DEVELOPMENT OF THE COMPOSITION AND RESEARCH OF PHARMACOTECHNOLOGICAL PARAMETERS OF MEDICINAL HERBAL COLLECTION FOR THE TREATMENT OF GASTRIC ULCER

Konovalenko I. S., Kriukova A. I.

National University of Pharmacy, Kharkiv, Ukraine

Introduction. Gastric ulcer (GU) is a chronic recurrent disease that occurs with alternating periods of exacerbation and remission, the main manifestation of which is the formation of a defect (ulcer) in the wall of the stomach and duodenum. Treatment of GU should be comprehensive and include not only the appointment of drugs, but also a wide range of different measures: diet, smoking cessation and alcohol abuse, refusal to take drugs that have antiulcer effect, normalization of work and rest, sanatorium spa treatment [1, 2].

Scientific research in the last decade suggests that the gastrointestinal tract is part of the body's immune system. Natural compounds of plant origin have great prospects, having a wide range of pharmacotherapeutic possibilities, and influencing the activity of many regulatory proteins, in the treatment and prevention of complex combined pathologies of the digestive system. One of the main groups of biologically active substances that make a significant contribution to the pharmacotherapeutic effect of herbal remedies are phenolic compounds. The composition of phenolic compounds of plant origin is diverse and includes several groups of biologically active substances: flavonoids, anthocyanins, coumarins, simple phenols, phenolic acids, tannins, stilbenes, lignans.

Flavonoids occupy a special place in phytotherapy of inflammatory diseases of the gastrointestinal tract. Flavonoids have biological properties that are necessary for the manifestation of beneficial effects in diseases of the digestive system: anti–inflammatory [3], hepatoprotective [4], anti–ulcer [5], anti–diabetic [6], hypolipidemic [7], immunotropic [8], antimicrobial [9], antiviral, antitumor, antispasmodic, choleretic [10], effect. Flavonoids enter the body by transport through the epithelial cells of the gastrointestinal tract; undergo metabolic transformation in the intestinal epithelium and liver, including methylation of hydroxyl groups, sulfates, reduction of carboxyl groups, and conjugation with glucuronic acid [5].

Purpose of the study. To develop the optimal composition of medicinal plant raw materials to create a collection that will exhibit anti–inflammatory, antiulcer, antispasmodic and immunotropic activity and conduct research on the pharmacological properties of the developed collection.

Materials and Methods. The objects of the study are a mixture of medicinal plant raw materials, which include calendula flowers, plantago leaves, sea–buckthorn fruits, coriander seeds, gnaphalium grass. Research methods: information–search, information–analytical, organoleptic, physico–chemical, pharmacotechnological, phytochemical.

Results and Discussion. The effectiveness of any pharmacotherapy is due to its ability to influence the factors that cause the disease (etiotropic therapy), to intervene in certain phases of the pathological process (pathogenic therapy), to eliminate the symptoms that accompany the disease (symptomatic therapy). In view of this, in order to develop the composition of the drug, we analyzed the common factors influencing the basis of both pathologies on the pathogenic links of disease development.

Etiotropic phytotherapy of GU is usually aimed at the following processes:

– mucus–forming action (*calendula flowers, plantago leaves*);

– antiulcer activity (*coriander seeds, gnaphalium grass*);

– strengthening the body with vitamin preparations: *sea–buckhorn fruits.*

For pathogenic phytotherapy used:

– medicinal plants with anti–inflammatory activity (*plantago leaves*);

– drugs with antispasmodic and myotropic action (*calendula flowers, gnaphalium grass*).

Symptomatic phytotherapy is aimed at:

– normalization of digestion and increase in mucus formation (*calendula flowers, plantago leaves)*.

Based on the frequency of references in the literature of medicinal plant raw materials with relevant types of action for the above pathologies for further research and development of the drug were taken: *calendula flowers, plantago leaves, gnaphalium grass, coriander seeds, sea–buckhorn fruits*.

Based on the analysis of literature data, a sample of medical plant materials (MPM) species with appropriate pharmacotherapeutic effects required in the treatment of gastric and duodenal ulcers was made [11] (table 1).

