

Chromatographic Profiles Analysis of Fruits of *Crataegus* L. Genus by High-Performance Thin-Layer Chromatography

Original Paper

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Abstract It was known that hawthorn - *Crataegus* L. is a polymorphic genus. Two hawthorn species and their hybrids are included in the European Pharmacopoeia, twelve – in Ukrainian pharmacopoeia. Determination of chromatographic profiles of hawthorn fruits species native to Ukraine and other countries that are non-pharmacopoeial, but have sufficient plant raw material base, is essential for quality control of drugs.

Aim. To analyze and compare the chromatographic profiles of fruits of 23 *Crataegus* L. species on phenolic compounds, evaluated by means of high-performance thin-layer chromatography procedure (HPTLC), and determine the specific features of chromatographic fingerprints.

Materials and Methods. A total of 39 samples of fruits of 23 hawthorn species that are native to Europe, Asia and North America, such as *Crataegus monogyna*, *C. laevigata*/C. *oxyacantha*, *C. leiomonogyna*, *C. curvisepala*, *C. pseudokyrstostyla*, *C. fallacina*, *C. subrotunda*, *C. ambigua*, *C. pentagyna*, *C. sanguinea*, *C. chlorosarca*, *C. almaatensis*, *C. pseudoheterophylla* subsp. *turkestanica*, *C. pinnatifida*, *C. pentagyna* subsp. *pseudomelanocarpa*, *C. punctata*, *C. pringlei*, *C. festiva*, *C. douglasii*, *C. holmesiana*, *C. submollis*, *C. flabellata*, *C. canadensis* were investigated. The analysis has been done following the TLC method from European Pharmacopoeia modified into HPTLC, using automated HPTLC herbal system (CAMAG, Switzerland).

The results have shown that chromatographic profiles of phenolic constituents of nine *Crataegus* L. species of Europe, both pharmacopoeial and non-pharmacopoeial, were quite similar, despite the significant morphological distinctions. The chromatographical profiles of three species of Asia were similar to the pharmacopoeial species; three other species looked different and had specific marker zones. In addition, eight *Crataegus* L. species of North America had specific markers helping for discriminative analysis from pharmacopoeial species.

Conclusion. The findings could help to identify the possible adulterations and prevent the falsification of finished products. The results will be taken into consideration during revision of the Ukrainian national pharmacopoeial monograph for hawthorn fruits.

Keywords Hawthorn – identification – phenolic compounds – high-performance thin-layer chromatography

INTRODUCTION

Hawthorn berries (*Crataegi fructus*) is the herbal raw material that has been traditionally used for cardiac failure, myocardial weakness, paroxysmal tachycardia, hypertension, arteriosclerosis and Buerger's disease.^[1] It is widely used in the commerce of Ukraine as bulk, extracts, tinctures and tablets.^[2-4] The monograph on «hawthorn berries» is included in the European Pharmacopoeia and the State Pharmacopoeia of Ukraine.^[5,6] According to these monographs, two species such as *Crataegus monogyna* Jacq. and *C. laevigata* (Poir.) DC. (*C. oxyacantha* L.) and their hybrids are allowed to be used as a herbal medicine. The national Ukraine monograph

on Hawthorn fruits^[6] besides the *C. laevigata*/C. *oxyacantha* and *C. monogyna* includes 10 more other related Hawthorn species. Out of these pharmacopoeial species, there are four, namely *C. monogyna*; *C. laevigata*; *C. pentagyna* Waldst. a Kit. ex Willd.; *C. curvisepala* Lindm., that are native to Ukraine flora, while others are cultivated or can be exported.^[7,8] Meanwhile, there are great numbers of other non-pharmacopoeial *Crataegus* L. species representative of the flora of Ukraine and other countries that have sufficient herbal raw material base. The identification of its chromatographic profiles is essential for quality control of finished herbal drugs.

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Thus, the **purpose** of this paper was the analysis and comparison of chromatographic profiles of phenolic constituents of fruits of 23 *Crataegus* L. species, growing in Europe, Asia and North America, evaluated by means of high-performance thin-layer chromatography (HPTLC), and the determination of specific distinguishing markers of its fingerprints.

