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Method Article

The method of establishing the authenticity and quality of *Hypericum perforatum* L. and *Salvia officinalis* L.

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A B S T R A C T

The paper presents methods for the criteria for quality control, authenticity and stability of preparations and raw materials based on *Hypericum perforatum* L. and *Salvia officinalis* L. Various methods of extracting the most valuable components that make up the studied plants, as well as methods for their chromatographic determination, were proposed, metrological characteristics were obtained.

- The criteria for quality control and stability of drugs and raw materials were substantiated
- The ratio of rutin to hyperforin determines the quality of *Hypericum perforatum* L.
- The ratio of carnosic acid to carnosol characterizes Salvia officinalis L.

A R T I C L E I N F O

Method name: The method of establishing the authenticity and quality of *Hypericum perforatum* L. and *Salvia officinalis* L.
Keywords: *Hypericum perforatum* L., *Salvia officinalis* L., HPLC-DAD-MS, Hyperforin, Rutin, Carnosic acid, Carnosol, quality, Authenticity
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Method details

This paper accompanies the paper entitled "Stability of some biologically active substances in extracts and preparations based on St. John's Wort (*Hypericum perforatum* L.) and sage (*Salvia officinalis* L.)" [1].

Background

A large variety of preparations based on medicinal plant raw materials are available on the pharmaceutical market. Among them, preparations based on St. John's Wort (*Hypericum perforatum* L.) and sage (*Salvia officinalis* L.) occupy a special niche. *Hypericum perforatum* L. has one of the leading positions on the pharmaceutical market, in particular, its extracts are the best-selling herbal medicines in the world for the treatment of depressive conditions in humans [2–7]. The main components responsible for this type of activity are phloroglucinols and naphthodianthrons, which are unstable and are subject to degradation under the influence of external factors [8,9] as well as possible natural variability among the same species [10]. A wide range of biologically active substances are present in *Salvia officinalis* L.: anthocyanins, phenolic acids, flavonoid glycosides and others. The authors [11–13] noted anti-inflammatory, antimicrobial activity against a number of neurological diseases. In most publications on sage, the component composition of essential oil is analyzed [14,15], while phenolic acids and flavonoids are studied to a lesser extent, although there is evidence [16] that the antioxidant properties of sage are due to the presence of these compounds.

Evaluation of the authenticity and quality of raw materials used in the manufacture of medicines is highly relevant, since falsification of products is observed by introducing other plant chemotypes [17] or using other plant species [18]. The issues of active substances stability during storage of plant material, obtaining extracts and preparations based on it, as well as the establishment of degradation products are very problematic.

Materials and method

Samples

St. John's Wort (*Hypericum perforatum* L.) from OAO Krasnogorskleksredstva (lot № 012015) (Moscow Region, Krasnogorsk), OOO Travy Kavkaza (lot № 030415) (Herbs of the Caucasus, Krasnodar Region, Goryachy Klyuch), OOO PKF FitoFarm (lot № 010213) (Krasnodar Region, Anapa), OOO Valery (lot № 3515) (Rostov Region, Oblivskaya), ZAO Ivan-chai (lot № 020514) (Moscow, Gorki-Leninskiye Settlement), OOO Faros-21 (lot № 05022015) (Krasnodar Region, Krasnodar) was used. Sage (*Salvia officinalis* L.) produced by OOO Travy Kavkaza (lot № 122014) (Herbs of the Caucasus, Krasnodar Region, Goryachy Klyuch), PKF OOO FitoFarm (lot № 040714) (Krasnodar Region, Anapa), ZAO Zdorovie (lot № 111214) (Moscow Region, Nakhabino village), OOO Altai Farm (lot № 10114) (Altai Region, Barnaul), OOO Faros-21 (lot № 05112014) (Krasnodar Region, Krasnodar) was used throughout the experiment. Medicinal preparations containing *Salvia officinalis* L.: NaturProdukt resorption tablets (lot № 046890417) (Herkel B.V. (Netherlands)), VitaLife lozenges (lot № 042020) (Guslitsa LLC, Russia)

and FarmProduct biologically active food supplement (lot № 020917) (Pharmproduct LLC, Russia) were used.

