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Polyphenols extract from *Eriobotrya japonica* L. by-product mitigates hyperlipidemia: In vivo study and computational mechanism analysis.

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ABSTRACT

Hyperlipidemia is the most known cause of metabolic complications and tissue toxicity such as liver steatosis, atherosclerosis and obesity. The present work aimed to study the hypolipidemic effect of loquat peel extract (PE) in a high fat-high fructose diet (HFFD) fed mice and then identified the major phenolic compounds present in the extract. The *in vivo* study was conducted in HFFD-fed mice and treated simultaneously with the PE at 100 and 200 mg/kg or fenofibrate (hypolipidemic drug) for 45days. The plasma, liver, and fecal matter lipids levels were undertaken using enzymatic methods, while the polyphenol profile was determined through HPLC analysis. Additionally, *in silico* docking analyses were executed utilizing the SwissDock docking analysis tool. The results demonstrated a significant restoration in lipid metabolism, plasma as well as lipid indices. High-Performance Liquid Chromatography (HPLC) revealed the presence of five major phenolics in the extract, with neochlorogenic acid being notably abundant. Moreover, these phenolics exhibited varying interaction capacities with enzymes and receptors implicated in lipid homeostasis. The loquat peel extract could be considered as a functional drink to prevent lipid metabolism disorders and the resulting health complications.

1. Introduction

Hyperlipidemia is a group of metabolic disorders characterized by elevated levels of total cholesterol (TC), triglycerides (TG), and low-density lipoprotein (LDL) in the plasma, significantly increasing the risk of atherosclerosis and cardiovascular diseases [1, 2]. This condition also leads to an increased production of reactive oxygen species (ROS) through lipid peroxidation, promoting LDL oxidation a crucial step in atherosclerosis [3]. Recent studies have shown that polyphenol-rich medicinal plants, such as grapes, apples, cacao, olive, and tea, can mitigate cardiovascular risk factors like dyslipidemia, oxidative stress, inflammation, and endothelial dysfunction, often with fewer side effects compared to pharmaceuticals [4, 5].

Loquat (*Eriobotrya japonica* Lindl) belonging to the Rosaceae family is an evergreen fruit tree originated in China but widely cultivated in temperate and subtropical zones including Mediterranean regions, Turkey, Pakistan, India, and Brazil [6]. In Morocco, Loquat trees cover a large area of about 600 ha in the province of Berkane (Oriental Morocco), which represents more than 80% of the overall area devoted to this sector at the national level. This area is spread over the communes of Zegzel, Takerboust, Tazaghine and Ouaoullout. Loquat is traditionally used in Asian and Mediterranean regions for both its fruit and medicinal properties. It has been employed in folk medicine to address conditions such as cough, bronchitis, diabetes, and cancer [7, 8]. Scientific studies suggest that loquat extracts exhibit antidiabetic, antihyperlipidemic, anti-obesity, and antioxidant effects [9, 10, 11]. The fruit is rich in bioactive compounds, including caffeic acid, chlorogenic acid derivatives, ellagic acid, and essential minerals like potassium, magnesium, and zinc [12, 13]. This study aims to scientifically investigate the potential benefits of loquat fruit peel extract on hyperlipidemia while also exploring the underlying mechanisms through in-silico methods.

2. Materials and Methods

2.1. *Plant material and extraction*

Loquat fruit (*Eriobotrya japonica* Lindl.) was collected in May 2022 from Zegzel valley, Berkane, Morocco. The peels were air-dried for 25 days, ground, and extracted

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using hot water infusion to obtain loquat peel extract (PE). The yield of the dried aqueous extract was 16.5%.

2.2. Total phenolic, flavonoid, and tannin content

The quantification of total polyphenol and flavonoid as well as the identification of individual phenolic compounds were undertaken using our previously established methods [14,15].

2.3. Preparation of HFFD

The high-fat, high-fructose diet (HFFD) was formulated by supplementing the standard mice diet with beef fat (16%), cholesterol (1.5%), fructose (10%), egg yolk (10%), and deoxycholic acid (0.2%).

2.4. Experimental protocol

The animals were allocated into five groups: the normolipidemic control group (NCG), fed a standard diet and gavaged with distilled water; the hyperlipidemic control group (HCG), fed a HFFD and gavaged with distilled water; two groups treated with loquat fruit peel extract (PTG100 and PTG200), fed HFFD and gavaged with loquat fruit peel extract and a group treated with fenofibrate (FTG), fed HFFD and gavaged with fenofibrate. Blood samples were collected every 15 days for plasma lipid analysis.

