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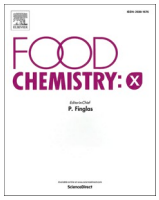

Effects of high-pressure homogenization on phenolics profile, antioxidant activity, α-glucosidase inhibitory activity, and insulin resistance of peach juice during simulated gastrointestinal digestion

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ABSTRACT

This study underscores the potential of high-pressure homogenization (HPH) as a non-thermal processing technique to improve the bioavailability and health benefits of phenolic compounds in peach juice. Following HPH treatment at 300 MPa, the retention of total phenolic and flavonoid content after gastrointestinal digestion increased by 28 % and 20 %, respectively. The bioactivities of peach juice were significantly improved, as evidenced by enhanced antioxidant activity, with DPPH and ABTS free radical scavenging capacities rising by 8.58 % - 26.68 %, and α-glucosidase inhibition improving by 21.40 % - 32.98 %. Furthermore, glucose consumption in insulin-resistant HepG2 cells increased by 17.15 % - 30.00 %. Molecular docking analysis further revealed that key phenolic compounds, including phlorizin and quercetin, interacted effectively with IRS1/PI3K/AKT pathway proteins, contributing to the alleviation of insulin resistance. These findings highlighted HPH as an innovative strategy for developing functional fruit-based beverages with enhanced nutritional and therapeutic value.

1. Introduction

As a non-thermal processing technology, high-pressure homogenization (HPH) is currently being developed for the processing of heat-sensitive liquid foods, such as fruit and vegetable juices, for the purpose of sterilizing and inactivating enzymes, as well as improving the turbidity stability of fruit juices (Inguva et al., 2024). The effects of strong shear, cavitation, and turbulence during HPH processing can also disrupt the tissue structure of plant cells, thereby promoting the solubilization and release of phenolics from the food matrix. On the other hand, cell rupture caused by HPH may allow contact between cytoplasmic polyphenol oxidase and phenolics, thus leading to the oxidative degradation of phenolics (dos Santos Aguilar et al., 2018; He et al., 2016; Liu et al., 2009). Numerous studies have shown that HPH altered the contents and composition of phenolics in different juices, but most studies only focused on the changes in total phenolic content (TPC) and total flavonoid content (TFC). For example, compared to non-treated kiwifruit, the TPC of kiwifruit juice significantly increased by 17.14 % and 22.86 % after being treated with 2 and 3 passes of HPH at 200 MPa, respectively (Patrignani et al., 2019). Similarly, the TPC of strawberry juice rose by 11.54 % after 2 passes of HPH at 100 MPa (Karacam et al., 2015). In contrast, the TPC of orange juice and apple juice showed no notable variation after HPH at pressures ranging from 100 to 300 MPa (Suárez-Jacobo et al., 2011; Velázquez-Estrada et al., 2013). Interestingly, lettuce juice exhibited a 46.43 % reduction in TPC after HPH at 150 MPa (Plazzotta & Manzocco, 2019).To better understand the change of phenolics in the juice after treated by HPH, our previous study found that the TPC of peach juice in free (FP), esterified (EP), and insoluble-bound (IBP) phenolic fractions were all enhanced after HPH at 300 MPa, with increasing values of 21.04 %, 48.33 %, and 29.53 %, respectively, but their phenolic compositions were all not changed (Bie et al., 2024).

Phenolics, as secondary metabolites in plants, have a variety of bioactivities and have been shown to be effective hypoglycemic

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compounds, which can lower blood glucose by regulating human blood glucose levels through six main pathways: inhibition of gluconeogenesis, inhibition of dipeptidyl peptidase IV (DPP-IV) activity, improvement of insulin resistance (IR), inhibition of α-glucosidase activity and α-amylase, and enhancement of sensitivity (Golovinskaia & Wang, 2023). Recently, a growing number of studies have suggested the potential benefits of phenolics in natural foods for improving levels of human blood glucose by inhibiting activities of DPP-IV and α-glucosidase. For instance, Bento et al. (2018) reported that six varieties of peaches from Portugal were characterized with a total of 17 major phenolic compounds, and their phenolic extracts showed good inhibitions of α-glucosidase. Our study has also shown that the FP, EP, and IBP in peach effectively inhibited α-glucosidase and DPP-IV activities, with IC_{50} in the ranges of 7.27–44.12 μg/mL and 50.96–312.22 μg/mL, respectively (Bie et al., 2024). These studies highlighted the unique advantages of phenolics derived from natural foods as a safe and sustainable component for blood glucose regulation. Moreover, phenolics offer lower toxicity and fewer side effects compared to synthetic drugs while delivering additional health benefits, including superior antioxidant, anti-inflammatory and cardiovascular protective properties (Shahidi & Ambigaipalan, 2015).

Insulin resistance is one of the main pathological features of metabolic diseases, like type II diabetes, which occurrence is closely related to disturbances in the insulin signaling pathway and abnormalities in the function of insulin receptors. It has been shown that insulin receptor substrate 1 (IRS1), and protein kinase B (AKT), phosphatidylinositol 3-kinase (PI3K) are common insulin signaling pathway proteins that affect glucose uptake and transport. Thus, the IRS1/PI3K/AKT signaling pathway is considered a potential target to improve insulin resistance (Cao et al., 2023). Previous studies have shown that phenolics extracted from black quinoa alleviated IR in HepG2 cells by improving glucose consumption and glycogen synthesis through upregulation of the IRS1/PI3K/Akt/glucose transporters (GLUTs) signaling pathway (Cao et al., 2023). The phenolics extracted from Rosaroxburghii Tratt Fruit regulated the expression of PI3K and phosphorylation of AKT, which further regulated the expression of both FOXO1 and p-GSK3β proteins, thereby promoting glycogen storage and inhibiting gluconeogenesis (Chen et al., 2022).

Accompanying changes in phenolic profile in natural food, their bioactivities were also affected by HPH. For instance, the scavenging capacity of kiwifruit juice against ABTS radicals increased by 13.2 % after HPH at 250 MPa (Patrignani et al., 2019). Meanwhile, the value of composite pear juice against DPPH radicals increased by 15.8 % after HPH at 250 MPa (Liu et al., 2022). Our previous study showed that the scavenging capacities of the three phenolic fractions in peach juice against DPPH radicals were all significantly elevated after HPH treatment at 300 MPa, and their IC_{50} values were reduced by 28.96 % - 66.48 %, and the IC_{50} values for the inhibition of DPP-IV activities and α-glucosidase were reduced by 30.83 % - 62.58 % and 37.25 % - 63.42 %, respectively (Bie et al., 2024). Whereas, orange juice showed no change in antioxidant capacity after HPH at 200 and 300 MPa (Velázquez-Estrada et al., 2013). Conversely, the scavenging capacity of apple juice against ABTS radicals decreased by 39.1 % after HPH at 250 MPa (He et al., 2016).

Furthermore, health effects of phenolics are closely linked to their bioavailability, that is, phenolics can only exert their true effects when they are ingested, absorbed through the intestines, and undergo a complex process of digestion in the human body (Ben Hlel et al., 2019). The bioavailability of phenolics varies with the type of food matrix, processing technology, digestion processing, and other factors. Thus, HPH might affect phenolics in different food matrices differently, which in turn causes changes in bioavailability. Interestingly, Rohilla and Mahanta (2024) reported that 75 MPa HPH resulted in increases of 30 %, 23 %, and 17 % in the TPC of purple, yellow, and red tamarillo, respectively, meanwhile, after gastrointestinal digestion, those values correspondingly increased by 22 % - 34 % and 25 % - 41 % compared to non-treated group, respectively. Therefore, HPH can be applied as a potential technique to enhance the bioavailability of phenolics in foods during digestion. However, there is a limited study focused on the changes in phenolics and their bioactivities of HPH-treated juice after digestion and their regulatory mechanisms on insulin resistance activity. Our previous studies also indicated a lack of sufficient evidence demonstrating that HPH enhanced the bioaccessibility of phenolic compounds in peach juice. Thus, it is crucial to clarify the underlying mechanisms by which HPH enhances the bioavailability of phenolics in fruit juices throughout digestion.