Before analysis, raw material and medicinal preparations were ground to a particle size of 0.5–1 mm.

Chemicals and materials

Acetonitrile (HPLC-S, BiosolveBV, Netherlands), formic acid (85%, LenReactiv, Russia) were used for HPLC. Ascorbic acid (imp., OAO Reaktiv, Russia) and ethyl alcohol (rectified, 95–96%) were used for extraction. A Milli-Q-UV (Millipore, France) installation was used to produce deionized water with a resistivity of 18.2 MΩ·cm (at 25 °C).

For the identification of components, the following standard samples were used: hyperforin (purity ≥ 85%, lot № SLBD8421V), carnosic acid (≥ 97%, lot № BCBN2021V), protocatechuic acid (≥ 97%, lot № BCBK6716V), chlorogenic (3-O-caffeoylquinic) acid (≥ 95%, lot № 110M1174V), neochlorogenic (5-O-caffeoylquinic) acid (≥ 98%, lot № BCBF0422V), (-)-epicatechin (≥ 97%, lot № BCBN0886V), I3,II8-biapigenin (≥ 95%, lot № BCBJ7473V), rutin (≥ 95%, lot № 1380505V), rosmarinic acid (≥ 96%, lot № BCBN6363V), caffeic acid (≥ 98%, lot № MKBR1977V), luteolin-7-*O*-glycoside (≥ 98%, lot № BCBP5178V) (Sigma-Aldrich, Steinheim, Germany), quercetin (≥ 95%, lot № R035P0) (USP, Rockville, USA), carnosol (≥ 98.7%, lot № 00003199-080) (ChromaDex, Irvine CA, USA) and hyperoside (≥ 93.51%, batch № HWI00286-1), hypericin (≥ 89.76%, batch № HWI01272), isoquercitrin (≥ 96.23%, batch № HWI00960), quercitrin (≥ 91.7%, batch № HWI01112), luteolin-7-*O*-β-D-glucuronide (≥ 85%, batch № HWI01321-1) (HWI ANALYTIK GmbH, Rülzheim, Germany).

Each sample was dissolved in acetonitrile to prepare the stock solution. Working solutions for obtaining calibration curves were prepared by serial dilution of stock solutions with 70% ethanol in chromatography vials.

Instrumentation

The analysis was performed using an LC 20 Prominence chromatograph (Shimadzu, Japan) consisting of a DGU-20A5 degasser, an LC20AD pump, an SIL-20A automatic dispenser, a CTO-20AC column thermostat, an SPD-M20A diode array spectrophotometric detector, an LCMS2010EV quadrupole mass detector (nebulizer and drying gas is nitrogen). The chromatographic separation of phenolic acids, flavonoids and diterpenes was carried out using a Luna C18, 100 Å column (250 × 2.0 mm, 5 μm), protected with a C18 precolumn (4 × 2.0 mm, 5 μm) (Phenomenex, United States). The chromatographic separation of hyperforin and hypericin derivatives was carried out using an Onyx Monolithic C18 column (50 × 2.0 mm) with an Onyx C18 monolithic precolumn (4 × 2.0 mm) (Phenomenex, United States). The compounds were identified using UV spectra as well as the retention times related to the retention times of standard substances. Quantitative data in two selected chromatographic separation systems were obtained using calibration curves of the compounds. The data were processed in the LCMS Solution software (Shimadzu, Japan).

