biology and life sciences forum

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Proceeding Paper

Characterisation and Quantification of Phenolic Compounds in Honeys from Sierra Nevada (Granada) †

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† Presented at the 4th International Electronic Conference on Foods, 15–30 October 2023; Available online: https://foods2023.sciforum.net/.

Abstract: Some of the properties that have been attributed to honey are antioxidant, anti-inflammatory, and antimicrobial effects, especially due to its content of bioactive compounds, mainly phenolic compounds (PCs), whose content varies greatly depending on the variety, origin, agronomic conditions, harvest season, and climate. The aim of the present study is to characterise 21 honeys from Sierra Nevada (Granada). High-performance liquid chromatography coupled to quadrupole-time of flight mass spectrometry (HPLC-ESI-QTOF-MS) was used. Mass accuracy and true isotopic patterns in both MS and MS/MS spectra enabled the tentative identification of 58 PCs, including flavonoids, phenolic acids and derivatives. The average content of PCs was 83.01 ± 16.36 μg/g, with flavonoids accounting for more than 85%. The most abundant compounds were naringenin (16.88 ± 3.15 μg/g), pinocembrin (12.33 ± 2.92 μg/g), chrysin (12.21 ± 2.09 μg/g), carnosol (9.52 ± 2.90 μg/g), galangin (5.41 ± 1.68 μg/g), and apigenin (5.24 ± 0.89 μg/g). Due to this interesting composition, more studies are necessary to determine if the extreme environmental conditions of Sierra Nevada cause abiotic stress in the plants located there, fostering this concentration of PCs.

Keywords: honey; phenolic compounds; Sierra Nevada; HPLC-ESI-QTOF-MS

Citation: Palma-Morales, M.; Balzani, A.; Huertas, J.R.; Mercolini, L.; Rodríguez-Pérez, C. Characterisation and Quantification of Phenolic Compounds in Honeys from Sierra Nevada (Granada). *Biol. Life Sci. Forum* **2023**, *26*, 74. https://doi.org/10.3390/Foods2023-15513

Academic Editor: Joana Amaral

Published: 31 October 2023

1. Introduction

Honey, a natural product crafted by honeybees (Apis mellifera), is renowned for its nutritive and healthful qualities. Its composition exhibits considerable variability based on factors like botanical and geographical origin [1,2]. Honey primarily consists of sugars (constituting 80–85% of its composition), water (15–17%), and proteins (0.1–0.4%). Additionally, to a lesser extent, it contains enzymes, organic acids, vitamins, minerals, and phenolic compounds, all of which significantly contribute to its sensory and functional attributes [3]. Honey has been associated with various beneficial effects, including antioxidant, anti-inflammatory, and antimicrobial properties [4]. These health-promoting properties are particularly linked to its content of bioactive compounds, mainly phenolic compounds (PCs). PC content varies substantially depending on factors such as honey variety, origin, agronomic conditions, harvest season, and climate. Plants synthetise PCs

under both normal and stressful conditions, with functions that encompass attracting pollinating insects and safeguarding against pathogens and ultraviolet (UV) radiation [4]. Recent studies have reported a wide range of total phenolic content (TPC) values in honey, spanning from 6.5 ± 4.2 to 841.7 ± 304.0 μg/g [5]. While many researchers have analysed the content of bioactive compounds in some Spanish honeys, there are no previous studies on the content of those compounds in honeys from Sierra Nevada (Granada), where plants are exposed to extreme environmental conditions such as UV radiation, extreme temperatures, and altitude (hypoxia), which could influence the content of PCs. Thus, the aim of the present study is to characterise and quantify PCs in 21 honeys from Sierra Nevada, which is a national park with a great variety of vegetation exposed to abiotic stresses that could increase the concentration and/or variety of PCs contained in the honeys produced there.

