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Administration of extract ethanol of Lime peel (Citrus aurantiifolia) effective as anti-hyperlipidaemia : In vivo study

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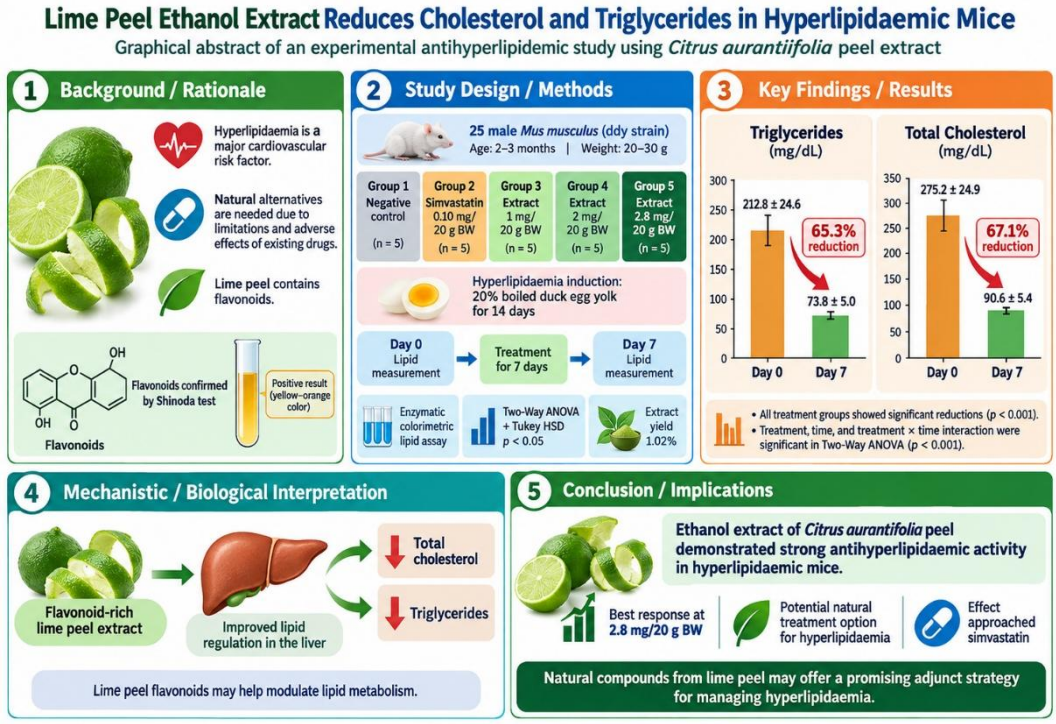
Graphical Abstract



Abstract: The quest for natural alternatives to existing pharmaceutical therapies for hyperlipidaemia has been prompted by the known harmful effects of these medications, which are a major risk factor for cardiovascular disease. Lime (*Citrus aurantiifolia*) peel ethanol extract was tested for its antihyperlipidemic effects on total cholesterol and triglyceride levels in mice that had been hyperlipidaemic due to a high-fat diet. In a genuine experimental study with a pre- and post-test control group design, twenty-five male Mus musculus (ddy strain), two to three months old, weighing twenty to thirty grams each, were split into five groups: one served as a negative control, another as a positive control (simvastatin 0.10 mg/20g BW), and the three treatment groups that received lime peel extract (1, 2, and 2.8 mg/20g BW) were also given a weight. The 96% ethanol maceration process yielded 1.02% of the final extract. Boiling duck egg yolk at a 20% concentration for 14 days caused hyperlipidaemia. There was confirmation of flavonoids by the Shinoda test.

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Enzymatic colorimetric techniques were used to evaluate lipid levels on both Day 0 and Day 7. Two-Way ANOVA and Tukey's HSD were used for data analysis ($p<0.05$). Flavonoids were validated by phytochemical screening. Lipid reductions were statistically substantial ($p<0.001$) across all treatment groups. Similar to simvastatin, the most significant decrease was shown in triglycerides (from 212.8±24.6 to 73.8±5.0 mg/dL) and cholesterol (from 275.2±24.9 to 90.6±5.4 mg/dL) at the optimum dose of 2.8 mg/20g BW. Treatment, time, and their interaction were shown to have significant impacts according to Two-Way ANOVA ($p<0.001$). With 2.8 mg/20g BW showing excellent antihyperlipidemic action, an ethanol extract of *Citrus aurantiifolia* peel successfully reduces total cholesterol and triglyceride levels in hyperlipidaemic mice, indicating its promise as a natural treatment option.

