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Research Article

SCOBY-Fermented *Citrus x aurantium* L. Peel with Enhanced Antioxidant and Cholesterol-Lowering Effects

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ABSTRACT

Citrus peels are rich sources of phenolic and flavonoid compounds with antioxidant and lipid-lowering effects, yet the bioactive profile of *Citrus x aurantium* L. (Gerga), a local Indonesian cultivar, has not been thoroughly investigated. Fermentation with a symbiotic culture of bacteria and yeast (SCOBY) offers a promising strategy to biotransform phytochemicals and enhance their functional potential. This study compared the total phenolic content (TPC), total flavonoid content (TFC), antioxidant activity, and antihypercholesterolemic effect of *C. x aurantium* peel infusion and its SCOBY-fermented product. TPC and TFC were quantified spectrophotometrically. Antioxidant activity was evaluated using the DPPH radical scavenging assay, and cholesterol-lowering efficacy was assessed in hypercholesterolemic mice. Data were analyzed using an independent t-test for total phenolic content (TPC) and total flavonoid content (TFC), while lipid-lowering efficacy was evaluated using one-way ANOVA. Fermentation significantly increased TPC (26.5±0.01 to 42.9±0.03 mg GAE/g) and TFC (20.9±0.05 to 32.7±0.03 mg QE/g) ($p < 0.05$). The SCOBY-fermented product also exhibited stronger antioxidant activity (IC_{50} = 11.98 vs. 14.64 mg/mL) and a greater reduction in serum total cholesterol compared with *C. x aurantium* peel infusion (29.84±1.03% vs. 27.71±0.25%). These findings indicate that SCOBY fermentation enhances the phenolic and flavonoid content, antioxidant potential, and antihypercholesterolemic activity of *C. x aurantium* peel infusion. This bioprocessing approach may provide a sustainable strategy for developing functional beverages from citrus by-products.

Keywords: Antioxidant, Antihypercholesterolemic, *Citrus x aurantium* L., Phenolic content, SCOBY fermentation

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Introduction

Cardiovascular diseases remain the leading cause of mortality worldwide, with hypercholesterolemia recognized as a major modifiable risk factor [1]. Elevated cholesterol levels not only accelerate atherosclerosis but also increase the incidence of hypertension, stroke, and coronary heart disease [2, 3]. Cholesterol is a vital lipid that supports hormone synthesis, maintains cell membrane integrity, aids vitamin D and bile acid production, and supports brain function. However, dietary intake of animal fat can cause pathological increases in cholesterol levels [4]. Hypercholesterolemia, defined as total cholesterol concentrations exceeding 200 mg/dL, often necessitates long-term pharmacotherapy, which can induce adverse effects such as rhabdomyolysis, myopathy, and myoglobinuria [5]. These limitations, together with growing health awareness and the global "back-to-nature" movement, have fueled interest in natural, safe, and effective alternatives.

Indonesia, renowned for its exceptional biodiversity, harbors a wide variety of indigenous plant species with significant potential for functional food and pharmaceutical development. Among these, *C. x aurantium*—locally known as Gerga, an orange variety cultivated in Kerinci, Jambi Province—stands out. This cultivar bears fruit year-round, offering a continuous supply of biomass. Despite this availability, Gerga fruit remains underutilized; only the pulp is consumed, while the peel, is discarded. This is paradoxical given that citrus peels are widely recognized as rich sources of valuable phytochemicals. Specifically, preliminary data indicate that Gerga peel contains around 3.24% flavonoids, including hesperidin, naringenin, hesperetin, and nobiletin—compounds linked in literature with lipid-lowering and cardioprotective actions [6, 7]. Complementing this, broader phytochemical profiling of *C. aurantium* peels confirms that they are rich in flavonoids, phenolic acids, and essential oils. For example, peel extracts may contain ~23% flavonoids and ~74% phenolic acids, with limonene often dominant among volatiles (~90%). Previous pharmacological studies support the potential of citrus peel for anti-cholesterol activity [6].