2. Methodology

2.1. Extraction of Phenolic Compounds

The extraction of PCs was performed using a previously described method [6,7] with some modifications. Sixty grams of each of the selected honeys was mixed with 150 mL of acidified water (pH 2.0). The mixture was stirred for 10 min at room temperature on a magnetic stirrer and then filtered through cotton wool to remove solid particles. The filtrate was mixed with 40 g Amberlite XAD-2 and stirred for 10 min at room temperature on a magnetic stirrer. The Amberlite particles were packed in a 33 cm long, 24 mm inner diameter gravimetric column (Sigma-Aldrich). Then, the column was washed with 100 mL of acidic water (pH 2.0) and then with 300 mL of milliQ water. In this way, PCs present in the honey were retained in the column while sugars and other polar compounds were eluted with the aqueous solvent. To collect the phenolic fraction, 300 mL of methanol was used. Then, the phenolic fraction was dried in a rotary evaporator at a temperature of 30 °C. The residue was dissolved in 5 mL of milliQ water and extracted in triplicate with diethyl ether (5 mL × 3). The ether extracts were combined and the ether was removed with a rotary evaporator. The residue was dissolved in 1 mL of methanol, filtered through a 45μm membrane filter, transferred to an HPLC vial, and frozen at −20 °C until analysis.

2.2. Analysis of Phenolic Compounds

The analytical technique used was high-performance liquid chromatography coupled to mass spectrometry (HPLC-MS-MS/MS). Specifically, an Acquity HPLC system (Waters Corporation, Milford, MA, USA) coupled to an electrospray ionisation (ESI) source operating in negative mode and a quadrupole time-of-flight (QTOF) mass spectrometer (Waters) was used. To separate the compounds of interest effectively, an ACQUITY UPLC BEH Shield RP18 column (1.7 μm, 2.1 × 100 mm; Waters Corporation, Milford, MA, USA) was used. Acidified H_2O with 1% acetic acid and methanol as solvents A and B, respectively, were used for the mobile phases. A linear gradient was applied so that at the start, 95% of the mixture was solvent A and 5% was solvent B; at minute 30, 23.9% was solvent A and 76.1% solvent B; and at minute 33, 100% was solvent B. The initial conditions were maintained for 6 min before each analysis. Column temperature was maintained at 40 °C and the injection volume was 0.5 mL/min.

2.3. Characterisation of Phenolic Compounds

MassLynx 4.1 software (Waters Corporation, Milford, MA, USA) was used to process the chromatographic data. The characterisation strategy was based on the exact mass and fragment information provided by the compound-specific MS and MS/MS spectra determined by the QTOF mass analyser. For the acquisition of information on the chemical structure of the compounds, in addition to consulting previously published research, the following databases were used: SciFinder Scholar (http://scifinder.cas.org (accessed on 12 December 2023)), FoodDb (https://foodb.ca/ (accessed on 12 December 2023)), MassBank (http://massbank.jp (accessed on 12 December 2023)), Pubchem (https://pubchem.ncbi.nlm.nih.gov (accessed on 12 December 2023)), Metfrag (https://msbi.ipb-halle.de/MetFrag/

(accessed on 12 December 2023)), METLIN (http://metlin.scripps.edu (accessed on 12 December 2023)), National Institute of Standards and Technology (https://www.nist.gov/ (accessed on 12 December 2023)), and the National Institute of Health (NIH) database. Additionally, SIRIUS 4 (https://bio.informatik.uni-jena.de/sirius/ (accessed on 12 December 2023)) was used to obtain metabolite structure information. Six analytical standards (catechin, chlorogenic acid, ferulic acid, rutin, phloridizin, quercetin, phloretin, and vanillic acid) were employed to estimate the amount of phenolic compounds present in the honeys.

3. Results and Discussion

Fifty-eight phenolic compounds were characterized in the 21 honeys, including flavonoids, phenolic acids, and derivatives (Table 1).

