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RESEARCH

Identification of α-Glucosidase-Inhibitors in *Edgeworthia gardneri* (Wall.) Meisn. Using UPLC-Q-TOF-MS/MS Analysis

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Abstract

Edgeworthia gardneri (Wall.) Meisn., a member of the genus *Edgeworthia* in the family Thymelaeaceae, has long been applied as an edible and medicinal plant in China. *E. gardneria* has a hypoglycemic effect and is used to prepare daily drinks for the prevention and treatment of diabetes. However, the hypoglycemic substances involved remain unknown. The present study aimed to screen the α-glucosidase-inhibitors of *E. gardneri* and analyze its chemical profile using a ultraperformance liquid chromatography-quadrupole time-of-flight mass spectrometry (UPLC-Q-TOF-MS/MS) method. As a result, the ethyl acetate fraction (EAF) had significant α-glucosidase-inhibitory and antioxidant activities but did not show an α-amylase-inhibitory activity. A total of 67 compounds were identified in the EAF by UPLC-Q-TOF-MS/MS analysis; among them, 48 compounds were first discovered in the genus *Edgeworthia*. Additionally, five flavonoids, namely, isoorintin, secoisolariciriniol, tiliroside, chrysin, and kaempferol, had α-glucosidase-inhibitory activities. Rutin had a α-amylase-inhibitory activity. Daphnoretin, a kind of coumarin, has α-glucosidase and α-amylase-inhibitory activities. These findings enrich the chemical library of *E. gardneria*. EAF has a selective α-glucosidase-inhibitory activity, and flavonoids and coumarins may be the active components of EAF. *E. gardneria* has important value for developing multiple-target hypoglycemic drugs.

Keywords *Edgeworthia gardneri* (Wall.) Meisn · Ethyl acetate fraction · Selective α-glucosidase-inhibitory activity · Flavonoids · Coumarins

Introduction

According to the latest report, approximately 529 million people worldwide were diagnosed with diabetes in 2021, and the global number of diabetes patients may reach a staggering 1.31 billion by the year 2050 [1]. Diabetes has emerged as a significant public health concern globally. It is a complex metabolic disorder characterized by high blood sugar levels and involves several pathological mechanisms, including insulin resistance, oxidative stress, and inflammation [2].

α-Glucosidase inhibitors have been used as a therapeutic approach for managing diabetes by slowing glucose absorption and reducing blood sugar levels [3]. However, currently available clinical α-glucosidase inhibitors such as acarbose, voglibose, and miglitol can inhibit α-glucosidase and α-amylase activity at the same time. This dual inhibition often leads to unpleasant side effects, including nausea, diarrhea, and bloating [4]. Therefore, there is an urgent need to discover new and selective α-glucosidase inhibitors that can effectively reduce blood glucose levels without causing such adverse reactions.

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Edible and medicinal plants are important resources for accessing natural α-glucosidase inhibitors and have attracted the attention of researchers in this field [5, 6]. *Edgeworthia gardneri* (Wall.) Meisn., which belongs to the Thymelaeaceae family, is found primarily in the Himalayan Mountains and is considered a valuable and unique botanical resource exclusive to Tibet [7]. People in southwestern China are fond of using the dried flower of *E. gardneri* to prepare daily drinks for the prevention and treatment of diabetes [8]. Previously, water extracts of *E. gardneri* were found to reduce fasting blood glucose in type 2 diabetes mellitus mice [9]. Additionally, structurally interesting phenolic constituents, including flavonoids and coumarins, were isolated from *E. gardneri* and identified [10]. However, to date, the hypoglycemic substances present in *E. gardneri* have not been identified, which has hindered further study of this edible and medicinal plant.