The Symbiotic Culture of Bacteria and Yeast (SCOBY), a microbial consortium forming a gelatinous biofilm, transforms sugars into bioactive metabolites during fermentation [8]. This process has been shown to enhance phenolic and flavonoid contents, thereby increasing antioxidant potential [9, 10]. Leveraging this biotransformation, the present study aims to utilize gerga peel infusion—a fruit processing byproduct—as a substrate for fermented herbal tea production, and to evaluate its total phenolic content and antihypercholesterolemic activity. By integrating waste valorization and functional beverage development, this research offers a sustainable strategy for managing hypercholesterolemia while promoting local agricultural value chains.

Materials and Methods

Plant material

The *C. x aurantium* peel was collected from Lolo Gedang Village, Bukit Kerman District, Kerinci Regency, Jambi Province, Indonesia. The plant material was identified and authenticated by

Dr. Nurainas, M. Si., a taxonomist at the Andalas University Herbarium (ANDA), and a voucher specimen (No. 53/K-ID/ANDA/I/2023) was deposited.

Research instrument

A UV–Vis spectrophotometer (Genesys® 10S UV–Vis), hot plate stirrer (AREX Digital Pro), laboratory oven (Memmert), water bath (Memmert), and a blood cholesterol test device (Autocheck®) were used in this study.

Research material and reagent

All chemicals used in this study were of analytical grade, including methanol p.a. (Emsure, Germany), sodium carboxymethyl cellulose (NaCMC, Sigma-Aldrich, USA), Folin–Ciocalteu reagent (Supelco, USA), sodium hydroxide (NaOH, Supelco, USA), aluminum chloride ($AlCl_3$, Sigma-Aldrich, USA), sodium acetate (CH_3COONa, Supelco, USA), quercetin (Sigma-Aldrich, USA), gallic acid (Sigma-Aldrich, USA), 2,2-diphenyl-1-picrylhydrazyl (DPPH, Sigma-Aldrich, USA), simvastatin (Sigma-Aldrich, USA), propylthiouracil (PTU, Sigma-Aldrich, USA), and distilled water. The symbiotic culture of bacteria and yeast (SCOBY) was purchased commercially through e-commerce.

Ethics statement and animal preparation

All experimental procedures were reviewed and approved by the Health Research Ethics Committee of Politeknik Kesehatan Kementerian Kesehatan Jambi, Indonesia (Approval No. LB.02.06/2/78/2023), and conducted in accordance with institutional regulations and internationally recognized standards for the care and use of laboratory animals. Male mice (*Mus musculus*), 2–3 months old and 20–30 g were obtained for the antihypercholesterolemic assay and maintained under controlled conditions at the Department of Pharmacy, Universitas Jambi, with unrestricted access to standard feed and water. Baseline health status was verified through physical examination and behavioral observation prior to the study. Animals exhibiting any signs of illness, pain, or distress were excluded from subsequent experimental procedures.

Preparation of C. x aurantium peel infusion and kombucha

The 5% (w/v) infusion was prepared by weighing 5 g of *C. x aurantium* peel and adding it to 100 mL of distilled water, followed by heating at 70 °C for 15 minutes, with slight modifications from Xu et al. and Antolak et al. [11, 12]. After heating, the extract was filtered, and the volume was readjusted to 100 mL by rinsing through the peel residue. The infusion was cooled to approximately 25 °C, then supplemented with 10 g of sugar and 3 g of SCOBY culture. Fermentation was performed at room temperature in a container covered with gauze to prevent contamination and protect from direct sunlight, and the mixture was incubated for 14 days. The fermentation product was then characterized organoleptically [13].

Determination of total phenol content

Total phenolic content of the *C. x aurantium* peel infusion and kombucha was determined using the Folin–Ciocalteu method as described in the Indonesian Herbal Pharmacopoeia [14]. Gallic acid (10 mg) was dissolved in 25 mL ethanol to obtain a 400 µg/mL stock solution, which was diluted to prepare standards of 25–60 µg/mL. One milliliter of each standard or sample was mixed with 5 mL of 7.5% Folin–Ciocalteu reagent, allowed to stand for 8 min, and then combined with 4 mL of 1% NaOH. After 1 h incubation, absorbance was measured at 730 nm. Phenolic content was calculated from the gallic acid calibration curve and expressed as milligrams gallic acid equivalents (mg GAE) per gram dry simplicia.

