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Evaluation of Bioactive Functions and Quantitative Analysis of Phenolic Compounds of *Glehnia littoralis* from Different Regions

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Abstract: *Glehnia littoralis* F. (GLF), a perennial herb indigenous to the coastal areas of northern Pacific countries is widely utilized in medicine for various diseases and symptoms. The current study aimed to determine the relationship between phytochemicals and their diverse functional abilities. High-performance liquid chromatography and a photodiode array detector were used to identify chlorogenic acid (**1**), rutin (**2**), isoquercitrin (**3**), psoralen (**4**), 8-methoxy psoralen (**5**), and bergapten (**6**). 2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) ($ABTS^+$)- and 2,2-diphenyl-1-picrylhydrazyl (DPPH)-radical-scavenging assays were conducted. It was found that GLF from the Chungnam Province had a higher content of compounds **4**–**6** contents of approximately 51.29 μmoL/g, which was primarily composed of bergapten (**6**) (44.44 μmoL/g). Moreover, GLF from Jeju Island exhibited the strongest $ABTS^+$- and DPPH-radical-scavenging activities, with IC_{50} values of 6.69 mg/mL and 10.26 mg/mL, respectively, followed by Chungnam Province and Jeonnam Province. In contrast, the radical-scavenging activities of GLF did not correlate with compounds **4**–**6** (furanocoumarins) and were predicted to be related to compounds **1**–**3**. These differences in chemical composition and biological functions are consistent with differences in environmental conditions. Therefore, GLF with high amounts of flavonoid compounds such as rutin and isoquercitrin could potentially be utilized as herbal medicines; however, further research into their additional biological effects is needed.

Keywords: *Glehnia littoralis*; radical-scavenging activity; HPLC/PDA; regional difference

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1. Introduction

Glehnia littoralis F. (GLF), a member of the Apiaceae family, is endogenous to the coastal regions of the northern Pacific [1]. The sandy beach environments that GLF usually inhabits are beneficial for initial rooting and subsequent rhizome development, making the species an economically important tool for averting soil erosion [2]. GLF is a perennial herb found in mainland China, Korea, and Japan, with edible and significantly profitable fresh sprouts [3,4]. GLF has been widely utilized for various medicinal purposes, such as in the treatment of bladder infections, as an analgesic, and for inducing perspiration [5]. Its roots and rhizomes are used in the treatment of lung disease, and for rapid alleviation of cough [6]. A recent study by Choe et al. showed that the hot water extract of GLF possessed skin-whitening and anti-wrinkle properties [7].

This study was conducted to evaluate the bioactive characteristics of indigenous GLF samples from different regions and to investigate the relationship between phytochemicals