MATERIALS AND METHODS

Standards

Hyperoside, batch 33520F, was purchased from USP; rutin, batch A0299493, and chlorogenic acid, batch A0290470, were purchased from EDQM.

Samples

A total of 39 hawthorn samples of 23 *Crataegus* L. species obtained from Botanical Garden of V.N. Karazin Kharkiv National University, Ukraine and different States and regions, and purchased from the market were investigated in this study. All the samples were properly identified by botanist V.I. Shatrovska, Botanical Garden of V.N. Karazin Kharkiv National University, Ukraine according to the National floristic datasets.^[7-9] Voucher specimens are deposited at the Herbarium of the Department Technology of Drugs, National University of Pharmacy, Kharkiv, Ukraine. Details and voucher specimen numbers are shown in Table 1.

Source Of The Method

TLC method for *C. laevigata*/*C. oxyacantha* and *C. monogyna* from European Pharmacopoeia^[5] was modernized into HPTLC method; 21 other different *Crataegus* L. species, growth worldwide (Table 1), were included in the method.

Chromatographic Conditions

Analyses were conducted on Merck HPTLC silica gel F₂₅₄ (Darmstadt, Germany). The following mobile phase was used: *anhydrous formic acid R*, *water R*, *methyl ethyl ketone R*, *ethyl acetate R* (10:10:30:50). For identification 6 µL of standard solutions and 6 µL of sample solutions were applied to the plate.

Visualization Of Fingerprints

The multiple detection modes used were white light and 366 nm after derivatization. Plates were heated at 100–105°C for 5 min and derivatized by dipping (speed of 3, t = 0), while still hot in NP/PEG reagents. The plate was evaluated after about 30 min. The NP/PEG reagent was prepared as follows: Solution A: 1.0 g of diphenylborinic acid aminoethylester is dissolved in 100 mL of methanol. Solution B: 10 g of polyethylene glycol 400 is dissolved in 200 mL of dichloromethane.

Preparation Of Samples And Standards

The sample solution of different Crataegus L. fruits: 1.0 g of dried powdered sample was mixed with 10 mL of methanol absolute, sonicated for 10 min and centrifuged or filtered. The supernatant/filtrate was used as the sample solution
Standard solution A: 0.25 mg/mL of hyperoside in methanol; 0.35 mg/mL of rutin in methanol.
Standard solution B: 2.5 mL of Standard solution A was diluted with 10.0 mL of methanol.
System suitability solution (SST): 0.3 mg/mL of chlorogenic acid and 0.25 mg of hyperoside was diluted with 10.0 mL of methanol.

Instruments And Reagents

Instruments: A CAMAG HPTLC system (Muttensz, Switzerland) included a visualizer, an Automatic TLC Sampler 4, an Automatic Developing Chamber 2, and a Scanner 4 controlled by visionCATS software.
Reagents: ethyl acetate (purity 99.5%), lot № AO355705, anhydrous formic acid (purity 98%), lot AO343914, were purchased from Acros Organics. Methanol (HPLC Ultra Gradient Grade), lot № 1042801 was purchased from CarlRoth GmbH.

RESULTS AND DISCUSSION

The taxonomical classification of hawthorn genus is quite diffuse as all *Crataegus* L. species are quite variable and tend to hybridize with each other. For instance, according to the Flora of SSSR,^[9] Russian and European authors often do not differentiate between *C. kyrtostyla* and *C. monogyna*, despite their significant morphological differences. From the other side, as is evident from Red Flora of URSR,^[7] *C. kyrtostyla* is a generalized species and includes *C. curvisepala*, *C. pseudokyrtostyla* Klovov, *C. subrotunda* Klovov, *C. fallacina* Klovov.

Most of the identified *Crataegus* L. species used in the analysis conformed to the worldwide accepted database "The Plant list".^[10] At the same time, some hawthorn species, that according to the national floristic datasets^[7] have distinctive morphological features (Fig. S1), are listed in "The Plant List"^[10] as synonyms (*C. oxyacantha*; *C. curvisepala*; *C. pseudokyrtostyla*; *C. subrotunda* are listed as synonym for *C. rhipidophylla* Gand. and *C. leiomonogyna* Klovov is listed as synonym for *C. monogyna*) or have unresolved status (*C. fallacina*, *C. festiva* Sarg.). These findings testify that "The Plant List" classification could be improved.