2.5. Tissue and fecal lipid analysis

Lipids were extracted from the liver, abdominal adipose tissue, and feces using the method outlined by Dos Santos [16]. TC and TG levels were then measured using enzymatic assays.

2.6. In silico 3D docking analysis

Molecular docking was used to examine potential binding interactions between major polyphenols and key enzymes/transcription factors regulating lipid metabolism. The docking analysis was performed using SwissDock (www.swissdock.ch/docking), with protein 3D structures obtained from UniProt (www.uniprot.org) and polyphenol structures from PubChem (https://pubchem.ncbi.nlm.nih.gov). Five proteins involved in lipid metabolism were selected, including HMG-CoAR, ABCG1, ABCG1, LXRα, RXRα. Binding capacities were expressed in kcal/mol, with values below -7 kcal/mol indicating probable interactions.

2.7. Statistical analysis

Statistical analysis was performed by one-way analysis of variance (ANOVA) followed by Tukey's post hoc test using GraphPad Prism 9.5.0 software. Statistically significant was considered at $P < 0.05$. Data were expressed as mean values ± standard error of the means (SEM).

3. Results

3.1. Total phenol content in loquat fruit peel extract

The loquat fruit peel extract contains 189.23 ± 0.84 mg/g of polyphenolic compounds. Flavonoids are the predominant component, constituting 54% of the total polyphenols (103.45 ± 0.42 mg/g), followed by tannins at 37% (71.12 ± 0.13 mg/g). HPLC analysis reveals that 5-O-caffeoylquinic acid is the most abundant phenolic compound, making up 46.51% of the extract, followed by chlorogenic acid at 17.44%. Ferulic acid and quercetin each account for 13.6%, while caffeic acid comprises 8.91%.

3.2. Induction of hyperlipidemia

In this study, all mice except those in the normal control group were fed a high-fat, high-fructose diet (HFFD) for 45 days. Plasma lipid parameters were assessed on days 0, 15, 30, and 45. From day 15, HFFD significantly increased TC, TG and LDL cholesterol (LDL-C), while decreasing HDL cholesterol (HDL-C). After 15 days, TC, TG, and LDL-C levels rose significantly, and HDL-C decreased slightly. After 45 days, TC, TG, and LDL-C levels showed further significant increases, with HDL-C continuing to decrease. The atherogenic index (AI) and LDL-C/HDL-C ratio also increased significantly, indicating a more pronounced effect on lipid metabolism over time (Table 1 and figure1).

3.3. Loquat PE and fenofibrate's effect on plasma lipid parameters and atherogenic indices

Treatment of HFFD-fed animals with loquat fruit peel extract (100 and 200 mg/kg) showed dose- and time-dependent effects on plasma lipid parameters. After 15 days, there were no significant changes. However, after 30 and 45 days, 100 mg/kg of the extract significantly reduced TC and TG at both time points. LDL-C decreased after 30 and 45 days, while HDL-C increased significantly. At a dose of 200 mg/kg, the extract showed more pronounced effects, significantly reducing TC, TG, and LDL-C, and increasing HDL-C after 30 and 45 days. The AI decreased, and the LDL/HDL ratio was significantly reduced. Fenofibrate, used as a standard hypolipidemic drug at 200 mg/kg, led to a notable increase in HDL-C and significant decreases in plasma TC, TG, LDL-C, AI, and LDL/HDL ratio after 30 days and 45 days respectively (Table 1 and figure1).

Table 1
Effect of loquat fruit peel extract and fenofibrate on plasma TC, TG, LDL-C and HDL-C levels in HFFD fed mice.