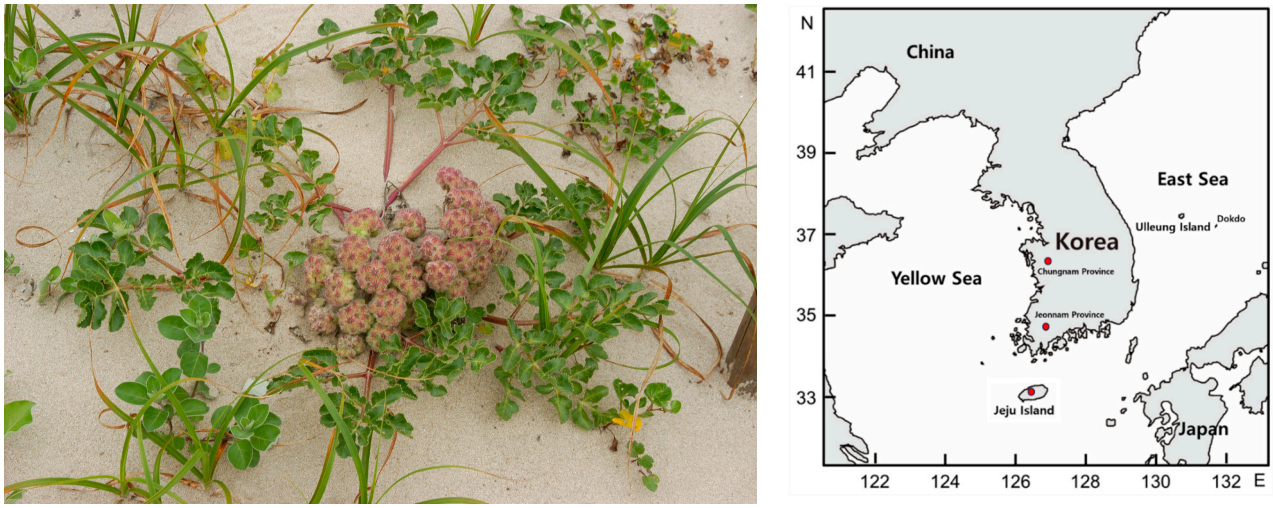
and their pharmaceutical activities. Previous studies were consulted to identify the indicator compounds in GLF. Masuda et al. [8] isolated psoralen, xanthotoxin, and bergapten from GLF via bioassay-directed chromatographic separation. In addition, Park et al. [9] developed a high-performance liquid chromatography (HPLC) method to detect 16 phytochemicals from the aerial parts of GLF, including chlorogenic acid, rutin, isoquercetin, psoralen, and bergapten. In addition, these compounds have been studied for their contribution to the ABTS-radical-scavenging activity of GLF via the online HPLC-ABTS approach. Furthermore, the effect of modified atmosphere package treatment on the postharvest quality of GLF has been studied [10]. In this study, several phenolic compounds were detected and quantified, including rutin, chlorogenic acid, bergapten, and isoquercitrin, using HPLC. Xu et al. [11] isolated novel lignan and neolignan glycosides from the roots of GLF such as glehlinoside G and H, using a preparative HPLC. There are several studies about bioactive properties of GLF, such as antioxidant, anti-inflammatory, immunomodulatory, and antibacterial activities [12]. However, there is still a lack of research regarding the differences of such activities based on regions.

Six compounds were selected as candidates for HPLC analysis and evaluation of their biological functions. The current study aimed to investigate the relationship between the $ABTS^{+}$-DPPH-radical-scavenging activities of GLF extracts collected from different regions and their chemical composition.

2. Materials and Methods

2.1. Plant Materials

This study was conducted using methanol (MeOH) extracts of whole parts of dried GLF from Jeju Island (KPM016-008), Jeonnam Province (KPM030-008), and Chungnam Province (KPM036-005) provided from the Natural Product Central Bank in KRIBB, Daejeon, Korea (Figure 1). All samples were identified and deposited at the herbarium of the Natural Product Central Bank in KRIBB, Daejeon, Korea.



(**a**) (**b**)

Figure 1. GLF sample from Jeonnam Province (**a**) and collection sites of GLF (**b**).

2.2. Equipment and Reagents

A quantitative analysis of GLF samples was performed using an HPLC instrument (Waters Alliance 2695 Separations Module, MA, USA) and the photodiode array detector (PDA, Waters 2998 PDA detector, Miliford, CT, USA). A YMC Pack Pro C_{18} column (4.6 × 250 mm, 5 µm) was used for isolation. HPLC/grade solvents such as MeOH, water, and acetonitrile (ACN) were purchased from J. T. Baker (Philipsburg, PA, USA). Triflu-

oroacetic acid (HPLC/grade) was purchased from Thermo Fisher Scientific (Waltham, MA, USA).

2.3. Chemical Compounds

Chlorogenic acid (**1**), rutin (**2**), isoquercitrin (**3**), psoralen (**4**), 8-methoxypsoralen (**5**), and bergapten (**6**) were obtained from the Natural Product Institute of Science and Technology (www.nist.re.kr, accessed on 10 January 2024) in Anseong, Korea (Figure 2).