Peaches (*Prunus persica* L.) have a long history of cultivation in China (Liao et al., 2019). Lijiang snow peach, a late-maturing variety grown in the Lijiang Plateau area of Yunnan Province, is particularly rich in phenolic compounds, making it a promising candidate for functional food application. The study uniquely explore the impact of HPH on the phenolics bioavailability in peach juice during simulated gastrointestinal digestion. The investigation encompassed changes in phenolics profile, content, antioxidant activity, and α-glucosidase inhibitory effects. Then, the effects of phenolics on glucose consumption were analyzed on the insulin-resistant HepG2 cell model. Additionally, computer simulations were employed to analyze the binding interactions of different phenolic compounds with key proteins in IRS1/PI3K/AKT signaling pathways. This study aimed to evaluate the feasibility of HPH as an innovative non-thermal processing technology to enhance the bioavailability of phenolics in fruit juices. It sought to elucidate the underlying mechanisms contributing to their health benefits and to offer a practical alternative technology for developing functional health foods targeting metabolic conditions such as type II diabetes.

2. Materials and methods

2.1. Materials and chemicals

Peaches were bought from Lijiang, Yunnan Province, China, and stored at 4 °C. The peaches were washed and juiced, and then filtered with gauze. The obtained juices were immediately frozen with liquid nitrogen and placed at −40 °C before use.

Solid phase extraction (SPE, Clover - C18N, 500 mg, 6 mL) columns were bought from Zhongjian WeiKang Biotechnology Ltd. (Beijing, China). Porcine pepsin (3500 units/mg protein), trypsin (from porcine pancreas, 8 × USP specification), and bile salts were purchased from Merck (Darmstadt, Germany). The glucose assay kit was obtained from Jiancheng Bioengineering Institute (Nanjing, China). Standards, including (+) - catechin, neochlorogenic acid, procyanidin B1, chlorogenic acid, hyperoside, phloridzin, and quercetin were purchased from Desite Biological Technology (≥ 98 %, Chengdu, China). 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenylte-trazolium bromide (MTT), 2,2′-azinobis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), and 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) were obtained from Sigma-Aldrich (MO, USA). Fetal bovine serum (FBS), penicillin, Dulbecco's modified Eagle's medium (DMEM), and streptomycin were obtained from Gibco (CA, UAS). Acarbose, *p*-nitrophenyl-α-D-glucopyranoside (*p*NPG), and recombinant human insulin were bought from Solarbio Science & Technology Co., LTD. (Beijing, China). α-Glucosidase (≥26.5 units/mg protein) was provided by Yuanye Biological Technology (Shanghai, China). HepG2 cells were obtained from Kunming Cell Bank.

2.2. High-pressure homogenization (HPH) processing

Peach juice was obtained by completely thawing at 4 °C overnight and mixed thoroughly. The juice was treated by a microchannel jet HPH equipment (FPG12805, Standard Fluid Power Ltd., Essex, UK). The temperature of equipment was pre-cooled to 4 °C by a cooling circulation system, and the pressure was adjusted. After the pressure stabilized, 400 mL of juice was treated by 1 pass of HPH at pressures of 50, 200, and 300 MPa with a flow rate of 40–50 mL/min, respectively. Among these,

50 and 200 MPa were selected as representative pressures for conventional homogenization and HPH, respectively, while 300 MPa represented the maximum pressure capacity of our equipment. Then, the treated peach juice was immediately filled into aluminum foil bags and frozen using liquid nitrogen, and then stored at −20 °C for use.

2.3. Simulated gastrointestinal digestion

Simulated gastrointestinal digestion based on the method of Ben Hlel et al. (2019) with slight modifications, the gastric simulated digestion fluid and intestinal simulated digestion fluid were prepared. Frozen sample was thawed by placing it at 4 °C overnight and thoroughly mixed. Prior to the simulated digestion, both the peach juice and simulated solutions were preheated to 37 °C, and all experiments were performed in the dark.

A total of 20 mL of peach juice was added with 12.8 mL of gastric simulated digestion fluid. Then, 3.2 mL of porcine gastric pepsin solution with an enzyme activity of 25,000 U/mL and 10 μL of 0.3 M $CaCl_2$ solution were added. The pH was adjusted to 3.00 with 1 M NaOH solution, and the volume was brought to 40 mL by adding gastric simulated digestion fluid. The mixture was incubated in the dark on a shaker at 100 rpm for 2 h.

After gastric digestion, 20 mL mixture was taken out, and the remaining 20 mL of the mixture was added with 11 mL of intestinal simulated digestion fluid. Then, 5.0 mL pancreatic trypsin solution with an enzyme activity of 800 U/mL, 2.5 mL bile salt solution, and 40 μL 0.3 M $CaCl_2$ solution were mixed. The pH of mixture was adjusted to 7.00 with 1 M NaOH solution, and the volume was brought to 40 mL with intestinal simulated digestion fluid. The mixture was placed in the dark on a shaker at 100 rpm for 2 h. After intestinal digestion, the pH was adjusted to 3.00 to stop the digestion. The digested mixture was then centrifuged, and the obtaining supernatant was collected and purified using SPE small columns, then frozen using liquid nitrogen for further use. The phenolic extract was obtained by mixing 1 mL peach juice or gastric/intestinal digestion fluid with 4 mL of 80 % methanol and then stored at −80 °C for analysis of TPC, TFC, phenolics profile, and antioxidant activity. The dried extract powder was obtained by a freeze dryer (LGJ-25JY, Bafangzhongda Technology Development Co., Ltd., Beijing, China) and then stored at −80 °C to analyze α-glucosidase inhibition and insulin resistance.

2.4. Analysis of total phenolic content (TPC) and total flavonoid content (TFC)

The TPC and TFC of peach juice at different digestion stages were determined following a previous study with slight modifications (Gao et al., 2022). Five hundred microliters of Folin-Ciocalteu (10-fold diluted with water) reagent were added into 50 μL of phenolic extract, followed by adding 450 μL of 7.5 % Na_2CO_3 solution (*w/v*) and then reacted for 1 h in darkness. The absorbances of the reaction solution at 765 nm was determined by a microplate reader (Epoch 2, Agilent Technologies Inc., California, USA). The TPC was calculated using gallic acid, which was expressed as gallic acid equivalent (GAE) mg/g.

For TFC determination, 200 μL of the phenolic extract was added with 30 μL of 5 % $NaNO_2$, and after 5 min, 30 μL of 5 % $AlCl_3$ was added. After 6 min, 200 μL of 1 M NaOH was added. The mixture was allowed to react in the dark for 30 min, and then the absorbance of sample was determined at 760 nm using a microplate reader. The TFC was calculated using rutin, which was expressed as rutin equivalent (RE) mg/g.

2.5. Identification and quantification of phenolics by UHPLC-ESI-HRMS/MS

Phenolic compounds were analyzed by a Thermo Fisher Ultimate 3000 UHPLC System equipped with a Q-Exactive Orbitrap mass spectrometer (Thermo Fisher Scientific, Bremen, Germany). Separation of 2 μL methanolic extract was carried out on a ZORBAX SB-C18 (2.1 mm × 100 mm, 1.8 μm, Agilent, CA, USA) with a column temperature of 35 °C and a flow rate of 0.2 mL/min. The mass spectrometry conditions were in positive ion scan mode for anthocyanin and negative ion scan mode for the rest of the phenolic compounds, with a scanning range of *m/z* 100–1500. The mobile phase contained an aqueous solution containing ultrapure water with 0.1 % formic acid (solvent A, *v*/v) and a pure acetonitrile solution (solvent B, v/v). The detailed gradient elution procedures of anthocyanin and non-anthocyanin were referred to by Bie et al. (2024).

2.6. Determination of antioxidant activity

2.6.1. Scavenging activity of DPPH radical

DPPH free radical scavenging activity was determined with reference to Zhou et al. (2019) with slight modifications. In detail, DPPH (0.1 mM) was dissolved in pure methanol, and the phenolic extract was diluted with 80 % methanol to the appropriate concentration. Subsequently, 50 μL of diluted phenolic extract and 200 μL of 0.1 mM DPPH solution were mixed and reacted for 30 min in the dark. The absorbance of the mixture was measured at 517 nm using a microplate reader and Vc as a positive control.

2.6.2. Scavenging activity of ABTS radical

ABTS free radical scavenging activity was determined with reference to Zhang et al. (2022) with slight modifications. First, 25 mL of ABTS solution (7 mM) was mixed with 440 μL of $K_2S_2O_8$ solution (0.14 M) and reacted at room temperature for 12–16 h, and the solution was then diluted 35-fold with ethanol. Then the phenolic extract was diluted with 80 % methanol to the appropriate concentration. Subsequently, 50 μL of diluted phenolic extract and 400 μL diluted ABTS solution were mixed and reacted for 30 min in the dark. The absorbance of the mixture was measured at 734 nm using a microplate reader and Vc as a positive control.