The average TPC of the Sierra Nevada honeys analysed was 83.01 ± 16.36 μg/g, being above the average of other Spanish honeys such as Galician honeys, which contain an average of 38 μg/g [8]. Flavonoids accounted for more than 85% of the TPC. Figure 1 shows the content of phenolic acids, flavonoids, other phenolic compounds, and total phenolic compounds in each honey. The most abundant compounds were naringenin (16.88 ± 3.15 μg/g), pinocembrin (12.33 ± 2.92 μg/g), chrysin (12.21 ± 2.09 μg/g), carnosol (9.52 ± 2.90 μg/g), galangin (5.41 ± 1.68 μg/g), and apigenin (5.24 ± 0.89 μg/g). Naringenin is noted for its positive effects on the cardiovascular system through antioxidant, anti-inflammatory, antiatherogenic, and antiapoptotic actions [9]. Pinocembrin is a flavanone with antioxidant, antimicrobial, and anti-inflammatory properties, and has recently been studied for its potential to inhibit histidine decarboxylase as a new natural antiallergic drug candidate [10]. Chrysin has shown significantly greater antiproliferative activity on cancer cell growth than other compounds [11]. It also has antioxidant, antiobesity, anti-inflammatory, antidiabetic, and neuroprotective activity [12]. Carnosol is a phenolic diterpene with demonstrated antioxidant, anti-inflammatory, and anticancer activity [13,14]. Positive effects of carnosol have also been reported in ischaemic stroke by inhibiting apoptosis and attenuating oxidative damage and cellular inflammation [15]. The main positive effects of galangin are attributed to its anti-inflammatory, antioxidant, anticancer, and antineoplastic properties [16]. Apigenin has shown therapeutic functions through cell cycle arrest, apoptosis, and anti-inflammatory effects. In addition, apigenin contributes to counteracting oxidative stress by enhancing the expression of antioxidant enzymes such as glutathione synthase, catalase, and superoxide dismutase. After its absorption into the digestive tract, apigenin is able to reach the brain and could have antidepressant and antianxiety effects [17].

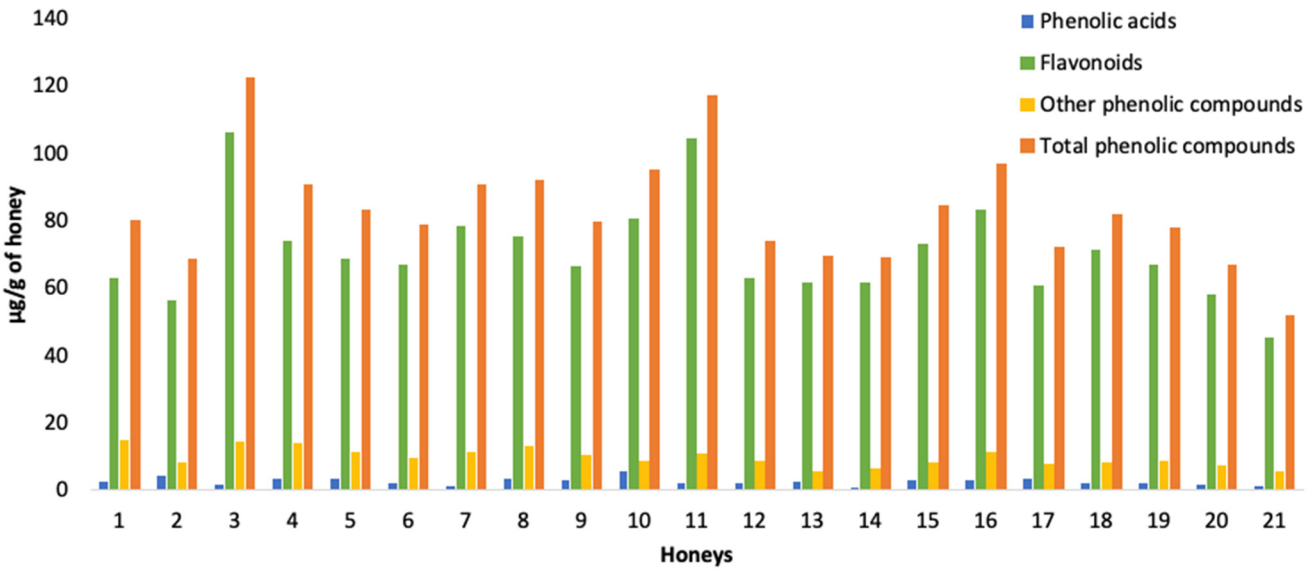

Figure 1. Content of phenolic compounds of Sierra Nevada honeys.

Table 1. Phenolic compounds characterised in the 21 honeys.