Despite that it is possible to discriminate different hawthorn species using morphological features when the fruits are intact, it is an analytical challenge for the finished dosage forms. It was established that hawthorn fruits are characterized by its phenolic constituents, in particular, the flavonoid components to which many of the pharmacological

Table 1: Description of the samples analyzed

N	Species	Voucher Specimens Number	Amount	Growth	Source, Year/Lot	Pharmacopoeia
1	<i>C. laevigata</i> (Poir.) DC. / <i>C. oxyacantha</i> L.	S15232	2	¹ CE, ² EE	Botanic Garden, Kharkiv, Ukraine, 2015	⁷ EPh, ⁸ SPhU
		S15195			'Likarski roslyny', Kharkiv, Ukraine, 2014	
2	<i>C. monogyna</i> Jacq.	S15231	3	CE, EE	Botanic Garden, Kharkiv, Ukraine, 2015	EPh, SPhU
		S15237			Ireland, 2015	
		S15194			'Fitosvit', Ukraine, 2014	
3	<i>C. leiomonogyna</i> Klokov	S15227	1	CE, EE	Botanic Garden, Kharkiv, Ukraine, 2015	-
4	<i>C. curvisepala</i> Lindm.	S15229	3	CE, EE	Botanic Garden, Kharkiv, Ukraine, 2015	SPhU
		S15202			'Viola', Zaporizhzhia, Ukraine, 01012012	
		S15203			'Likarski roslyny', Kharkiv, Ukraine, 2014	
5	<i>C. pseudokyrstostyla</i> Klokov	S15228	7	CE, EE	Botanic Garden, Kharkiv, Ukraine, 2015	-
		S15197			Kharkiv, Ukraine, 2014	
		S15198			'Ahrofirma', Mykolaiv, Ukraine, 2015	
		S15206			Kharkiv, Ukraine, 2012	
		S15207			'Zdorovia', Kharkiv, Ukraine, BMP-081014	
		S15208			'Ternofarm', Ternopil, Ukraine, P. 415/06.14	
		S15210			'Sumyfitofarmatsiia', Sumy, Ukraine, 6612.Y.1211	
6	<i>C. fallacina</i> Klokov	S15230	1	CE, EE	Botanic Garden, Kharkiv, Ukraine, 2015	-
7	<i>C. subrotunda</i> Klokov	S15205	1	CE, EE	'Chysta flora' Vyshneve, Ukraine, 2014	-
8	<i>C. ambigua</i> C.A.Mey. ex A.K. Becker	S15226	1	CE, EE	Botanic Garden, Kharkiv, Ukraine, 2015	-
9	<i>C. pentagyna</i> Waldst. & Kit. ex Willd.	S15196	1	CE, EE	Kharkiv, Ukraine, 2015	SPhU
10	<i>C. pseudoheterophylla</i> subsp. <i>turkestanica</i> (Pojark.) K.I.Chr.	S15216	2	³ CA, ⁴ EA	Botanic Garden, Kharkiv, Ukraine, 2014	-
		S15236			Botanic Garden, Kharkiv, Ukraine, 2015	
11	<i>C. sanguinea</i> Pall.	S15199	3	Siberia, ⁵ ME	Anapa, Russia, 051014	SPhU
		S15200			Anapa, Russia, 2014	
		S15201			Anapa, Russia, 2015	
12	<i>C. chlorosarca</i> Maxim.	S15235	1	CA, EA	Botanic Garden, Kharkiv, Ukraine, 2015	-
13	<i>C. pentagyna</i> subsp. <i>pseudomelanocarpa</i> (Popov ex Pojark.) K.I.Chr.	S15217	1	CA, EA	Botanic Garden, Kharkiv, Ukraine, 2015	-
14	<i>C. pinnatifida</i> Bunge	S15233	1	CA, EA	Botanic Garden, Kharkiv, Ukraine, 2015	-
15	<i>C. almaatensis</i> Pojark.	S15214	2	CA, EA	Botanic Garden, Kharkiv, Ukraine, 2014	-
		S15215			Botanic Garden, Kharkiv, Ukraine, 2015	