2.7. Determination of α-glucosidase inhibitory activity

The α-glucosidase inhibitory activity was determined with reference to Tan et al. (2017) with slight modifications. First, phenolic extract (0.05–1 μg/mL), pNPG solution (4 mM), and α-glucosidase solution (1 U/mL) were dissolved in phosphate buffer (1 M, pH 6.8), respectively. Subsequently, the reaction mixture, including 160 μL of phenol extract, 200 μL of pNPG solution, and 40 μL of α-glucosidase solution reacted at 37 °C for 10 min in a water bath. The absorbance of the mixture was measured at 734 nm using a microplate reader and acarbose (0.05–1 μg/mL) as a positive control.

2.8. Cell culture, cell viability assay, and insulin resistance (IR)

The HepG2 cells were grown in DMEM supplemented with 1 % penicillin-streptomycin and 10 % fetal bovine serum. The cells were incubated at a constant temperature of 37 °C in a cell culture incubator with 5 % CO_2.

The effects of different concentrations of insulin and phenolic extracts on cell viability was measured by MTT method. HepG2 cells were seeded in a 96-well plate with a density of 1×10^5 cells/mL in 200 μL of culture medium per well. After 24 h of incubation, insulin with concentrations of 1×10^{-9} to 1×10^{-5} mol/L or phenolic extracts and standards diluted in fresh culture medium were added to the wells. After 20 h of incubation, 0.5 mg/mL MTT solution was added to each well. After incubated for 4 h, 200 μL of DMSO was added to each well and the absorbance was determined at 570 nm.

An insulin resistance model was built according to a previous method with modifications (Cao et al., 2023). HepG2 cells were inoculated in a 6-well plate with a density of 5×10^4 cells/mL in 2.0 mL of culture medium per well. After incubated for 24 h, the model group and control

group were cultured in an incomplete culture medium. After incubated for 24 h, insulin with concentrations of 1×10^{-9} to 1×10^{-5} mol/L diluted in culture medium were added. The final concentration of insulin was determined by measuring glucose consumption.

Once the insulin resistance model was established successfully, the model group was treated with rosiglitazone (5×10^{-6} mol/L), while the sample group was treated with post-digested peach juice or a 5 μmol/L standard. After 24 h of incubation, the supernatant was obtained, and the glucose content was determined by a glucose assay kit as the instructions provided by Jiangsu Jiancheng Bioengineering Institute in China.

2.9. Molecular docking

The three-dimensional crystal structures of AKT (PDB ID: 1H10), IRS1 (PDB ID: 1K3A), and PI3K (PDB ID: 4WWP) were obtained from the Protein Data Bank (https://www.pdb.org/). Ligands, unnecessary water molecules, and ions were removed from the structures. The structures of phenolic compounds were obtained from the PubChem molecular database (https://pubchem.ncbi.nlm.nih.gov/). Before docking, the protein structures with missing residues were hydrogenated and assigned Gaussian charges using AutoDock Tools (ADT, version 1.5.7). Docking boxes were created to enclose the entire protein, with the following dimensions: 1. Box 1: center_x = 23.411, center_y = 14.461, center_z = 9.895, x = 50, y = 50, z = 50. 2. Box 2: center_x = 18.055, center_y = 22.719, center_z = 43.445, x = 56, y = 52, z = 58. 3. Box 3: center_x = 35.225, center_y = 2.95, center_z = 28.708, x = 90, y = 78, z = 70. The AutoDock Vina software (version 1.1.2) was used for semi-flexible molecular docking. The exhaustiveness value was set to 100, and the docking model was set to 20. Then, the binding sites and intermolecular interactions between ligands and proteins were analyzed using PyMol and BIOVIA Discovery Studio 2016 Client.

2.10. Statistical analysis

The results are expressed as mean ($n = 3$) ± standard deviation. Data was statistically analyzed using one-way analysis of variance (ANOVA) in SPSS 2 (SPSS, IBM, Armonk, NY, USA), followed by Tukey's significant difference, with significance set at $p < 0.05$.

3. Results and discussion

3.1. Total phenolic and total flavonoid retention

As shown in Fig. 1a. the total phenolic content (TPC) of peach juice did not change significantly after HPH, regardless of the applied pressure. However, its value varied greatly during the digestion process. Fig. 1 showed that the total phenolic content (TPC) of peach juice showed no significant change after HPH, regardless of pressure applied, while its value varied greatly during in vitro digestion process. After gastric digestion, the TPC in non-treated and peach juice after HPH at 50 and 200 MPa showed no significant difference from that of the undigested sample, whereas when the pressure increased to 300 MPa, the value after gastric digestion was significantly increased to 129.69 %. It might be explained by that both the acidic environment generated during gastric digestion and the action of related enzymes leads to the hydrolysis of phenolics, thus increasing phenolic content (Elejalde et al., 2024). In addition, HPH improved the release of phenolics during gastric digestion. It was deduced that the shear force and cavity effect of HPH can disrupt the physical structure of the cell wall in peach juice, and the particle size became smaller, thus increasing the release of phenolics from peach juice during digestion (Marszałek et al., 2023). On the other hand, the strong mechanical effect of HPH might promote the conversion of difficult to extract IBP and EP to FP (Hossain et al., 2022).

After intestinal digestion, the TPC of non-treated peach juice was decreased to 82.29 %, indicating that degradation or transformation of the phenolics in peach juice occurred during intestinal digestion. This might be partly due to that phenolics and proteins or other macromolecules formed high molecular weight complexes through covalent or non-covalent bonds, which precipitated and were removed when centrifuged after intestinal digestion, resulting in lower retention rates (Rodríguez-Roque et al., 2013). Similarly, Quan et al. (2018) found that the TPC of apple juice and orange juice extracts increased by 47.23 % and 15.09 % after gastric digestion, respectively, and then decreased by 7.80 % and 25.30 % after intestinal digestion. It also has been reported that digestion significantly affected the conversion of hydroxycinnamic acid in *Viburnum opulus* fresh juice, where a decrease in chlorogenic acid content contributed to a remarkably increase in its isomer content (Pietrzyk et al., 2021). In addition, the polymerization and glycosylation patterns of phenolics may reduce their bioavailability (Chen et al., 2022). Importantly, the TPC of peach juices treated by HPH after

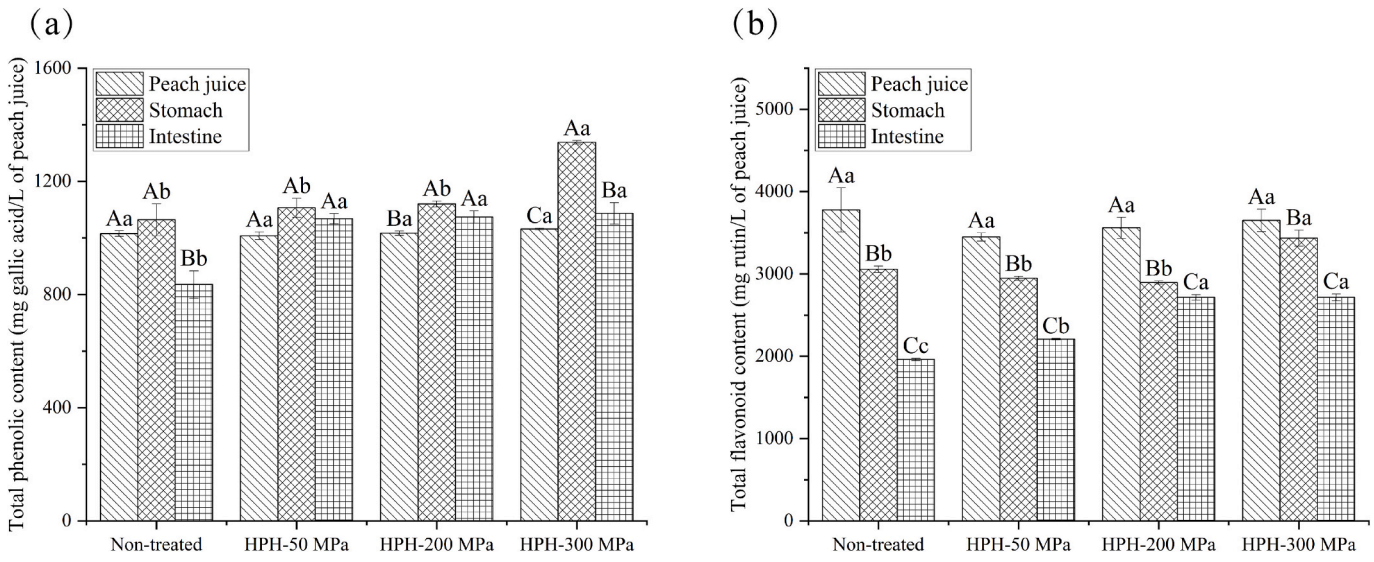

Fig. 1. Retention of total phenolics and total flavonoids in the gastrointestinal tract of peach juice after in vitro digestion simulation. All values are expressed as mean ± SD (n = 3). "a-c" represent significant differences between peach juices before and after HPH treatment. "A-C" represent significant differences between different digestion stages of peach juices with the same treatment ($p < 0.05$).

intestinal digestion was more stable than non-treated juice. Although the values were lower than after gastric digestion, they were still around 28 % higher than those of non-treated peach juices, regardless of the pressure applied. That was to say, HPH improved the stability of phenolics in the peach juice during the gastrointestinal tract.