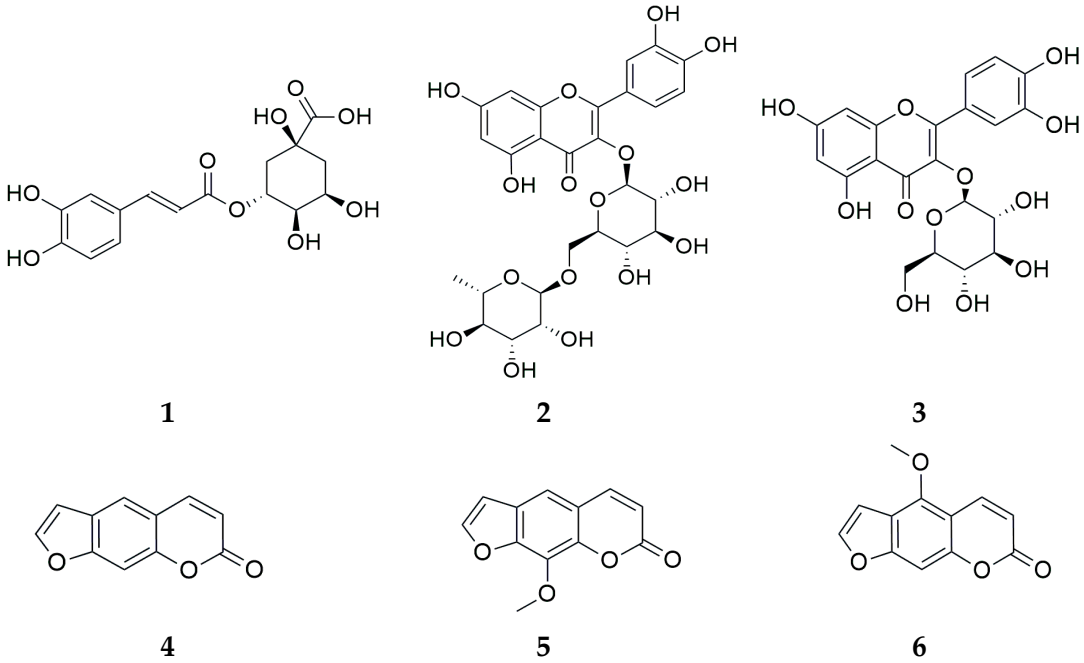


Figure 2. Chemical structures of compounds **1**–**6** (**1**: chlorogenic acid, **2**: rutin, **3**: isoquercitrin, **4**: psoralen, **5**: 8-methoxy psoralen, **6**: bergapten).

2.4. Sample Preparation

Dry GLF samples (20 mg) were diluted in 1 mL MeOH (20 mg/mL). Compounds **1**–**6** (1 mg) were dissolved in MeOH (1 mg/mL) to obtain the standard solutions. Each sample and standard solution was dissolved via sonication and filtered using a 0.45 µm polyvinylidene fluoride filter before analysis.

2.5. 2,2-Diphenyl-1-picrylhydraxyl (DPPH)-Radical-Scavenging Assay

The radical-scavenging assays were performed as described by previous studies [13,14]. Briefly, dry GLF samples (50 mg) were diluted in 1 mL MeOH to create sample stocks and were then sequentially diluted (50–3.125 mg/mL). The standards (1 mg) were diluted in 1 mL of methanol (1 mg/mL) and serially diluted (1–0.125 mg/mL). An amount of 10 mg of the sample was applied to a 96-well culture plate, followed by the addition of 200 µL of DPPH stock solution. In the control group, the DPPH solution was replaced with 95% ethanol. After 30 min of reaction in a dark room, the absorbance was read at 514 nm using a microplate reader. Vitamin C was used as a reference substance.

2.6. 2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) ($ABTS^+$)-Radical-Scavenging Assay

To create the sample stock solution, 40 mg of dry GLF samples were diluted in 1 mL MeOH and sequentially diluted (40–2.5 mg/mL). The standards (1 mg) were diluted in 1 mL methanol and serially diluted (1–0.0625 mg/mL) before conducting the assay. An amount of 10 mg of samples and standards were applied to a 96-well culture plate, followed by the addition of 200 µL $ABTS^+$ solution. The $ABTS^+$ solution was replaced with 200 µL water in the control group. As reference compound, vitamin C was used.