In the present study, we aimed to employ a comprehensive approach to study the hypoglycemic substances of *E. gardneri*. First, the total flavonoid/phenol/coumarin contents of the extract and various sites were tested, after which their inhibitory activities against α-glucosidase and α-amylase, as well as their antioxidant activities, were evaluated. Considering both the secondary metabolite content and bioactivity, we screened out the best antidiabetic site. Subsequently, UPLC-Q-TOF–MS/MS combined with the establishment of Traditional Medicine Library based on collecting information on relevant fragments of chemical standards was adopted to systematically identify the components of the screened site. Finally, the identified compounds were evaluated for their α-glucosidase and α-amylase-inhibitory activities. Taken together, these results provide a solid theoretical foundation for the development of α-glucosidase-inhibitors derived from *E. gardneria*.

Materials and Methods

The material and methods section is presented as supplementary material.

Results and Discussion

Total Flavonoid, Total Phenol, and Total Coumarin Content

The 95% ethanol extract (EEE) of *E. gardneri* were extracted to get the petroleum ether fraction (PEF), the ethyl acetate fraction (EAF), the *n*-butanol fraction (NBF), and the aqueous fraction (AF). The total phenol, total flavonoid and total coumarin contents of the EEE, PEF, EAF, NBF, and AF are shown in Table 1. The total flavonoid contents ranged from 38.0 ± 0.5 to 199.3 ± 0.3 mg RUE/g. The order from high to low was EAF > NBF > EEE > PEF. The total flavonoid content in the EAF was significantly higher than those in the PEF, NBF and EEE (all $p < 0.001$). The total phenol content ranged from 18.6 ± 2.2 to 191.7 ± 3.5 mg GAE/g. The order of total phenol content from high to low was also EAF > NBF > EEE > PEF. The total phenol content in the EAF was obviously higher than those in the PEF, NBF, and EEE (all $p < 0.001$). Moreover, the total coumarin contents of the five samples ranged from 23.4 ± 2.8 to 624.1 ± 13.8 mg 7-HCE/g. The total coumarin content varied from high to low according to the sequence: EAF, NBF, EEE, PEF and AF. The total coumarin content in the EAF was significantly higher than those in the PEF, NBF, EEE, and AF (all $p < 0.001$). All the results indicate that flavonoids, phenols, and coumarins are well enriched in the EAF after extraction. Notably, the high total coumarin content in EAF suggests that coumarins are the main components of EAF. Chemical composition studies of this genus have primarily focused on *E. gardneri* and *E. chrysantha*, with coumarins

Table 1 Total flavonoid, total phenol and total coumarin contents of samples prepared from *Edgeworthia gardneri*

Samples	Total flavonoid content (mg RUE/g)	Total phenol content (mg GAE/g)	Total coumarin content (mg 7-HCE/g)
EEE	57.4 ± 3.3***	56.6 ± 1.8●●●***□□□	220.7 ± 15.5●●●***□□□■■■
PEF	38.0 ± 0.5***	18.6 ± 2.2***□□□	70.7 ± 5.4***□□□■■■
EAF	199.3 ± 0.3□□□	191.7 ± 3.5□□□	624.1 ± 13.8□□□■■■
NBF	64.2 ± 3.5	102.0 ± 6.4	280.1 ± 3.8■■■
AF	-	-	23.4 ± 2.8

"-" indicates not detected. Compared with the petroleum ether fraction (PEF): ●●● $p < 0.001$; compared with the ethyl acetate fraction (EAF): $^{***}p < 0.001$; compared with the *n*-butanol fraction (NBF): □□□ $p < 0.001$; compared with the aqueous fraction (AF): ■■■ $p < 0.001$. EEE: 95% ethanol crude extract of *E.gardneri*

and flavonoids being the main components [10, 11]. Our results are consistent with these previous findings.