Determination of total flavonoid content

Total flavonoid content of *C. x aurantium* peel infusion and kombucha was also determined using the method described in the Indonesian Herbal Pharmacopoeia [14]. Quercetin (10 mg) was dissolved in ethanol to prepare a 400 µg/mL stock solution, which was serially diluted to yield standards of 3–75 µg/mL. For each standard or sample, 1.5 mL ethanol, 0.1 mL of 10% aluminum chloride, 0.1 mL of 1 M sodium acetate, and 2.8 mL distilled water were added. After incubation at room temperature for 30 min, absorbance was recorded at 415 nm. Flavonoid content was calculated from the quercetin calibration curve and expressed as milligrams quercetin equivalents (mg QE) per gram dry simplicia.

Determination of antioxidant activity

Antioxidant activity was assessed using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay, adapted from Rusdi et al. [15]. Briefly, 0.2 mL of the extract solution (1.56–100 µg/mL in methanol) was mixed with 3.8 mL of a 50 µM DPPH solution. The mixtures were incubated in the dark for 30 minutes to ensure complete reaction. Absorbance was measured at 517 nm, with a blank containing DPPH and methanol. The radical scavenging activity (RSA, %) was calculated as:

$$\% \text{ scavenging of DPPH} = \frac{\text{A\_control} - \text{A\_sample}}{\text{A\_control}} \times 100$$

The IC_{50} value, representing the extract concentration required to inhibit 50% of DPPH radicals, was determined by plotting RSA (%) against extract concentration and applying linear regression ($y = a + bx$). The IC_{50} was calculated using:

$$IC_{50} = \frac{50 - a}{b}$$

Evaluation of antihypercholesterolemic activity

This study employed a completely randomized design (CRD) with a posttest control group approach. Twenty-five male white mice (2–3 months old, 20–30 g) were acclimatized for seven days under standard housing conditions with ad libitum access to food and water. Hypercholesterolemia was

induced by administering 13 mg/kg propylthiouracil (PTU) in combination with a high-fat diet (HFD), following previously reported protocols, for a duration of 14 days [16–18]. Following induction, the mice were fasted for 12–18 hours, and total cholesterol levels were measured. Mice with total cholesterol levels >130 mg/dL were classified as hypercholesterolemic and randomly divided into four groups (n = 5 per group). The groups were as follows: (1) negative control (PTU and HFD treatment only), (2) positive control (PTU, HFD, and 1.3 mg/kg simvastatin suspension), (3) Treatment 1 (PTU, HFD, and a 5% infusion of *C. x aurantium* peel at 0.4 mL/20 g), and (4) Treatment 2 (PTU, HFD, and a 5% SCOBY-fermented infusion of *C. x aurantium* peel at 0.4 mL/20 g). Treatments were administered for 14 consecutive days. The procedure was adapted from Arief et al. [19], who studied the water extract of orange peel, with slight modifications. The percentage reduction in total cholesterol was calculated using the following formula:

$$\text{Reduction } (\%) = \frac{\text{Initial cholesterol level - Final cholesterol level}}{\text{Initial cholesterol level}} \times 100$$

where the initial and final cholesterol levels (mg/dL) were measured before and after treatment, respectively.

Data analysis

Data were analyzed using an independent t-test for total phenolic content (TPC) and total flavonoid content (TFC), whereas lipid-lowering efficacy was assessed using one-way ANOVA at a 95% confidence level. Post-hoc comparisons were performed using Duncan's multiple range test, and a p-value < 0.05 was considered statistically significant.

Results and Discussion

Physicochemical and sensory characteristics of Gerga orange peel infusion and kombucha

This study aimed to evaluate the potential of fermented *C. x aurantium* peel as an antihypercholesterolemic agent, while also assessing its organoleptic characteristics and phytochemical composition. The infusion method was selected for extracting bioactive compounds from Gerga peel due to its simplicity, cost-effectiveness, and short processing time, making it particularly suitable for community-level applications. Infusion employs water as a polar solvent, enabling efficient extraction of polar phytochemicals according to the principle of "like dissolves like," wherein solvents preferentially dissolve solutes with similar polarity [20]. This technique is especially advantageous for recovering hydrophilic compounds such as phenolics and flavonoids, which are associated with antioxidant activity and various health-promoting effects [21]. The use of water as the extraction medium was also strategically aligned with the subsequent fermentation process using a Symbiotic Culture of Bacteria and Yeast (SCOBY), serving not only as the solvent but also as a growth medium for the bacteria and yeast in the SCOBY matrix. This integrated approach offers practical feasibility for household-scale SCOBY

fermentation, supporting community-based production of functional beverages with potential benefits in cholesterol management.

