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ARTICLES

Determination of Phenolic Compounds in Medicinal Plants from the Lamiaceae Family

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Abstract—A procedure for the determination of Phenolic compounds in extracts from the medicinal plants of the Lamiaceae family—garden sage (*Salvia officinalis* L.), creeping thyme (*Thymus serpyllum* L.), wild marjoram (*Origanum vulgare* L.), and common balm (*Melissa officinalis* L.)—obtained under different extraction conditions was developed. The identification of the extracted compounds was performed and their qualitative and quantitative composition was established by HPLC with diode array and mass-spectrometric detection with consideration for the obtained characteristics of the standard samples of individual components. The test samples of medicinal herbs contained caffeic acid (0.19–0.62 mg/g) and rosmaric acid (4–23 mg/g); the highest rosmaric acid content (23 mg/g) was found in wild marjoram, and the lowest content (4 mg/g), in creeping thyme. The extracts of wild marjoram contained the greatest amounts of Phenolic compounds; rosmaric acid and luteolin-7-O-β-D-glucuronide were major components, whereas protocatechuic, 3-O-caffeoylquinic, and caffeic acids were minor components.

Keywords: medicinal herbs of the Lamiaceae family, garden sage, creeping thyme, wild marjoram, common balm, Phenolic compounds, extraction, HPLC, mass spectrometry

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Sage, thyme, wild marjoram, and balm are plants from the Lamiaceae family that are widely used in medicine. The essential oil of these medicinal plant raw materials is of special interest for pharmacology; it is used as spasmolytic, sedative, expectorant, antipyretic, and bactericidal agents [1–3]. The production of essential oil from Lamiaceae medicinal plant raw materials is reduced to hydrodistillation or steam distillation, and its qualitative and quantitative composition was studied in sufficient detail (Table 1).

Components such as phenol carboxylic and cinnamic acids and flavonoids are most frequently not taken into consideration in quality assessment procedures and studies of the pharmacological activity of Lamiaceae medicinal plant raw materials. On the other hand, the antioxidant and proliferating properties of sage are caused by the content of Phenolic substances [15].

Usually, the Phenolic components are extracted from the Lamiaceae medicinal plant raw materials under varied conditions. Procedures for the extraction of Phenolic components are maceration, ultrasonic extraction, extraction at elevated pressures, etc. [16–24] with the use of different extractants [25–27]. Pharmacopoeia articles [28–30] specify total flavonoids in terms of luteolin or its glycoside as a quantitative quality index for thyme and wild marjoram. However, the contributions of individual Phenolic compounds to this index are of undoubted interest for evaluating the pharmacological activity of medicinal plant raw materials; for this purpose, it is necessary to determine their concentrations. Liquid chromatography with spectrophotometric [31–35] and mass-spectrometric (MS) detection [16, 36, 37] and a combination of several detection techniques with the application of NMR spectroscopy, which increases the reliability of analyte identification [17–20], are used for this purpose (Table 2).

The identification of Phenolic compounds in garden sage by a comparison of the UV spectra and retention times of analytes and reference samples was described [25, 31, 32, 38]. This approach was used for establishing the qualitative composition of the extracts of garden sage and the presence of acids such as gallic acid, vanillic acid, ferulic acid, and other phenol carboxylic and cinnamic acids in them. However, the majority of the above phenolic acids were not identified in garden sage with the use of MS and NMR-spectroscopic techniques [17–19]; because of this, it is difficult to establish the authentic qualitative composition and to develop general approaches to its standardization. Analogous identification problems also occur in the cases of wild marjoram [20, 27, 34, 37] and common balm [16, 35, 39]. In this context, in spite of the interest of researchers in the Lamiaceae

Table 1. Data on the study of the qualitative composition of the essential oil of medicinal plant raw materials from the Lamiaceae family

Medicinal plant raw material	Number of identified compounds	Essential oil extraction method	Determination technique	References
Rosmarinus officinalis L. *Salvia officinalis* L.	50	Hydrodistillation	GC–MS	[4]
Salvia L.	15	The same	GLC–FID	[5]
S. macroclamys, S. verticillata, ssp. *amasiaca, S. virgata, S. multicaulis, S. firigida, S. microstegia, S. kronenburgii*	33	"	GC–MS	[6]
Salvia officinalis L.	27	Steam distillation	GC–MS	[7]
Thymus L.	66	Hydrodistillation	GC–MS	[8]
Origanum spp. L.	52	Steam distillation	GC–MS	[9]
Origanum rotundfolium L.	39	Hydrodistillation	GC–MS	[10]
Origanumvulgare L.	40	Steam distillation	GC–MS, HPLC–DAD	[11]
Melissa officinalis L.	43	Hydrodistillation	GC–MS	[12]
Melissa officinalis L.	52	The same	GC–MS	[13]
Melissa officinalis L.	33	"	GC–MS	[14]