As shown in Fig. 1b, HPH also showed no significant influence on the total flavonoid content (TFC) in peach juice, but showed a continuous decrease after gastrointestinal simulated digestion. The TFC in non-treated peach juice decreased by 19.12 % and 48.09 % after gastrointestinal digestion, respectively. HPH improved the stability of flavonoids in peach juice after both stomach and intestinal digestion. Especially, the TFC in peach juice after HPH at 300 MPa after stomach and intestinal digestion were 10.06 % and 19.97 % higher than those values after digestion in non-treated juice, respectively. Compared to other phenolics, it was indicated that flavonoids in peach juice were more unstable during simulated digestion. Similar study has shown that flavonoids in soft date kiwifruit continued to be degraded or transformed during simulated digestion, and the flavonoids in gastric digestion phase were more stable than intestinal digestion phase (Li et al., 2024). The reason might be that flavonoids are easily catabolically converted during digestion. For example, flavanones in orange juice were converted to chalcones during gastrointestinal digestion (Hou et al., 2019).

3.2. Identification and quantification of phenolic compounds

Table 1 showed that 19 phenolic compounds were detected in all samples, including 6 flavonoids, 9 phenolic acids, and 4 tannins. Among them, quinic acid, chlorogenic acid, procyanidin Bl, and (+)-catechin were the most predominant phenolics in non-treated peach juice, ranging from 5.57 (procyanidin Bl) - 70.21 (chlorogenic acid) mg/L, whereas only trace amounts of salicylic acid and (−)-epicatechin were detected (Tables S1-S3). The variation in the profiles of phenolics in non- and HPH-treated peach juice before and after simulated gastrointestinal digestion were investigated by means of clustered heat maps, as shown in Fig. 2. The trends of most phenolics in peach juice after HPH and during digestion were both consistent with those changes of TPC and TFC. Most phenolics in the sample were not changed significantly after HPH treatment, while the content of procyanidin B1 and (+)-catechin was elevated after HPH, especially their contents were increased by 42.85 % and 22.43 % after 300 MPa. It was suggested that HPH might be beneficial for the protection of anthocyanin analogues and the promotion of their release. On the contrary, the content of ferulic acid in peach juice decreased after all HPH treatments, indicating it was susceptible to HPH.

After gastric digestion, the content of most phenolic compounds increased, with quinic acid, procyanidin Bl, chlorogenic acid, and (+)-catechin remaining the most predominant phenolics in peach juice. Notably, the content of quinic acid isomer I in peach juice decreased significantly after gastric digestion, dropping from 19.24 to 20.85 mg/mL to 12.47–14.23 mg/mL, which might be attributed to the weak resistance to gastric digestion, making it susceptible to degradation by stomach acid and pepsin (Pinto et al., 2023). All phenolic compounds in the peach juice treated by HPH showed significant increases after gastric digestion compared to the non-treated sample. Notably, their contents rose with increasing pressure, showing an increase of 13.31 % - 30.90 % when after HPH at 300 MPa. Among them, chlorogenic acid, procyanidin Bl, and (+)-catechin showed the most significant increases, with rises of 24.05 %, 22.29 %, and 25.24 %, respectively. After intestinal digestion, most phenolic compounds in all peach juice were digested and broken down, resulting in significant decreases in their content compared to gastric digested samples. da Silva Haas et al. (2019) also found that gastric digestion of grape juice sediment resulted in an increase in most phenolic compounds, while intestinal digestion caused a significant resuction in nearly all phenolic compounds. However, the content of quinic acid isomer I increased significantly, possibly due to the elevated pH in the intestine. This increase might also attributed to the conversion of quinic acid isomer I from its bound form to a free form during digestion (Caicedo-Lopez et al., 2019). Notably, our previous study identified quinic acid isomer I as the most abundant bound phenolic in the bound phenolic fraction (Bie et al., 2024). A similar phenomenon was observed for cryptochlorogenic acid and phlorizin.

Most phenolic compounds in HPH treated juice were obviously higher than those in non-treated samples after intestinal digestion, with increases ranging from 3.90 % - 57.56 % at 300 MPa. Notably, procyanidin Bl, (+)-catechin and quercitrin exhibited the greatest increases, with rises of 47.61 %, 57.56 %, and 19.68 %, respectively. Previous study also showed that processing methods affected the phenolic profiles during food digestion. For example, compared to thermal processing (72 °C/1 min), high-pressure processing (HPP, 600 MPa/1 min) enhanced the retention of phenolic compounds in strawberry juice after gastric digestion, especially the content of anthocyanin was increased by 38 % - 47 % (Stübler et al., 2020). Our findings suggest that HPH contributes to the stability of phenolic compounds during the digestion process. Moreover, both HPH and simulated gastrointestinal digestion did not alter the overall phenolic composition of peach juice, but rather affected the content of individual phenolics.

3.3. Antioxidant activities

As shown in Table 2, peach juice showed effective scavenging of

Table 1
The phenolic compounds identified from peach juice before and after in vitro digestion simulation by UHPLC-ESI-HRMS/MS in negative mode.

Peak	t_R(min)	Compounds	Molecular Formula	$[M-H]^-$(m/z)	Error (ppm)	MS/MS Fragment ions
1	1.27	Quinic acid isomerI	$C_7H_{12}O_6$	191.0552	1.180	191.0554(100.00), 85.0281(97.84), 93.0332(35.96)
2	7.05	Chlorogenic acid	$C_{16}H_{18}O_9$	353.0877	2.836	191.0554(100.00), 135.0440(60.96), 179.0342(56.61)
3	8.15	Salicylic acid	$C_7H_6O_3$	137.0233	0.004	136.0156(39.24), 108.0205(28.55), 93.0333(5.77)
4	8.58	Procyanidin B1 isomerI	$C_{30}H_{26}O_{12}$	577.1353	2.075	289.0719(100.00), 407.0773(87.05), 125.0232(74.78)
5	8.93	Procyanidin B1 isomerII	$C_{30}H_{26}O_{12}$	577.1353	2.179	289.0719(100.00), 407.0774(88.59), 125.0232(84.05)
6	8.95	3-p-coumaroyl quinic acid	$C_{16}H_{18}O_8$	337.0931	3.726	163.0391(100.00), 119.0490(69.34), 191.0557(13.41)
7	9.45	(+)-Catechin	$C_{15}H_{14}O_6$	289.0717	3.547	109.0282(100.00), 123.0440(74.19), 125.0230(60.43)
8	9.49	Quinic acid isomerII	$C_7H_{12}O_6$	191.0553	1.494	191.0554(100.00), 85.0281(66.40), 93.0331(28.34)
9	9.50	Neochlorogenic acid	$C_{16}H_{18}O_9$	353.0877	2.751	191.0554(100.00), 192.0586(7.89), 85.0281(4.37)
10	9.77	Methyl chlorogenic acid	$C_{17}H_{20}O_9$	367.1034	2.810	193.0499(100.00), 134.0362(88.06), 173.0448(3.97)
11	9.84	Ferulic acid	$C_{10}H_{10}O_4$	193.0497	0.905	134.0362(100.00), 61.9870(98.45)
12	9.93	Quercitrin	$C_{21}H_{20}O_{11}$	447.0949	4.098	284.0330(100.00), 285.0404(74.33)
13	10.46	Procyanidin B1 isomerIII	$C_{30}H_{26}O_{12}$	577.1355	2.508	289.0719(100.00), 407.0774(94.33), 125.0232(90.99)
14	10.77	Cryptochlorogenic acid	$C_{16}H_{18}O_9$	353.0880	3.601	191.0555(100.00), 192.0589(7.74), 85.0281(6.17)
15	11.02	(−)-Epicatechin	$C_{15}H_{14}O_6$	289.0719	4.170	109.0282(100.00), 123.0440(85.18), 125.0233(62.03)
16	11.89	Procyanidin B1 isomerIV	$C_{30}H_{26}O_{12}$	577.1355	2.508	289.0719(100.00), 125.0232(93.37), 407.0775(57.78)
17	12.89	Rutin	$C_{27}H_{30}O_{16}$	609.1460	1.623	609.1462(100), 300.0277(55.15), 301.0349(49.39)
18	13.34	Hyperoside	$C_{21}H_{20}O_{12}$	463.0886	2.953	300.0276(100.00), 301.0343(54.09), 271.0246(12.38)
19	15.64	Phlorizin	$C_{21}H_{24}O_{10}$	435.1304	4.267	273.0774(100.00), 167.0341(68.36), 125.0232(9.32)