Continued Table 1: Description of the samples analyzed

N	Species	Voucher Specimens Number	Amount	Growth	Source, Year/Lot	Pharmacopoeia
16	<i>C. punctata</i> Jacq.	S15218	1	⁶ NA	Botanic Garden, Kharkiv, Ukraine, 2015	-
17	<i>C. pringlei</i> Sarg.	S15219	1	NA	Botanic Garden, Kharkiv, Ukraine, 2015	-
18	<i>C. festiva</i> Sarg.	S15220	2	NA	Botanic Garden, Kharkiv, Ukraine, 2014	-
		S15221			Botanic Garden, Kharkiv, Ukraine, 2015	
19	<i>C. douglasii</i> Lindl.	S15223	1	NA	Botanic Garden, Kharkiv, Ukraine, 2015	-
20	<i>C. holmesiana</i> Ashe	S15224	1	NA	Botanic Garden, Kharkiv, Ukraine, 2015	-
21	<i>C. submollis</i> Sarg.	S15225	1	NA	Botanic Garden, Kharkiv, Ukraine, 2015	-
22	<i>C. flabellata</i> (Bosc ex Spach) K.Koch.	S15234	1	NA	Botanic Garden, Kharkiv, Ukraine, 2015	-
23	<i>C. canadensis</i> Sarg.	S15238	1	NA	Botanic Garden, Kharkiv, Ukraine, 2015	-

¹CE – Central Europe; ²EE – East Europe; ³CA – Central Asia; ⁴EA – Eastern Asia; ⁵ME – Middle East; ⁶NA – North America; ⁷EPh – European Pharmacopoeia; ⁸SPhU – State Pharmacopoeia of Ukraine.

properties have been attributed.^[1,8,11,12] Moreover, flavonoids are used for pharmacopoeial standardization of hawthorn fruits. That is why, our investigation included modification of existing TLC method from European Pharmacopoeia into modern and reproducible HPTLC method that can help to detect an adulteration,^[13,14] the inclusion of new *Crataegus* L. species and comparison of their chromatographic profiles.

For the proposed HPTLC method, the stationary phase, sample and standard preparations, application volume, documentation were modified, and acceptance criteria were set.

The derivatization reagent NP/PEG used in the method for the visualization of results in UV 366 nm allowed us to distinguish phenolic constituents of different *Crataegus* L. species, depending on its structure.^[15] Thus, the obtained HPTLC fingerprints showed orange-yellow fluorescent (fl) zones due to flavanols: quercetin, myricetin and their glycosides, and yellow-green fl zones due to kaempferol, isorhamnetin and their glycosides; orange fl zones due to flavones: luteolin and their glycosides, and yellow-green fl zones due to apigenin and their glycosides; blue fl zones due to phenol carboxylic acids (caffeic acid, chlorogenic acids) and coumarins.

Comparison of HPTLC fingerprints of different samples of 23 *Crataegus* L. species on phenolic constituents is shown in Fig. 1. As we can see in Fig. 1, *Crataegus* L. species, which are widespread in Central and East Europe, both pharmacopoeial and non-pharmacopoeial, such as: *Crataegus monogyna*, *C. laevigata* (*C. oxyacantha*), *C. leiomonogyna*, *C. curvisepala*, *C. pseudokyrstostyla*, *C. fallacina*, *C. subrotunda*, *C. ambigua*

C.A.Mey. ex A.K. Becker, *C. pentagyna* Waldst. & Kit. ex Willd., and species, which are widespread in Central and Eastern Asia, such as *C. sanguinea* Pall., *C. chlorosarca* Maxim., *C. almaatensis* Bunge, show quite similar fingerprints without specific discriminative features. Below, the acceptance criteria for these species are proposed.