Keywords: Hyperlipidemia; Citrus aurantiifolia; Flavonoids; Cholesterol; Tryglicerides.

INTRODUCTION

One important factor in the development of cardiovascular disease is hyperlipidemia, which is defined as an abnormally high level of circulating lipids, namely, atherosclerosis is brought on by an imbalance between good and bad cholesterol levels, namely a rise in total cholesterol and a decrease in HDL[1,2]. This process leads to ischemic heart disease, which is a leading killer on a global scale. Medications such as fibrates and statins are now a part of treatment plans. The use of statins, for example, can cause hepatotoxicity and rhabdomyolysis, and gemfibrozil can increase the risk of certain coronary events when used for an extended period of time[3]. The need for non-pharmacological approaches that are derived from natural sources is emphasized by these limitations[4].

Cardiovascular disorders, such as myocardial infarction, dyslipidaemia, and coronary artery disease, are significant contributors to morbidity and death in Western nations. Consequently, discerning successful treatment strategies and comprehending their fundamental biological signaling pathways continue to pose significant hurdles in medicine. There is strong evidence from several epidemiological studies that eating foods high in flavonoids can reduce cardiovascular risk factors and mortality rates. With about 95% being flavanones, the flavonoids found in citrus fruits including lemons, oranges, bergamots, and grapefruit are gaining attention due to their substantial nutraceutical potential[5,6].

In this context, *Citrus aurantiifolia* (lime), especially its peel, which is often discarded as an agricultural by-product, represents a promising source of bioactive compounds. The peel contains various phytochemicals, including polyphenols, essential oils, and flavonoids such as naringin, hesperidin, and rutin. These compounds are believed to contribute to improving lipid profiles and exerting protective effects on the cardiovascular system. Therefore, the utilization of *Citrus aurantiifolia* peel as a natural source of flavonoids is of significant interest for further research, particularly in developing alternative, plant-based therapeutic strategies for the prevention and management of cardiovascular diseases

Citrus aurantiifolia (lime) peel, a frequently discarded agricultural by-product[7], represents a potential source of bioactive compounds. It contains various phytochemicals, including polyphenols, essential oils, and flavonoids such as naringin, hesperidin, and rutin[8]. Flavonoids act as potent antioxidants[8,9], and lime peel extracts have demonstrated high antioxidant capacity (IC_{50} 5.81 µg/ml)[10]. The peel itself possesses a higher concentration of flavonoids compared to the juice or pulp[11]. These compounds are postulated to modulate lipid metabolism by enhancing the activity of lipoprotein lipase (LPL) and inhibiting key enzymes in cholesterol synthesis and absorption, thereby attenuating oxidative stress, a key driver in atherosclerosis progression[12,13]. Although several studies have reported on the bioactivity of Citrus species[14–16], the antihyperlipidemic mechanism of ethanol-extracted flavonoids from lime peel requires further elucidation in well-defined animal models. Therefore, this study aims to rigorously investigate the in vivo effect of a characterized ethanol extract of *Citrus aurantiifolia* peel on total

cholesterol and triglyceride levels in a mouse model of diet-induced hyperlipidaemia.

MATERIAL AND METHOD

This research utilized a full experimental design with pre- and post-tests alongside control groups. The study was performed in the Clinical Pathology Laboratory and the Pharmacology Laboratory of STIKes Ngudia Husada Madura from March to April 2024. Ethical permission was obtained from the Health Research Ethics Committee of STIKes Ngudia Husada Madura (No: 1949/KEPK/STIKES-NHM/EC/XII/2023). Lime (Citrus aurantiifolia) fruits were procured at a local market in Bangkalan, Madura. The peels were segregated, meticulously cleaned, and air-dried at ambient temperature. Five hundred grams of dried peels were pulverized and macerated in 750 mL of 96% ethanol for five consecutive 24-hour periods at ambient temperature, shielded from light. The solution was filtered, and the solvent was removed to produce a concentrated extract. The extract yield was determined as a percentage of the original dry mass. Phytochemical screening for flavonoids was conducted on the extract utilizing the Shinoda test (including the addition of magnesium powder and concentrated hydrochloric acid), with a positive result signified by the emergence of an orange to red hue.