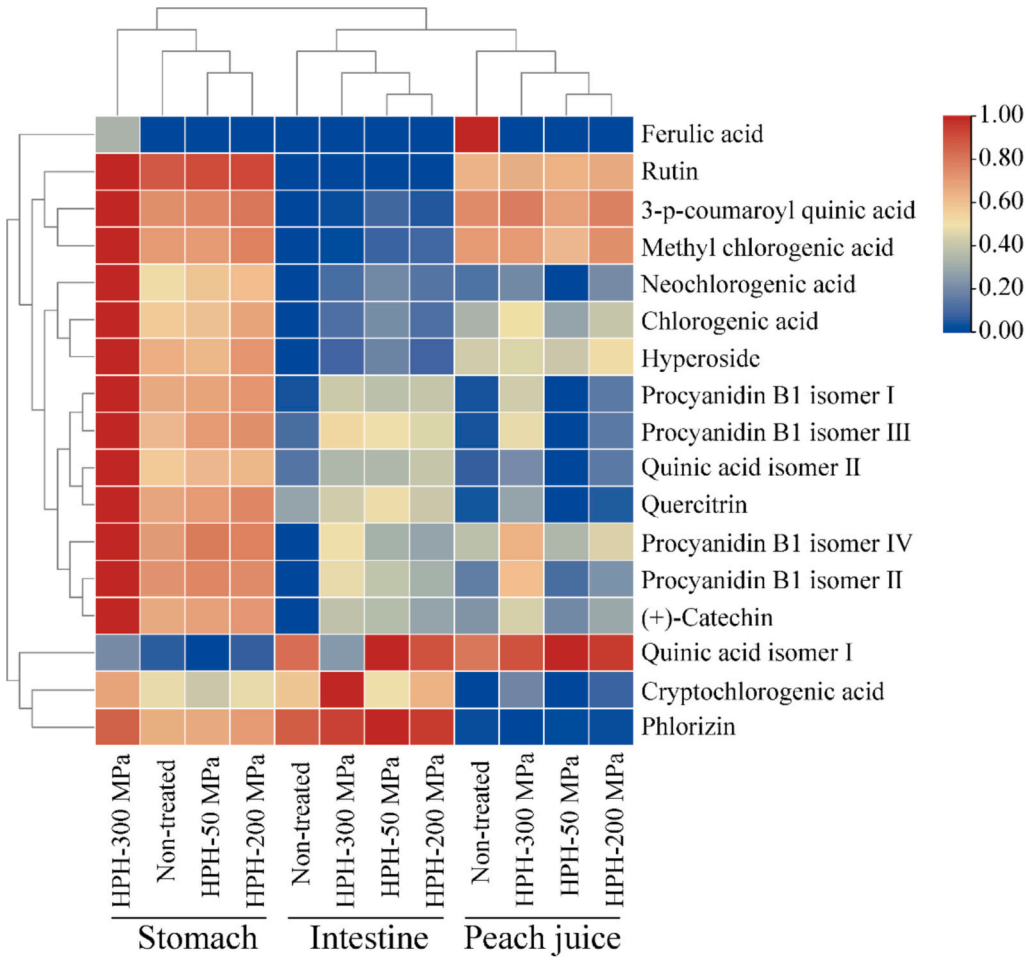

Fig. 2. Thermogram analysis of phenolic compounds before and after in vitro simulated digestion of peach juice before and after HPH treatment, respectively.

Table 2
IC50 values (μg/mL) of DPPH, ABTS free radical scavenging capacity and inhibition of α-glucosidase in HPH-treated peach juice after simulated digestion in vitro.

Parameter	Digestive stage	Non-treated	HPH-50 MPa	HPH-200 MPa	HPH-300 MPa
DPPH	Control	27.04 ± 2.25^{Ba}	25.44 ± 0.26^{Ba}	27.10 ± 1.36^{Ba}	25.20 ± 0.08^{Ba}
	Stomach	27.31 ± 0.32^{Ba}	29.20 ± 0.50^{Aa}	28.06 ± 0.25^{Ba}	22.47 ± 0.31^{Cb}
	Intestine	33.35 ± 0.45^{Aa}	29.68 ± 0.26^{Ab}	30.49 ± 0.50^{Ab}	26.67 ± 0.54^{Ac}
ABTS	Control	30.75 ± 0.18^{Ba}	31.77 ± 0.37^{Aa}	31.20 ± 0.42^{Aa}	31.09 ± 0.09^{Aa}
	Stomach	25.99 ± 0.60^{Ca}	27.78 ± 0.63^{Ba}	26.57 ± 0.86^{Ba}	23.14 ± 0.15^{Cb}
	Intestine	38.00 ± 0.21^{Aa}	32.44 ± 1.02^{Ab}	32.78 ± 0.15^{Ab}	27.86 ± 0.02^{Bc}
α-Glucosidase	Control	29.95 ± 0.76^{Ba}	30.49 ± 0.26^{Aa}	31.36 ± 0.26^{Aa}	30.43 ± 2.55^{Aa}
	Stomach	25.79 ± 0.24^{Ca}	27.09 ± 0.24^{Ba}	28.52 ± 0.50^{Ba}	21.79 ± 0.16^{Bb}
	Intestine	40.66 ± 0.51^{Aa}	31.96 ± 0.10^{Ab}	27.47 ± 2.00^{Bc}	27.25 ± 2.99^{Ac}

All the values are presented as mean ± SD (n = 3). "A-C" represent the significant differences between the different stages of digestion of the same treatment 'Lijiang snow' peach juice, "a-d" represent the significant differences between the same stages of digestion from the non-treated and high pressure homogenization treated 'Lijiang snow' peach juice, respectively ($p < 0.05$).

DPPH and ABTS, exhibiting a dose-dependent relationship. Similarly, the DPPH and ABTS radical scavenging capacities of phenolics in peach juice showed no significant change after HPH, regardless of the pressure applied. Overall, the radical scavenging capacity of peach juice decreased during simulated gastrointestinal digestion, as indicated by an increase in the IC_{50} value. This reduction is likely due to the significant decrease in phenolic content in gastrointestinal digestion, which leads to lower absorption of phenolic compounds by the body, thus decreasing their bioavailability (Altuntas & Korukluoglu, 2024). Similar results were observed in many foods, such as blueberries, coffee, and pomegranate, where free radical scavenging capacity decreases after gastrointestinal digestion, consistent with the reduction in phenolic content (Correa-Betanzo et al., 2014; Mall & Patel, 2023; Yu et al., 2025). Additionally, the bioactivity of phenolics is generally higher in acidic environments than in alkaline conditions. This is because, under alkaline conditions, the hydroxyl groups of phenolics are more likely to undergo protonation, resulting in structural alterations (Spínola et al., 2018).