Designations: GC–MS, gas chromatography with mass-spectrometric detection; GLC-FID, gas–liquid chromatography with a flame-ionization detector; and DAD, a diode array detector.

plant materials, data on the qualitative composition of the Phenolic compounds of garden sage, creeping thyme, wild marjoram, and common balm are contradictory, and they should be refined.

Data on the concentrations of individual Phenolic compounds in medicinal plants within a family are also insufficiently studied and contradictory. Thus, conditions for the extraction and determination of the Phenolic compounds of different plants from the Lamiaceae family were compared [25, 40, 41]; however, either methods for the determination of total Phenolic acids and flavonoids or liquid chromatography with UV and visible region detection without the application of other detailed identification methods are used for these purposes.

The aim of this work was to identify the Phenolic compounds extracted from garden sage (*Salvia officinalis* L.), creeping thyme (*Thymus serpyllum* L.), wild marjoram (*Origanum vulgare* L.), and common balm (*Melissa officinalis* L.) of the Lamiaceae family using different extraction methods.

EXPERIMENTAL

The samples of garden sage (*Salvia officinalis* L.), creeping thyme (*Thymus serpyllum* L.), wild marjoram (*Origanum vulgare* L.), and common balm (*Melissa officinalis* L.) of the Travy Kavkaza trade mark (Goryachii Klyuch, Krasnodar krai) were used as test materials. Before the extraction of Phenolic compounds, the source materials were ground to sizes of 0.5–1 mm.

Chemical reagents, solvents, and standard reference samples. Acetonitrile (high-purity grade from Kriokhrom) and imported concentrated formic acid (Len-Reaktiv) were used for the chromatography of the samples. High-purity rectified ethanol was used for the extraction. Deionized water was obtained on a Milli-Q-UV system (Millipore, France). The following standard reference samples were used for identification and calibration purposes: protocatechuic acid (≥97%), chlorogenic acid (≥95%), neochlorogenic acid (≥98%), rosmaric acid (≥96%), caffeic acid (≥98%), carnosic acid (≥97%), luteolin-7-O-glycoside (≥98%) (Sigma-Aldrich, Germany), and luteolin-7-O-β-D-glucuronide (≥85%) (HWI ANALYTIK GmbH, Germany). Gallic acid (≥99%), vanillic acid

Table 2. Determination of Phenolic compounds in the Lamiaceae medicinal plant raw materials

Medicinal plant raw material	Analytes	Extraction	Determination technique	References
Salvia officinalis L.	Phenolic acids, flavonoids, and coumarins	Extraction with methanol	HPLC–DAD	[31]
Salvia L.	Phenolic acids	Maceration, ultrasonic extraction (methanol, 2-propanol)	HPLC–DAD	[32]
Salvia officinalis L.	Phenolic acids	Water bath (water)	HPLC–DAD, GC–MS	[33]
Origanum vulgare L.	Flavones	Water bath (acetone)	TLC, HPLC–UV/Vis	[34]
Melissa officinalis L.	Benzoic acids	Soxhlet extraction (methanol–water)	HPLC–DAD	[35]
Thymus L.	Flavonoids	Infusion (diethyl ether)	HPLC–DAD–MS	[36]
Origanum vulgare L.	Phenolic acids and flavonoids	Infusion, concoction (water), alcohol extraction	HPLC–DAD–MS	[37]
Melissa officinalis L.	Caffeic acid derivatives, polyphenols, etc.	Enzymatic extraction, solvent extraction under pressure	HPLC–DAD–MS/MS	[16]
Rosmarinus officinalis L., *Salvia officinalis* L.	Diterpenes, flavonoids, triterpenoids, etc.	Soxhlet extraction (hexane, ethyl acetate)	HPLC–DAD–MS^n, NMR	[17]
Salvia officinalis L.	Diterpenes and their derivatives	Oleoresin	Semipreparative HPLC–DAD, IR, MS, NMR	[18]
Salvia officinalis L.	Phenolic acids, flavonoids, etc.	Infusion (ethanol)	LC, IR, MS, NMR	[19]
Origanum vulgare L.	Hydroxybenzoic acids, caffeic acid derivatives, etc.	Percolation (ethanol)	TLC, HPLC, preparative HPLC, IR, MS, NMR	[20]

Designations: TLC, thin-layer chromatography; LC, liquid chromatography.