The components of raw materials were extracted using a UZV-4.0/1 TTTs ultrasonic bath (Sapfire, Russia) or an ETHOS EX installation for microwave extraction (Milestone, Italy). For the dynamic extraction of biologically active substances at elevated temperature and pressure, we used a pilot plant consisting of a tubular electric heater, the temperature of which was maintained with a TRM-101 electron unit, and a thermoelectric converter. The extractant was pumped by an LC20AD liquid chromatography pump (Shimadzu, Japan); a steel case of chromatographic column (150 × 4.6 mm) was used as an extraction cell, which was connected to the installation by means of two steel capillaries. To prevent the boiling of extractant and to maintain the desired pressure in the system, a *P*-455 backpressure limiter (Upchurch Scientific, United States) was used. The nominal backpressure of the limiter was 68 atm upon passing water at a flow rate of 1 mL/min. The extract was collected in glass containers at the output from the system.

Sample extraction

The extraction of sage by heating on a water bath was carried out according to the pharmacopoeia requirements [19]. A 1.0 g sample of ground raw material was placed in a conical flask with a capacity of 250 ml, then 100 ml of 70% ethanol was added. The flask was attached to a reflux condenser, heated in a boiling water bath for 60 min and periodically shaken to flush the particles of raw material from the walls. Then, the resulting extract was filtered through cotton wool into a 100 ml flask. Then, it was cooled to room temperature and, if necessary, brought to the initial mass with alcohol.

The extraction of hypericum by heating on a water bath was carried out according to the pharmacopoeia requirements [20]. A 1.0 g sample of ground raw material was placed in a conical flask with a thin section with a capacity of 250 ml, 30 ml of 50% ethanol was added. The flask was attached to a reflux condenser, heated in a boiling water bath for 30 min and periodically shaken to flush the particles of raw material from the walls. Then, the resulting extract was filtered through cotton wool into a 100 ml flask so that the particles of the raw material did not fall on the cotton wool. 30 ml of 50% ethanol was added to the extraction flask and the extraction was repeated twice more under the conditions described above, the extract was filtered into the same volumetric flask. After cooling, the volume of the extract was brought up to the mark with 50% ethanol and mixed.

Ultrasound extraction (USE): 0.5 g of ground raw material was placed in a conical flask, 25 ml of 70% ethanol was added, and the flask was placed in an ultrasonic bath for 30 min. After that, the resulting extract was filtered through cotton wool into a 25 ml flask. The raw material in the flask was washed several times with eluent, the resulting solution was adjusted to the mark.

Microwave extraction (MWE): A weighed portion of ground raw material weighing 0.5 g was poured into quartz flasks, 25 ml of 70% ethanol was added, and this mixture was placed in a microwave extraction unit for 30 min (excluding solvent preheating). After that, the obtained extracts were cooled to room temperature, filtered into 25 ml flasks through cotton wool and adjusted to the mark with 70% ethanol.

For dynamic extraction with heating and pressure (DEHP) a portion of raw material (0.2 g) was placed in the extraction cell; the inlet and outlet capillaries were connected. 70% ethyl alcohol solution was purged with nitrogen to remove dissolved oxygen; then the system was filled with the extractant using a pump, and the heating to 120 °C was turned on. Next, 70% ethanol was fed into the system at a flow rate of 1 mL/min. A typical value of pressure in the system, according to pump pressure gauge readings, was 100–150 atm.

Note: in all methods for the extraction of compounds, the sample: extractant ratio was 1:50 with the exception of extraction of raw materials by heating on a water bath-the sample: extractant ratio was 1:100.

The effect of the stabilizer on the stability of carnosic acid and carnosol: a 0.5 g sample of ground raw material was placed in a conical flask, 25 ml of 70% ethanol containing 5% ascorbic acid was added, and the flask was placed in an ultrasonic bath for 30 min. After every 5 min of extraction, 0.5 ml of the obtained extract was taken into a vial. After 30 min, the extract was filtered through cotton wool into a 25 ml flask, the raw material was poured with a new portion of the eluent and put in an ultrasonic bath for 30 min. Sampling was carried out similarly to the method described above. The total extraction time was 90 min.

Sample preparation of drugs: a sample of the drug was ground, placed in a 10 ml volumetric flask, 70% ethyl alcohol was added and placed in an ultrasonic bath for 30 min.

