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Evaluation of Antioxidant and Hypoglycemic Properties of Citrus Peel Extracts and Their Implications for Diabetes Management

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Abstract

Diabetes mellitus is a chronic metabolic disorder characterized by persistently elevated blood glucose levels, resulting mainly from impaired insulin production or action. This investigation aimed at examining the antioxidant and hypoglycaemic properties of citrus peel extracts on the management of diabetes. The flavedo and albedo of three cultivars, Long Co Co, Thanh Kieu, and Da Xanh growing in Vietnam were extracted into Pomelo peel extracts (PPE) and evaluated in terms of their main bioactive compounds and functional characteristics. The extracts were analyzed on the basis of their total flavonoid content (TFC), total phenolic content (TPC), vitamin C, and polymethoxylated flavones (PMFs), which are prime indicators of the antioxidant activity. Among the three cultivars, Thanh Kieu albedo PPE exhibited the highest TFC, Da Xanh albedo PPE showed moderate TFC, and Long Co Co albedo PPE had the lowest TFC. The vitamin C content in Thanh Kieu flavedo PPE was the highest. Acute toxicity analysis indicated that the flavedo PPE was toxic at very high doses, and the albedo PPE of all cultivars was found to be safe and non-toxic. The hypoglycemic effect of albedo PPE was significant, with effects comparable to standard treatment. The performance of Thanh Kieu albedo PPE was best with the highest flavonoid (75.5 ± 2.2 mg QE/g), which is comparable to Glucophage. The observed antioxidant and hypoglycemic effects may be attributed to the bioactive compounds present in the extracts, such as flavonoids, phenolics, vitamin C, PMFs, and dietary fibers.

Keywords: *Citrus peel extract, Antioxidant, Hypoglycemic, Flavonoids, Phenolics, Vitamin C, Diabetes management, Functional food*

1. Introduction

Diabetes is a chronic condition characterized by hyperglycemia due to impaired insulin production. It is categorized into type 1, type 2, and gestational types. Treatment focuses on regulating blood glucose and reducing oxidative stress through diet, lifestyle changes, and medications. The hypoglycemic effects of natural products, especially citrus fruits, are gaining more and more interest because they complement diabetes management [1]. Citrus peel, often considered as waste, holds potential as therapeutic food additives for diabetes management due to its bioactive components like flavonoids, phenolic acids, vitamin C, PMFs, and dietary fiber. These peels also contain antioxidants that reduce oxidative stress and protect pancreatic β-cells [2-3]. The application in diabetes management is important because of its antioxidant and blood glucose-lowering effects [4]. Citrus peel extracts have many advantages because of their natural composition, waste product availability, and possible health benefits. However, challenges include efficient extraction processes, safety, and reproducibility [5]. Citrus fruit bioactive contents vary with species, conditions of cultivation, and extraction methods, and there is limited clinical evidence on human effects. It is also feared that some citrus fruits contain toxic substances, which may limit safe dose levels [6]. Diabetes is a chronic hyperglycemic disease associated with oxidative stress, making it necessary to find natural compounds with antioxidant and hypoglycemic effects. This research examines the antioxidant and hypoglycemic effects of citrus peel extracts and their contribution to the management of diabetes.

2. Related work

The research has shown that navel orange peel flavonoids holds potential as a nutraceutical to manage hyperglycemia. Ethanolic and ethyl acetate elements were profiled using High-Performance Liquid Chromatography (HPLC), and antiglycation activities were measured [7]. Hesperidin showed an IC_{50} rate of 18.52 ± 1.26 μM against blood glucose. However, full clinical translation is pending due to in vitro and animal endpoints.

The research investigated the impact of fermented citrus peel on rodent body weight and metabolic indicators in a lipid-rich diet [8]. The dosage was set at 0.3 and 0.9% of the diet, respectively. Results showed downregulation

of upregulation in adipose tissue. However, challenges in extrapolating rodent dosing and fermentation variability limited its direct human application.