HPH with higher pressure significantly increased the free radical scavenging capacity of peach juice after gastrointestinal digestion. After gastric digestion, the IC_{50} values for DPPH radical scavenging in peach juice treated by HPH at 50 and 200 MPa showed no significant difference compared to the non-treated group. However, after intestinal digestion, the IC_{50} values were reduced by 11 % and 8.57 % in peach juice treated at 50 and 200 MPa, respectively. In contrast, peach juice treated at 300 MPa showed a 17.72 % reduction in the IC_{50} value for DPPH scavenging after gastric digestion compared to the non-treated group, and a 20.03 % reduction after intestinal digestion. A similar

trend was observed for ABTS radicals scavenging. After gastric digestion, the IC_{50} values for ABTS radical scavenging in peach juice treated by HPH at 50 and 200 MPa were not significantly different from the non-treated group. However, after intestinal digestion, the IC_{50} values decreased by 14.63 % and 13.74 % for peach juice treated at 50 and 200 MPa, respectively. Notably, for peach juice treated at 300 MPa, the IC_{50} value for ABTS scavenging decreased by 10.97 % after gastric digestion and by 26.68 % after intestinal digestion compared to the non-treated group. The changes in IC_{50} values for scavenging of DPPH and ABTS in peach juice treated with HPH were basically consistent with the trend observed in TPC and TFC, suggesting that higher pressure HPH enhanced phenolics retention and their bioactivities, especially the higher pressure of HPH might have better effects. Similar study have shown that HPP significantly increased the antioxidant activity of phenolics in apple juice after gastrointestinal digestion, with ABTS, DPPH, and FRAP scavenging capacities of HPP-treated juice increased by 24 %, 14 %, and 28 %, respectively, compared to non-treated juice (Fernández-Jalao et al., 2020). Similarly, the tamarillo after HPH treatment at 75 MPa showed a 10 % - 20 % increase in DPPH and ABTS radical scavenging capacity after in vitro simulated digestion compared to the non-treated sample (Rohilla & Mahanta, 2024). Overall, the ability of HPH to improve the antioxidant activity of food phenolics is largely caused by its capacity to modify the physical state and chemical properties of phenolic compounds in food, facilitating their release and stability and thereby enhancing their antioxidant activity (Liu et al., 2024).

3.4. Inhibition of α-glucosidase

As shown in Table 2, peach juice, both before and after HPH, demonstrated strong α-glucosidase inhibition following intestinal digestion, with IC_{50} values ranged from 21.79 to 40.66 μg/mL. The inhibitory mechanism of phenolics on α-glucosidase involves the hydroxyl group in phenolics forming intermolecular hydrogen bonds with the enzyme's amino acid residues, thereby targeting its active site and reducing enzyme activity (Gong et al., 2020). Prior to digestion, there was no significant difference in α-glucosidase inhibitory ability between HPH-treated and non-treated peach juice. However, gastric digested samples exhibited the strongest α-glucosidase inhibitory capacity compared to undigested and intestinally digested samples. Notably,

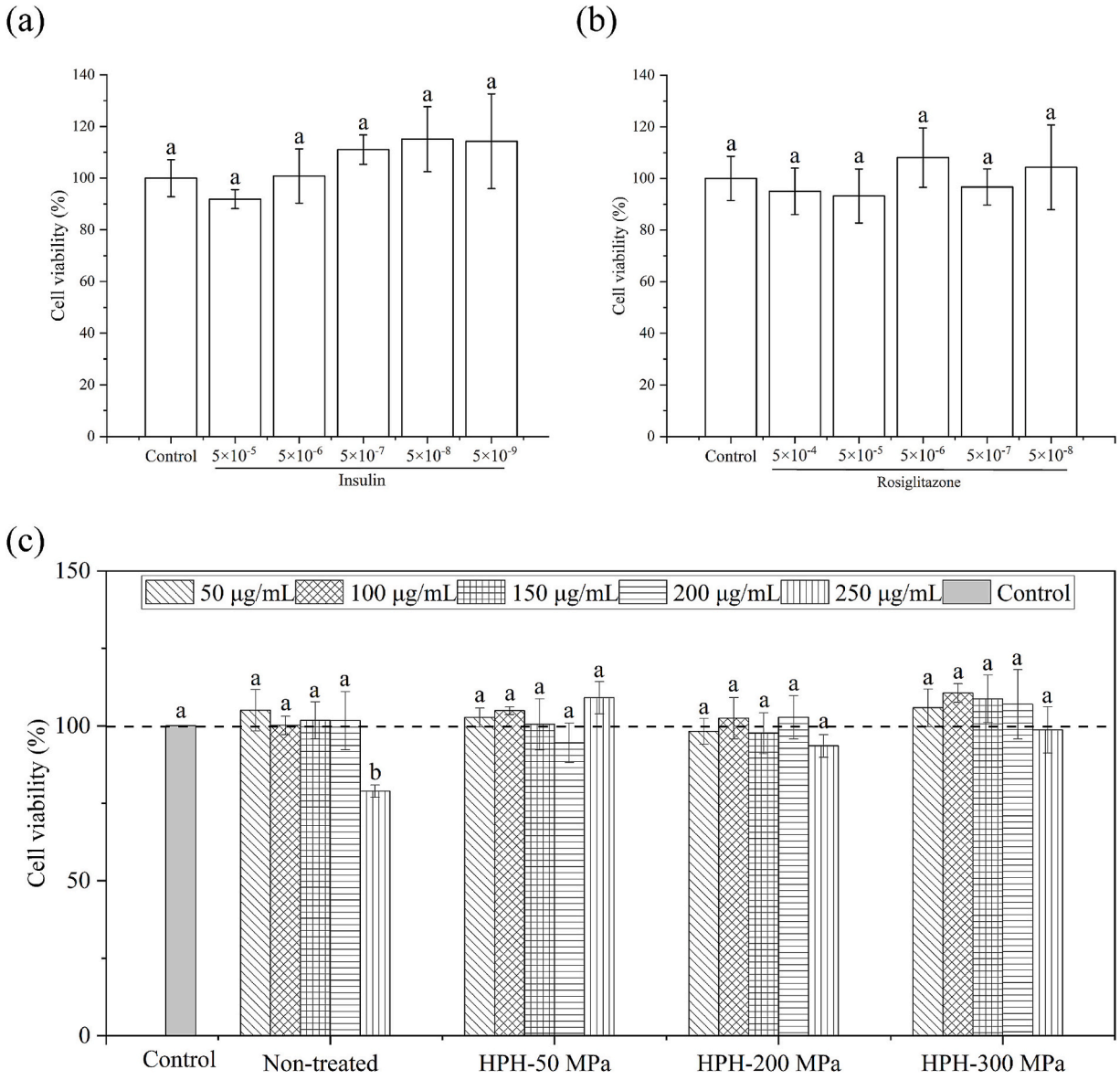

Fig. 3. Effect of different concentrations of insulin, rosiglitazone and phenolic extracts of peach juice on cell viability. All values are expressed as mean ± SD ($n = 3$). "a-d" represent significant differences between samples of different concentrations and controls, respectively ($p < 0.05$).

peach juice after HPH at 300 MPa had the lowest IC_{50} value of 21.79 after gastric digestion, 15.51 % lower than the non-treated sample. This enhanced inhibition can be attributed to the phenolic content and composition, as higher phenolic contents typically correlate with stronger α-glucosidase inhibition. Key compounds in peach juice, including chlorogenic acid, quinic acid, procyanidin Bl, and (+)-catechin, have been shown to exhibit significant α-glucosidase inhibitory effects (Xu et al., 2024).

After intestinal digestion, the IC_{50} of α-glucosidase inhibition for the non-treated peach juice was 40.66 μg/mL, which decreased to 31.96, 27.47 and 27.25 μg/mL when HPH at 50 MPa, 200 MPa and 300 MPa applied, respectively, 21.40 %, 32.44 % and 32.98 % lower than that value of non-treated juice, respectively. HPH improved the α-glucosidase inhibitory capacity of peach juice after digestion. Similarly, Alongi et al. (2019) applied HPH to coffee beverages at pressures ranging from 0 MPa to 150 MPa and found that samples treated at higher pressures, specifically 100 MPa and 150 MPa, exhibited improved α-glucosidase inhibition after intestinal digestion. In addition, a decrease in α-glucosidase inhibition after intestinal digestion was also observed for raspberry fruits, with IC_{50} values decreased from 1.39 mg/mL to 1.87 mg/mL (Qin et al., 2018).