0.20 or 0.45 μm nylon filters were used to filter the extracts before HPLC analysis (Millipore, USA).

HPLC analysis of phenolic compounds

(a) Conditions of the HPLC-DAD-ESI-MS determination of biologically active substances of Hypericum perforatum *L*

System 1: The conditions for determining phenolic acids and flavonoids were the same as described in [21]. Acetonitrile (A) and water containing 0.1% formic acid (B) were the components of the mobile phase. The following gradient elution mode was set: 0–2 min, from 95 to 90% of B; 2–2.01 min, 90%

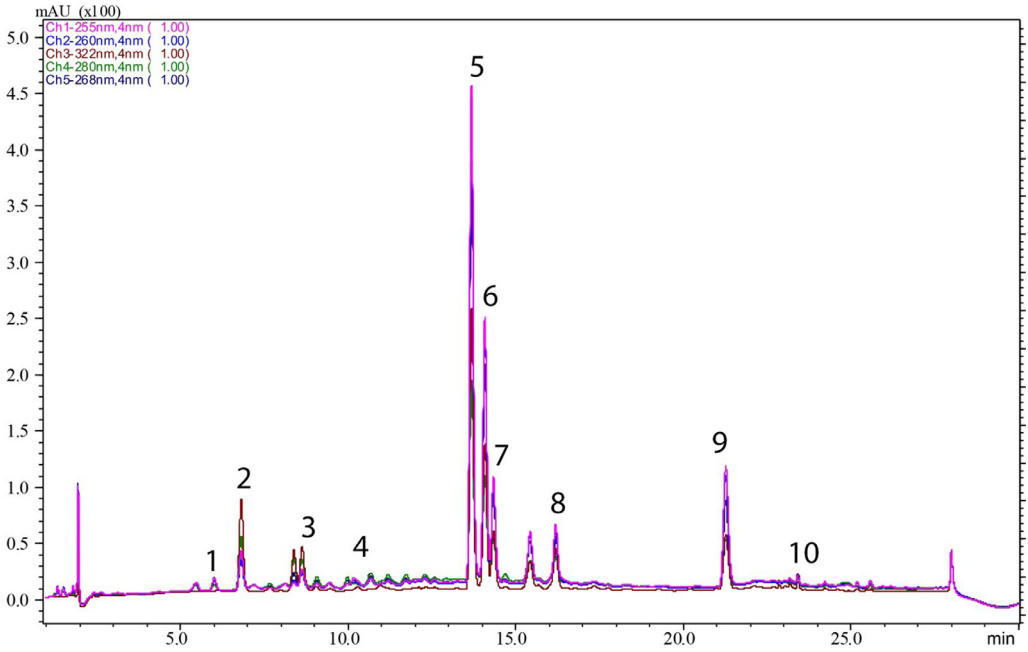

Fig. 1. Chromatogram of *Hypericum perforatum* L. extract obtained by HPLC-DAD (Separation system 1): 1 – Protocatechuic acid; 2 – Neochlorogenic acid; 3 – Chlorogenic acid; 4 – (-)-epicatechin; 5 – Rutin; 6 – Hyperoside; 7 – Isoquercitrin; 8 – Quercitrin; 9 – Quercetin; 10 – I3,II8-biapigenin.

of B; 2.01–10 min, from 90 to 80% of B; 10–18 min, from 80 to 70% of B; 18–25 min, from 70 to 10% of B, and 25.05–30 min, 95% of B. The mobile phase flow rate was 0.4 mL/min. The column oven temperature was 40 °C; the sample injection volume was 5 μL. Data were collected using a diode array detector (DAD) in the range of 190–800 nm. The parameters of the mass spectrometric (MS) detector were the following: interface voltage, 4.5 kV; detector voltage, 2.0 kV; desolvation line temperature, 200 °C; drying gas flow rate (nitrogen), 1.5 L/min; electrospray ionization. Spectra were recorded in the negative ion mode in the *m/z* range of 120–650 at the scanning frequency of 2000 amu/s. The chromatograms obtained under these conditions are presented in Fig. 1.