Acceptance criteria. Under UV 366 nm, 30 min after derivatization, the chromatogram of the test solutions shows in the lower part of the chromatogram a very faint or faint yellow or orange fl zone at $R_f \sim 0.32$, corresponding to the reference substance rutin. In the middle part of the chromatogram, a faint to equivalent yellow or orange fl zone at $R_f \sim 0.52$ corresponding to the reference substance hyperoside and another faint yellow or orange fl zone at $R_f \sim 0.56$ above the position of reference substance hyperoside are present; one or two faint light blue fl zones at $R_f \sim 0.43$ (chlorogenic acid) and at $R_f \sim 0.47$ below the zone corresponding to the reference substance hyperoside are present. Close to the solvent front, one or two blue fl zones are seen.

Furthermore, other very faint or faint green fl zone at $R_f \sim 0.35$ above the zone corresponding to the reference substance rutin (green arrows), light-blue fl zone at $R_f \sim 0.62$ (blue arrows) and yellow or orange fl zones at $R_f \sim 0.16$ and $R_f \sim 0.24$ (yellow arrows) can be present.

Some other non-pharmacopoeial *Crataegus* L. species, which are widespread in Central and Eastern Asia – *C. pseudoheterophylla* subsp. *turkestanica* (Pojark.) K.I.Chr., *C. pinnatifida* Bunge, *C. pentagyna* subsp. *pseudomelanocarpa*



C.laevigata (Poir.) DC. /
C.oxyacantha L.



C.monogyna Jacq.



C.leiomonogyna Klokov



C.curvisepala Lindm.



C.pseudokyrstostyla Klokov



C.fallacina Klokov



C.ambigua C.A.Mey.ex A.K.
Becker



C.pentagyna Waldst. & Kit.
ex Willd.



C. pentagyna subsp.
pseudomelanocarpa (Popov
ex Pojark.) K.I.Chr.



C.pseudoheterophylla subsp.
turkestanica (Pojark.)
K.I.Chr.



C.pinnatifida Bunge



C.chlorosarca Maxim.

Figure 1S: Pictures of some *Crataegus* L. species

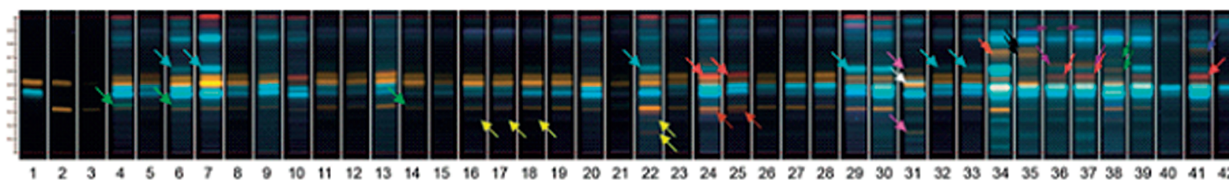
*C.almaatensis* Pojark.*C.pringlei* Sarg.*C.festiva* Sarg.*C.punctata* Jacq.*C.submollis* Sarg.*C. flabellata* (Bosc ex Spach) K.Koch.Continued Figure 1S: Pictures of some *Crataegus* L. species

Figure 1. Comparison of HPTLC fingerprints of phenolic compounds of 23 *Crataegus* species. Fruits. Developing solvent: anhydrous formic acid, water, methyl ethyl ketone, ethyl acetate (10:10:30:50); derivatization: NP/PEG; detection: 366 nm.

Tracks: 1 – SST: Chlorogenic acid, hyperoside; 2 – R: Rutin, hyperoside; 3 – R1/4: Rutin, hyperoside; 4-5 – *C. laevigata*/*C. oxyacantha*; 6-8 – *C. monogyna*; 9 – *C. leiomonogyna*; 10-12 – *C. curvisepala*; 13-19 – *C. pseudokyrstostyla*; 20 – *C. fallacina*; 21 – *C. subrotunda*; 22 – *C. ambigua*; 23 – *C. pentagyna*; 24-25 – *C. pseudoheterophylla* subsp. *turkestanica*; 26-28 – *C. sanguinea*; 29 – *C. chlorosarca*; 30 – *C. pentagyna* subsp. *pseudomelanocarpa*; 31 – *C. pinnatifida*; 32-33 – *C. almaatensis*; 34 – *C. punctata*; 35 – *C. pringlei*; 36-37 – *C. festiva*; 38 – *C. douglasii*; 39 – *C. holmesiana*; 40 – *C. submollis*; 41 – *C. flabellata*; 42 – *C. canadensis*.