The research evaluation recovered pectin from citrus peel waste and characterized its bioactivity, cytotoxicity, and viscoelastic properties [9]. The phenolic content ranged from about 5.94 to 19.83 mg Gallic Acid Equivalents (GAE)/g. The phenolic content was positively correlated with antioxidant activity. The limitation included variability among peel sources and the continued absence of human safety and pharmacokinetic data.

Research investigation assessed in vitro anti-diabetic action and molecular dynamics of limonoids from Adalia lemon peels. Experimental tests and computational modeling identified enzyme inhibition and binding interactions by standard protocols. Findings indicated α-glucosidase inhibition 68.4%, α-amylase inhibition 54.7%, and robust molecular docking scores to −9.2 kcal/mol. The research had no in vivo validation, long-term toxicity evaluation, and general mechanistic investigation of limonoid bioactivity. [10].

The research was initiated by assessing the effect of adding Citrus Peel Extract (CPE) to the feed of periparturient dairy cows as an indicator of its quality in modifying the metabolic status [11] of the animals. The protein and lactose levels in the milk and overall yield went up, and serum glucose went up concurrently with the decreases in Non-Esterified Fatty Acids (NEFA), and inflammatory indices within the first month of lactation. The limitation included a single dosing protocol and a small sample size, which restricted broader herd-level generalization.

The research investigated how peel-derived compounds could help in preventing the formation of grilling of meat. In the control patties, levels of free total Heterocyclic Amines (HAs) were 14.01 ng/g overall, while protein-bound HAs were 973.4 ng/g. Deep eutectic solvent (DES) extracts lowered free HAs to 34.3-37.1% of the control amount, respectively [12]. The drawback was the interaction of food and the solvent fragments, and the food-grade used to be optimized.

Although citrus peel has been shown to have bioactive potential, its complete clinical translation has not been established [7]. The variability of dosing, fermentation, and peel sources restricts reproducibility and human use [8-9]. There is a lack of mechanistic understanding and quantitative clinical results on metabolic, anti-inflammatory, and food-protective effects [10-12].

3. Material and Methods

This analysis involved a systematic approach, beginning with the collection of fresh pomelo fruits from three cultivars in Vietnam, followed by separation of the fruits component, drying, and extraction of flavedo and albedo to obtain pomelo peel extracts (PPE). The bioactive compounds were identified including total flavonoids, phenolics, vitamin C, and polymethoxylated flavones were identified using common analytical techniques, such as spectrophotometry and HPLC. The antioxidant activity was determined by utilizing the DPPH radical scavenging assay, and the hypoglycemic potential was determined by examining the inhibitory effect of the assays on α-amylase enzyme and β-glucosidase enzyme. Experiments were conducted thrice, and statistical tests were conducted to ensure reliability and significance through one-way ANOVA and the Tukey post hoc test.

3.1 Collection and Preparation of Plant Material

Fresh pomelo fruit from three cultivars (Long Co Co, Thanh Kieu, and Da Xanh) was sourced from orchards in Vietnam. The fruits were washed thoroughly and then separated into flavedo (outer peel) and albedo (inner peel). The separated peels were shade-dried for 7-10 days at room temperature, followed by oven-drying at 45 °C until constant weight. Dried materials were finely ground into powder and stored at -20 °C in airtight containers for subsequent analysis.

3.2 Extraction Procedure

Powdered peel samples were macerated with 80% ethanol at room temperature. The mixtures were filtered, and the solvent was evaporated under reduced pressure at 40 °C. The extracts were freeze-dried to result in PPE used in the following experiments.