3.5. Analysis of insulin resistance

Cytotoxicity of insulin and rosiglitazone was assayed using the MTT assay, with samples tested at various concentrations of insulin and rosiglitazone. As shown in Fig. 3a and Fig. 3b, insulin concentrations ranging from 5×10^{-9} - 5×10^{-5} mol/L and rosiglitazone concentrations from 5×10^{-4} - 5×10^{-8} mol/L were not cytotoxic to cells. As shown in Fig. 3c, cell viability for cells treated with phenolic extract of peach juice at concentrations up to 250 μg/mL remained above 90 %, indicating no toxicity to the cells. As shown in Fig. 4a, glucose consumption in cells treated with high concentrations of insulin was significantly reduced from 3.87 to 8.66 mmol/L. However, both rosiglitazone and phenolic extracts significantly reduced insulin resistance and maintained normal cellular glucose consumption. In the rosiglitazone-treated group, glucose consumption was recovered to 7.85 mmol/L. The phenolic extract from non-treated peach juice after intestinal digestion improved the glucose consumption in cells from 3.87 to 6.12 mmol/L, with further increases to 7.17, 7.96, and 7.72 mmol/L for peach juice after HPH treatment at 50 MPa, 200 MPa, and 300 MPa, respectively. These results suggest that phenolics are effective in alleviating insulin resistance and increasing cellular glucose consumption, and the potential of phenolics to mitigate insulin resistance has been studied in numerous studies. For example, phenolics in black quinoa and coffee by-products have also been shown to alleviate insulin resistance in different cell types (Cao et al., 2023; Rebollo-Hernanz et al., 2019). Rodríguez-González et al. (2018) found that phenolic-rich peach juice by-products reduced blood glucose and insulin levels in mice by 17 % and 25 %, respectively, compared to dietary fiber-rich peach juice by-products. A clinical study also demonstrated that consuming 600 mg of apple phenolic extract daily for 12 weeks significantly improved subjects' sugar intolerance and alleviated insulin resistance, with postprandial blood glucose levels significantly lower in the apple phenolic group (164.0 ± 7.4 mg/dL) compared to the control group (194.7 ± 10.4 mg/dL) (Shoji et al., 2017). In addition, the improvement in insulin resistance observed with HPH was closely associated with the increased retention of total phenols in peach juice after digestion by HPH.

To identify the key phenolic compounds in peach juice that significantly alleviate insulin resistance, seven phenolic compounds, including (+)-catechins, phlorizin, procyanidin B1, quercetin, hyperoside, chlorogenic acid, and neochlorogenic acid were chosen for further investigation. Fig. 4b showed that rosiglitazone and most of these phenolics demonstrated comparable effects in reducing insulin resistance compared to the model group, except for neochlorogenic acid. Among the compounds, glucose consumption in the rosiglitazone-treated group

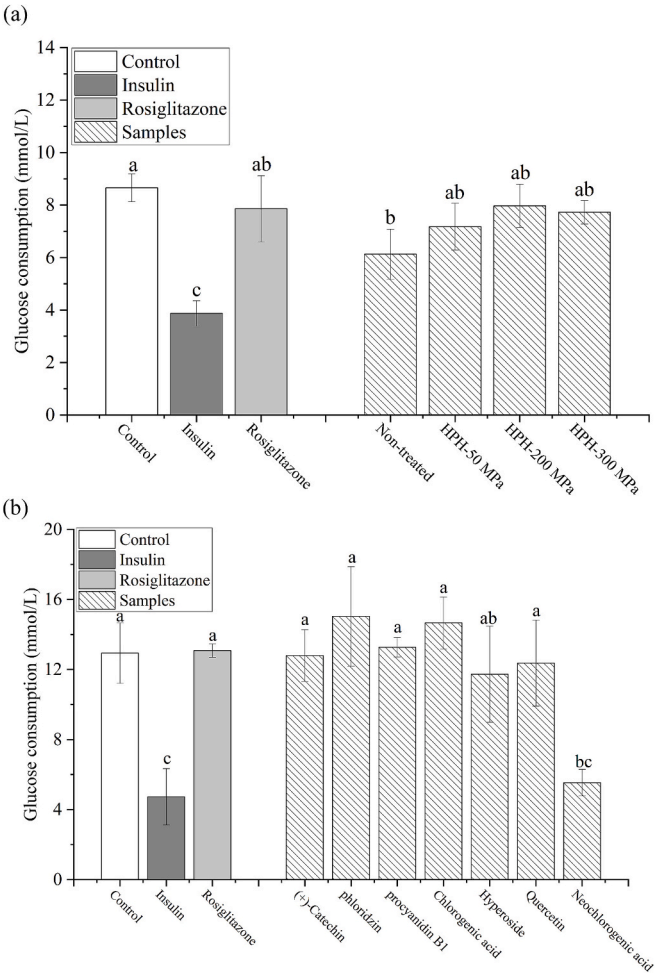

Fig. 4. Effect of intestinally digested phenolic extracts (a) of peach juice treated by HPH at different pressures and seven phenolic compounds (b) on glucose consumption in a model of insulin resistance. All values are expressed as mean ± SD (n = 3). "a-c" represent significant differences between samples ($p < 0.05$).

was restored to 13.07 mmol/L, while the phenolics restored glucose consumption to levels ranging from 5.53 (neochlorogenic acid) - 15.03 (phlorizin) mmol/L. Notably, phlorizin and quercetin were the most effective in alleviating insulin resistance, nearly three times higher than that of neochlorogenic acid. Huang et al. (2015) reported that common phenolics such as quercetin, kaempferol, and lignans could enhance glucose uptake in insulin resistance in HepG2 cells. Xia et al. (2021) reported that eleven phenolic compounds, including (+)-catechins, vanillic acid, and p-hydroxybenzoic acid, in Zhenjiang balsamic vinegar ameliorated high glucose-induced cellular insulin resistance by inhibiting IRS-1 expression and activating PI3K/AKT in HepG2 cells. Furthermore, procyanidins from grape seeds have demonstrated efficacy in alleviating insulin resistance, and results showed that HepG2 cells treated with 6.25 μg/mL procyanidins exhibited a 52 % increase in glucose consumption compared to the insulin resistance model group (Zhang et al., 2009). These results suggest that phenolic compounds have the potential to alleviate insulin resistance and enhance cellular glucose consumption, as demonstrated in cell models. However, the absence of direct evidence regarding protein levels changes necessitates further validation to strengthen the interpretation of these findings.

3.6. Molecular docking

The docking scores of the seven phenolic compounds with the three

pathway proteins AKT, IRS1, and PI3K are presented in Table S4. Among the compounds, neochlorogenic acid and (−)-catechin have lower docking scores compared to the others. As detailed in Table 3, all seven phenolic compounds interacted with the active amino acid residues of AKT, IRS1, and PI3K through hydrogen bonding (Hbs) and van der Waals (Vdws) forces. Notably, procyanidin B1 formed the most number of seven Hbs with six amino acid residues (GLU9, TRP99, LYS8, GLU95, TRP11, and HIS13) of AKT and formed five Vdws. Similarly, hyperoside formed seven Hbs with five amino acid residues (ARG23, ARG86, ASN53, ILE19, and TYR18) of AKT, along with five Vdws. In contrast, phlorizin showed the weakest binding to AKT, forming only one Hb with GLN47.

The binding effects varied significantly across the phenolic compounds and proteins. In the docking analysis with IRS1, chlorogenic acid exhibited the strongest binding affinity, forming seven Hbs with six amino acid residues (HIS1030, GLN1084, GLU1241, GLU1088, PHE1117, LYS1081), and ten Vdws. Meanwhile, procyanindin B1 formed only three Hbs with three amino acid residues (GLY1122, ASN1110, ASP1056). Although phlorizin also formed three Hbs with IRS1, it demonstrated the highest number of Vdws (fourteen) in this interaction. Regarding PI3K binding, phlorizin showed strong binding affinity by forming nine Hbs with five amino acid residues (ARG690, ASP788, TYR787, ARG849, and CYS869). Conversely, procyanidin B1, which exhibited strong binding with AKT, formed only four Hbs with ARG849 and HIS658 of PI3K. In general, a greater number of Hbs and Vdws indicates stronger binding between the phenolic compound and the protein, which is often associated with improved insulin resistance alleviation (Majewski et al., 2019). In this study, phlorizin showed the best effect in alleviating insulin resistance, probably due to its stronger binding interactions with IRS1 and PI3K compared to AKT. However, quercetin did not form the highest number of Hbs or Vdws with the three proteins but emerged as one of the most effective compounds for alleviating insulin resistance.

To further investigate, three phenolic compounds with varying effects on insulin resistance were selected, including quercetin (good efficacy), hyperoside (moderate efficacy), and neochlorogenic acid (poor efficacy), as shown in Fig. 5. The average Hb bond lengths for interaction with AKT were 2.30 Å (quercetin) < 2.39 Å (hyperoside) < 2.45 Å (neochlorogenic acid). Similarly, the average Hb bond lengths for interactions with PI3K were 2.53 Å < 2.67 Å < 2.73 Å, respectively. Shorter bond lengths indicate tighter binding (Scheiner, 2020). Additionally, previous studies revealed that rutin binds to GLU880, ASN299, LEU864, and LYS298 in PIK3. But, LYS298 and GLU880 formed Hb with quercetin and neochlorogenic acid in this study, respectively, indicating that LYS298 might serve as a key amino acid residue in PIK3 (Cao et al., 2023).