	Parameters (mg/dL)	Day 15	Day 30	Day 45
NCG	TC	80.16±1.6	80.94±1.3	83.75±3.12
	TG	50.12±1.6	51.12±1.72	50.82±1.6
	LDL-C	8.19±2.3	8.5±2.65	8.6±1.63
	HDL-C	20.02±0.65	20.45±0.5	21.1±0.70
HCG	TC	140.08±3.5$^{###}$	198.2±1.74$^{###}$	240.81±3.04$^{###}$
	TG	72.18±2.12$^{###}$	114.2±1.5$^{###}$	128.5±1.52$^{###}$
	LDL-C	59.8±7.10$^{###}$	58.2±2.86$^{###}$	92.1±1.68$^{###}$
	HDL-C	19.2±0.12	18.05±0.96$^{#}$	18.12±0.17$^{#}$
PTG 100 mg/kg	TC	138.13±2.23	194.12±0.51*	210.52±2.1*
	TG	69.3± 1.52	110.22±0.52*	115.81±2.03**
	LDL-C	47.01±3.5	50.21±1.18*	56.92±1.11***
	HDL-C	21.29±1.52	25.13±1.77**	38.94±2.5***
PTG 200 mg/kg	TC	137.01±2.15	180.5±2.5$^{***×××}$	153.01±1.1$^{***×××}$
	TG	68.1±1.13	98.9±3.65$^{**××}$	70.01±3.96$^{***×××}$
	LDL-C	44.12±2.78	45.81±0.16$^{***××}$	32.09±1.06$^{***×}$
	HDL-C	20.1±2.1	31.92±1.72$^{***×}$	49.32±1.10$^{***××}$
FTG 200 mg/kg	TC	138.14±1.32	183.3±1.24***	155.7±2.81***
	TG	73.1±2.36	96.53±5.1**	72.12±2.6***
	LDL-C	44.12±2.78	45.81±1.16***	32.09±1.06***
	HDL-C	20.33±1.52	30.06±0.6***	47.01±1.64***

*** ± SEM (n=8). $^{#}$P<0.05 and $^{###}$P<0.001 vs. NCG, *P<0.05, **P<0.01, ***P<0.001 vs. HCG. ×P<0.05, ××P<0.01 and ×××P<0.001 vs. PTG 100 mg/kg. TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol. NCG, normolipidemic control group; HCG, hyperlipidemic control group; PTG, loquat fruit peel extract-treated groups; FTG, fenofibrate treated group; HFFD, high fat-high fructose diet.

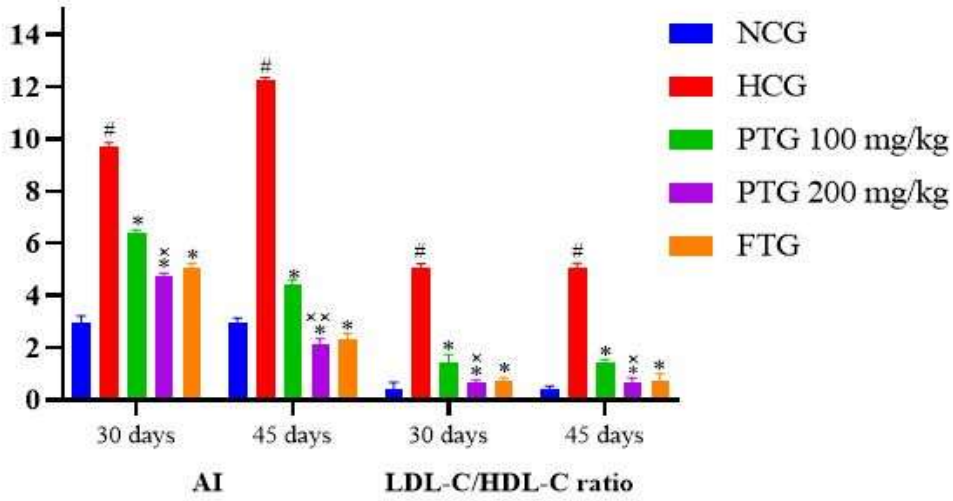

Fig. 1. Effect of loquat fruit peel extract and fenofibrate on atherogenic markers in HFFD-induced hyperlipidemic mice.

*** ±SEM (n=8). $^{#}$P<0.001 vs. NCG, *P<0.001 vs. HCG. $^{×}$P<0.01 and $^{××}$P<0.001 vs. PTG 100 mg/kg. AI, atherogenic index; LDL/HDL-C, ratio of low-density lipoprotein-cholesterol to high-density lipoprotein-cholesterol; NCG, normolipidemic control group; HCG, hyperlipidemic control group; PTG, loquat fruit peel extract-treated groups; FTG, fenofibrate treated group. HFFD, high fat-high fructose diet.