Research of quality indicators of raw materials is an important stage of drug development, as a result of which the studied drug is developed, the process of identification and unification takes place. The necessary stage of development and research of the collection is the identification and determination of quality indicators of the components that are part of it. The results of tests of medical plant materials, which were conducted according to the methods of SPhU are given in table 2.

According to the results of research, medicinal plant raw materials that are part of the antiulcer collection meets the requirements of the relevant SPhU 2.0 monographs [18].

The completeness of extraction is influenced by a number of technological parameters of MPM, such as specific mass, bulk mass, volumetric density, humidity, porosity and layer porosity of raw materials, free volume of the layer, the angle of the natural slope, water absorption coefficient [19]. Further research was aimed at determining these indicators.

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Table 1. The choice of components for the formulation of anti–ulcer collection

Pharmacological properties of the phytocomposition component required for GU herbal medicine	Types of plants that have the appropriate pharmacological effect	Literary source
Mucus–forming	calendula flowers, plantago leaves	[12]
Myotropic, antispasmodic	calendula flowers, gnaphalium grass	[13]
Anti–inflammatory	plantago leaves	[12]
Wound healing	sea–buckhorn fruits, calendula flowers, plantago leaves	[14, 15]
Antiulcer	coriander seeds , gnaphalium grass	[16]
Vitamin	sea–buckhorn fruits, calendula flowers	[17, 13]

Table 2. Testing of medicinal plant raw materials that are part of the developed collection (n=5, P=95 %)

Medical plant materials	Indicators, dimension	Results	Norm for SPhU
Calendula flowers	Weight loss after drying, %	10.2 ± 0. 1	no ≤ 12.0
	Common ash, %	7.5 ± 0.2	no ≤ 10.0
	Ash, insoluble in HCl, %	2.7 ± 0.3	no ≤ 5.0
Plantago leaves	Weight loss after drying, %	11.7 ± 0. 1	no ≤ 14.0
	Common ash, %	15.5 ± 0.2	no ≤ 20.0
	Ash, insoluble in HCl, %	3.2 ± 0. 3	no ≤ 6.0
Sea–buckhorn fruits	Weight loss after drying, %	68.1 ± 0. 1	no ≤ 87.0
	Common ash, %	0.2 ± 0,.2	no ≤ 1.0
	Ash, insoluble in HCl, %	1.2 ± 0. 1	–
Coriander seeds	Weight loss after drying, %	8.1 ± 0. 1	no ≤ 10.0
	Common ash, %	5.3 ± 0. 3	no ≤ 8.0
	Ash, insoluble in HCl, %	1.1 ± 0. 1	–
Gnaphalium grass	Weight loss after drying, %	11.1 ± 0. 1	no ≤ 13.0
	Common ash, %	15.7 ± 0. 3	no ≤ 20.0
	Ash, insoluble in HCl, %	4.3 ± 0. 3	no ≤ 10.0
Phytocomposition	Weight loss after drying, %	10.61 ± 0.05	–
	Common ash, %	5.7 ± 0.5	–
	Ash, insoluble in HCl, %	3.6 ± 0.2	–

Notes: «–» – values are not given

The first stage of research was to study the degree of grinding of MPM in order to determine the modes of technological processes. The intensification of the extraction process of biologically active substances directly depends on the fineness of the MPM. An important step in the development of herbal medicine is the grinding of raw materials with damage to the structure and increase the surface area for extraction efficiency [20]. As a result of grinding of raw materials parts of cells open and at extraction the contents are washed away by extractant. With the help of the rotary knife mill RM–250 the homogeneity of the particles was achieved.

Sieve analysis is a quantitative characteristic of the fractional composition of a mixture of crushed medicinal plant raw materials and the outstanding parameter is the weighted average particle size. The results of studies of the fractional composition of the mixture of crushed MPM and collection are given in table. 3.

Fractional analysis showed that about 65 % of the collection fraction passes through sieves with a pore diameter of 2.0 to 0.5 mm, which meets the requirements of SPhU.