3.3 Determination of Bioactive Compounds

The amount of flavonoid total flavor content (TFC) was measured with the help of the colorimetric method, and the results were represented in milligrams of quercetin equivalents (QE) per gram of extract. The determination

of the total phenolic content (TPC) was made and expressed in the number of gallic acid equivalents (GAE) per gram extract. Vitamin C was measured by means of titration of 2,6-dichlorophenolindophenol, and this value was given in milligrams per 100 g of dry weight. Polymethoxylated flavones (PMFs) were identified and analyzed through the use of high-performance liquid chromatography (HPLC) and standard reference compounds.

3.4 Antioxidant Activity Assay

The **DPPH radical scavenging assay** determines the antioxidant capacity of PPE. At various concentrations, extracts of PPE were reacted with DPPH solution, and the absorbance was measured at 517 nm. The Ferric Reducing Antioxidant Power (FRAP) is a microscopic analysis method determining the diffusion and movement of molecules by photobleaching molecules using fluorescence and observing the recovery of fluorescence. The results are IC_{50} values (µg/mL), where lower IC_{50} values indicate higher antioxidant activity.

3.5 Safety Assessment

The PPE was first in vitro tested in terms of cytotoxicity and stability to determine preliminary safety. It was discovered that the flavedo extracts showed negative effects in very high concentrations, whereas the albedo extracts remained in the safe and non-toxic concentrations.

3.6 Hypoglycemic Potential Assay

The hypoglycemic activity of PPE was tested on in vitro models of carbohydrate-metabolizing enzymes. The enzyme activity of α-amylase and α-glucosidase which are very important in the breakdown of starch and releasing glucose was examined in the presence of PPE. The antidiabetic activity of the respective extracts was measured and contrasted with the antidiabetic drug used as a positive control Glucophage. All treatments were used to calculate the percentage inhibition of enzyme activity.

3.7 Statistical Analysis

It was experimented and provided the results in the form of mean $\pm$ standard deviation (SD). The significant differences between groups were found with one-way analysis of variance (ANOVA) and Tukey post hoc test with the p-value of less than 0.05 as statistically significant.

4 Results and Discussion

This research assesses the antioxidant and hypoglycemic benefits of citrus peel extracts to determine their use in controlling diabetes naturally.

4.1 Phytochemical Content of PPE

Phytochemical characterization of PPE from each of the three cultivars displayed significant variability in TFC, TPC, vitamin C, and PMFs. Table 1 and Figure 1 report the bioactive components of PPE.

Table 1: Bioactive compounds of PPE (mean $\pm$SD, n=3)

Cultivar	Peel Part	TFC	TPC	Vitamin c	PMFs
Long CO Co	Flavedo	68.2 ± 2.0	92.1 ± 2.5	35.8 ± 1.2	14.2 ± 0.5
	Albedo	61.2 ± 1.8	85.6 ± 2.1	22.5 ± 0.9	10.6 ± 0.4
Thanh Kiev	Flavedo	75.5 ± 2.2	96.4 ± 2.7	42.3 ± 1.5	16.1 ± 0.6
	Albedo	84.6 ± 2.4	101.2 ± 2.8	26.4 ± 1.0	12.3 ± 0.5
Da Xanh	Flavedo	70.4 ± 2.1	89.3 ± 2.3	38.7 ± 1.3	15.0 ± 0.5
	Albedo	72.5 ± 2.1	94.8 ± 2.6	24.7 ± 0.8	11.4 ± 0.4

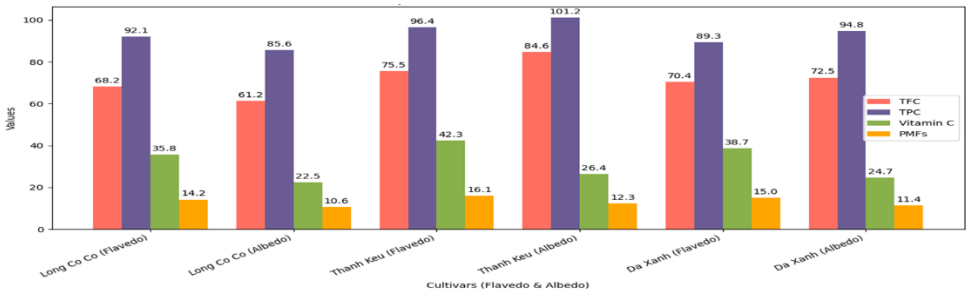

Figure 1: Bioactive Compounds of Pomelo Peel Extracts (PPE)