System 2: When determining naphthodianthrones and phloroglucinols, the mobile phase consisted of acetonitrile (A) and water containing 0.1% formic acid (B). The following gradient elution conditions were set: 0–10 min, from 0 to 20% of B; 10–20 min, 0% of B; 20–21 min, from 0 to 20% of B; and 21–25 min, 20% of B. The mobile phase flow rate was 0.6 mL/min; the column oven temperature was 40 °C; and the sample injection volume was 5 μL. The DAD data were collected in the range of 190–800 nm. The MS detection of substances was performed with electrospray ionization. Spectra were recorded in both negative and positive ion modes as follows: 0.00–1.00 min, negative ion mode; 1.00–2.00 min, negative + positive ion mode, and 2.00–25.00 min, negative ion mode. In the negative ion mode, the interface voltage was 4.5 kV, and the desolvation line temperature was 200 °C. In the positive ion mode, the interface voltage was 3.5 kV, and the desolvation line temperature was 250 °C. In both modes, the detector voltage was 2.0 kV, and the flow rate of drying gas (nitrogen) was 1.5 L/min. In the negative ion mode, ions were recorded in the *m/z* range of 120–650 with the scanning frequency of 1000 amu/s, and in the negative + positive ion mode in the *m/z* range of 120–650 with the scanning frequency of 6000 amu/s. The chromatograms obtained under these conditions are presented in Fig. 2.

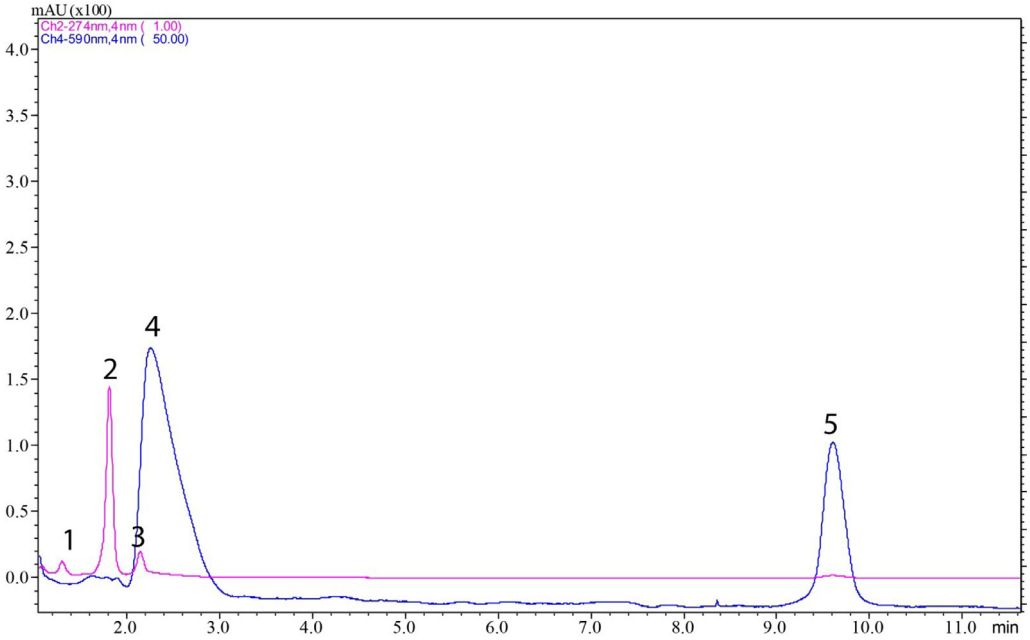

Fig. 2. Chromatogram of *Hypericum perforatum* L. extract obtained by HPLC-DAD (Separation system 2): 1 – Furohyperforin; 2 – Hyperforin; 3 – Adhyperforin; 4 – Pseudohypericin; 5 – Hypericin.

