 |
| HDL-C (mg/dL)      | Before (mean±SD) | 51.70±12.23            | 45.52±10.42         | 6.17             | −12.55 to 0.82  |
|                   | After (mean±SD) | 51.53±12.76            | 43.18±9.11          | 8.35             | −14.96 to −2.72 |
|                   | MD within groups | −0.16                   |                      | −2.34            |                  |
|                   | 95% CI         | −1.27 to 1.59           | −0.11 to 4.79       |                  | −14.96 to −2.72 |
| Cardio-risk ratio (cholesterol/HDL-C) | Before (mean±SD) | 4.36±1.04             | 4.88±1.30           | −0.52            | −0.08 to 1.18  |
|                   | After (mean±SD) | 3.94±0.93              | 4.76±1.55           | −0.82            | −0.18 to 1.50  |
|                   | MD within groups | −0.42                   |                      | −0.12            |                  |
|                   | 95% CI         | 0.23 to 0.61            | −0.38 to 0.62       |                  |                  |

Data within and between groups compared with ANOVA test. Data are presented as mean and standard deviation with a 95% confidence interval (CI).

Significant difference at *P<0.05.

MD, mean deviation; CI, confidence interval; SD, standard deviation; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol.
DISCUSSION

This study used FiberCreme, a nondairy creamer mainly made of fully hydrogenated coconut oil (trans-free oil) and oligosaccharides IMO. IMO improves metabolic disorders (e.g., hyperlipidemia and reduces cardiovascular disease risks). Animal and human studies have shown that IMO improves lipid profiles. Mice fed a diet with cellulose replaced with IMO had lower total plasma lipid, CH, and triglyceride levels than the control group (Chen et al., 2001). A study indicated that daily supplementation with 10 g of IMO for 4 weeks effectively reduced the total plasma and LDL-C levels (Yen et al., 2011). Wang et al. (2001) reported that giving 30 g of IMO to patients receiving hemodialysis for 4 weeks could significantly reduce total CH and triglyceride levels and increase HDL-C levels.

These results showed that the FiberCreme cookies could significantly reduce CH, triglyceride, and CRR scores, whereas the control cookies did not significantly change the lipid profiles and CRR scores. CH and HDL-C values can be used to predict the atherogenic coefficient (AC) and CRR, which are good predictors of future cardiovascular events. The formula for calculating the AC is (CH−HDL-C)/HDL-C, and the CRR is CH/HDL-C (Lafta, 2014). In a 17-year follow-up cohort study, Cox regression results showed that the CH/HDL-C ratio was significantly associated with the incidence of myocardial infarction in the Women’s Health in the Lund Area study. Therefore, the CH/HDL-C ratio and CRR are good predictors of high-risk myocardial infarction (Calling et al., 2019).

Furthermore, a prospective multicenter cohort study involving 630 patients who received peritoneal dialysis (PD) showed that a significantly higher CH/HDL-C ratio was related to an increased risk of all-cause mortality in incident patients with PD (Noh et al., 2021). In this study, the decrease in CH levels was 11.30% in the FiberCreme group, which was significantly higher than 6.67% in the control group. Also, based on the CH and HDL-C levels, the decrease in CRR score (−10.66%) in the FiberCreme group was much greater than (−2.61%) in the control group. As mentioned above, FiberCreme contains IMO, and the fiber content in FiberCreme cookies is higher than in the control cookies. IMO consists mainly of oligomers containing α(1−6) glycosidic bonds, which are resistant to enzymatic digestion in humans so that they can replace DF. The benefits of DF in decreasing blood CH were reported in South African Bantu in 1954 (Higginson and Pepler, 1954). Moreover, it is currently recommended as an adjuvant to statins to reduce the risk of cardiovascular diseases by lowering blood CH levels (Soliman, 2019).

DF can interfere with the emulsification, digestion, and absorption of lipids. It also increases bile acid deconjugation leading to increased excretion of fecal bile acids and lowers CH levels by stimulating the liver to synthesize bile from circulating CH. In mice fed a high-CH diet, cereal fiber reduced absorption and increased intestinal CH efflux and clearance. However, this happens by modulating PPARα, LXRα, and SREBP signaling pathways in CH metabolism to lower CH levels (Han et al., 2019). Caz et al. (2015) showed that the oyster mushroom’s (P. ostreatus) PDF induces mRNA expression of CH-related genes (e.g., DGAT1, FDFT1, SOAT1, and SREBF1) which can exhibit CH-lowering effects in Caco-2 cell cultures.

Additionally, indigestible fibers, including IMO, enter the colon and are fermented by colonic bacteria to produce SCFAs, especially acetate, propionate, and butyrate, which alter the composition of the microbiota, contributing to the hypocholesterolemia effect of fibers (Soliman, 2019). IMO has been applied as a functional food ingredient that is partially enzymatically indigestible in humans but can stimulate beneficial microbiota in the GIT. According to Singh et al. (2017), IMO affects metabolism alteration in the mice induced by a high-fat diet by preventing dysbacteriosis of the gut. In rats, IMO stimulates and increases Lactobacillus diversity (Ketabi et al.,
2011). Interactions between *Lactobacillus* spp. and metabolism in the host’s digestive tract can indirectly control metabolism (Drissi et al., 2017). IMO also stimulates the secretion of SCFAs in the intestinal tract and increases colonic microbiota in rats (Lan et al., 2020). Additionally, propionic acid inhibits CH synthesis in isolated hepatocytes. Supplementation of 10 g/d with a low fiber diet for 8 weeks improved the colonic microflora profile and increased propionic acid levels by 3.5-fold compared with placebo in elderly subjects suffering from constipation (Yen et al., 2011).

Besides reducing the levels of blood CH, the FiberCreme cookies also reduced the triglyceride levels (−11.84%), whereas the control cookies increased them (5.38%; Fig. 1). High blood plasma triglyceride levels are associated with insulin resistance. Weitkunat et al. (2017) reported that supplementation with 5% SCFAs in the diet decreased triglycerides in the liver and increased insulin sensitivity. Cronin et al. (2021) reported that propionic acid significantly reduces blood fatty acid levels, whose mechanism depends on G-protein-coupled receptor 43, causing a decrease in cellular lipolytic activity. Additionally, the dextrin resistance intervention (5 g/kg body weight) for 10 weeks decreased CH and lipid deposition in the liver and improved insulin resistance in rats induced by a high-fat and high-fructose diet (Hu et al., 2020). Therefore, FiberCreme cookies have several benefits in reducing the risk of cardiovascular diseases and improving insulin resistance.

The main limitation of this study was the difficulty of matching the indicators of BMI and age of the subject groups. Dropouts occurred during the recruitment, leading to the BMI and age distributions deviating from the initial estimates. Another limitation was using the Semi-quantitative Food Frequency Questionnaire assessment of dietary consumption based on the subject’s memory. A 1-month dietary recall may yield inaccuracy when determining the amount of fiber consumed.

Based on the results from this study, FiberCreme cookies containing 5.78% fiber could significantly improve blood lipid profile, reduce the risk of cardiovascular disease, and potentially improve insulin resistance by lowering triglyceride levels.

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**AUTHOR DISCLOSURE STATEMENT**

The authors declare no conflicts of interest.

**AUTHOR CONTRIBUTIONS**

Concept and design: S, HM, YM, DLNF, AM. Analysis and interpretation: S, NY. Data collection: S, HM, NY. Writing the article: S, NY, YM. Critical revision of the article: S. Final approval of the article: all authors. Statistical analysis: S. Obtained funding: YM, S, DLNF, AM. Overall responsibility: S.

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