The organoleptic and physicochemical properties of the *C. x aurantium* peel infusion, prior to SCOBY fermentation, were characterized by a dark brown color, a characteristic citrus aroma, a bitter taste, and an initial pH of approximately 4 (Table 1). These sensory traits are consistent with the presence of phenolic compounds, flavonoids, and natural pigments such as carotenoids and tannins, which contribute to the brown coloration commonly observed in hot-water plant infusions [11]. The citrus aroma is largely attributable to volatile essential oils, particularly limonene, the major constituent of citrus peels [22]. Bitterness can be ascribed to flavanones such as naringin and limonoids such as limonin, both commonly found in citrus peels [23]. The mildly acidic pH 4 likely results from organic acids, including citric acid, which is abundant in citrus fruits. Following SCOBY fermentation, the infusion retained its dark brown color but developed a distinctive fermentation aroma, indicative of secondary metabolites such as acetic acid, ethanol, and other volatiles produced during microbial activity [24]. The taste shifted from bitter to markedly sour, correlating with a pH reduction to around 2. This decrease reflects the accumulation of organic acids—particularly acetic and gluconic acids—synthesized by *Acetobacter spp*. during fermentation [25]. Such acidity not only modifies sensory characteristics but also enhances microbial stability by inhibiting pathogenic growth, consistent with the optimal safety pH range of 2.5–4.2 for kombucha [26]. These changes parallel findings in other citrus-based fermented beverages; for example, kombucha prepared from *Citrus nobilis* orange peel showed a progressive decline in pH, increased acidity, and elevated flavonoid and vitamin C content over prolonged fermentation [27]. Overall, SCOBY fermentation of *C. x aurantium* peel infusion induces notable alterations in sensory and physicochemical properties. The pronounced acidity, enhanced sourness, transformed aroma, and stable color may improve its biological activities [28].

Table 1 Organoleptic characteristics of *C. x aurantium* peel infusion and SCOBY-fermented infusion.

Characteristics	Infusion	SCOBY-Fermented Infusion
Color	Dark brown	Yellowish brown
Aroma	Citrus-like	Fermented-like
Taste	Bitter	Sour
pH	4	2

Total phenolic content and total flavonoid content

The total phenolic content (TPC) in *C. x aurantium* peel infusion and its fermented product measured via the Folin–Ciocalteu method with a gallic acid standard, was determined using a calibration curve described by the equation y=0.0158x-0.1997 (R^2= .9931). The infusion contained 26.5±0.01 mg GAE/g, which significantly increased to 42.9±0.03 mg GAE/g after SCOBY fermentation ($p<0.05$) (Table 2). This significant enhancement (≈1.6-fold) is consistent with previous reports showing that SCOBY fermentation can increase the total phenolic content (TPC) of tea through enzymatic hydrolysis

of phenolic conjugates and the release of bound forms, with increases of up to 3.5-fold [29]. In kombucha and related fermented beverages, this trend is consistently observed as a result of microbial actions, such as the activity of glucosidases and other hydrolytic enzymes, liberating free phenolics from complex matrices [30]. Similarly, total flavonoid content (TFC), assessed using the $AlCl_3$ colorimetric method with quercetin as the standard, showed a calibration equation $y=0.0046x-0.0127$ ($R^2=0.9959$). The infusion had 20.9±0.05 mg QE/g, which rose significantly to 32.7±0.03 mg QE/g post-fermentation, 1.6-fold increase ($p<0.05$) (Table 2). This is consistent with several studies indicating that SCOBY fermentation enhances flavonoid levels, often via deconjugation of glycosides into more bioactive aglycone forms [31]. The parallel elevation of both phenolic and flavonoid contents highlights their biochemical interrelationship: flavonoids are a subclass of polyphenols, and both groups contribute synergistically to antioxidant capacity. The fermentation-induced enzymatic hydrolysis appears to increase the extractability and bioavailability of these compounds, enhancing their radical-scavenging activity) [32].