A registered breeder provided twenty-five male mice (*Mus musculus*, ddy strain) that were two to three months old and weighed twenty to thirty grams. In a controlled environment with a 12-hour light/dark cycle, free access to water, and a regular pellet meal, the animals were allowed to acclimate for a duration of 7 days. Following a high-fat diet (HFD) for 14 days caused hyperlipidaemia in all groups except the negative control. The HFD consisted of 80% standard pellet feed mixed with 20% boiled duck egg yolk[17]. Induction of hyperlipidaemia was confirmed by measuring baseline (Day 0, post-induction) lipid levels before treatment administration. Following the 14-day induction period, the 25 mice were randomly divided into five groups (n=5 per group):

a. Group I (Negative Control): Received standard diet and were orally administered 1% CMC solution (vehicle) once daily for 7 days.
b. Group II (Positive Control): Received HFD and were orally administered simvastatin (0.10 mg/20g body weight (BW), suspended in 1% CMC) once daily for 7 days. The simvastatin dose was converted from the human therapeutic dose (40 mg/70kg).
c. Group III (Dose 1): Received HFD and were orally administered lime peel extract (1 mg/20g BW in 1% CMC) once daily for 7 days.
d. Group IV (Dose 2): Received HFD and were orally administered lime peel extract (2 mg/20g BW in 1% CMC) once daily for 7 days.
e. Group V (Dose 3): Received HFD and were orally administered lime peel extract (2.8 mg/20g BW in 1% CMC) once daily for 7 days.

Extract doses were derived from a previous study on rats, converted to mouse doses using standard conversion tables[18,19]. All treatments were administered via oral gavage.

Two times, one after the 14-day induction of a high-fat diet (Day 0, pre-treatment) and another after the 7-day treatment period (Day 7, post-treatment), blood samples were taken from the tail vein of each mouse after a fasting period of 16-18 hours. The serum was separated by centrifuging the blood at 3000 rpm for 15 minutes after it had coagulated in microtubes. Our laboratory utilized the GPO-PAP enzymatic colorimetric approach to measure serum triglyceride level. Cholesterol Oxidase-Phenol + Amino phenazone, or CHOD-PAP, was the technique used to measure total cholesterol levels. Following the instructions provided by the manufacturer, the absorbance was measured at a wavelength of 546 nm using a photometer.

The mean ± standard deviation (SD) was used to express the data. We used SPSS (version 25.0) for all of our statistical analysis. The Shapiro-Wilk test was employed to evaluate the normality of data distribution. A Two-Way ANOVA was employed to examine the impact of therapy and time on lipid levels. Upon detecting a significant difference ($p < 0.05$), Tukey's Honestly Significant Difference (HSD) post-hoc test was employed to ascertain particular group differences. A p-value below 0.05 was deemed statistically significant.

RESULTS AND DISCUSSION

The maceration of 500 g of dried lime peel powder with 96% ethanol produced 5.1 g of concentrated extract, resulting in a yield of 1.02% (w/w). Phytochemical screening by the Shinoda test verified the presence of flavonoids in the extract, indicated by the development of a reddish-orange hue.

The mean serum triglyceride levels for all groups at Day 0 (post-induction, pre-treatment) and Day 7 (post-treatment) are presented in Table 1. After 14 days on a high-fat diet, all HFD-fed groups (II, III, IV, V) exhibited mean triglyceride levels well above the normal range (>150 mg/dL), indicating successful induction of hypertriglyceridemia. The negative control group maintained normal levels throughout the study. After 7 days of treatment, all intervention groups (positive control and all three extract doses) showed a significant reduction in triglyceride levels compared to their respective Day 0 values ($p < 0.001$ for all). The most pronounced reduction was observed in the Dose 3 group (2.8 mg/20g BW), where levels decreased from 212.8 ± 24.6 mg/dL to 73.8 ± 5.0 mg/dL.

Table 1. Effect of *Citrus aurantiifolia* Peel extract on Serum Triglyceride Levels (mg/dL) in Mice.