(b) Conditions of the HPLC-DAD-ESI-MS determination of biologically active substances of Salvia officinalis *L*

The conditions for determining biologically active substances of *Salvia officinalis* L. were the same as described in [22]. When determining flavonoids, phenolic acids, hydroxy derivatives of cinnamic acid and diterpenes, the mobile phase consisted of acetonitrile (A) and water containing 0.1% formic acid (B). The gradient elution conditions were different with consideration for the specific character of the analyzed plant samples: 0–2 min, from 95 to 90% of B; 2–2.01 min, 90% of B; 2.01–10 min, from 90 to 80% of B; 10–18 min, from 80 to 70% of B; 18–28 min, from 70 to 10% of B; 28–30 min, 10% of B; 30–31 min, 10–95% of B; and 31–35 min, 95% of B. The mobile phase flow rate was 0.4 mL/min. The column oven temperature was 40 °C; the sample injection volume was 5 μL. Data were collected using a diode array detector (DAD) in the range of 190–800 nm. The parameters of the mass spectrometric (MS) detector were the following: interface voltage, 4.5 kV; detector voltage, 2.0 kV; desolvation line temperature, 200 °C; drying gas flow rate (nitrogen), 1.5 L/min; electrospray ionization. Spectra were recorded in the negative ion mode in the *m/z* range of 120–720 at the scanning frequency of 2000 amu/s. The chromatograms obtained under these conditions are presented in Fig. 3.

Parameters of identification of the biologically active substances by their retention times, absorption spectra and mass spectra and performance characteristics of the procedure for the HPLC-DAD-MS determination of biologically active substances are shown in Table 1 and Table 2, respectively.

Establishing the ratio of the components that make up the plant raw materials

The relationship between rutin and hyperforin contents in Hypericum perforatum L. extracts

In the study of *Hypericum perforatum* L. extracts, a relationship was found between the contents of hyperforin and rutin in the raw materials of various trademarks and places of plant growth.