3.4. Effect of PE on lipid levels in hepatic and adipose tissue

After 45 days of a high-fat high-fructose diet (HFFD), mice in the hyperlipidemic control group exhibited significantly elevated levels of TC and TG in the liver compared to the normal control group. Administration of PE at a dose of 100 mg/kg led to a notable reduction in both hepatic TC and TG. The 200 mg/kg dose of the extract proved even more effective, significantly lowering these liver lipids. Similarly, fenofibrate treatment resulted in a substantial decrease in hepatic TC and TG. In terms of adipose tissue, the HFFD increased TC and TG compared to the normal control group. Loquat fruit peel extract treatment effectively decreased these elevated levels in a dose-dependent manner. The extract at 100 mg/kg and 200 mg/kg resulted in significant reductions in adipose tissue TC and TG. Fenofibrate also significantly reduced adipose tissue TC and TG compared to the hyperlipidemic control group (Table 2).

Table 2
Effect of loquat fruit peel extract and fenofibrate on hepatic and adipose tissue lipid profile in HFFD fed mice.

	Parameters	NCG	HCG	PTG 100 mg/kg	PTG 200 mg/kg	FTG
Liver	TC (mg/g)	10,37±0.89	20.72±1.21$^{\#}$	16.34±0.13*	12.23±0.70$^{***\times\times\times}$	11.16±0.73***
	TG (mg/g)	4.72±0.63	22.84±2.06$^{\#}$	17.82±0.06*	14.2±0.19$^{***\times\times}$	9.96±0.42***
Adipose tissue	TC (mg/g)	1.93±0.05	3.42±0.14$^{\#}$	2.91±0.12*	2.5±0.07$^{***\times}$	2.17±0.09***
	TG (mg/g)	7.68±0.73	27.53±0.32$^{\#}$	22.05±0.57**	18.93±1.19$^{***\times}$	17.02±0.51***

*** ± SEM (n=8). #P <0.001 vs. NCG. *P<0.05. **P<0.01. ***P<0.001 vs. HCG. ×P<0.05. ××P<0.01 and ×××P<0.001 vs. PTG 100 mg/kg.TC, total cholesterol; TG, triglycerides; NCG, normolipidemic control group; HCG, hyperlipidemic control group. PTG, loquat fruit peel extract-treated groups; FTG, fenofibrate treated group; HFFD, high fat-high fructose diet.

3.4. Effect of PE on fecal TC and TG

The levels of TC and TG in feces were analyzed. Mice subjected to a high-fat, high-fructose diet (HFFD) for 15 days exhibited higher excretion of TC and TG compared to those on a standard diet. Initially, treatment with loquat fruit peel extract did not alter fecal cholesterol and triglyceride excretion. However, at a dose of 100 mg/kg, the PE significantly enhanced the excretion of TC and TG in hyperlipidemic mice after 30 and 45 days. A dose of 200 mg/kg further increased the fecal excretion of TC and TG at both time points. Fenofibrate also markedly improved the excretion of TC and TG, with more substantial effects evident after 45 days (Figure 2).

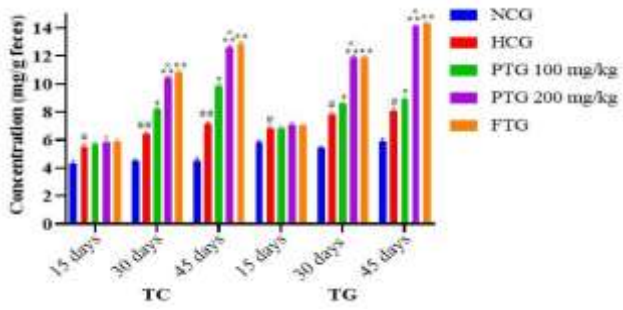

Fig. 2. Effect of loquat fruit peel extract and fenofibrate on fecal excretion of TG and TG in HFFD-induced hyperlipidemic mice.

*** ±SEM (n=8). $^{\#}$P<0.01, $^{\#\#}$P<0.001 vs. NCG. *P<0.01, **P<0.001 vs. HCG. $^{\times}$P<0.001 vs. PTG 100 mg/kg. TC, total cholesterol; TG, triglycerides; NCG, normolipidemic control group; HCG, hyperlipidemic control group; PTG, loquat fruit peel extract-treated groups; FTG, fenofibrate treated group.