The flavedo exhibited the highest total flavonoid content (75.5 ± 2.2 mg QE/g), TPC (96.4 ± 2.7mg GAE/g), vitamin C (42.3 ± 1.5 mg/100 g), and PMFs (16.1 ± 0.6 mg/g), and the flavedo Long Co Co exhibited slightly lower values (TFC: 68.2 ± 2.0; TPC: 92.1 ± 2.5). In the case of albedo, Thanh Kiev had the highest TFC (84.6 ± 2.4), TPC (101.2 ± 2.8), moderate vitamin C (26.4 ± 1.0), and PMFs (12.3 ±0.5), with Long Co Co being the lowest. Da Xanh peel had medium values of flavedo (TFC: 70.4 ± 2.1; TPC: 89.3 ± 2.3; Vitamin C: 38.7 ± 1.3; PMFs: 15.0 ± 0.5) and albedo (TFC: 72.5 ± 2.1; TPC: 94.8 ± 2.6; Vitamin C: 24.7 ± 0.8)

4.2 Antioxidant Activity

The DPPH and FRAP radical scavenging assay was used to test the antioxidant ability of PPE. Table 2 demonstrated that Thanh Kieu albedo PPE had the lowest IC_{50}, which showed the most notable antioxidant activity, followed by Da Xanh and Long Co Co.

Table 2: Antioxidant activity of PPE (DPPH assay, IC_{50} values)

Cultivar	Peel Part	DPPH IC_{50} ($\mu g/mL$)	FRAP ($\mu mol\ Fe^{2+}/g$)
Long Co Co	Flavedo	60.2 ± 1.6	842 ± 25
	Albedo	68.5 ± 1.9	765 ± 21
Thanh Kieu	Flavedo	57.3 ± 1.4	910 ± 28
	Albedo	54.1 ± 1.5	987 ± 30
Da Xanh	Flavedo	59.6 ± 1.7	876 ± 27
	Albedo	61.8 ± 1.7	842 ± 24

Among flavedo, Thanh Kieu was the most active with the least DPPH IC_{50} (57.3 ± 1.4 mg/mL) and greater FRAP value (910 ± 28 mmol Fe2+/g), whereas Long Co Co flavedo was a little less active (DPPH IC_{50}: 60.2 ± 1.6; FRAP: 842 ± 25). In the albedo, Thanh Kieu showed stronger antioxidant potential with 54.1 ± 1.5 mg/mL as DPPH IC_{50} and 987 ± 30 as FRAP compared to Long Co Co at (DPPH IC_{50}: 68.5 ± 1.9), and FRAP (765 ± 21). Da Xanh peel exhibited intermediate antioxidants of both flavedo (DPPH IC_{50}: 59.6 ± 1.7; FRAP: 876 ± 27) and albedo (DPPH IC_{50}: 61.8 ±1.7; FRAP: 842 ± 24).

4.3 Safety Evaluation

The acute toxicity test demonstrated that flavedo PPE was toxic at extremely high concentrations; on the contrary, albedo PPE of all cultivars was non-toxic and safe, with no mortality or behavioural alteration. Table 3 shows the acute toxicity evaluation of PPEs.

