Food and Chemical Toxicology 127 (2019) 182–187

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Chlorogenic acid and caffeic acid from *Sonchus oleraceus* Linn synergistically attenuate insulin resistance and modulate glucose uptake in HepG2 cells

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ARTICLE INFO

Keywords:
Sonchus oleraceus Linn
Chlorogenic acid
Caffeic acid
Insulin resistance
Glucose metabolism
Short title: phenolic acids synergistically effect on insulin-resistance

ABSTRACT

The crude extract of *Sonchus oleraceus* Linn (CE) and its main phenolic acids (PA), chlorogenic acid and caffeic acid have anti-diabetic activity, but the mechanisms for their effects on glucose intake remain largely unknown. Aim of this study was to examine the synergistic effect of chlorogenic and caffeic acid from *S. oleraceus* Linn attenuate insulin resistance and modulate glucose uptake in HepG2 cells. Major phenolic acids in SOL were isolated and identified by HPLC. Insulin-resistance HepG2 cell model was used to elucidate the effect of CE on glucose metabolism. Pre-treatment of HepG2 cells with CE or PA enhanced levels of glucose production and avoided the decrease total levels of IRS-1 triggered by high insulin concentration. CE or PA pre-treatment also could prevent the inactivation of the PI3K/AKT pathway, as well as the diminution of GLUT4 levels induced by high glucose. These findings suggested that CE and its main phenolic acids improved insulin sensitivity of HepG2 cells treated with insulin, preventing or delaying a potential hepatic dysfunction through the attenuation of the insulin signaling blockade and the modulation of glucose consumption.

1. Introduction

Type 2 diabetes mellitus (T2DM) is known as a sort of metabolic disturbance, which is characterized by a chronic hyperglycemic condition either caused by an insulin deficiency of impaired insulin signaling and non-autoimmune etiology, or due to a decreased insulin sensitivity present primarily in the adipose tissues, liver, and skeletal muscles (Teng et al., 2018). A widely held notion is that T2DM is a heterogeneous and polygenic disorder resulting from genetic susceptibility, characterized by impaired insulin signaling, also known as insulin resistance, as well as a relative insulin deficiency of non-autoimmune etiology, and environmental factors such as obesity, over eating, lack of exercise, and stress as well as aging (Chen et al., 2018). The major contributor to the pathogenesis of T2DM is insulin resistance. Clinically, the terminology of insulin resistance is a condition in which insulin in the body does not exert sufficient action proportional to its blood concentration to conserve a normo-glycemia. On cell level, it is defined as deficient insulin signaling strength from downstream receptor to the final substrates in multiple and mitogenic aspects of cellular functions (Simons et al., 2016). In insulin resistant plight, the impairment of insulin action in major target organs such as liver and muscles does not properly respond to insulin and by that inducing hyper-glycaemia and a reactive escalation of insulin excretion by β cells of pancreas (Bakar et al., 2015). At those conditions, the poor insulin responsiveness can only be reimbursed for limited time only, which only further impairs insulin resistance (Baena et al., 2016). This depraved cycle finally points to brawl of fragile balance between insulin resistance and β cell functions, which leads to manifestation of T2DM.

During the last decades, our research team has focused on the investigation of underutilized functional foods, with the hope to find an efficient way to improve their comprehensive utilization (Chen et al., 2018a,b; Chen et al., 2016; Teng et al., 2017; Zhao et al., 2018a and 2018b). *Sonchus oleraceus* Linn. (SOL) is widely consumed as a delicious daily diet, and in the South of China, especially in Fujian province, it is a low price and popular dish for rural people (Cui et al., 2004; Xia et al., 2011). Some studies have reported that extracts of SOL are beneficial for human physiology with antioxidant activity (Yin et al., 2007), antibacteria activity (Xia et al., 2011), anxiolytic activity (Vilela et al., 2010), and anti-inflammatory activity (Vilela et al., 2010). Phytochemicals isolated from the SOL included chlorogenic acid, celeryin, kaempferol, acacetin, isorhamnetin, apigenin-7-O-β-D- glucuronatemethyl, apigenin-7-O-β-D glucuronide, and luteolin- 7-O- β-D-