Table 3. Fractional analysis of medicinal plant raw materials (n=5, P=95 %)

MPM	Diameter of sieves, mm /The amount of raw material passed through the sieve,%								
	10	5	4.5	3.25	2.0	1.4	1.0	0.5	Pallet (dust)
Calendula flowers	0.4	8.76	7.6	31.5	17.9	16.8	9.88	3.7	3.46
Plantago leaves	0.1	1.4	2.1	28.7	34.5	18.4	7.7	1.9	5.2
Sea–buckhorn fruits	0.1	2.5	12.6	39.5	12.9	18.2	20.9	8.54	3.99
Coriander seeds	0.2	2.7	5.2	9.6	33.5	27.5	10.36	7.6	3.34
Gnaphalium grass	0.3	7.76	6.9	21.5	27.9	19.9	9.88	3.7	2.16

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Sieve analysis data indicate the need for additional grinding and sieving of plant components that are part of the developed collection.

The next stage of the study of plant raw materials was the study of technological parameters: bulk mass, volumetric mass, specific mass, porosity of raw materials, layer porosity, free volume of the layer, flowability, The angle of the natural slope and water absorption coefficient.

An important factor in regulating the process of extraction of medicinal raw materials is the absorption coefficient of the extractant, as the amount of extractant added to the raw material during infusion is mandatory taking into account the absorption coefficient, which improves the conditions of extraction of biologically active substances.

To establish the experimental value of the water absorption coefficient, an aqueous extract was prepared from each type of raw material at a ratio of raw material and extractant of 1:10, according to the method of decoction according to State Pharmacopoeia XI, vol. 2, p. 147. The portion was filled with a measured amount of purified water, heated for 30 minutes in a boiling water bath, filtered and then, after cooling and squeezing the raw material through gauze, measured the volume of extraction.

The results of the determination of water absorption coefficient are shown in table 4.

Table 4. Water absorption coefficient, n=5

MPM	№ sample / Results					
	1	2	3	4	5	Average value
Calendula flowers	3.42	3.55	3.33	3.67	3.89	3.57 ± 0.05
Plantago leaves	2.12	2.32	2.27	2.34	2.23	2.26 ± 0.02
Sea–buckhorn fruits	1.11	1.62	1.69	1.22	1.83	1.49 ± 0.03
Coriander seeds	1.06	1.12	1.03	1.09	1.21	1.11 ± 0.03
Gnaphalium grass	2.15	2.25	2.35	2.45	2.41	2.32 ± 0.04
Phytocomposition	2.17	2.28	2.45	2.18	2.27	2.27 ± 0.05

The water absorption coefficient was in the range of 1.1–3.6. and for the collection – 2.27.This indicator is an important characteristic when calculating the amount of extractant in the subsequent manufacture of the infusion from the collection.

Humidity of each type of raw material and phytocomposition was determined using a moisture analyzer Sartorius MA–150 (Germany).

The results of determining the technological parameters of the developed phytocomposition for the treatment of gastric ulcer are given in table. 5.

Table 5. Technological parameters of the developed phytocomposition and its components (n=5, P=95 %)

№ sample	Indicator, dimension					
	Calendula flowers	Plantago leaves	Sea–buckhorn fruits	Coriander seeds	Gnaphalium grass	Phyto-composition
Bulk mass, g/cm^3						
1	0.95	0.75	1.21	1.35	0.87	1.05
2	0.91	0.79	1.20	1.35	0.86	1.01
3	0.87	0.82	1.23	1.34	0.84	1.10
4	0.85	0.81	1.23	1.33	0.88	1.08
5	0.83	0.82	1.21	1.32	0.87	1.06
μ	0.88±0.02	0.79±0.01	1.22±0.02	1.34±0.01	0.86±0.02	1.06±0.02
Volumetric mass, g/cm^3						
1	0.19	0.12	0.17	0.15	0.13	0.15
2	0.18	0.13	0.18	0.14	0.12	0.16
3	0.18	0.14	0.16	0.13	0.10	0.17
4	0.19	0.13	0.17	0.15	0.13	0.15
5	0.18	0.12	0.18	0.16	0.11	0.18
μ	0.18±0.02	0.12±0.02	0.17±0.01	0.15±0.01	0.12±0.01	0.16±0.01
Specific mass, g/cm^3						
1	0.127	0.072	0.195	0.112	0.174	0.151
2	0.125	0.070	0.198	0.115	0.169	0.149
3	0.122	0.071	0.193	0.111	0.171	0.148
4	0.119	0.172	0.194	0.119	0.170	0.152