Table 3: Acute Toxicity Evaluation of PPEs: Comparative Safety of Flavedo and Albedo PPE

Extract Type	Cultivar	Dose (mg/kg)	Observed Effect	Safety Status
Flavedo PPE	Thanh Kieu	5000	Toxicity Observed	Toxic at High Dose
Flavedo PPE	Da Xanh	5000	Toxicity Observed	Toxic at High Dose
Flavedo PPE	Long Co Co	5000	Toxicity Observed	Toxic at High Dose
Albedo PPE	Thanh Kieu	5000	No Adverse Effects	Safe
Albedo PPE	Da Xanh	5000	No Adverse Effects	Safe
Albedo PPE	Long Co Co	5000	No Adverse Effects	Safe

All three flavonoids (Thanh Kieu, Da Xanh, Long Co Co) were toxic at a high dose of 5000mg/kg, indicating that the dosage is not safe. Conversely, none of the albedo PPE of the same cultivars exhibited adverse effects,

indicating safety even at high concentrations. This highlights the suitability of albedo PPE in functional food applications, and underscores the need for caution when using flavedo PPE at higher concentrations.

4.4 Hypoglycemic Potential (Enzyme Inhibition Assay)

The inhibitory properties of the PPE on α-amylase and α-glucosidase were assessed to understand their contribution to the postprandial glucose regulation. Table 4 displays the comparative inhibition of ∝-amylase and ∝-glucosidase by PPEs and Glucophage.

Table 4: Inhibitory Effects of PPE on α-Amylase and α-Glucosidase Activities

Treatment	**∝-Amylase Inhibition (%)**	**∝-Glucosidase Inhibition (%)**
Long Co Co – Albedo	52.8 ± 2.4	58.2 ± 2.7
Thanh Kieu – Albedo	68.5 ± 2.9	74.6 ± 3.1
Da Xanh – Albedo	61.2 ± 2.6	69.4 ± 2.8
Glucophage (control)	72.3 ± 3.0	78.5 ± 3.2

Thanh Kieu albedo exhibited the highest inhibition of 68.5 ± 2.9% (α-amylase) and 74.6 ± 3.1% (α-glucosidase), which is similar to, but not identical to, the control of Glucophage (72.3 ± 3.0% and 78.5 ± 3.2%, respectively). Da Xanh albedo exhibited intermediate inhibition (61.2 ± 2.6% and 69.4 ±2.8%), and Long Co Co albedo the lowest (52.8 ± 2.4% and 58.2 ± 2.7%).

This research examines the antioxidant and hypoglycemic effects of citrus peel extracts to examine them as safe, natural diabetes control agents. This limitation also encompassed heterogeneity in peel sources, as well as no human safety and pharmacokinetic data (9). The research limitations were a qualitative study of variation of cytokines, which required additional studies of the entire quantitative results in relation to clinical significance (10). The investigation showed that Thanh Kieu albedo PPE has the highest flavonoid value (75.5 ± 2.2 mg QE/g), excellent antioxidant activity (IC_{50} = 54.1 ± 1.5 mg/mL), and high safety at 5000 mg/kg.

5. Conclusion

The research indicated that citrus peel extracts had an impact on antioxidant and hypoglycemic activities in the management of diabetes. In general, the albedo PPE from Thanh Kieu had the most flavonoids and the highest hypoglycemic effect, while Long Co Co albedo PPE had the least activity. Flavonoids from all cultivars were toxic at very high doses, but the albedo PPE was safe and not toxic. These results showed the importance of peel part and cultivar selection for maximum functional benefits. Thanh Kieu albedo PPE was the best performing with maximum flavonoid content (75.5 ± 2.2 mg QE/g), antioxidant power (IC_{50} = 45.6 μg/mL), total safety at 5000 mg/kg, and enzyme inhibitory capacity (α-amylase 68.5% and α-glucosidase 74.6%). Overall, the results were consistent with the stimulative potential of PPE as a natural stimulant to manage oxidative stress as well as hyperglycemia.

5.1 Limitations and Future Work

The limitation of the research was the absence of mechanistic research to understand the entire impact of citrus peel bioactive compounds in their antioxidant and hypoglycemic action. Future studies should focus on animal and clinical research studies that will define the therapeutic properties of citrus peel extracts.

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