Abbreviations: SOL, *Sonchus oleraceus* Linn; PA, phenolic acids; NPA, none-phenolic acids fraction; T2DM, Type 2 diabetes mellitus; ERK, extracellular signal-regulated kinase; GLUT-4, Glucose transporter type 4

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https://doi.org/10.1016/j.fct.2019.03.038
Received 2 February 2019; Received in revised form 15 March 2019; Accepted 20 March 2019
Available online 23 March 2019

glucoside and etc. (Yin et al., 2007). Crude extract of *S.* Linn (CE) (Ahmed et al., 2011) and its main phenolic acids have anti-diabetic effects (Oboh et al., 2015), however, studies are still essential to identify the chemical structure to fully understand and realize its potential in the future. Based on the traditional claims surrounding SOL, this context was aimed at evaluating the positive effects for the traditional use of SOL with insulin resistance-HepG2 cells.

2. Materials and methods

2.1. Materials

SOL used as raw material was a local variety "Kucai" obtained from the regions of Ningde, Fuzhou, China. Samples were collected after taking the part of above ground, pressing the mash; freeze dried and sealed in polyethylene bags, then kept at 4 °C until further use. Plant species authentication was performed by Prof. Dr. Gongxi Chen, the executive director of Chinese National Medical Association-Jishou University-where a voucher specimen is deposited under NP-002.

2.2. Extraction

Extraction of SOL was performed according to previous study (Chen and Kang, 2014). Briefly, leaves were thawed and cut into small pieces with a laboratory blade cutter to 100 mesh. One gram of dried leaves powder (1 g) was weighted into Erlenmeyer flasks and extracted with 20 mL 95% ethanol at room temperature for 24 h under shaking, using a KS 500 laboratory shaker. Extracts were filtered through a 0.2 μm membrane syringe filter (ADVANTEC Ltd, Toyo, Japan), the residue was re-extracted with 20 mL of the solvent for 30 min to ensure an exhaustive extraction. Supernatants were combined, and the organic solvent was removed by evaporation in vacuum at 40 °C.

2.3. Isolation

The AcOEt soluble fraction was chromatographed over a SiO_2 column (6 × 60 cm, 63–200 μm particle size, Merck) and eluted with AcOEt-MeOH (50:1 → 1:1, each 1.0 L) yielded three fractions (F1-F3). Fraction F3 was subjected to a SiO_2 column (4 × 50 cm, 40–63 μm particle size Merck), eluted with $CHCl_3$-MeOH (30:1 → 1:1, each 0.5 L) to afford sub-fractions of PA and NPA. They were isolated and structurally elucidated from the whole plant of SOL and determined by HPLC analyses. Stock solutions of tested compounds in DMSO were prepared, kept at −70 °C, and diluted to the desired final concentrations.

2.4. HPLC analysis

The major component of SOL were profiled and identified as previously reported methods (Chen and Kang, 2014) by high performance liquid chromatography (HPLC, Shimadzu, AQUITY, MA, USA) along with ODS HYPERSIL column and a photodiode array (PDA) detector (Waters Corporation) at 335 nm. The column temperature was maintained at 35 °C, and the mobile phase consisted of 2% (v/v) acetic acid in water (eluent A) and 0.5% acetic acid in water and acetonitrile (50:50, v/v, eluent B) using the following gradient program: 0–5% B (35 min), 5–20% B (45 min), 20–100% B (30 min), 100% B isocratic (3 min), 100-0% B (10 min) at a flow rate of 0.8 mL/min. The injection volume varied between 10 μL. The peak of major component was profiled by comparing the retention times between the standard peaks and our published study (Chen et al., 2017). All measurement was carried out in triplicate.