2.7. HPLC Conditions

Quantitative analysis of the GLF stock solution was performed using reverse-phase chromatography. A YMC Pack Pro C_{18} column (4.6 × 250 mm, 5 μm) was used to isolate the compounds. Water (0.1% TFA) (A) and acetonitrile (ACN) (B) were used as the mobile phases, and the analysis was performed using the gradient method. The elution conditions were 90% A at 0 to 5 min, 75% A at 15 min, 60% A at 35 min, 0% A at 45 to 50 min, and 90% A at 55 to 65 min. The injection volume of the sample was set to 10 μL, the temperature of the column was set to 35 °C, and the UV wavelength was set to 254 nm. The flow rate was set at 1 mL/min. Each sample was processed in triplicate.

2.8. Calibration Curves

Stock solutions of compounds **1**, **3**, and **5** were sequentially prepared (500, 250, 125, 62.5, 31.3, 15.6, and 7.8 μg/mL). Stock solutions of compounds **2**, **4**, and **6** were dissolved (125, 62.5, 31.3, 15.6, 7.8, 3.9, and 2.0 μg/mL) to form a calibration curve. The value of the *y*-axis (mAU) indicates the area of the peak, and the *x*-axis value (μg/mL) signifies each concentration of the standard solution. The total content of the standard (mg/g) was calculated by multiplying C, V, D, and P, followed by dividing by W (C: standard concentration in the test solution, V: total volume of the test solution, D: dilution factor, P: standard purity, W: sample weight). The calibration curve of standards exhibited good linearity, with an R-squared value of 0.9999 to 1.

2.9. Statistical Analysis

The results are presented as means and standard deviations, and statistical significance was evaluated by an analysis of variance (ANOVA) followed by Duncan's multiple range test. Minitab 16 software (Minitab Inc., State College, PA, USA) was used for statistical analyses.

3. Results

3.1. Radical-Scavenging Activities

The GLF MeOH extracts from the Jeonnam Province showed the weakest activity for scavenging $ABTS^+$ and DPPH radicals, with half-maximal inhibitory concentration (IC_{50}) values of 30.11 mg/mL and 40.41 mg/mL, respectively (Figure 3).

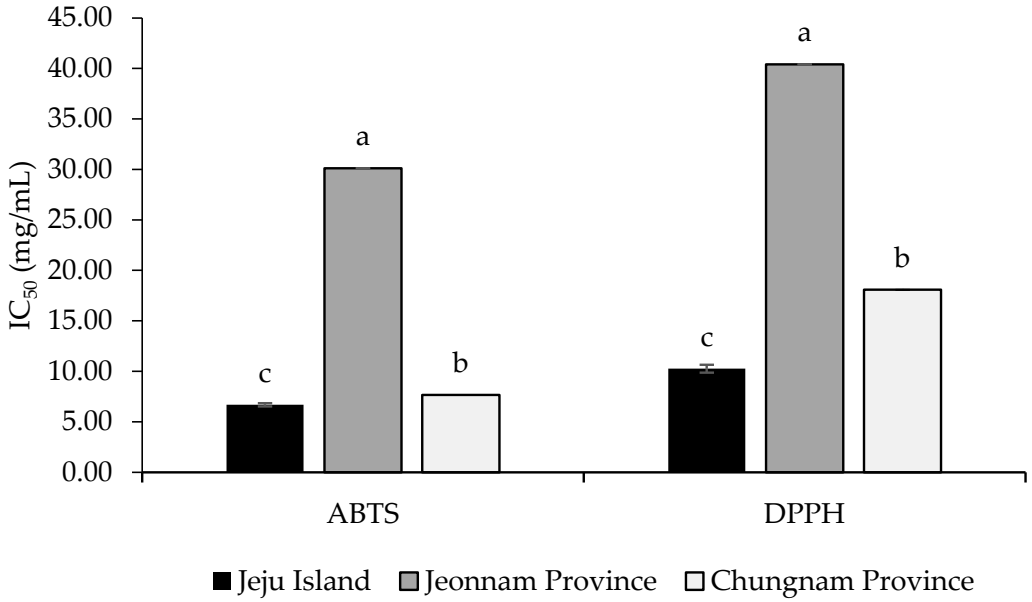


Figure 3. $ABTS^+$- and DPPH-radical-scavenging activity of *G. littoralis* extracts. Statistically significant differences are represented by lowercase letters.