Measurement of Antioxidant Activity

Recent studies have shown that oxidative stress plays an important role in regulating diabetes, especially type 2 diabetes. [2] Antioxidants can eliminate ROS, reduce the degree of oxidative stress, protect pancreatic beta cells from damage, promote normal secretion and action of insulin, improve the pathological process of diabetes, reduce the risk of complications, and improve the overall health of patients [2]. Therefore, we first evaluated the antioxidant activity of sites. 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2′-azino-bis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assays are commonly performed to evaluate the antioxidant activity of extracts and compounds. Therefore, the ability of sites to scavenge DPPH and ABTS free radicals was evaluated to determine their antioxidant activity. The results are presented as the IC_{50} values. According to Table S1, the order of DPPH radical scavenging activity from strong to weak was EAF > NBF > EEE > PEF, and that of ABTS radical scavenging activity from strong to weak was EAF > NBF > EEE. The AF didn't exhibit DPPH and ABTS radical scavenging activities, and PEF didn't show ABTS radical scavenging activity. Among the tested samples, the EAF had the strongest antioxidant activity, with an IC_{50} values both below 100 μg/mL, which indicates that the EAF may contain abundant antioxidant substances and has potential application prospects.

Measurement of α-Glucosidase/ α-Amylase-Inhibitory Activity

α-Glucosidase is an enzyme found in the brush border cells of intestinal villi. Its main function is to break down disaccharides and oligosaccharides into α-D-glucose, allowing them to enter the bloodstream through the intestinal wall. α-Amylase is present in saliva and pancreatic fluid, and its role is to break down starch into simpler disaccharides, oligosaccharides, and low-molecular-weight carbohydrates. When α-glucosidase is inhibited, it cannot effectively break down disaccharides and oligosaccharides into α-D-glucose, resulting in a decrease in glucose entering the bloodstream, which helps control high blood sugar levels. However, currently used α-glucosidase inhibitors (such as acarbose, miglitol, and voglibose) inhibit both α-glucosidase and α-amylase activities, leading to adverse effects such as bloating, diarrhea, feelings of fullness, and discomfort. These side effects occur due to the inhibition of α-amylase, which leads to the fermentation of undigested carbohydrates [12]. Therefore, when designing new selective α-glucosidase inhibitors, it is necessary to consider their significant inhibitory effect on α-glucosidase without inhibiting α-amylase activity to effectively reduce blood sugar levels and minimize adverse gastrointestinal reactions [12]. The results shown in Table 2 revealed the following order of α-glucosidase-inhibitory activity from strong to weak: EAF > NBF, with EEE, PEF, and AF showing no activities. The NBF showed an α-amylase-inhibitory activity, and the EEE, PEF, EAF and AF didn't exhibit α-amylase-inhibitory activities. The results demonstrated that the NBF could simultaneously inhibit α-glucosidase and α-amylase, while the EAF had a significant α-glucosidase-inhibitory activity with a low IC_{50} value of 32.7 ± 0.1 μg/mL. These findings indicate that the EAF has potential for the development of multi-target antidiabetic drugs.

Identification of the Chemical Constituents of the EAF

UPLC-Q-TOF–MS/MS data analysis was performed using Unifi 2.0 software to filter out ion features from the raw data (detector counts > 1500, response > 200). The selected feature ions were subsequently matched against Waters' Traditional Medicine Library. The filtering criteria included a mass error (mDa) between -5 and + 5 mDa and > 2 total fragments. The retention times and fragment information were compared with those in the relevant literature for preliminary characterization of the compounds. Finally, compound identification was achieved by combining the accurate molecular weight and fragmentation patterns of compounds from the literature, as well as the predicted fragmentation patterns from reference mass spectral databases such as MassBank Europe.

The total ion chromatogram (TIC) and base peak intensity chromatogram (BPI) of the positive and negative ion mode low-energy channel and high-energy channel of the EAF are shown in Figures S1-S2. A total of 67 compounds were identified based on the data analysis and identification using Unifi 2.0 software. The screened results had matching parent ions (mass error < 2 mDa) and at least one diagnostic fragment ion, greatly improving the

Table 2 α-Glucosidase and α-amylase-inhibitory activities of samples prepared from *E. gardneri.* (IC_{50}, μg/mL)

Samples	α-glucosidase	α-amylase
EEE	Na	Na
PEF	Na	Na
EAF	32.7 ± 0.1□□□	Na
NBF	183.3 ± 0.9	264.9 ± 6.4
AF	Na	Na
Acarbose	4.6 ± 0.2	2.1 ± 0.2