2.5. Cell viability

The HepG2 cells (1×10^4 cells per well) were seeded in a 96-well flat-bottomed culture plate and incubated at 37 °C overnight in a humidified environment of 5% CO_2 and 95% air to allow cell adherence. Cells were then treated with SOL or pure compounds at different concentrations for another 24 h, followed by removing of the medium. And 1 mg/mL of MTT in DMEM solution was added into each well for further incubation of 4 h to allow formazan crystal formation. The supernatant was then carefully removed, and 100 μL of DMSO was added into each well to dissolve the MTT formazan crystal. The absorbance was measured at 570 nm with a microplate reader (BioTek Instruments). The complete growth medium served as the blank.

2.6. HepG2 cell culture and establishment of an insulin resistant model

The methods were performed according to our previous report (Teng et al., 2016). HepG2 cells were preserved in the molecular nutrition laboratory of Fujian Agriculture and Forestry University. Cultures were maintained in 10% FBS in DMEM containing 1% antibiotic antimycotic solution (100 ×) with 1% DMSO in liquid nitrogen. Before establishment of the insulin resistance model, HepG2 cells were seeded into cell culture bottles in high-glucose DMEM supplemented with 10% FBS and 1% antibiotic antimycotic solution at 37 °C in a humidified atmosphere containing 5% CO_2 to be activated. The cells were then subcultured until the density reached 5×10^4 cells/mL. After activation treatment, HepG2 cells were incubated in high-glucose DMEM with 1% antibiotic antimycotic solution for 12 h. The medium was then replaced with serum-free high-glucose DMEM with 5×10^{-7} M recombinant human insulin for 48 h, and the cells were cultured in high-glucose DMEM supplemented with 10% FBS and 1% antibiotic antimycotic solution at 37 °C as a negative control. Insulin resistant HepG2 cells had already been established. Finally, glucose uptake assays were performed using glucose oxidase method (GOD) kits to evaluate anti-diabetic effects after treatment of insulin resistant HepG2 cells with different concentrations of samples.

2.7. Western blotting

HepG2 cells were collected and lysed in a buffer containing 62.5 mM Tris-HCl (pH 6.8), 2% SDS, 10% glycerol, 50 mM dithiothreitol, and a protease inhibitor cocktail tablet (Roche Diagnostics; Mannheim, Germany). The total protein concentration of the lysates was determined with the BCA Protein Assay Reagent (Pierce). Proteins in the lysates were separated on a 10–12.5% SDS polyacrylamide gel and transferred to a polyvinylidene difluoride membrane (GE Healthcare Life Sciences; Piscataway, NJ, USA). Membranes were blocked in 5% BSA overnight at 4 and then incubated overnight at 4 with the following primary antibodies: GLUT4, β-actin, Akt, IRS-1, and p-Akt. Membranes were incubated with horseradish peroxidase-conjugated secondary antibodies overnight at 4 °C. The protein expression levels were detected accordingly by WB.

2.8. Statistical analysis

All analyzes were conducted in triplicate and statistical analyzes were performed using the Statistical Package for DPS 16.05 system (Zhejiang University, Hangzhou, China). Results were expressed as the mean ± standard deviation (SD). The analysis of variance was performed at the 5% level of significance.

3. Results and discussion

3.1. Isolation and characterization of PA and NPA fractions of CE

The methanol extract of SOL was suspended in hot water and partitioned to afford hexane, AcOEt, BuOH, and H_2O soluble fractions, respectively (Fig. 1). Based on the α-glucosidase inhibitory activity of the plant extracts observed relative to acarbose, the AcOEt fraction was selected for further separation using a variety of chromatographic