Table 2 TPC, TFC and Antioxidant activity of *C. x aurantium* peel infusion and SCOBY-fermented infusion.

Samples	TPC (mgGAE/g)	TFC (mgQE/g)	IC_{50} (mg/mL)
C. x aurantium peel infusion	26.5 ±0.01	20.9 ± 0.05	14.64
SCOBY-Fermented *C. x aurantium* peel infusion	42.9 ±0.03	32.7 ±0.03	11.98
Gallic acid	-	-	0.028

Antioxidant activity

The antioxidant activity of *C. x aurantium* peel infusion and its SCOBY-fermented derivative was assessed using the DPPH radical scavenging assay, with results expressed as IC_{50} values (Table 2). The SCOBY-fermented sample exhibited a lower IC_{50} (11.98 mg/mL) than the unfermented infusion (14.64 mg/mL), indicating a stronger antioxidant effect post-fermentation, although still weaker than gallic acid used as a reference standard. This enhancement corresponds with the significant increases in total phenolic and flavonoid contents observed in the fermented sample. Phenolic compounds, particularly flavonoids, are recognized as potent hydrogen donors and metal chelators, effectively neutralizing free radicals and disrupting oxidative chain reactions [33, 34]. The improved antioxidant potential following SCOBY fermentation is likely due to microbial enzymatic hydrolysis, which releases bound phenolics and flavonoids from the plant matrix, thereby increasing their extractability, bioavailability, and radical scavenging capacity [35, 36]. Gallic acid, used as the reference standard, displayed the highest activity (IC_{50}=0.028 mg/mL), validating the assay's sensitivity. The strong positive correlation between total phenolic and flavonoid levels and antioxidant activity is consistent with previous reports identifying these compounds as the principal contributors to plant-derived antioxidant capacity [37].

Evaluation of antihypercholesterolemic activity

The total phenolic and flavonoid contents in *C. x aurantium* peel infusion and its SCOBY-fermented product are key contributors to their biological activity. These compounds exhibit strong antioxidant properties through free radical scavenging and lipid oxidation inhibition [38, 39], which are crucial in preventing oxidative stress-induced atherosclerosis in hypercholesterolemia. The anti-hypercholesterolemic assay demonstrated that both the infusion and its fermented counterpart significantly reduced cholesterol levels by 27.71% and 29.84%, respectively, compared with the negative control ($p=0.001$; $p<0.05$). These effects were statistically comparable to the reduction observed with simvastatin treatment (30.34%) (Figure 1 and Table 3).

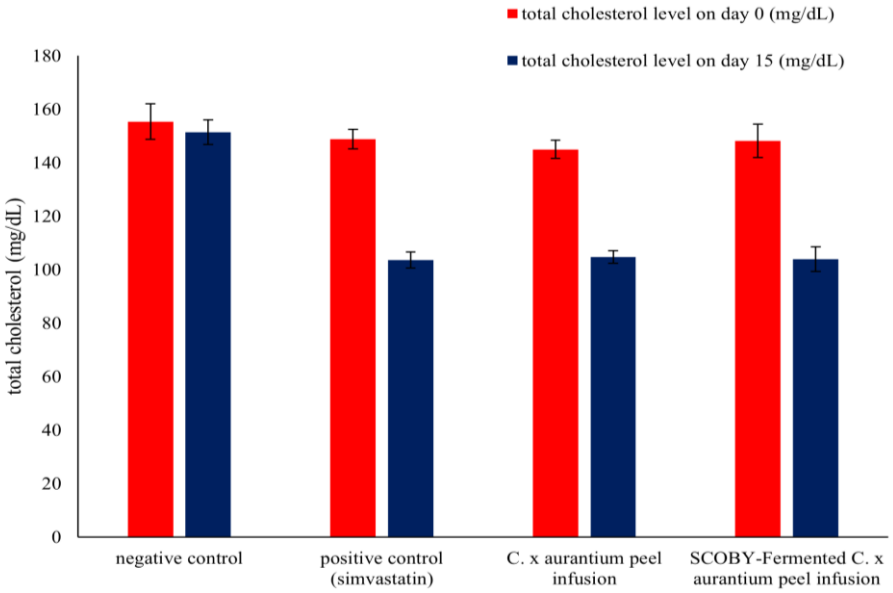

Figure 1 Total cholesterol levels of the treatment groups on day 0 and day 15.