GLF from Jeju Island showed the strongest activity, with IC_{50} values of 6.69 mg/mL for $ABTS^+$ and 10.26 mg/mL for DPPH, followed by GLF from Chungnam Province, with IC_{50} values of 7.66 mg/mL ($ABTS^+$) and 18.08 mg/mL (DPPH). Among the compounds, compounds **4**–**6** did not exhibit notable differences in their optical density values according to their concentrations (Table 1). The radical-scavenging activities of other compounds have been shown as relative vitamin C-equivalent-antioxidant-capacity (VCEAC) value. Overall, rutin (**2**) showed the strongest radical-scavenging activity in both radicals, with relative VCEAC values of 2.27 and 1.31 for $ABTS^+$ and DPPH, respectively. Chlorogenic acid (**1**), had a radical-scavenging activity higher than that of vitamin C for $ABTS^+$, with a relative VCEAC value of 1.12, but exhibited a relatively weak scavenging ability for DPPH, with a relative VCEAC value of 0.96.

Table 1. $ABTS^+$- and DPPH-radical-scavenging activity of compounds **1**–**6**.

Compound	$ABTS^+$-Scavenging Activity (Relative VCEAC Values [a])	DPPH-Scavenging Activity (Relative VCEAC Values)
Chlorogenic acid (**1**)	1.12	0.96
Rutin (**2**)	2.27	1.31
Isoquercitrin (**3**)	0.57	0.54
Psoralen (**4**)	-	-
8-Methoxy psoralen (**5**)	-	-
Bergapten (**6**)	-	-
Vitamin C [b]	1.00	1.00

[a] Relative VCEAC value = VCEAC of each compound/radical-scavenging capacity of vitamin C. [b] Vitamin C was used as a positive control.

3.2. Characterization of Phenolic Compound Content by HPLC

To identify the major phytochemicals in GLF samples, an HPLC/PDA analysis was conducted for chlorogenic acid (**1**), rutin (**2**), isoquercitrin (**3**), psoralen (**4**), 8-methoxypsoralen (**5**), and bergapten (**6**). The calibration curves of compounds **1**–**6** showed great linearity, exhibiting correlation factors of 0.9999 or 1 (Table 2).

Table 2. Calibration curves of compounds **1**–**6**.

Compound	tr [a]	Calibration Equation [b]	R-Value [c]
Chlorogenic acid (**1**)	11.7	Y = 10,686x + 9024.1	0.9999
Rutin (**2**)	17.5	Y = 19,141x − 766.57	1
Isoquercitrin (**3**)	18.2	Y = 26,810x + 40,996	0.9999
Psoralen (**4**)	30.6	Y = 35,255x + 5221.5	0.9999
8-Methoxy psoralen (**5**)	32.2	Y = 49,634x + 24,987	1
Bergapten (**6**)	36.3	Y = 27,694x + 13,860	1

[a] retention time. [b] Y = peak area, X = concentration of the standard (μg/mL). [c] R-value = correlation coefficient for the five data points in the calibration curve.

The retention times of compounds **1**–**6** were 11.7, 17.5, 18.2, 30.6, 32.2, and 36.3 min, respectively. Compounds **1**–**6** and GLF from the three different regions were analyzed simultaneously (Figure 4). The quantitative analysis of the six compounds in the GLF samples revealed chlorogenic acid (**1**) contents of 4.34, 0.88, and 10.31 μmoL/g in the GLF from Jeju Island, Jeonnam Province, and Chungnam Province, respectively (Table 3).