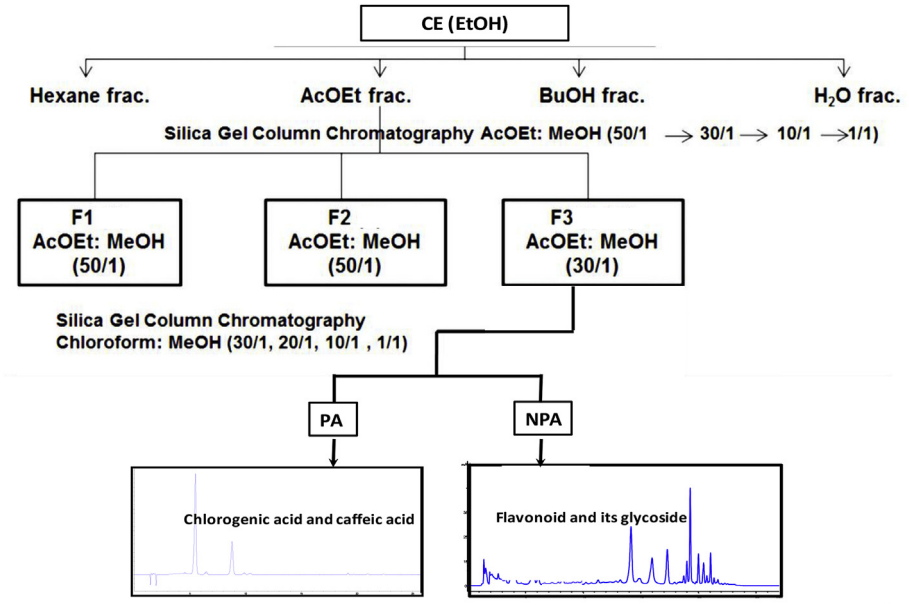

Fig. 1. A flow chart showing the fractionation procedures of SOL and its phenolic acid fraction (PA) or non-phenolic acid fraction (NPA).

methods (data not shown). This resulted in the isolation of 2 major fractions including phenolic acids (PA) fraction and non-phenolic acid fraction (NPA) (Fig. 1). In PA chlorogenic acid was the most abundant chlorogenic acid, followed by caffeic acid. Rutin and other flavonoid glycosides were also found with lower amounts in NPA.

3.2. Establishing an insulin-resistance HepG2 cell lines

For establishment of insulin-resistance model, HepG2 cells were accordingly treated with a wide range of insulin dose requirements from 5×10^{-5} to 5×10^{-9} M for 36 h (Fig. 2A). The highest glucose was determined in culture medium at an insulin dose of 5×10^{-7} M (Fig. 2A), negatively it means the lowest glucose uptake occurred in this condition. Therefore, HepG2 cells were exposed to 5×10^{-7} M insulin to screen the incubation time and the results demonstrated that insulin-induced glucose uptake was lowest at 24 h (Fig. 2B). Consequently, the insulin-resistance model conducted in this study was: 5×10^{-7} M insulin administered to the HepG2 cells for 24 h. Furthermore, the protein expression level of selective insulin doses to confirm insulin resistance was determined by WB (Fig. 2C). Fig. 2C showed that 5×10^{-7} insulin decreased the protein expression level of p-Akt in insulin resistance HepG2 cells compared to controls, which is directly related to the insulin signaling pathway. These results suggest that insulin at a concentration of 5×10^{-7} M may possess resistance in HepG2 cells (Fig. 2D). This was in agreement with previous study which has verified that a significant decrease ($p < 0.05$) of extracellular glucose occurred