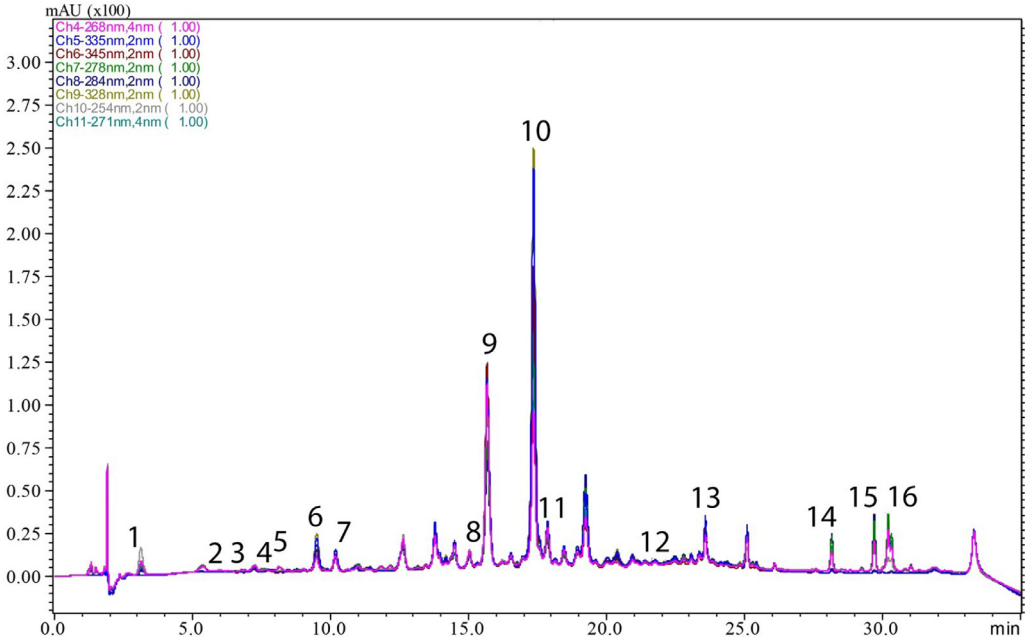

Fig. 3. Chromatogram of *Salvia officinalis* L. extract obtained by HPLC-DAD: 1 – Quinic acid; 2 – 3,4-dihydroxyphenyllactic acid; 3 – Protocatechuic acid; 4 – Chicoric acid; 5 – Protocatechuic aldehyde; 6 – Caffeic acid; 7 – Luteolin-7-*O*-β-D-rutinoside; 8 – Luteolin-7-*O*-β-D-glucoside; 9 – Luteolin-7-*O*-β-D-glucuronide; 10 – Rosmarinic acid; 11 – Apigenin 7-glucoside; 12 – Luteolin; 13 – Apigenin; 14 – Carnosol; 15 – Carnosic acid; 16 – Methyl carnosate.

Table 1
Parameters of identification of the biologically active substances by their retention times, absorption spectra and mass spectra.

Compound	Retention time, min	λ_{max}, nm	m/z	Theoretical monoisotopic mass
Protocatechuic acid	6.0	259, 294	152.9	154.1
Neochlorogenic acid	6.8	221, 327	352.9	354.3
Chlorogenic acid	8.6	238, 327	352.9	354.3
(-)-epicatechin	9.9	227, 279	288.9	290.3
Rutin	13.6	255, 354	609.0	610.5
Hyperoside	14.0	255, 354	462.9	464.3
Isoquercitrin	14.3	255, 354	463.0	464.3
Quercitrin	16.1	255, 349	446.9	448.3
Quercetin	21.2	255, 370	300.9	302.2
I3,II8-Biapigenin	23.1	268, 331	536.9	538.4
Furohyperforin	1.3	274	553.0	552.8
Hyperforin	1.8	272	535.4	536.8
Adhyperforin	2.1	272	549.3	550.8
Pseudohypericin	2.2	548, 591	519.0	520.4
Hypericin	9.6	548, 591	502.9	504.4
Carnosic acid	30.2	234, 285	331.0	332.4
Carnosol	28.6	231, 284	329.0	330.4
Luteolin-7-*O*-β-D-glucuronide	15.6	255, 347	461.0	462.3
Luteolin-7-*O*-β-D-glycoside	14.4	255, 347	446.9	448.3
Caffeic acid	9.4	323	178.9	180.1
Rosmarinic acid	17.3	329	358.9	360.3

Table 2
Performance characteristics of the procedure for the HPLC determination of biologically active substances.

Compound	Analytical range, μg/mL	Calibration equation	Correlation coefficient (r)	LOQ, μg/mL	LOD, μg/mL
Protocatechuic acid	1–100	$y = (45.2 \pm 0.7) \times 10^3 x$	0.9991	0.78	0.13
Neochlorogenic acid	1–100	$y = (29.7 \pm 0.5) \times 10^3 x$	0.9992	0.49	0.10
Chlorogenic acid	1–100	$y = (31.1 \pm 0.6) \times 10^3 x$	0.9993	0.60	0.10
(-)-epicatechin	1–100	$y = (9.19 \pm 0.13) \times 10^3 x$	0.9999	0.49	0.07
Rutin	1–200	$y = (25.37 \pm 0.19) \times 10^3 x$	0.9992	0.43	0.10
Hyperoside	1–100	$y = (27.11 \pm 0.25) \times 10^3 x$	0.9999	0.73	0.10
Isoquercitrin	1–100	$y = (31.0 \pm 0.8) \times 10^3 x$	0.9995	0.34	0.07
Quercitrin	1–100	$y = (36.5 \pm 0.4) \times 10^3 x$	0.9996	0.32	0.10
Quercetin	1–100	$y = (40.1 \pm 0.7) \times 10^3 x$	0.9999	1.2	0.20
I3,II8-Biapigenin	1–100	$y = (53.6 \pm 0.9) \times 10^3 x$	0.9996	0.29	0.05
Hyperforin	0.2–125	$y = (6.97 \pm 0.10) \times 10^3 x$	0.9997	0.24	0.16
Hypericin	0.2–20	$y = (19.0 \pm 0.5) \times 10^3 x$	0.9996	0.30	0.10
Carnosic acid	0.8–100	$y = (6.4 \pm 0.1) \times 10^3 x$	0.9997	0.75	0.28
Luteolin-7-*O*-*β*-D-glucuronide	0.5–200	$y = (27.8 \pm 0.4) \times 10^3 x$	0.9995	0.48	0.30
Luteolin-7-*O*-*β*-D-glycoside	0.4–100	$y = (36.2 \pm 0.2) \times 10^3 x$	0.9994	0.36	0.19
Carnosol	1.4–100	$y = (3.8 \pm 0.1) \times 10^3 x$	0.9995	1.4	0.70
Caffeic acid	0.2–200	$y = (59.6 \pm 0.8) \times 10^3 x$	0.9998	0.24	0.12
Rosmarinic acid	0.3–200	$y = (34.8 \pm 0.5) \times 10^3 x$	0.9998	0.25	0.16