"Na" denotes no activity. Compared with the NBF: □□□ $p < 0.001$

accuracy of the results. For compounds with no matches among the high-intensity components, structural analysis tools combined with the publicly available online database ChemSpider, which contains compound entries from more than 500 databases and is embedded in the UNIFI software, were used for database searches. The initial matching results were subsequently confirmed through structural analysis of the fragment ions. Among the 67 identified compounds, 21 flavonoids, 11 phenylpropanoids, 6 coumarins, 5 lignans, 4 alkaloids, 4 terpenes, 4 organic acids, 3 sterols, 3 volatile oils, 1 phenanthrene, 1 quinone, and 4 other compound types were found. By analyzing the molecular weights, retention times, and fragmentation patterns of the reference standards, 16 compounds (adenosine, syringin, neochlorogenic acid, umbelliferone, daphnetin, caffeic acid, rutin, kaempferol-3-*O*-rutinoside, isoorientin, secoisolariciresinol, isoliquiritigenin, tiliroside, 2H-1-benzopyran-2-one, chrysin, kaempferol and daphnoretin) were confirmed. The chemical structures of identified compounds are shown in Figure S3, and detailed identification information can be found in Table S2.

Among the 67 identified compounds, 49 were discovered in *E. gardneri* for the first time. Except for adenosine, the other 48 were all discovered in the genus *Edgeworthia* for the first time. Based on the peak areas of the liquid chromatography results, tiliroside, daphnoretin, buddlenoid A, apocynin B, and isoorientin were found to be present at relatively high concentrations. Tiliroside, apocynin B, buddlenoid A and isoorientin are flavonoids. Daphnoretin is a coumarin.

Identification of the Flavonoids in the EAF

Flavonoid compounds are mostly connected by three ring structures: A-C-B. The glycosidic bonds at the 7th position of the A ring and the 3rd position of the C ring are easily broken, resulting in fragments such as $[M\text{-}H_2O]^-$, $[M\text{-}H\text{-}rha]^-$, $[M\text{-}H\text{-}glc]^-$, and $[M\text{-}H\text{-}rutinose]^-$. The C–O–C bond in the C ring can also break or undergo rearrangement. Under MS conditions, these compounds responded well in positive ion mode. Taking tiliroside [kaempferol-3-*O*-(6-*p*-coumaroyl)-glucoside] as an example, its pseudomolecular ion peak is at m/z 595.14547 $[M+H]^+$, suggesting a molecular formula of $C_{30}H_{26}O_{13}$. During the fragmentation process, the following fragmentation pathways occur (Figure S4): 595.14547 $[M+H]^+$, 287.05541 [kaempferol + H]$^+$, 147.04394 [*p*-coumaroyl + H]$^+$, and 119.04888 [*p*-coumaroyl + H–CO]$^+$. By analyzing the m/z values of the secondary mass spectrometry ion fragments obtained from fragmentation and comparing them with the MS/MS values in the relevant literature [13], the compound was identified on a preliminary basis. After verification with a reference standard, the compound was confirmed to be tiliroside.

Identification of Phenylpropanoids in the EAF

Phenylpropanoids are a class of natural compounds formed by the polymerization of a benzene ring and three straight-chain carbons (C6-C3 moiety). Their fragmentation pattern typically involves the loss of H_2O, CO, and CO_2 to generate fragment ions. Taking caffeic acid as an example, its molecular ion peak is observed at m/z 179.03471 $[M\text{-}H]^-$, suggesting a molecular formula of $C_9H_8O_4$. The secondary fragment ions include 179.03471 $[M\text{-}H]^-$, 135.04487 $[M\text{-}H\text{-}CO_2]^-$, and 107.05036 $[M\text{-}H\text{-}CO_2\text{-}CO]^-$ (Figure S5). The analysis of the m/z values of the secondary mass spectrometry fragment ions obtained from fragmentation, in comparison with relevant literature [14], tentatively identified this compound as caffeic acid. After verification with a reference standard, the results were able to be confirmed.