(≥99.7%), *p*-coumaric acid (≥99.5%), 4-hydroxybenzoic acid (≥98%), and cinnamic acid (≥99.7%) (Sigmabiosintez) and *trans*-ferulic acid (≥99%) and rutin (≥95%) (Sigma-Aldrich, Germany) were also used for the identification of components.

Instrumentation. The chromatographic determination of Phenolic compounds in the extracts of medicinal plant raw materials was conducted using an LC-20 Prominence HPLC system (Shimadzu, Japan) with an SPD-M20A spectrophotometric diode array detector and an LCMS2010EV mass-spectrometric detector. A Luna C18 100A column (250 × 2.0 mm; 5 μm; Phenomenex, the United States) and a C18 precolumn (5 μm, 4 × 2.0 mm; Phenomenex, the United States) were used for the separation of Phenolic compounds.

A UZV–4.0/1 TTTs ultrasonic bath (Sapfir) was used for the extraction of components from medicinal plant raw materials, and an ETHOS EX microwave extraction system (Milestone, Italy) was used for microwave exposure. The experimental system described previously [42] was used for the dynamic extraction of Phenolic compounds at elevated temperature and pressure. The resulting extracts were collected in glass vessels.

Parameters of the HPLC determination of Phenolic compounds. The conditions of chromatographing and detecting Phenolic compounds were analogous to those described elsewhere [43]. The gradient elution conditions were different with consideration for the specific character of the analyzed plant samples: 0–2 min, from 95 to 90% W; 2–2.01 min, 90% W; 2.01–10 min, from 90 to 80% W; 10–18 min, from 80 to 70% W; 18–28 min, from 70 to 10% W; 28–30 min, 10% W; 30–31 min, 10–95% W; and 31–35 min, 95% W. Electrospray ionization was used in the MS detection of substances. The mass spectra were obtained under the conditions of negative ion monitoring in an m/z range of 120–720 with a scanning frequency of 2000 amu/s. Data were processed using the LCMS Solution software (Shimadzu, Japan).

The calibration functions for the HPLC–DAD system were obtained for the protocatechuic acid, chlorogenic acid, neochlorogenic acid, rosmaric acid, caffeic acid, carnosic acid, luteolin-7-O-glycoside, and luteolin-7-O-β-D-glucuronide with the use of standard samples. The linearity of response signals

Table 3. Metrological characteristics of a procedure for the determination of Phenolic compounds in the medicinal plants

Compound	Analytical range, μg/mL	Determination limit, μg/mL	Detection limit, μg/mL
Protocatechuic acid	0.8–100	0.78	0.13
5-O-Caffeoylquinic acid	0.5–100	0.49	0.10
3-O-Caffeoylquinic acid	0.6–100	0.60	0.10
Caffeic acid	0.2–100	0.24	0.12
Luteolin-7-O-glycoside	0.4–100	0.36	0.19
Luteolin-7-O-β-D-glucuronide	0.5–200	0.48	0.30
Rosmaric acid	0.3–200	0.25	0.16
Carnosic acid	0.8–100	0.75	0.28

was determined for 10–11 concentration levels of protocatechuic acid, chlorogenic acid, neochlorogenic acid, caffeic acid, carnosic acid, and luteolin-7-O-glycoside and for 15 concentration levels of the solutions of the main components rosmaric acid and luteolin-7-O-β-D-glucuronide in 70% ethanol; in each particular case, no less than three parallel measurements were carried out for a solution concentration. All of the calibration functions were constructed based on the data of six parallel measurements; their correlation coefficients were ≥0.999.

Extraction of Phenolic compounds. Phenolic compounds were extracted from garden sage, creeping thyme, wild marjoram, and common balm under the following conditions: (1) batch extraction on heating (I) analogously to pharmacopoeia requirements [28–30]; (2) batch extraction under the action of ultrasound (II) analogously to previously chosen conditions [43]; (3) batch microwave extraction of Phenolic compounds (III) analogously to previously chosen conditions [43]; and (4) dynamic extraction of Phenolic compounds on heating under pressure (IV) analogously to previously chosen conditions [43].

Before chromatographing, the extracts prepared were centrifuged and filtered through a Whatman polypropylene filter (pore size, 0.45 μm).