Interestingly, the average bond lengths of Hb formed between IRS1 and quercetin, hyperoside, and neochlorogenic acid were 2.58 Å > 2.36 Å > 2.3 Å, respectively, which was contrary to results observed with AKT and PIK3. Notably, both quercetin and hyperoside were found to bind to GLN997 and MET1052, indicating that these amino acid residues might play a key role in the interaction with IRS1. However, no single phenolic compound exhibited superior binding to all pathway proteins tested, indicating a coordinated effect of multiple phenolic compounds may be more effective in mitigating insulin resistance. Liu et al. (2018) found that galangin and pinocembrin might synergistically alleviate insulin resistance through the Akt/mTOR signaling pathway. Thus, the phenolic compounds in peach juice can interact with the insulin receptor, inducing conformational changes and enhancing insulin receptor sensitivity, thereby alleviating insulin resistance. However, further experiments are required to confirm the underlying mechanism of phenolics in alleviating insulin resistance at the protein level through techniques such as Western blotting.

4. Conclusion

HPH significantly enhanced the retention of phenolic compounds during digestion. After gastrointestinal digestion, the TPC and TFC of peach juice treated by HPH at 300 MPa increased by 28 % and 19.97 %, respectively, compared to the non-treated samples. Nineteen phenolic compounds were identified in peach juice, with quinic acid, chlorogenic acid, procyanidin Bl, and (+)-catechin as the primary phenolics. Most of these phenolic compounds increased after gastric digestion but decreased after intestinal digestion. HPH disrupted the physical structure of peach juice cell walls through mechanical shear and cavitation effects, resulting in smaller particle sizes and enhanced release of phenolic compounds during digestion. After gastrointestinal digestion, the levels of procyanidin Bl, (+)-catechin and quercitrin in peach juice treated by HPH at 300 MPa increased by 47.61 %, 57.56 %, and 19.68 %, respectively, compared to non-treated samples. Phenolic compounds are key contributors to biofunctional activity. The increased retention of phenolics after digestion was closely associated with significant

Table 3
Docking results of seven phenolic compounds with three pathway proteins AKT, IRS1 and PI3K.

	Compounds	Pubchem ID	AKT(1H10)		IRS1(1K3A)		PI3K(4WWP)	
			Amino Acid Residues Forming Hydrogen Bonds	Van der Waals Force	Amino Acid Residues Forming Hydrogen Bonds	Van der Waals Force	Amino Acid Residues Forming Hydrogen Bonds	Van der Waals Force
1	Phlorizin	6072	GLN47 (1)	5	GLY1122, MET1052, GLY1055 (3)	14	ARG690, ASP788, TYR787, ARG849, CYS869 (9)	13
2	(+)- Catechin	9064	LEU52, ARG41, ALA50 (3)	6	GLU1088, TYR1060, GLU1241 (3)	6	ASP654 (1)	7
3	Chlorogenic acid	1,794,427	GLU40, ALA50, GLN47 (3)	6	HIS1030, GLN1084, GLU1241, GLU1088, PHE1117, LYS1081 (7)	10	ARG690, ARG849, GLU880 (3)	14
4	Quercitrin	5,280,459	GLU17, ARG23, ASN53, ARG86 (5)	3	GLN977, SER979, MET1052 (4)	6	PRO866, ARG277, LYS298 (3)	11
5	Neochlorogenic acid	5,280,633	HIS89, TRP11, LYS8, GLU95 (4)	5	THR1118, GLN1084, PHE1117, LYS1081 (5)	10	CYS869, ARG277, ARG690, ARG849, GLU880 (7)	12
6	Hyperoside	5,281,643	ARG23, ARG86, ASN53, ILE19, TYR18 (7)	5	LYS1003,ARG1109, MET1052, GLN977 (4)	12	GLN846, ARG690, ARG849, GLN291, HIS658 (7)	11
7	Procyanidin B1	11,250,133	GLU9, TRP99, LYS8, GLU95, TRP11, HIS13 (7)	5	GLY1122, ASN1110, ASP1056 (3)	10	ARG849, HIS658 (4)	16

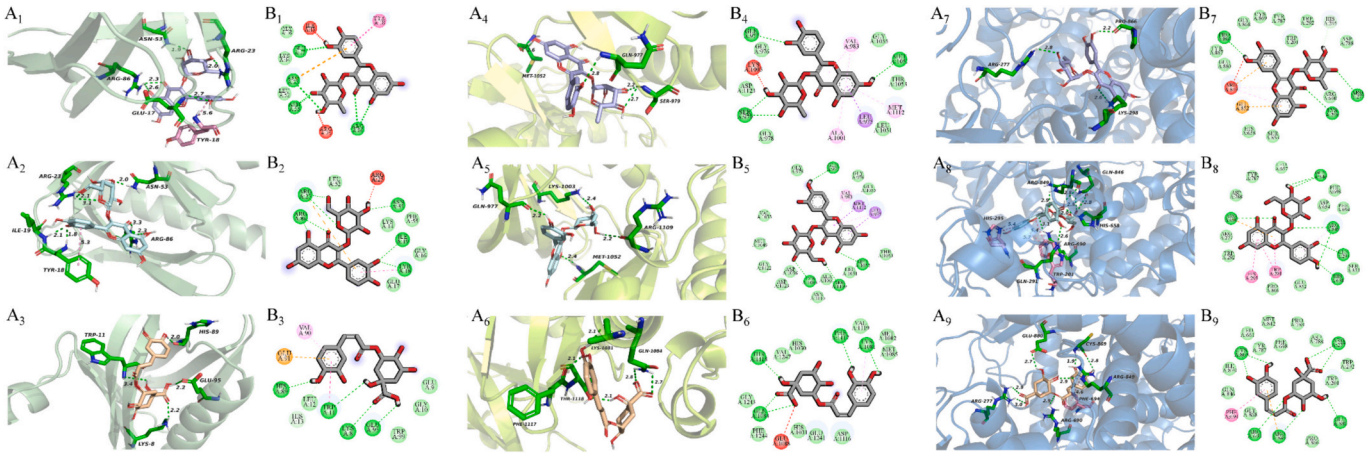

Fig. 5. Docking results of quercetin, hyperoside, and neochlorogenic acid with three pathway proteins, AKT (A_1-A_3, B_1-B_3), IRS1 (A_4-A_6, B_4-B_6), and PI3K (A_7-A_9, B_7-B_9). A_1-A_9 is the three-dimensional conformation of the hydrogen bonds with hydrophobic interactions. B_1-B_9 is the two-dimensional conformation of the hydrogen bond.

improvements in antioxidant activity and α-glucosidase inhibition in HPH-treated peach juice. For samples treated with HPH at 300 MPa after gastrointestinal digestion, the IC_{50} values for scavenging DPPH and ABTS free radicals decreased by 20.03 % and 26.68 %, respectively, and the IC_{50} value for inhibiting α-glucosidase activity decreased by 32.98 % compared with non-treated samples. Additionally, HPH treated peach juice reduced insulin resistance in HepG2 cells, increasing glucose consumption by 17.15 %, 30.00 %, and 26.14 % after 50, 200, and 300 MPa, respectively. Combining the in vitro results of individual phenolics on insulin resistance and the docking analysis, found that hydrogen bonding and van der Waals forces were the primary interactions between pathway proteins and phenolic compounds. Phlorizin and quercetin emerged as key compounds in peach juice for reducing insulin resistance. Although our study demonstrated that HPH is an effective technique for enhancing the bioaccessibility of phenolics, it is limited by the lack of direct evidence regarding protein-level changes, which may influence the interpretation of the results. Further study is needed to clarify the underlying mechanisms by which phenolics affect protein expression and modification. Specific bioregulatory pathways should be further validated though techniques such as Western blotting, combined with proteomic analyses and functional assays, to provide more comprehensive insights and reinforce the findings. In the future, integrating HPH with other food processing technologies could not only showcase its potential in enhancing the nutritional value of functional beverages but also expand its applications in developing health-focused food products. This approach holds particular promise for addressing metabolic disorders, such as insulin resistance, demonstrating HPH's potential as a valuable tool in the advancement of health-oriented food innovations.

CRediT authorship contribution statement

Yijin Peng: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Shenke Bie:** Methodology, Data curation. **Shengbao Cai:** Resources, Funding acquisition. **Linyan Zhou:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Chaofan Guo:** Writing – review & editing, Resources, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fochx.2025.102263.

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