(Popov ex Pojark.) K.I.Chr., look slightly different and have specific marker zones. For instance, *C. pseudoheterophylla* subsp. *turkestanica* shows reddish fl zone at $R_f \sim 0.57$ above orange fl zone corresponding to the reference substance hyperoside (red arrows); right below the position of reference substance rutin, there is another yellow fl zone (brown arrows). *C. pinnatifida* shows additional light-blue zone at $R_f \sim 0.52$ between two orange zones (white arrow); shows additional faint yellow zones at $R_f \sim 0.16$ and at $R_f \sim 0.6$ (pink

arrows). *C. pentagyna* subsp. *pseudomelanocarpa* does not show orange or yellow fl zone at the position of reference substance hyperoside.

Most of the species that are widespread in North America – *C. punctata* Jacq., *C. pringlei* Sarg., *C. festiva*, *C. douglasii* Lindl., *C. holmesiana* Ashe, *C. submollis* Sarg., *C. flabellata* (Bosc ex Spach) K.Koch., *C. flabellata* (Bosc ex Spach) K.Koch. show different profiles of phenolic compounds in the upper half of the plate compared to pharmacopoeial species.

Discriminative features of these species that can be helpful for identification are shown below. Thus, *C. punctata* does not show orange or yellow fl zone at the position of reference substance hyperoside. It shows additional yellow fl zone at $R_f \sim 0.73$ (orange arrow). *C. pringlei* shows additional yellow fl zones at $R_f \sim 0.72$ and at $R_f \sim 0.75$ (black arrows). In the chromatogram of the test solution zone corresponding to reference substance, the hyperoside is overlapped with light-blue fl zone, above this zone reddish fl zone at $R_f \sim 0.57$ is seen (red arrows); in the upper third of chromatogram additional yellow fl zones at $R_f \sim 0.65$ and at $R_f \sim 0.92$ are present (violet arrows) (*C. festiva*). *C. douglasii* shows additional faint orange fl zone at $R_f \sim 0.61$ above the position of reference substance hyperoside and a very faint orange fl zone above it (dark green arrows). In the chromatogram of the test solution zone corresponding to the reference substance, the hyperoside is overlapped with light-blue fl zone (*C. holmesiana*). *C. submollis* does not show orange or yellow fl zones corresponding to the reference substances rutin and hyperoside. *C. flabellata* shows reddish fl zone at $R_f \sim 0.57$ above yellow fl zone corresponding to the reference substance hyperoside (red arrows) and additional orange fl zone at $R_f \sim 0.75$ (dark blue arrows). *C. canadensis* does not show yellow or orange fl zone at the position of reference substance rutin.

CONCLUSIONS

1. The evaluation and comparison of HPTLC fingerprints on phenolic constituents of 23 *Crataegus* L. species spread worldwide have been done.

2. Despite the slight variations, the similarity of phenolic constituents of nine *Crataegus* L. species native to Central and East Europe and three hawthorn species native to Central and Eastern Asia have been established. Further, phytochemical and pharmacological investigations are necessary.
3. The discriminative features in HPTLC chromatographic fingerprints for three other *Crataegus* L. species native to Central and Eastern Asia and eight hawthorn species native to North America have been established.

The data about the similarity of phenolic constituents of both pharmacopoeial and non-pharmacopoeial *Crataegus* L. species could be a ground for including new species into pharmacopoeial analysis and broadening of the herbal raw material base for the pharmaceutical market. The findings concerning discriminative features of phenolic fingerprints for some species could help to identify the possible adulteration and falsification. The results can be used for further chemotaxonomic investigation of hawthorn genus and improving "The Plant List", and should be taken into consideration for revising pharmacopoeial monograph for hawthorn fruits.

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