RESULTS AND DISCUSSION

Metrological characteristics of a procedure for the determination of Phenolic compounds in the medicinal plants. The main metrological characteristics of the results of the determination of Phenolic compounds with the use of standard samples were determined with consideration for the above conditions of chromatographing and detecting Phenolic compounds (Table 3). The calibration functions for rosmaric acid and luteolin-7-O-β-D-glucuronide were linear to 200 μg/mL or to 100 μg/mL for protocatechuic, chlorogenic, neochlorogenic, caffeic, and carnosic acids and luteolin-7-O-glycoside.

Identification of Phenolic compounds in the test medicinal plants. The identification was based on the following three measured parameters: retention time, UV spectrum, and mass spectrum. For this purpose, the extracts of medicinal plants containing different phenol carboxylic and cinnamic acid, flavonoids, and diterpenes were analyzed. Table 4 summarizes the results of the identification of Phenolic compounds in the extracts of garden sage *Salvia officinalis* L.), creeping thyme (*Thymus serpyllum* L.), wild marjoram (*Origanum vulgare* L.), and common balm (*Melissa officinalis* L.).

Quinic acid, 3,4-dihydroxyphenyllactic acid, caffeic acid, and rosmaric acid, which is a characteristic marker of this family of plants [50], were identified in all of the test samples of medicinal plant raw materials. In creeping thyme, 3-O-, 4-O-, and 5-O-caffeoylquinic acids were also identified, whereas only 3-O-caffeoylquinic acid was identified in wild marjoram.

Taking into account published data [25, 31, 32, 38], for establishing the possible concentrations of gallic, *trans*-ferulic, vanillic, *p*-coumaric, 4-hydroxybenzoic, and cinnamic acids in the extracts of plants, we chromatographed the extracts with the use of the standard samples of these compounds in the gradient elution mode with increasing the fraction of acetonitrile in the eluant from 5 to 90% and with a 100% aqueous phase content at the first step of the gradient elution mode. These experiments resulted in the absence of the above components.

Quantitative evaluation of the concentrations of Phenolic compounds in the medicinal plants under the conditions of their extraction. For evaluating the concentrations of Phenolic compounds in the medicinal plants under the conditions of their extraction, we analyzed medicinal plant raw materials by different methods based on sage as an example; we used a pharmacopoeia procedure, ultrasonic extraction, microwave and subcritical extractions at a fixed ratio between the weight of raw material and the extractant volume (1 : 50) and a constant extractant composition (70% ethanol, by volume). Table 5 summarizes the results. The great relative standard deviations (s_r) for carnosic acid, as compared with those for other substances, are due to its instability under the action of

Table 4. Results of the identification of Phenolic compounds in the medicinal plants

Phenolic compound	Garden sage (*Salvia officinalis* L.)	Creeping thyme (*Thymus serpyllum* L.)	Wild marjoram (*Origanum vulgare* L.)	Common balm (*Melissa officinalis* L.)
Quinic acid	+ [25]*	+	+	+
3,4-Dihydroxyphenyllactic acid (*Danshensu*)	+ [44]	+	+	+ [16, 39]
Protocatechuic acid	+ [24]	+ [45]	+ [37, 27]	+ [16, 35, 26]
5-O-Caffeoylquinic acid	–**	+	–	–
Chicoric acid	+	–	–	–
Protocatechuic aldehyde	+	+	+	+
Caftaric acid	–	–	–	+ [16]
3-O-Caffeoylquinic acid	–	+ [45, 46]	+ [37]	–
4-O-Caffeoylquinic acid	–	+	-	–
Caffeic acid	+ [24, 25, 38, 44]	+ [45–47]	+ [27, 41]	+ [16, 26]
Luteolin-7-O-β-D-rutinoside	+ [25]	+ [47]	-	-
Salvianolic acid derivative	–	–	–	+ [26]
Rutin	–	+ [45, 46]	–	–
Luteolin-7-O-glycoside	+ [24, 48]	+ [45, 46]	–	+ [49]
Luteolin-7-O-β-D-glucuronide	+ [48]	+ [45, 47]	+ [37]	–
3,5-Dicaffeoylquinic acid	–	+	–	–
Apigenin-7-glycoside	+ [17, 24]	–	–	+
Rosmaric acid	+ [17, 19, 24, 25, 38, 44]	+ [45–47]	+ [27, 37, 41]	+ [16, 26, 49]
Apigenin 7-glucuronide	+	+ [45]	+ [37]	–
Lithospermic acid	–	–	–	+ [16, 39]
Luteolin	+ [24, 31]	+ [45, 47]	+ [34]	+
Apigenin	+ [17, 24, 31]	+ [46]	+ [34]	–
Gispidulin	+ [17, 38]	–	–	–
Carnosol	+ [17, 18, 23, 38]	+	–	–
Carnosic acid	+ [17, 18, 23, 25, 38]	+	–	–
Methyl carnosate	+ [17, 18, 38]	+	–	–

* Reference to analogous published data.