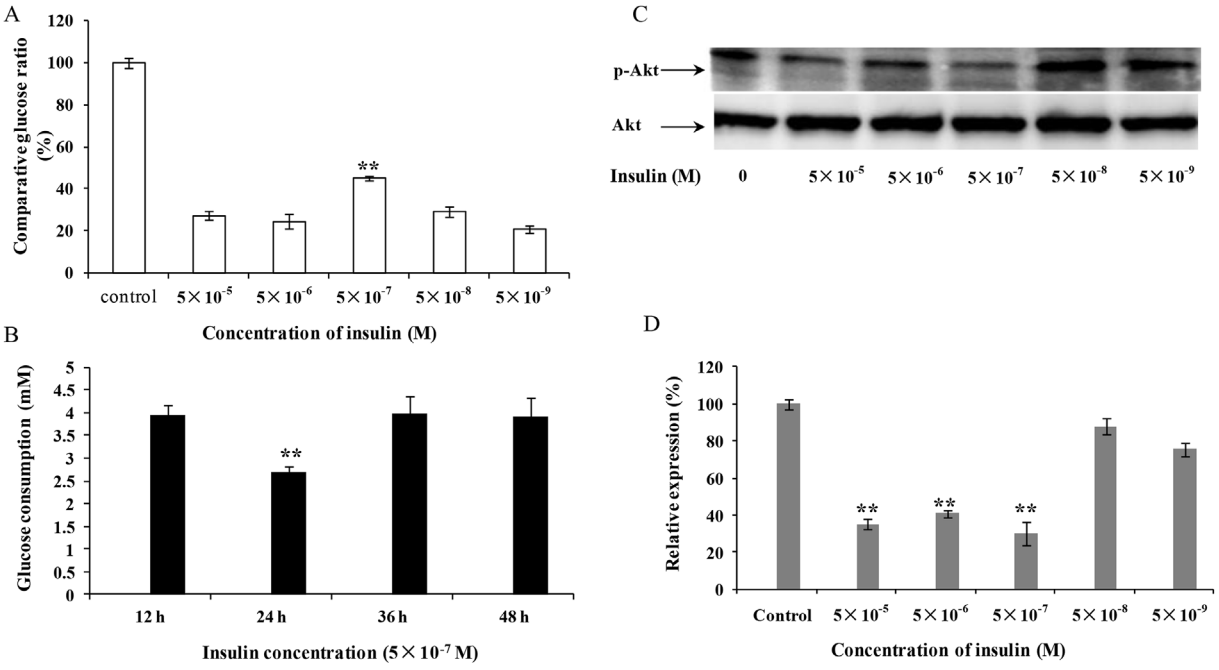

Fig. 2. Effect of insulin dose (5×10^{-5}-5×10^{-5} M) (A) nd insulin time (12 h-48 h) (B) insulin-induced glucose uptake; p-Akt expression and relative ratios of p-Akt and Akt, and glucose uptake of 5×10^{-7} M insulin treatment for 24 (C). Protein band intensities were quantified by densitometric analysis (D) in HepG2 cells. The glucose uptake assay was performed using the fluorescent D-glucose.

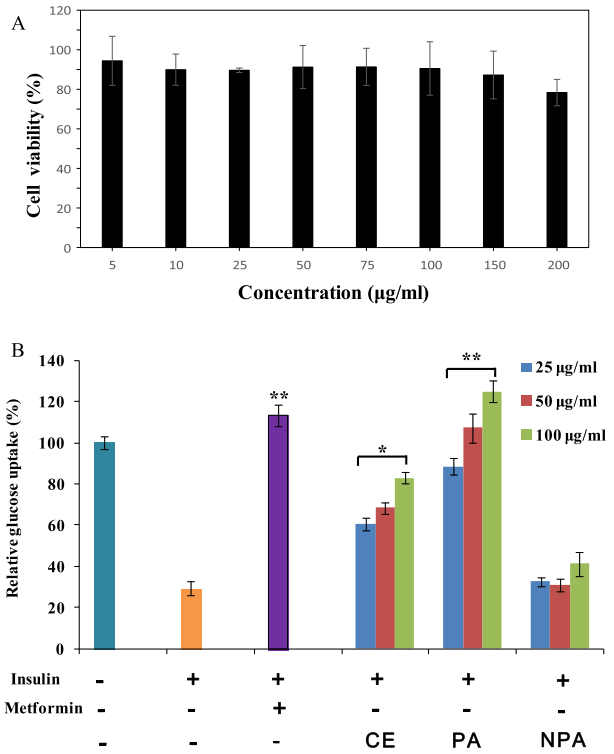

Fig. 3. Effect of CE on cytotoxicity (Up) and effect of CE, PA, and NPA on insulin-stimulated glucose uptake in insulin-resistant HepG2 cells (Down). The glucose uptake assay was performed using the fluorescent D-glucose analogue 2-NBDG, and 5×10^{-7} M insulin was used for insulin resistance. The insulin-resistant HepG2 cells were treated with different concentrations of CE, PA, and NPA for 24 h, and insulin-stimulated 2-NBDG uptake was measured. Values are the mean ± standard deviation of three independent experiments; **P < 0.01 and *P < 0.001 indicate significant differences from the 5×10^{-7} M insulin-treated control group, metformin at concentration of 10 μM was used a positive control.

after the incubation of HepG2 cells with 5×10^{-7} M insulin for 24 h.