[M-H]$^-$	RT	Molecular Formula	Proposed Compound	Fragments	Reference
135.0433	2.189	$C_8H_8O_2$	Phenylacetic acid	117	[18]
135.0438	2.01	$C_8H_8O_2$	Vinylcatechol	134, 133, 105	[19]
137.0222	4.014	$C_7H_6O_3$	Hydroxybenzoic acid	93	[20]
153.0208	4.852	$C_7H_6O_4$	Protocatechuic acid	109, 137	[21]
163.0386	3.225	$C_9H_8O_3$	Cumaric acid (Isomer 1)	145, 119	[20]
163.0396	3.341	$C_9H_8O_3$	Cumaric acid (Isomer 2)	119, 117	[20]
165.0547	2.458	$C_9H_{10}O_3$	4-hydroxicinnamic acid	161, 133, 132, 122	[22]
165.0558	3.448	$C_9H_{10}O_3$	L-(-)-phenylactic acid	147	[23]
167.0337	2.065	$C_8H_8O_4$	Homogentisic acid	134, 137, 131, 117, 108	[24]
177.0181	1.769	$C_9H_6O_4$	Esculatin	145, 125, 120, 144	[25]
193.0495	2.095	$C_{10}H_{10}O_4$	Coniferic/ferulic acid	133	[26]
195.0659	1.995	$C_{10}H_{12}O_4$	4-methoxyphenylactic acid	133, 177, 149	[27]
197.0442	2.16	$C_9H_{10}O_5$	Siringic acid (Isomer 1)	106	[20]
197.0455	2.262	$C_9H_{10}O_5$	Siringic acid (Isomer 2)	121, 123	[20]
211.0599	4.875	$C_{10}H_{12}O_5$	Methylsyringate	181	[28]
221.0804	3.45	$C_{12}H_{14}O_4$	3-hydroxy-1-(2-methoxyphenyl)penta-1,4-dione (Isomer 1)	133	[29]
221.0811	3.605	$C_{12}H_{14}O_4$	3-hydroxy-1-(2-methoxyphenyl)penta-1,4-dione (Isomer 2)	133	[29]
223.0609	3.228	$C_{11}H_{12}O_5$	Sinapic acid	144, 116, 142, 160	[21]
223.0968	6.851	$C_{12}H_{16}O_4$	Vanillin 1,2-butylene glycol	151, 136, 108	[30]
253.0497	12.928	$C_{15}H_{10}O_4$	Chrysin	209, 143, 145, 119,195	[31]
255.0659	12.128	$C_{15}H_{12}O_4$	Pinocembrin	171, 133, 213, 134, 169	[32]
269.0439	10.498	$C_{15}H_{10}O_5$	Apigenin	117,149, 201, 145, 183, 107	[33]
269.0441	9.803	$C_{15}H_{10}O_5$	Baicalein	129, 143, 151	[25]
269.0445	13.681	$C_{15}H_{10}O_5$	Galangin	211, 239, 195,167, 151	[34]
271.0600	7.979	$C_{15}H_{12}O_5$	Pinobanksin	253, 197,225, 209, 125	[35]
271.0603	8.406	$C_{15}H_{12}O_5$	Naringenin	253,197, 161,125, 225	[20]
283.0597	11.218	$C_{16}H_{12}O_5$	Prunetin	211, 238, 167, 165	[36]
283.0604	13.878	$C_{16}H_{12}O_5$	Biochanin A	268, 211, 239, 269, 195	[37]
283.0605	13.469	$C_{16}H_{12}O_5$	Genkwanin	134, 175, 168, 148, 159	[38]
283.0969	13.161	$C_{17}H_{16}O_4$	Phenylethyl caffeate	135, 133, 161, 134	[34]
285.0381	10.787	$C_{15}H_{10}O_6$	Kaempferol (Isomer 1)	151, 184, 245, 255, 273	[39]
285.0392	6.831	$C_{15}H_{10}O_6$	Luteolin (Isomer 1)	151, 257	[40]
285.0394	13.682	$C_{15}H_{10}O_6$	Kaempferol (Isomer 2)	269, 268, 211, 239	[39]
285.0396	8.691	$C_{15}H_{10}O_6$	Luteolin (Isomer 2)	255, 133, 283, 151	[40]
285.0404	7.646	$C_{15}H_{10}O_6$	Kaempferol (Isomer 3)	255, 227, 211, 284	[39]
285.0408	9.135	$C_{15}H_{10}O_6$	Luteolin (Isomer 3)	241, 133	[40]
285.0772	12.291	$C_{16}H_{14}O_5$	5-O-Methylnaringenin	188, 191, 255, 243, 158	[20]
287.0555	5.52	$C_{15}H_{12}O_6$	Eriodictyol	161, 269, 251	[41]
299.0545	11.479	$C_{16}H_{12}O_6$	Kaempferide (Isomer 1)	284, 227, 256, 165, 269	[42]
299.0547	11.155	$C_{16}H_{12}O_6$	Kaempferide (Isomer 2)	284	[42]
301.0322	4.236	$C_{15}H_{10}O_7$	Quercetin	175, 183, 201, 225, 245	[42]
301.0339	4.077	$C_{15}H_{10}O_7$	Quercetin	255, 273, 213, 151	[42]
301.0354	9.343	$C_{15}H_{10}O_7$	Morin	273, 151, 257, 178, 255	[34]
301.0696	9.9400	$C_{16}H_{14}O_6$	Hesperetin (Isomer 1)	164	[43]
301.0713	5.3190	$C_{16}H_{14}O_6$	Hesperetin (Isomer 2)	151, 177	[43]
301.0717	5.4440	$C_{16}H_{14}O_6$	Hesperetin (Isomer 3)	177, 286	[43]
301.2008	8.5460	$C_{15}H_{10}O_7$	Tricetin	255, 151	[44]
315.0487	10.875	$C_{16}H_{12}O_7$	3-Methylquercetin/Isorhamnetin (Isomer 1)	241, 242, 270, 313, 300	[39]
315.0500	10.157	$C_{16}H_{12}O_7$	3-Methylquercetin/Isorhamnetin (Isomer 2)	300	[39]
315.0506	9.136	$C_{16}H_{12}O_7$	3-Methylquercetin/Isorhamnetin (Isomer 3)	241, 242, 270, 271, 300, 313	[39]
329.0650	9.824	$C_{17}H_{14}O_7$	Quercetin dimethyl ether (Isomer 1)	314	[45]
329.0664	11.956	$C_{17}H_{14}O_7$	Quercetin dimethyl ether (Isomer 2)	314	[45]
329.1744	15.415	$C_{20}H_{26}O_4$	Carnosol (Isomer 1)	285	[35]
329.1745	15.068	$C_{20}H_{26}O_4$	Carnosol (Isomer 2)	285	[35]
329.1753	15.708	$C_{20}H_{26}O_4$	Carnosol (Isomer 3)	285	[35]
329.1758	14.856	$C_{20}H_{26}O_4$	Carnosol (Isomer 4)	285	[35]
431.0974	7.651	$C_{21}H_{20}O_{10}$	Kaempferol-rharmnoside	285, 255, 227	[46]
461.1065	9.049	$C_{22}H_{22}O_{11}$	8-Methoxykaempferol 7-rhamnopyranoside	287, 299, 315, 259, 139	[46]