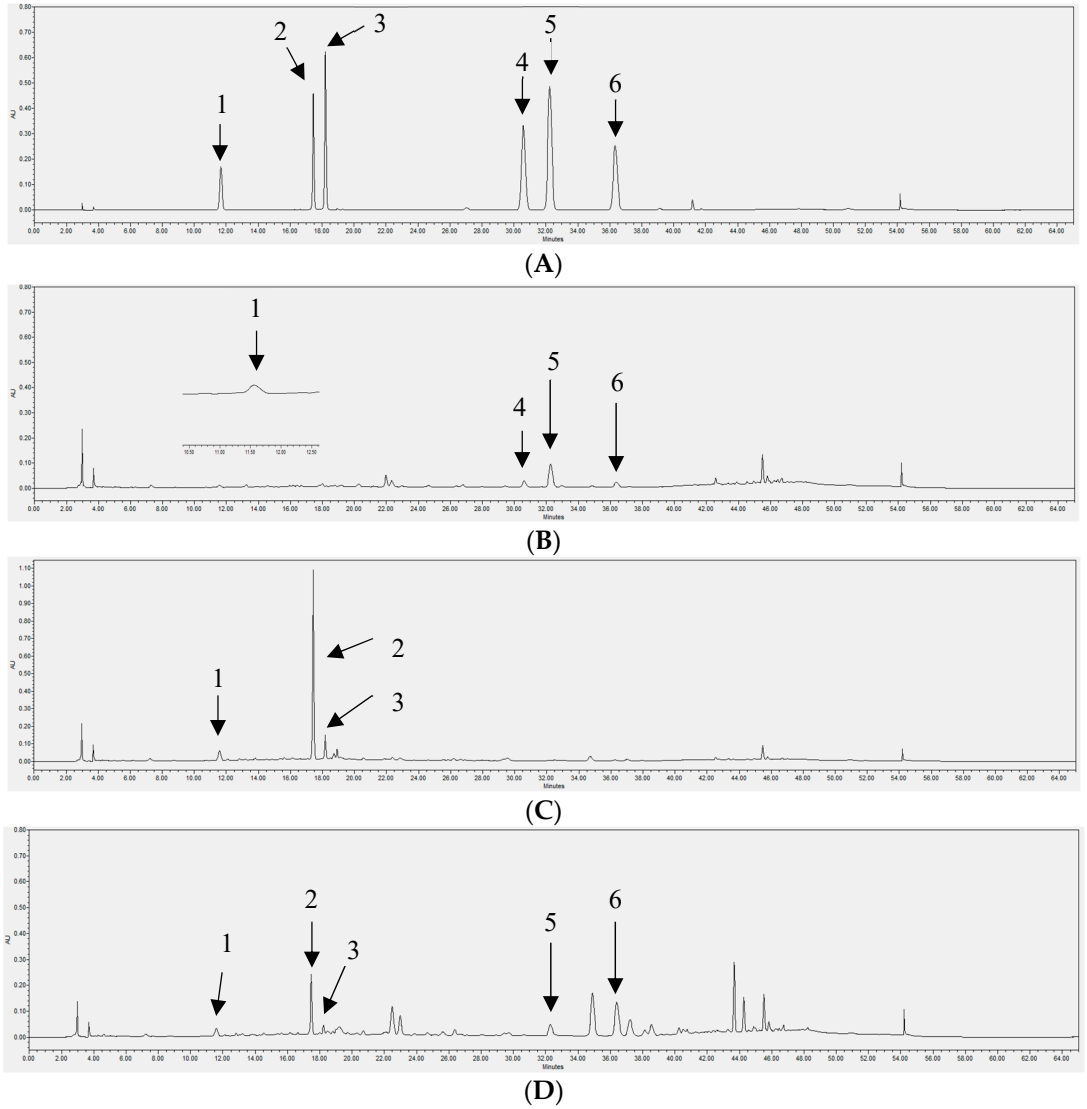


Figure 4. HPLC/PDA chromatograms of standards: (**A**) **1**: chlorogenic acid, **2**: rutin, **3**: isoquercitrin, **4**: psoralen, **5**: 8-methoxy psoralen, **6**: bergapten, Jeju Island (**B**), Jeonnam Province (**C**), and Chungnam Province (**D**).

Table 3. Content of compounds **1–6** in *G.littoralis.*

Compound	Jeju Island (μmoL/g)	Jeonnam Province (μmoL/g)	Chungnam Province (μmoL/g)
Chlorogenic acid (**1**)	4.34 ± 0.14 ^{b}	0.88 ± 0.00 ^{c}	10.31 ± 0.08 ^{a}
Rutin (**2**)	24.13 ± 0.03 ^{a}	tr	15.95 ± 0.02 ^{b}
Isoquercitrin (**3**)	2.69 ± 0.04 ^{a}	tr	1.55 ± 0.02 ^{b}
Psoralen (**4**)	ND	2.15 ± 0.05	tr
8-Methoxy psoralen (**5**)	ND	5.41 ± 0.05 ^{b}	6.85 ± 0.09 ^{a}
Bergapten (**6**)	tr	13.42 ± 0.05 ^{b}	44.44 ± 0.65 ^{a}
Total	31.16	21.86	79.10

tr: trace. ND: not detected. Statiscally significant differences are represented by lowercase letters.