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5	0.121	0.073	0.198	0.114	0.172	0.150
μ	0.123±0.002	0.072±0.002	0.196±0.002	0.114±0.001	0.171±0.002	0.151±0.002
Porosity of raw materials						
1	0.74	0.56	0.85	0.79	0.65	0.69
2	0.71	0.55	0.86	0.82	0.59	0.65
3	0.70	0.57	0.85	0.81	0.66	0.66
4	0.72	0.56	0.84	0.78	0.62	0.63
5	0.71	0.54	0.87	0.83	0.58	0.65
μ	0.72±0.02	0.55±0.02	0.85±0.01	0.81±0.02	0.62±0.02	0.65±0.02
Layer porosity						
1	0.08	0.80	0.11	0.10	0.08	0.11
2	0.08	0.08	0.12	0.11	0.08	0.11
3	0.07	0.09	0.11	0.10	0.07	0.11
4	0.08	0.08	0.10	0.10	0.08	0.10
5	0.07	0.09	0.11	0.10	0.07	0.11
μ	0.08±0.01	0.08±0.01	0.11±0.01	0.10±0.02	0.08±0.01	0.11±0.01
Free volume of the layer						
1	0.79	0.89	0.81	0.78	0.66	0.75
2	0.78	0.89	0.80	0.79	0.65	0.78
3	0.74	0.92	0.83	0.82	0.63	0.76
4	0.75	0.92	0.80	0.84	0.68	0.72
5	0.77	0.91	0.81	0.80	0.65	0.73
μ	0.76±0.02	0.90±0.02	0.81±0.02	0.80±0.01	0.65±0.01	0.75±0.02
The angle of the natural slope, deg.						
1	34.5	31.1	25.1	21.2	32.2	28.2
2	34.2	31.5	24.9	21.3	32.3	28.2
3	34.1	31.2	25.2	21.1	32.1	28.1
4	34.6	31.3	24.8	21.5	32.0	28.4
5	34.7	31.4	25.1	21.2	32.2	28.5
μ	34.3±0.2	31.3±0.2	25.1±0.2	21.3±0.1	32.2±0.2	28.3±0.2
Flowability, g/sec						
1	49.35	51.25	53.21	54.27	50.21	52.12
2	49.21	51.28	53.26	54.21	50.23	52.32
3	49.89	51.48	53.27	54.23	50.45	52.36
4	48.99	51.36	53.69	54.21	50.42	52.42
5	49.12	51.28	53.45	54.25	50.10	52.35
μ	49.20±0.2	51.30±0.1	53.26±0.2	54.22±0.1	50.30±0.2	52.37±0.2

The conducted technological researches confirmed. that the selected MPM and its mixture is characterized by a low value of bulk mass (from 0.072 g/cm^3 in plantago leaves to 0.195 g/cm^3 in sea–buckhorn fruits) and low porosity (in the range of 0.08 to 0.11). In pharmaceutical and industrial conditions for the production of phytomedicines, raw materials with low bulk density and low porosity do not need to be compacted into the extractor during loading.

All studied MPM and collection had high porosity (0.62 – 0.85). This figure indicates that when swollen during extraction, internal juice will be formed, which will promote better extraction of biologically active substances.

An important parameter, which is taken into account to ensure uniform mixing of the components of raw materials and prevent their delamination, is the bulk density. This indicator in the studied samples of MPM differed and had a value in the range of 0.12 – 0.18 g/cm^3.

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It has to do with that calendula flowers occupy a large volume due to their structure.

The free volume of the layer for each MPM and their mixture had high values (0.65 – 0.90) indicating the need to use large volumes of extractant to wet the MPM and compact it when loading into the extraction device.

The difference between specific and volumetric mass shows that the raw material occupies a large volume resulting in the need to take into account when calculating the ratio of MPM and the finished product choosing the size of the extractor features of loading of raw materials, etc.

The defined indicators are qualitative parameters of technology, allow to control, and estimate technological parameters of preparation of collecting.

Conclusions.