3.3. Effect of CE on glucose uptake in insulin-resistance HepG2 cells

The cytotoxic effects of CE were measured by MTT using spectrophotometric assays. As shown in Fig. 3 (Up), cells treated with 5–150 μg/mL CE showed no significant difference in cytotoxicity, while cells treated with CE concentration beyond 200 μg/mL showed significant difference in viability compared to control group. Therefore, the concentration between 5 and 100 μg/mL of CE was used to investigate whether phenolic acids (PA), major component derived from CE, might regulate glucose transport in HepG2 cells. PA treatment significantly potentiated insulin-stimulated glucose uptake in a concentration-dependent manner. As shown in Fig. 3 (down), insulin-stimulated glucose uptake in HepG2 cells treated with PA at 25, 50, or 100 μg/mL was approximately 3.0-, 3.6-, or 4.2-fold higher, respectively, than in the control culture without PA. The stimulatory effect of 100 μg/mL NPA was significantly lower than that of PA, CE and metformin controls. Previous publications have reported that chlorogenic acid could effectively regulate glucose and lipid metabolism disorders (Peng et al., 2015; Ma et al., 2015; Santana-Gálvez et al., 2017). Vinayagam, Jayachandran and Xu (2016) reported that chlorogenic acid could reduce blood glucose by increasing glucokinase activity via activating the PI3K/AKT-mediated pathway. Further studies have also found that supplemental phenolic acids would increase insulin secretion (Zuniga et al., 2018), modulate glucose transport (Zhu et al., 2018), reduce weight gain (Alristina et al., 2018), and normalize blood glucose levels (Moser et al., 2018).

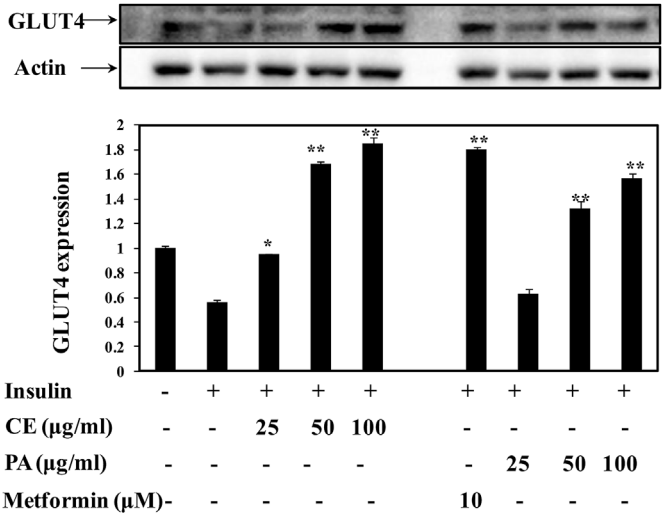

Fig. 4. Effect of CE and PA on expression levels of GLUT4 in HepG2 cells after 24 h of treatment. Cells were incubated with 5×10^{-7} M insulin for 24 min before the harvest. Bands of representative experiments for GLUT4 (Up). Densitometric quantification of GLUT4 (Down). Values are expressed as a percentage relative to the control condition (n = 3). Equal loading of Western blots was ensured by β-actin. **P < 0.01 and *P < 0.001 indicate significant differences from the 5×10^{-7} M insulin-treated control group, metformin at concentration of 10 μM was used a positive control.