4. Discussion

The current study focused on the radical-scavenging activity of GLF collected from three different regions and their correlation with their chemical compositions. Compounds **4–6** (furanocoumarins) exhibited no radical-scavenging activity. Furanocoumarin is a

type of phytochemical that is a combination of coumarin and a furan ring [15]. The most abundant linear furanocoumarins in higher plants include psoralen, xanthotoxin, and bergapten, which have the highest concentrations in Apiaceae, Leguminosae, Moraceae, and Rutaceae [16]. Among linear furanocoumarins, psoralen has been shown to possess numerous pharmacological properties, such as anti-osteoporotic, antimicrobial, anti-Alzheimer disease, and antiarrhythmic activities [17]. Furanocoumarins are formed in plants as a defense against pests and are studied for their bioactivities such as anti-fungal, anti-inflammatory, and anti-viral functions [18]. There was no direct connection between the radical-scavenging activities of GLF and furanocoumarins, since compounds **4**–**6** (furanocoumarins) did not exhibit notable radical-scavenging activity. The radical-scavenging assays of psoralen derivatives revealed that psoralen, 8-methoxy psoralen, and bergapten possess weaker $ABTS^+$ and DPPH activities than those of other psoralen derivatives [19]. This result could be due to the lack of phenolic hydroxyl groups in the benzopyrone moiety. The characterization of free-radical-scavenging activity found in betalains revealed that the presence of one phenolic hydroxy group created an increase of 1.6 units of Trolox-equivalent antioxidant capacity, and two phenolic hydroxy groups induced an increase of 3.4 units [20].

The current study observed some correlation between radical-scavenging capacities and phytochemical contents in GLF. The GLF from Jeju Island showed the strongest radical-scavenging activity, followed by the GLF from Chungnam Province and Jeonnam Province. This trend was also seen in the HPLC content of compounds **1**–**3**, where the sum of the three component contents was highest for the Jeju Island sample (31.16 μmoL/g), followed by the Chungnam Province sample (27.81 μmoL/g) and the Jeonnam Province sample (0.88 μmoL/g). Since compounds **4**–**6** showed no radical-scavenging activity, this trend can be attributed to the effects of compounds **1**–**3**. Wang et al. [21] identified five major antioxidant phytochemicals in *Hibiscus sabdariffa* leaf extracts using liquid chromatography/quadrupole-time-of-flight mass spectrometry, which included chlorogenic acid, rutin, and isoquercitrin. So et al. [22] found a variety of flavonoids with strong activity, with high radical-scavenging activity found in Korean *Chrysanthemum* flowers with high flavonoid content.

Rutin (**2**), otherwise known as quercetin-3-*O*-rutinoside, is a polyphenolic bioflavonoid named after *Ruta graveolens* from which it was first isolated and has been shown to have significant effects on lipid peroxidation assays [23–25]. It is abundantly found in natural sources, such as the flowers of pagoda trees or buckwheat seeds [26]. Antioxidant and anti-aging in vitro assays conducted by Girsang et al. [27] showed that rutin (**2**) exhibited significant activities, with an IC_{50} value of 12.09 μg/mL for scavenging hydrogen peroxide and 46.88 μg/mL for inhibiting elastase. Atanassova et al. [28] evaluated the rutin (**2**) content in twelve natural products and reported that *Rhus cotinus* had the highest rutin (**2**) content at 10.53% of the total.