To determine the rutin/hyperforin ratio, extracts were obtained by the methods described above and concentrations were found using calibration curves of the individual components. After that, their contents in St. John's wort (mmol/kg dry raw material [17,18]) were calculated by the formula 1:

$$X_{compound} = C \times V/m, \quad (1)$$

where $X_{compound}$ is the substance content in the sample, mmol/kg;

C is the concentration of the substance in the extract, mmol/l;

V is the volume of extract, l; m is the mass of dry raw materials, kg.

After calculation, the contents of rutin and hyperforin can be obtained. The ratio of the contents of rutin and hyperforin in the raw material of *Hypericum perforatum* L. can be used as an indicator of the authenticity and quality of the plant material. For the authentic and quality plant material, the ratio of rutin and hyperforin is close to 1.

The relationship between hyperforin and furohyperforin contents in extracts and preparations based on Hypericum perforatum *L*

Based on the data on the stability of hyperforins in *Hypericum perforatum* L. extract and their degradation during storage, differentiation of the antidepressant properties of *Hypericum perforatum* L. extracts is possible, which are used as a tincture and for the manufacture of medicines. Since the antidepressant properties of *Hypericum perforatum* L. are determined by the concentration of hyperforin and the biological activity of the extract decreases due to its degradation with the formation of furohyperforin, it can be assumed that hyperforin/furohyperforin ratio may be just such an indicator.

To determine the hyperforin/furohyperforin ratio, extracts were obtained by the methods described above and concentrations were found using calibration curves of the individual components. Next, their contents in St. John's wort (mmol/kg dry raw material) were calculated by the formula 1. After the calculation, the contents of hyperforin and furohyperforin were obtained. The ratio of their contents in the raw material was established.

The relationship between carnosic acid and carnosol contents in extracts and preparations based on Salvia officinalis *L*

To determine the carnosic acid and carnosol ratio, extracts were obtained by the methods described above and concentrations were found using calibration curves of the individual components.

Next, their contents in sage (mmol/kg dry raw material) were calculated by the formula 1. With an increase in the ratio of carnosic acid to carnosol, the quality of the raw material increases.

Conclusion

The optimal conditions for the chromatographic determination of phenolic compounds of *Salvia officinalis* L. and *Hypericum perforatum* L. were established. When studying extracts of *sage and* St. John's wort, a relationship was found between the contents of individual compounds. The ratio of hyperforin to furohyperforin allows to rank the raw materials of *Hypericum perforatum* L. by the place of growth, and the ratio of rutin to hyperforin is a marker of the quality of *Hypericum perforatum* L. The ratio of carnosic acid to carnosol is an indicator of the quality of *Salvia officinalis* L.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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