** The component was not detected.

external factors (light, atmospheric oxygen, etc.) already at the stage of extraction [18, 23, 52].

Taking into account the fact that the extraction of components with the use of method IV was maximal, we studied the dynamic extraction of Phenolic compounds from the samples of creeping thyme, common balm, and wild marjoram. Table 6 summarizes the results of the determination of Phenolic compounds in the extracts obtained. Based on these studies, we can conclude that a comparison of the UV spectra and retention times of analytes and standard samples is insufficient for the identification of Phenolic compounds in the medicinal raw materials. The additional use of mass-spectrometric data makes it possible to carry out this procedure with higher reliability. Table 6 indicates that all of the test samples were characterized by the presence of caffeic and rosmaric acids; the greatest and smallest concentrations of rosmaric acid were found in wild marjoram and creeping thyme, respectively. The maximum quantities of some Phenolic compounds were found in wild marjoram, where the major component concentrations were 23 ± 2 mg/g for rosmaric acid and 19 ± 1 mg/g for luteolin-7-O-β-D-glucuronide; protocatechuic, 3-O-caffeoylquinic, and caffeic acids were determined as minor components. A concentration of luteolin-7-O-

Table 5. Results (mg/g) of the determination of Phenolic compounds in garden sage (*Salvia officinalis* L.) under the conditions of extraction methods I–IV ($n = 5$, $P = 0.95$)

Compound	I		II		III		IV	
	mg/g*	s_r	mg/g*	s_r	mg/g*	s_r	mg/g*	s_r
Caffeic acid	0.41 ± 0.02	0.020	0.27 ± 0.02	0.047	0.49 ± 0.03	0.023	0.52 ± 0.05	0.042
Luteolin-7-O-glycoside	0.43 ± 0.03	0.032	0.40 ± 0.04	0.080	0.75 ± 0.07	0.035	0.55 ± 0.05	0.037
Luteolin-7-O-β-D-glucuronide	5.9 ± 0.1	0.008	3.4 ± 0.3	0.070	5.8 ± 0.2	0.013	6.0 ± 0.4	0.026
Rosmaric acid	6.2 ± 0.1	0.009	5.1 ± 0.3	0.047	5.8 ± 0.5	0.036	6.5 ± 0.1	0.006
Carnosic acid	3 ± 1	0.149	3.7 ± 0.6	0.122	3.4 ± 0.7	0.082	4 ± 2	0.041

* Weights are given on a dry matter basis [51].

Table 6. Results (mg/g) of the determination of Phenolic compounds extracted by method IV from the medicinal plant raw materials ($n = 5$, $P = 0.95$)

Phenolic compound	Garden sage (*Salvia officinalis* L.)	Creeping thyme (*Thymus serpyllum* L.)	Wild marjoram (*Origanum vulgare* L.)	Common balm (*Melissa officinalis* L.)
Protocatechuic acid	ND*	ND	0.68 ± 0.06	0.10 ± 0.01
5-O-Caffeoylquinic acid	ND	0.10 ± 0.02	ND	ND
3-O-Caffeoylquinic acid	ND	0.69 ± 0.20	0.3 ± 0.1	ND
Caffeic acid	0.52 ± 0.05	0.19 ± 0.01	0.62 ± 0.01	0.5 ± 0.1
Luteolin-7-O-glycoside	0.55 ± 0.05	0.20 ± 0.03	ND	0.31 ± 0.02
Luteolin-7-O-β-D-glucuronide	6.0 ± 0.4	4.0 ± 0.7	19 ± 1	ND
Rosmaric acid	6.5 ± 0.1	4.0 ± 0.7	23 ± 2	14 ± 2
Carnosic acid	4 ± 2	0.07 ± 0.04	ND	ND

* ND denotes that the compound was not detected.

β-D-glucuronide comparable with that of rosmaric acid was found in the samples of sage, thyme, and wild marjoram.

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