RT: retention time.

4. Conclusions

Due to the interesting composition of Sierra Nevada honeys, more studies are necessary to determine if the peculiar environmental conditions of Sierra Nevada, such as UV radiation, extreme temperature, or altitude (hypoxia), cause abiotic stress in the plants lo-

cated there, fostering an elevated concentration of PCs and thus increasing the antioxidant, antimicrobial, anti-inflammatory, and anticarcinogenic activity of these honeys.

Author Contributions: Conceptualization, C.R.-P.; investigation, M.P.-M. and A.B.; data curation, M.P.-M. and C.R.-P.; writing—original draft preparation, M.P.-M.; writing—review and editing, M.P.-M., A.B., J.R.H., L.M. and C.R.-P.; supervision, C.R.-P.; funding acquisition, J.R.H. All authors have read and agreed to the published version of the manuscript.

Funding: Contract for young research personnel financed by the Programa Operativo de Empleo Juvenil (Youth Employment Program) Ref: 8017, and contract to the Junta de Andalucía-Consejería de Universidad, Investigación e Innovación Research Project: P21_00777 M.P.-M.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data that support the findings of this study are available from the corresponding author, M.P.-M., upon reasonable request.

Acknowledgments: NUTRACMIEL research project (CDTI-FEDER 4162-00).

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

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