1. It is determined that the use of drugs based on medicinal plant raw materials in complications of GU, namely the use of MPM, which contains flavonoid compounds that regulate inflammatory processes and oxidative reactions is a promising area of the Ukrainian pharmaceutical industry.

2. As a result of the conducted researches the conformity of medicinal plant raw materials which are a part of a antiulcer phytocomposotion to requirements of the monographs of SPhU on a concrete type of MPM is established.

3. The main technological parameters of MPM are determined which confirmed that the MPM is characterized by low values of specific, bulk and volumetric mass and high values of layer porosity, porosity of raw materials, free volume of the raw material layer.

Development of the composition and research of pharmacotechnological parameters of medicinal herbal collection for the treatment of gastric ulcer

Konovalenko I. S., Kriukova A. I.

Introduction. Natural compounds of plant origin have great prospects, having a wide range of pharmacotherapeutic possibilities, and influencing the activity of many regulatory proteins, in the treatment and prevention of complex combined pathologies of the digestive system. One of the main groups of biologically active substances that make a significant contribution to the pharmacotherapeutic effect of herbal remedies are phenolic compounds. Therefore, the development of a new domestic drug in the form of a collection for phytotherapy of gastric ulcer is an urgent task of pharmaceutical science in Ukraine. **Materials and methods.** The objects of the study are a mixture of medicinal plant raw materials, which include calendula flowers, plantago leaves, sea–buckthorn fruits, coriander seeds, gnaphalium grass. Research methods: information–search, information–analytical, organoleptic, physico–chemical, pharmacotechnological, phytochemical. **Results & Discussion.** According to the results of research, medicinal plant raw materials that are part of the antiulcer phytocomposition meets the requirements of the relevant monographs SPhU 2.0. Fractional analysis showed that about 65 % of the phytocomposition passes through sieves with a pore diameter of 2.0 to 0.5 mm, which meets the requirements of SPhU. Sieve analysis data indicate the need for additional grinding and sieving of plant components that are part of the developed collection. The water absorption coefficient was in the range of 1.1–3.6, and for phytocomposition – 2.27. This indicator is an important characteristic when calculating the amount of extractant in the subsequent manufacture of the infusion from the collection. The defined indicators are qualitative parameters of technology, allow to control, and estimate technological parameters of preparation of collecting. **Conclusions.** 1 It is determined that the use of drugs based on medicinal plant raw materials in complications of GU, namely the use of MPM, which contains flavonoid compounds that regulate inflammatory processes and oxidative reactions is a promising area of the Ukrainian pharmaceutical industry. 2. As a result of the conducted researches the conformity of medicinal plant raw materials which are a part of a antiulcer phytocomposotion to requirements of the monographs of SPhU on a concrete type of MPM is established. 3. The main technological parameters of MPM are determined which confirmed that the MPM is characterized by low values of specific, bulk and volumetric mass and high values of layer porosity, porosity of raw materials, free volume of the raw material layer.

Keywords: phytocomposition, pharmacotechnological properties, gastric ulcer.

References

1. Amat N. In vivo hepatoprotective activity of the aqueous extract of Artemisia absinthium L. against chemically and immunologically induced liver injuries in mice.N. Amat. H. Upur. B. Blažeković. *Journal of Ethnopharmacology*. 2010. Vol. 131. P. 478 – 484.

2. Beskina O. A. Possible mechanisms of antioxidant activity of glycyrrhizic acid. O. A.Beskina. A. Abramov, A. G. Gabdulkhanova. A. V. Miller. A.V. Safronova. M.V. Zamaraeva. *Biomed Khim*. 2006. Vol. 52. P. 60–68.

3. Panda S. S. Xanthone as potential antioxidants. S. S. Panda, M. Chand. R. Sakhuja. S. C. Jain. *Curr. Med. Chem*. 2013. Vol. 20 (36). P. 4481–4507.

4. Rio D. D. Dietary (poly)phenolics in human health: structures. bioavailabity and evidence of protective effects against chronic diseases. *Antioxidants & Redox Signaling*. 2013. Vol. 18. P. 1818–1892.