Treatment group	Day 0 (Mean ± SD)	Day 7 (Mean ± SD)	Mean Reduction
Negative Control	130.08 ± 5.4	131.6 ± 5.0	-0.8
Positive Control	234.2 ± 24.5	90.6 ± 9.1	152.6
Dose 1 mg	228.2 ± 25.7	94.2 ± 5.3	134.0
Dose 2 mg	217.6 ± 24.7	91.8 ± 5.8	125.8
Dose 2.8 mg	212.8 ± 24.6	73.8 ± 5.0	139.0

A similar pattern was observed for total cholesterol levels (Table 2). The HFD effectively induced hypercholesterolemia in all treatment groups. Following the 7-day treatment period, all intervention groups demonstrated significant reductions in total cholesterol ($p < 0.001$). Again, the Dose 3 group exhibited the most substantial decrease, with mean cholesterol levels dropping from 275.2 ± 24.9 mg/dL to 90.6 ± 5.4 mg/dL, a value comparable to that achieved by the positive control group treated with simvastatin (89.8 ± 5.8 mg/dL).

Table 2. Effect of *Citrus aurantiifolia* Peel extract on Serum Cholesterol Levels (mg/dL) in Mice.

Treatment group	Day 0 (Mean ± SD)	Day 7 (Mean ± SD)	Mean Reduction
Negative Control	95.8 ± 4.3	95.6 ± 3.4	0.2
Positive Control	262.4 ± 27.6	89.8 ± 5.8	172.6
Dose 1 mg	241.6 ± 26.0	96.6 ± 5.5	145.0
Dose 2 mg	311.4 ± 27.0	105.4 ± 7.0	206.0
Dose 2.8 mg	275.2 ± 24.9	90.6 ± 5.4	184.6

The Shapiro-Wilk tests indicated that the data for all groups had normal distribution ($p > 0.05$). Two-Way ANOVA demonstrated a statistically significant impact of therapy, time, and their interaction on triglyceride and total cholesterol levels ($p < 0.001$). Tukey's HSD post-hoc analysis of the Day 7 triglyceride data revealed that the Dose 3 group (73.8 ± 5.0 mg/dL) exhibited a statistically significant difference from the positive control (90.6 ± 9.1 mg/dL, $p = 0.016$), Dose 1 (94.2 ± 5.3 mg/dL, $p = 0.001$), and Dose 2 (91.8 ± 5.8 mg/dL, $p = 0.004$), thereby affirming its superior efficacy. Likewise, the cholesterol decrease in the Dose 3 group was analogous to the positive control ($p = 0.999$) and considerably superior than the lower doses ($p < 0.05$).

This study provides robust evidence for the antihyperlipidemic efficacy of an ethanol extract of *Citrus aurantiifolia* peel in a mouse model of diet-induced hyperlipidemia. The results demonstrate that oral administration of the extract for seven days significantly reduces both elevated serum triglyceride and total cholesterol levels. The effect was dose-dependent, with the highest dose (2.8 mg/20g BW) producing the most marked reduction, comparable to the standard drug simvastatin. These findings address the editor's concerns by presenting data with appropriate measures of variability (SD) and by employing a clear, consistent statistical approach (Two-Way ANOVA with post-hoc analysis), which confirms the robustness of the observed effects. The observed hypolipidemic effect is attributed to the presence of bioactive flavonoids in the lime peel extract, confirmed by our phytochemical screening. This aligns with previous research indicating that Citrus peels are rich sources of flavonoids such as naringin, hesperidin, and rutin[20]. The high antioxidant capacity of lime peel extract (IC_{50} 5.81 µg/mL) reported by Novriyanti et al.[10] further supports its potential to mitigate the oxidative stress that accompanies and exacerbates hyperlipidemia.

The mechanism by which flavonoids lower serum lipids is multifaceted. They are recognized for augmenting the activity of Lipoprotein Lipase (LPL), the enzyme that hydrolyzes triglycerides transported by Very-Low-Density Lipoprotein (VLDL) and chylomicrons into free fatty acids and glycerol. Enhanced LPL activity results in more effective removal of triglyceride-rich lipoproteins from the bloodstream, thus reducing serum triglyceride concentrations, as demonstrated in our study.

The enhanced clearance of triglyceride-rich lipoproteins from the circulation, thereby lowering serum triglyceride levels as observed in our study, may also be complemented by the contribution of other bioactive constituents present in citrus peel. In addition to flavonoids, citrus-derived compounds are influenced by the activity of monoterpene synthases, which regulate the production of various volatile compounds found in citrus essential oils[21,22]. These compounds contribute not only to the biochemical profile but also to the biological activity of the extract.