This effect is likely mediated by flavonoids, particularly hesperidin and naringin abundant in citrus peel, which inhibit HMG-CoA reductase, a key enzyme in cholesterol biosynthesis Naringin supplementation lowers plasma lipids and enhances erythrocyte antioxidant enzyme activities in hypercholesterolemic subjects [40]. Additionally, phenolics and flavonoids can promote fecal bile acid excretion, enhancing cholesterol catabolism [41]. SCOBY fermentation may further increase bioavailability by hydrolyzing glycosides into more absorbable aglycones [35], potentially explaining the slightly greater cholesterol-lowering effect of second treatment despite only modest increases in phenolic and flavonoid content. These findings are consistent with previous studies, such as kombucha prepared from seagrapes (*Caulerpa racemosa*), which after four weeks at a concentration of 150 mg/kg produced a greater reduction in total cholesterol compared to the negative control (31.67 vs. 66.36 mg/dL) [42]. Similarly, another study in rats demonstrated that 16 weeks of kombucha green tea (*Camellia sinensis*) administration significantly reduced total cholesterol by 26%, compared with a 16% reduction in the control group [43].

Table 3 Total cholesterol levels (mg/dL) of treatment groups on day 0 and day 15, and percentage reduction in cholesterol.

Treatment groups	Total cholesterol level (mg/dL)±SEM		Percentage reduction (%)
	Day 0	Day 15	
negative control	155.4±6.71	151.4±4.61	2.34±1.75[a]
positive control	148.8±3.62	103.6±2.98	30.34±1.50[b]
C. x aurantium peel infusion	145.0±3.40	104.8±2.31	27.71±0.25[b]
SCOBY-Fermented *C. x aurantium* peel infusion	148.2±6.24	104.0±4.61	29.84±1.03[b]

Note: Values are expressed as mean±standard error of the mean (SEM). Different superscript letters in the same column indicate significant differences ($p < 0.05$).

Fermentation with SCOBY increased both TPC and TFC of *C. x aurantium* peel infusion, accompanied by enhanced radical-scavenging capacity, as indicated by a lower DPPH IC_{50} value. Mechanistically, this phytochemical enrichment may contribute to antihypercholesterolemic effects through multiple complementary pathways reported in previous studies. First, phenolics, including flavonoids, can mitigate oxidative stress by donating electrons or hydrogen atoms and chelating pro-oxidant metals, thereby preventing low-density lipoprotein (LDL) oxidation—a critical step in atherogenesis [44, 45]. Second, certain phenolic structures can modulate lipid metabolism by attenuating HMG-CoA reductase activity, upregulating LDL receptor expression, and activating AMPK and PPAR signaling pathways, which collectively lower circulating cholesterol and improve the lipid profile [46, 47]. Third, SCOBY fermentation produces organic acids (notably acetic and gluconic acids) and microbial enzymes that enhance the bioavailability of aglycone flavonoids, while also influencing bile-acid metabolism and intestinal cholesterol absorption [47]. Collectively, these effects are consistent with the observed higher TPC/TFC, improved antioxidant metrics, and greater reduction in total cholesterol in the fermented infusion compared to the non-fermented infusion.

Conclusions

SCOBY fermentation of *C. x aurantium* peel infusion significantly increased total phenolic and flavonoid contents, as well as antioxidant capacity, compared to the unfermented infusion. The fermented infusion also demonstrated a greater reduction in serum cholesterol levels in the tested model. These results indicate a possible relationship between fermentation-enhanced bioactive compounds and lipid-lowering activity. However, further studies involving compound-specific profiling, mechanistic assays, and clinical validation are needed before definitive conclusions and practical applications can be established.

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