3.4. CE and PA increase the expression of GLUT4

GLUT4 which belongs to the GLUT family is widely distributed in endosomes, trans-Golgi network, and tubular-vesicular structures, etc. After insulin stimulation and exercise, GLUT4 is distributed to the plasma membrane, and defects in this process in response to insulin resulting insulin-resistance, type 2 diabetes, and metabolic syndrome. To investigate the potential effect of PA and CE on modification of the expression and subcellular localization of GLUT4, Western blotting was used. As shown in Fig. 4, either CE or PA could significantly increase the expression of GLUT4 in HepG2 cell lysates (Fig. 4 up). Accordingly, GLUT4 expression in HepG2 cells treated with CE at 25, 50 and 100 μg/mL was approximately 1.6-, 2.9-, or 3.2-fold higher; respectively; treated with PA at 25, 50 and 100 μg/mL was approximately 1.1-, 2.3-, or 2.7-fold higher than in the control culture (Fig. 4 down). These results suggest that CE or PA may enhance glucose uptake in HepG2 cells via increased GLUT4 expression and translocation. In fact, caffeic acid has been clearly improved to increase insulin-independent glucose transport activity in skeletal muscle (Tsuda et al., 2012).

3.5. CE and PA activate Akt

AKT lays facilitating glucose uptake and glycogen synthesis in the liver, which plays a key role in mediating the metabolic effects of insulin signaling (Cordero-Herrera et al., 2014). Since CE and PA could increase glucose uptake through enhanced GLUT4 expression, we examined the expression levels of Akt and p- Akt proteins involved in the insulin signaling pathway by western blotting. Treatment of HepG2 cells with CE and PA evoked a significant increase in the phosphorylated levels of Akt (Fig. 5). Likewise, expression of p-Akt in HepG2 cells treated with CE at 25, 50, and 100 μg/mL was approximately 1.4-, 1.3-, or 1.4-fold higher, and treated with PA at the same concentration, was approximately 1.1-, 1.3-, or 1.5-fold higher, respectively, than in the control. Metformin was used in these experiments as a positive control showing expression of p-Akt was 1.7-fold higher, than in the control. These results indicated that CE and PA enhanced glucose uptake

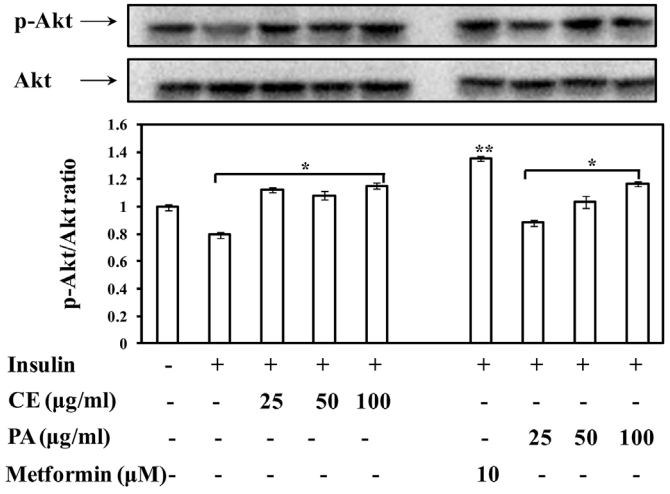

Fig. 5. Effect of CE and PA on expression levels of p-Akt and Akt in HepG2 cells after 24 h of treatment. Cells were incubated with 5×10^{-7} M insulin for 24 min before the harvest. Bands of representative experiments for p-Akt and Akt (Up). Densitometric quantification of p-Akt and Akt (Down). Values are expressed as a percentage relative to the control condition (n = 3). **P < 0.01 and *P < 0.001 indicate significant differences from the 5×10^{-7} M insulin-treated control group, metformin at concentration of 10 μM was used a positive control.