Concurrently, changes across citrus species, with variances in geographical origin and climatic circumstances, significantly influence the content and concentration of these beneficial chemicals. Previous investigations have revealed limonene as a prominent component in the essential oils of some citrus species, including Citrus grandis and Citrus microcarpa, constituting up to 81.6% and 94% of their total oil content, respectively. Although abundant, limonene is rather unstable when subjected to heat and light, and it does not substantially enhance the flavor and smell quality of essential oils. Consequently, its decrease is frequently essential in industrial processing to augment the concentration of more stable oxygenated chemicals and to boost product shelf stability [Lime (*Citrus aurantifolia* (Christm.) Swingle)] Essential Oils: Volatile Compounds, Antioxidant Capacity, and Hypolipidemic Effect.

Interestingly, lime essential oil (LEO) has been reported to contain lower levels of limonene compared to other citrus species [21]. This characteristic may offer an advantage by minimizing compound degradation during processing and preserving the integrity of other bioactive constituents. Consequently, the relatively low limonene content in *Citrus aurantiifolia* peel extract could contribute to maintaining its pharmacological efficacy, including its antihyperlipidemic activity, by reducing the loss of beneficial compounds and enhancing the stability of its active components[23].

Flavonoids have many effects on hepatocytes that lead to decreased cholesterol. In order for cholesterol to be esterified and included in very low density lipoprotein (VLDL) particles, they have the ability to inhibit the activity of Acyl-CoA Cholesterol Acyl Transferase (ACAT). The liver's production and release of very low-density lipoprotein (VLDL) is reduced when cholesterol esterification is

reduced. Also, flavonoids can reduce the levels of two proteins that are crucial for lipidation and the formation of very low density lipoprotein (VLDL): apolipoprotein B-100 (ApoB-100) and microsomal triglyceride transfer protein (MTP). A decrease in hepatic VLDL production subsequently reduces the circulating levels of its metabolic byproduct, Low-Density Lipoprotein (LDL) cholesterol, hence contributing to the overall reduction in total cholesterol. Our findings align with prior in vivo research indicating the hypocholesterolemic properties of Citrus peel extracts in hypercholesterolemic rat models[24].

One of the biggest problems in public health across the world is cardiovascular disease (CVD), which has two main causes: high blood pressure and high cholesterol. An imbalance in the metabolism of lipids causes hyperlipidemia, which is characterized by abnormally high levels of triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), and very low-density lipoprotein cholesterol (VLDL-c), and abnormally low levels of high-density lipoprotein cholesterol (HDL-c). The development of cardiovascular disease is greatly impacted by dietary patterns and lifestyle choices. It has been continuously shown that increasing the intake of fruits and vegetables lowers the risk. Bioactive compounds, such as the lycopene, dietary fiber, and flavonoids found in citrus fruits, are believed to be responsible for some of this protective impact.

Citrus fruits are notably abundant in flavonoids, including flavanone glycosides (such as rutin, hesperidin, hesperetin, and quercetin) and polymethoxyflavones (such as nobiletin and tangeretin), which are recognized for their role in atherogenesis prevention. These substances demonstrate considerable hypocholesterolemic effects, corroborating the findings of the current investigation. Moreover, flavonoid consumption has been demonstrated to have an inverse relationship with cardiovascular risk, non-fatal cardiovascular incidents, and overall mortality, even in groups with minimal intake of other well acknowledged flavonoid-rich foods like soy, tea, and cocoa[25]. This finding further strengthens the evidence that flavonoids, particularly those derived from citrus sources, play an important role in cardiovascular protection[21]. Hypocholesterolemic effects, which support the findings of the present study.

Flavonoids have many effects on hepatocytes that lead to decreased cholesterol. The enzyme Acyl-CoA Cholesterol Acyl Transferase (ACAT) is responsible for esterifying cholesterol so that it may be included in very low density lipoprotein (VLDL) particles, although they can hinder ACAT's action. The liver's production and release of very low-density lipoprotein (VLDL) is reduced when cholesterol esterification is reduced. In addition, flavonoids have shown that they can inhibit MTP activity and Apolipoprotein B-100 (ApoB-100) synthesis, which are both necessary for lipidation and the formation of very low density lipoprotein (VLDL). A reduction in total cholesterol levels is caused by a decrease in hepatic VLDL synthesis, which in turn decreases circulating levels of its metabolic byproduct, low-density lipoprotein (LDL) cholesterol. A complex relationship exists between citrus flavonoids' ability to modulate hepatic lipid metabolism and their cardioprotective effects. In line with previous in vivo studies showing that citrus peel extracts have hypocholesterolemic effects in rat models of hypercholesterolemia, our results lend credence to the idea that compounds derived from citrus fruits could be useful as natural therapeutic agents for the treatment and prevention of cardiovascular disease.