Identification of the Coumarins in EAF

The fragmentation patterns of coumarins can be described as follows: simple coumarins can lose a carbonyl or carbon dioxide from the pyran ring under certain conditions. When the core is substituted with a hydroxy group, alternating losses of carbonyl and carbon dioxide can occur. Furanocoumarins are prone to substitution cleavage at C-5 and C-8, potentially resulting in the loss of carbonyl or carbon dioxide groups. There is also the possibility of alternating losses of carbonyl and carbon dioxide groups. Coumarin compounds with hydroxy substitutions on the core can lose water, while those with methoxy substitutions can lose both water and the methoxy group. Coumarin glycosides usually first lose their sugar portion during fragmentation, followed by further fragmentation according to the cleavage patterns of the coumarin compounds. Taking daphnoretin as a case study, its quasimolecular ion peak was observed at m/z 353.06642 $[M+H]^+$, suggesting a molecular formula of $C_{19}H_{12}O_7$. During the fragmentation process, it undergoes the following fragmentation modes (Figure S6): In positive ion mode, the ions observed are 353.06642 $[M+H]^+$, 338.04278 $[M+H\text{-}CH_2]^+$, 192.04176 $[M+H\text{-}CH_2\text{-}C_9H_6O_2]^+$, and 179.03402 $[M+H\text{-}CH_2\text{-}C_9H_6O_2\text{-}C]^+$. By analyzing the m/z values of the secondary mass spectrometry ion fragments obtained from fragmentation and comparing them with relevant literature [15], the compound was initially determined. After confirmation using a reference standard, daphnoretin was conclusively identified.

Biological Activity Evaluation of Individual Compounds in the EAF

The results are shown in Table S3. Isoorientin, isoliquiritigenin, tiliroside, chrysin and kaempferol exhibited α-glucosidase-inhibitory activities, with IC_{50} values ranging from 22.3 ± 0.8

to 1071.6 ± 31.1 μM. However, these five compounds did not have inhibitory effects on α-amylase. Daphnoretin had inhibitory effects on both α-glucosidase and α-amylase. Additionally, rutin exhibited an α-amylase-inhibitory activity without inhibiting α-glucosidase. These findings indicate that the flavonoids and coumarins in the EAF may be the active ingredients responsible for its hypoglycemic effects. UPLC-Q-TOF–MS/MS analysis revealed that tiliroside and isoorientin were the main flavonoids in EAF, while daphnoretin was the main coumarin. These findings provide evidence supporting the notion that active components in traditional Chinese medicine are often the abundant ones [16]. Isoliquiritigenin and tiliroside exhibited obvious α-glucosidase-inhibitory activities, with IC_{50} values 22.3 ± 0.8 and 23.6 ± 0.3 μM, respectively. They were also identified in *Dalbergia odorifera* T. Chen and *Phlomis stewartii*, respectively, and were found to display obvious inhibition of α-glucosidase, which is consistent with our results [17, 18]. All the findings indicate that the α-glucosidase inhibitory activity of the EAF may be attributed to the types, contents, and interactions of secondary metabolites [6, 19].

Conclusions

In summary, 67 compounds were characterized by UPLC–Q-TOF–MS/MS analysis, enriching the chemical library of *E. gardneri*. The EAF has a selective α-glucosidase inhibitory activity. Flavonoids and coumarins may be the active components. *E. gardneri* has important value in the development of multiple-target hypoglycemic drugs and is worthy of in-depth research.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11130-024-01158-x.

Author Contributions Liang Liu and Xianwen Zhang contributed to the study conception and design. Lin Li, Qijun Da, and Bolin Zou performed the experiments. The first draft of the manuscript was written by Lin Li. Liang Liu and Yanyan Zhang completed the final version of the manuscript. All the authors have read and approved the final manuscript.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Ethics Approval This declaration is not applicable.

Competing interests The authors declare no competing interests.

Conflict of Interest The authors have no conflicts of interest to declare.

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