Unlike the Jeonnam Province sample, where rutin (**2**) was found in trace amounts, approximately 77.4% of the six compounds in the Jeju Island sample (24.13 μmoL/g) and 20.2% in the Chungnam Province sample (15.95 μmoL/g) were identified as rutin (**2**). Isoquercitrin (**3**), also known as quercetin-3-*O*-glucoside, is a natural flavonoid component that inhibits reactive oxygen species [29,30]. As a singular glucoside variant of quercetin, isoquercitrin (**3**) is a predominant flavonoid in nature which is extensively found in plants [31]. A compound isolated from *Aster yomena* has been investigated for its ability to induce fungicidal activity by disrupting cell membranes [32]. Isoquercitrin (**3**) was detected in all GLF samples, either in trace amounts or lower than 10% of the total content, with 2.69 μmoL/g in Jeju Island and 1.55 μmoL/g in Chungnam Province. Thus, compounds **1**–**3** are expected to affect to the radical-scavenging activities of GLF samples, due to the contribution of the flavonoid compounds. Mustafa et al. [33] studied the relationship between flavonoid compounds and DPPH-radical-scavenging activities of 21 tropical plants and figured out that flavonoid content is positively correlated with radical-scavenging activity. In more structural detail, the hydroxylation of the A-ring and B-ring of the flavonoid structure, and

the C2-C3 double bonds connected to the C-3 hydroxyl and C-4 carbonyl groups have been studied for their contributions [34].

Chlorogenic acid (**1**, 3-caffeoylquinic acid) is an ester structured between caffeic acid and quinic acid that exhibits numerous biological functions, such as regulating the nervous system and antioxidant activities [35,36]. It is effective in the alleviation of persistent ailments, and its prevalence in various food sources makes it a potential candidate for application in the food industry [37]. For instance, when Ma et al. [38] used chlorogenic acid (**1**) nanoparticles as a material in food packaging, the authors reported that it was effective in blocking ultraviolet (UV) A and also had a positive effect on the browning of bananas and bacterial growth in chicken samples. Chlorogenic acid (**1**) content was found to be relatively low in the Jeonnam Province sample, with less than 10% of the total content of compounds **1**–**6**, whereas it was approximately 13.9% and 13.0% in the Jeju Island sample and the Chungnam Province sample, respectively. Psoralen was found in trace amounts or was not detected in the Chungnam Province and Jeju Island samples, respectively, and 2.15 μmoL/g was found in the Jeonnam Province sample. The 8-methoxypsoralen contents were 5.41 μmoL/g and 6.85 μmoL/g, while the bergapten contents were 13.42 μmoL/g and 44.44 μmoL/g in the samples from Jeonnam Province and Chungnam Province, respectively.

These regional differences in content could be due to climate and soil nutrient status. Composition changes due to climate change and environmental influences, in addition to regional differences, are challenges that need to be overcome in the future. The accumulation of secondary metabolites is influenced by factors, such as the presence of water, soil composition, and UV exposure [39]. Even within the same country, vulnerabilities are observed differently, such as Yeosu in Jeonnam Province being vulnerable to floods and Boryeong in Chungnam Province being vulnerable to heatwaves [40]. The limitation of this study is the lack of specific comparison regarding the reasons for such difference.

5. Conclusions

The present study was conducted to uncover the correlations between the collection region of GLF samples and their phytochemical compositions. It was found that the sample from Jeju Island had the highest total content of the compounds studied, followed by the sample from Chungnam Province and the sample from Jeonnam Province. A similar trend was found in the radical-scavenging activities for $ABTS^+$ and DPPH radicals, which helped to dig out the relationship between the contents of phenolic compounds and certain biological functions of the extracts. Specifically, the radical-scavenging activity and the content of compounds **1**–**3** were highest in the Jeju Island sample with IC_{50} values of 6.69 mg/mL against $ABTS^+$ and 10.26 mg/mL against DPPH, followed by the Chungnam Province sample and the Jeonnam Province sample. It was expected to be more affected by other substances than furanocoumarins because such compounds **4**–**6** were found to have no significant radical-scavenging activities for both $ABTS^+$ and DPPH radicals. A similar trend was found in the result of the HPLC analysis, which helps to establish the correlation between phytochemical contents and biological functions. The Jeju Island sample also had the highest total content of compounds **1**–**3** (31.16 μmoL/g), followed by the Chungnam Province sample (27.81 μmoL/g) and the Jeonnam Province sample (0.88 μmoL/g). The difference between the regions could be attributed to differences in their climate or soil nutrition.

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Conflicts of Interest: The authors declare no conflicts of interest.

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