The dose-response relationship observed, particularly the superior efficacy of the 2.8 mg/20g BW dose, highlights the importance of optimizing extract concentration. This dose likely provides a sufficiently high concentration of flavonoid aglycones or their active metabolites to effectively modulate the aforementioned enzymatic pathways. While the 1 mg and 2 mg doses also produced significant reductions, the highest dose achieved levels closest to those of the simvastatin control, and in the case of triglycerides, was statistically superior.

This finding has practical implications for the potential development of this extract as a nutraceutical supplement. This study has several strengths, including its rigorous design, the use of a validated HFD induction model, detailed reporting of the extraction procedure, and comprehensive statistical analysis. The incorporation of a positive control (simvastatin) provides a clinically relevant benchmark for the extract's efficacy. However, some limitations should be acknowledged. The treatment duration was relatively short (7 days); longer-term studies are needed to assess the sustainability of the lipid-lowering effect and to evaluate potential toxicity. Furthermore, while the mechanism is discussed based on the known pharmacology of flavonoids, this study did not directly measure enzyme activities (e.g., LPL, ACAT) or gene expression. Future research should focus on these molecular aspects to confirm the proposed pathways and should also investigate the effect of the extract on other lipid parameters like HDL and LDL cholesterol.

The limitations of this study can be clearly linked to the broader discussion on the role of citrus flavonoids in preventing and managing cardiovascular disease (CVD).First, the relatively short treatment duration (7 days) represents a significant limitation. CVD is a chronic condition that develops over a long period, and although citrus flavonoids have been associated with improved cardiovascular outcomes, their long-term effectiveness and safety cannot be adequately assessed within such a brief timeframe. Therefore, longer-duration studies are necessary to evaluate the sustainability of lipid-lowering effects and to detect any potential toxicity.

Second, while the proposed mechanisms are based on the known pharmacological properties of flavonoids—such as antioxidant activity, improvement of insulin sensitivity, modulation of lipid metabolism, and anti-inflammatory effects, this study did not directly measure enzyme activities (e.g., lipoprotein lipase [LPL] and acyl-CoA: cholesterol acyltransferase [ACAT]) or gene expression. This is an important limitation, as current literature emphasizes that, despite the multiple beneficial effects of citrus flavonoids (including reducing oxidative stress, suppressing inflammation and apoptosis, and improving endothelial dysfunction), their precise mechanisms of action are not yet fully established. Without molecular-level data, the pathways underlying the observed lipid-lowering effects remain speculative.

Finally, the absence of analysis on additional lipid parameters, such as HDL and LDL cholesterol, further limits the interpretation of the findings. In the context of CVD, the balance between LDL (atherogenic) and HDL (protective) is crucial. Previous studies have shown that citrus flavonoids can improve overall lipid profiles and reduce the risk of atherosclerosis. Therefore, including these parameters in future research would provide a more comprehensive understanding of the extract’s cardioprotective potential.

These limitations highlight the need for more comprehensive future studies, including longer intervention periods, detailed biochemical assessments, and molecular investigations. Such approaches are essential to confirm and better understand the protective mechanisms of citrus flavonoids against CVD.

CONCLUSION

This research determines that the ethanol extract of lime (Citrus aurantiifolia) peel, standardized for flavonoid concentration, markedly decreases total cholesterol and triglyceride levels in a mouse model of hyperlipidemia produced by a high-fat diet. The impact is dose-dependent, with a dosage of 2.8 mg per 20 g of body weight exhibiting the most significant lipid-lowering efficacy, akin to the conventional medication simvastatin. These findings endorse the potential of this agricultural by-product as a source of bioactive chemicals for the

management of hyperlipidaemia, necessitating further exploration of its therapeutic use

AUTHORS' CONTRIBUTIONS
All authors contributed equally to this work

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DATA AVAILABILITY STATEMENT
The utilized data to contribute to this investigation are available from the corresponding author on reasonable request.

DISCLOSURE STATEMENT
All affiliated agencies with whom the writers are involved express no endorsement of the views or opinions expressed in this article, which are solely those of the writers. This information is unique since it is derived from the author's own research and has not been published elsewhere.

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