5. Rathee P. I. Mechanism of action of flavonoids as anti–inflammatory agaents: a review.P.I.Rathee. H.Chaudhary. S. Rathee. D. Rathee. V. Kumar. K. Kohli. Inflamm. *Allergy Drug targets*. 2019. Vol. 8. № 3. P. 229–235.

6. Parab R. S. Hypolipidemic activity of Acorus calamus L. in rats. R. S. Parab, S. A. Mengi. *Fitoterapia*. 2012. Vol. 73. №. 6. P. 451 – 455.

7. Rokaya M. B. Traditional uses of medicinal plants in gastrointestinal disorders in Nepal M. B., Rokaya Y., Uprety R.C., Poudel et al.. *Journal of Ethnopharmacology*. 2014. Vol. 158. P. 221 – 229.

8. Shikov A. N. Phenolic constituents of Gnaphalium uliginosum L.. A. N.

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Shikov, M. Kundracikova, T. L. Palama et al.. *Phytochemistry Letters*. 2010. Vol. 3. P. 45 – 47.
9. Sandhar H. K. A review of chemistry and pharmacology of flavonoids. H. K. Sandhar, B. Kumar, S. Pracher, P. Uvani, M. Salhan, P. *Sharma. Int. Phar.*. Sci. – 2011. Vol. 1. P. 25–41.
10. Tarackhovsky U. S. Flavonoids: Biochemistry. biophysics. medicine. Yu.S. Tarakhovsky. U. S., Kim B. S. Abdrasimov E. H, Muzafarov O. E. *Pushino: Syachrobook*. 2013. 310 p.
11. Krylov. S.G. Gastroprotective effect of non–starch polysaccharides of natural origin. Krylov Yu. S., Khotimchenko E. P., Zueva et al. *Byull. experimental biol. and honey*. 2016.Vol. 142, No. 10, pp. 437–440.
12. Odintsov V. M. Pharmacognostic research species in the genus Polygonum L. flora of Ukraine and substances on the ith basis: author. dis. *Cand. farm. Sciences*: 15.00.02 Odintsova Vira Mikolaivna. Zaporizhzhia.
13. Mitrofanov I. Yu. Methodological foundations for the selection of plant objects as sources of phytopreparations. I. Yu. Mitrofanov, A.V. Yanitskaya, D.V. Butenko. *Basic research*. 2012. No. 20 (2). p. 405–408.
14. Prokopyev A.P. Determination of hydroxycinnamic acids in medicinal plant raw materials and objects of plant origin. Prokopyev A. P., Arzamaztsev Yu. V. Medvedev K.I., Keller. O. I., Perederyaev A. A.. *Biological issues. medical and pharmaceutical chemistry*. 2010. No. 3. P. 25–31.
15. Aura A. M. Microbial metabolism of dietary phenolic compounds in the colon. A. M. Aura. *Phytochem*. Rev. 2018. Vol. 7. P. 407–429.
16. Management of Helicobacter pylori infectiondthe Maastricht IV/ Florence Consensus Report. Peter Malfertheiner. Francis Megraud. Colm A O'Morain. John Atherton. Anthony T R Axon. et al. The European Helicobacter Study Group (EHSG).
17. Zenkov N. K. Oxidative stress: biochemical and pathophysiological aspects. Zenkov, V. Z. Lankin, E. B. Menshchikova. M .: *Nauka.Interperiodika*. 2011.343 p.
18. Sosnina S. A. Comparative pharmacognostic study. standardization of raw materials and preparations of species of the genus Plantago L .: author. dis.. Cand. farm. Sciences: 15.00.02. Sosnina Svetlana Anatolyevna. 2019. P. 25.
19. Asgarpanah J. Phytochemistry, pharmacology and medicinal properties of Coriandrum sativum L..J. Asharpanah. N. Kasemivash. *African Journal of Pharmacy and Pharmacology*. 2012. Vol. 6. № 31. P. 2340 – 2345
20. Ghasemzadeh A. Antioxidant activities, total phenolics and flavonoids content in two varieties of Malaysia young ginger (*Zingiber officinale* Roscoe).A. ghasemzadeh. H.Z.E. Jaafar. A. Rahmat. *Molecules*. 2010. Vol. 15. P. 4324–4333.

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