3.5. *In silico interactions between major loquat fruit peel extract polyphenols and proteins involved in lipid regulation*

As presented above, the extract presents significant lipid-lowering properties. In order to understand the underlying mechanisms of this effect, we performed interactome analyses using *in silico* 3D docking. The results showed that the major phenolic compounds identified in the extract could bind to proteins (enzymes or transcription factors) involved in regulating lipid metabolism. Caffeoylquinic acid shows the highest binding affinity to HMG-CoA reductase with a value of -8.2 kcal/mol, followed closely by chlorogenic acid at -8.3 kcal/mol. Both of these compounds exhibit strong potential as inhibitors of cholesterol biosynthesis. In contrast, ferulic acid and caffeic acid demonstrate lower binding affinities, suggesting a less pronounced effect on HMG-CoA reductase inhibition compared to caffeoylquinic and chlorogenic acids. When assessing the interaction with ABCG1, quercetin displays the strongest binding affinity at -8.31 kcal/mol, which indicates a significant potential for facilitating cholesterol efflux and reverse cholesterol transport. Caffeoylquinic acid also shows a notable binding

affinity at -7.98 kcal/mol. Meanwhile, chlorogenic acid and caffeic acid exhibit weaker affinities, which may suggest less effectiveness in modulating cholesterol transport via ABCG1. In terms of binding to ABCG4, caffeoylquinic acid and chlorogenic acid both show similar binding affinities, -7.85 kcal/mol and -7.84 kcal/mol respectively. These results suggest that these compounds may effectively modulate cholesterol transport through ABCG4. The binding affinities of ferulic acid, caffeic acid, and quercetin are slightly lower, indicating a potentially lesser role in this process. Regarding the interaction with Liver X Receptor Alpha (LXRα), caffeoylquinic acid and quercetin exhibit the highest binding affinities at -8.12 kcal/mol and -8.1 kcal/mol respectively. This suggests that these compounds could significantly activate LXRα and influence cholesterol metabolism. Ferulic acid also shows substantial binding, while caffeic acid has a lower binding affinity, indicating a potentially reduced effect on LXRα activation. Lastly, for Retinoid X Receptor Alpha (RXRα), caffeoylquinic acid again leads with the strongest binding affinity of -8.23 kcal/mol. Caffeic acid and quercetin also exhibit strong interactions with RXRα, while chlorogenic acid and ferulic acid show weaker binding. This suggests that caffeoylquinic acid and these other compounds may significantly influence RXRα-mediated pathways.

4. Discussion

The habitual intake of high-fat and high-sugar diets is closely linked to the development of metabolic disorders such as hyperlipidemia, obesity, diabetes, and nonalcoholic fatty liver disease (NAFLD) [17]. These disorders, along with oxidative stress, are major risk factors for cardiovascular diseases (CVD), which have been a leading cause of morbidity and mortality globally [18]. In Morocco and many developing countries, herbal remedies and dietary supplements are widely used to treat hyperlipidemia and prevent CVD [19]. This study aimed to investigate the effects of loquat fruit peel extract on lipid metabolism in mice fed a high-fat high-fructose diet at doses of 100 and 200 mg/kg body weight. Feeding mice with the HFFD resulted in a significant increase in plasma lipids, consistent with previous studies [20]. However, treatment with loquat fruit peel extract corrected this imbalance, particularly by reducing LDL-C, an atherogenic lipid parameter targeted by hypolipidemic drugs [21]. This suggests that the extract may enhance the expression of LDL receptors in the liver and peripheral organs, thereby improving LDL-C absorption. These findings align with those of Abdelrahman et al. [11], who reported similar effects with other E. japonica extracts. Moreover, the extract increased HDL-C levels, indicating activation of reverse cholesterol transport (RCT). Our data support this hypothesis, showing that excess peripheral cholesterol was returned to the liver and excreted through the enterohepatic cycle. Molecular docking studies revealed that caffeoylquinic acid and quercetin bind strongly to proteins involved in RCT, such as ABCG1, ABCG4, and LXR-RXR. This interaction likely contributes to the observed effects on cholesterol metabolism. The increase in fecal cholesterol levels may result from biliary secretion and trans-intestinal cholesterol efflux (TICE), regulated by the LXR-RXR mechanism [22, 23, 24]. Furthermore, polyphenols in the loquat extract, including caffeoylquinic acid and quercetin, interact with HMG-CoA reductase, suggesting a potential modulation of cholesterol biosynthesis. This finding is consistent with previous reports on polyphenols from Thymus atlanticus [25].

5. Conclusion

In conclusion, the present study demonstrated that loquat fruit peel is a valuable source of active compounds with antihyperlipidemic activity. Our findings suggest that the aqueous extract could be used as substrate to produce phytotherapeutics drugs or dietary supplements to prevent hyperlipidemia, hyperglycemia and related cardiovascular diseases.

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Conflicts of interest statement

There are no conflicts to declare.

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