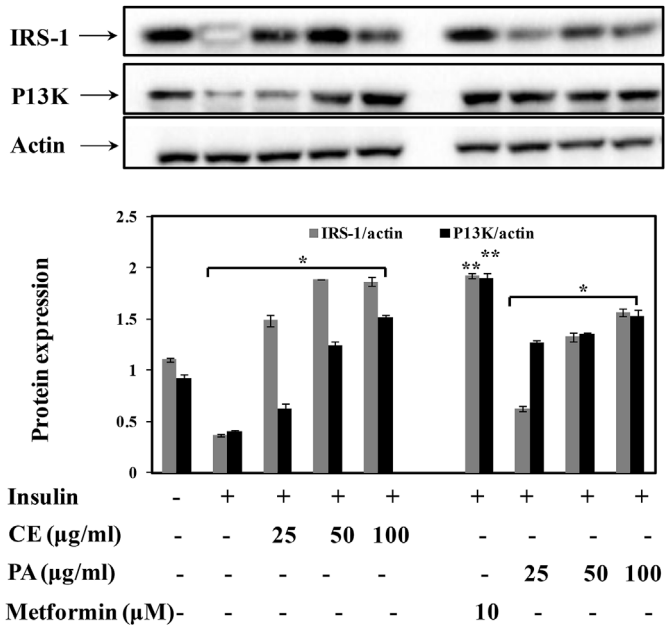

Fig. 6. Effect of CE and PA on expression levels of IRS-1 and PI3K in HepG2 cells after 24 h of treatment. Cells were incubated with 5×10^{-7} M insulin for 24 min before the harvest. Bands of representative experiments for IRS-1 and PI3K (Up). Densitometric quantification of IRS-1 and PI3K (Down). Values are expressed as a percentage relative to the control condition (n = 3). Qual loading of Western blots was ensured by β-actin. **P < 0.01 and *P < 0.001 indicate significant differences from the 5×10^{-7} M insulin-treated control group, metformin at concentration of 10 μM was used a positive control.

through Akt activation of the insulin signaling pathway.

3.6. CE and PA modulate IRS-1/PI3K

PI3K is related to glucose translocation and glycogen synthesis, whereas, activated IRS-1 stimulates glucose uptake in liver (McMullen et al., 2003). Therefore, IRS-1/PI3K could be considered as importance in glucose metabolism regulation and appear to contribute to the development of insulin resistance. In the present study, insulin resistance decreased the expression of PI3K and IRS-1 in HepG2 cells by 67.2% and 56.4% of the basal value, whereas CE and PA treatment increased the expression PI3K and IRS-1. CE increased the expression of PI3K by 65.2% of the basal value, whereas PA caused 66.7% increasing at the concentration of 100 μg/mL (Fig. 6). In addition, CE and PA increased IRS-1 expression in insulin-resistant HepG2 cells in a dose-dependent manner (Fig. 3). Restated, treatment with CE or PA increased the expression of IRS-1/PI3K in insulin-resistant HepG2 cells. Interestingly, earlier report declared that chlorogenic acid did not show effect on the expression of PI3K and had no association between PI3K and IRS-1, suggesting a positive role of caffeic acid presented in PA and CE on activation of IRS-1/PI3K. These results are consistent with the study by Tsuda et al. (2012) who found chlorogenic acid did not affect phosphorylation of PI3K and IRS-1, but observed that caffeic acid, a metabolite of chlorogenic acid, induced the phosphorylation of PI3K, IRS-1, and AMPK. In this regard, CE and PA pretreatment stimulated the increase in IRS-1 induced by insulin, showing comparable values to those of metformin.

4. Conclusion

Two phenolic acids fractions were isolated from crude extract of SOL (CE) as chlorogenic acid and caffeic acid were identified on the basis of structural elucidation and literature by HPLC. The glucose uptake assay showed CE and PA could regulate glucose metabolism by immediately targeting AKT on insulin resistance HepG2 cell line. In addition, the protein expression results for IRS-1, Akt, PI3K, and GLUT-4 showed significant up regulation in case of PA treated samples as compared to insulin resistance control. Here, we report for the first time that crude extraction of SOL and its main phenolic acid fraction improved insulin sensitivity in cultured HepG2 cells. All these data shed light on SOL could be exploited as a potential source of natural by delaying a potential hepatic dysfunction and alleviating the hepatic insulin resistance.

Acknowledgments

This work is supported by the National Natural Science Foundation of China (NSFC, Grant No. 31701520), China Postdoctoral Science Foundation Funded Project (No. 2018M642551), the Funds for Distinguished Young Scientists (Grant No. kxjq17012) at Fujian agriculture and forestry university of China.

Transparency document

Transparency document related to this article can be found online at https://doi.org/10.1016/j.fct.2019.03.038.

Conflicts of interest

The authors declare no competing financial interest.

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