Influence of some types of medicinal plant materials on the hemostasis system in vitro

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SUMMARY

The article presents studies on the study of antiaggregatory and anticoagulant activity of some types of medicinal plant materials containing various groups of biologically active substances. Experiments to determine the anticoagulant and antiaggregatory activity were carried out in vitro on human donor blood. Determination of anticoagulant activity was carried out by generally recognized clotting tests. The study of the effect on platelet aggregation was carried out according to the Born method. In the course of the experiment, it was found that all studied samples have a tendency to manifest anticoagulant activity, to one degree or another - antiaggregatory activity, some species are superior in action to the reference drug. The following types of medicinal plant materials have been identified,

Key words: antiaggregatory and anticoagulant activity, hawthorn, lemongrassChinese, gynostemma five-leafed, papaya, pomegranate, immortelle, fenugreek, wormwood, flavonoids, saponins.

RESUME

The article presents research the study of antiaggregation and anticoagulation activity of some types of medicinal plant raw materials containing various groups of biologically active substances. Experiments to determine anticoagulation and antiaggregation activity were performed in vitro on human blood. The determination of anticoagulation activity was carried out by generally recognized clotting tests. The study of the effect on platelet aggregation was carried out using the Born method. During the experiment, it was found that all the samples under study have a tendency to anticoagulation activity and revealed to some extent antiaggregation activity, the effect of some of them exceeds the action of the comparison drug. The following types of medicinal plant raw materials that exhibit antiaggregation and anticoagulant activity were identified:

Keywords: antiaggregation and anticoagulant activity, hawthorn, Chinese lemongrass, jiaogulan, papaya, common pomegranate, immortelle, fenugreek, annual wormwood, flavonoids, saponins.

Diseases of the circulatory system today are one of the most global problems of mankind due to the widespread prevalence, severity of the consequences and the highest mortality.

In recent years, special attention has been paid to the theory of the role of the systems of hemorheology and hemostasis, with

from the point of view of normal functioning, and in the formation of thrombosis, ischemia and heart attacks. One of the central links in the development of cardiovascular diseases is hemostatic activation with impaired rheological properties of blood and endothelial dysfunction, which occurs before the development of thrombus formation. The use of antithrombotic, hemangiocorrecting agents is considered as the most optimal method for restoring vascular patency and preventing thrombus formation [6, 11].

The main groups of drugs used in this pathology are thrombolytics, anticoagulants and antiplatelet agents. However, they have a lot of side effects. So, one of the most severe complications when using thrombolytic therapy is hemorrhage. To solve this problem, it is necessary to search for new effective drugs that do not have these complications. An example is herbal biologically active substances, which have a milder effect, are not toxic and do not cause such extensive side effects as synthetic drugs. In many experimental works, the influence of various biologically active substances of plants on the rheological picture of blood has been investigated. So, for example, antiplatelet, angioprotective, hypocholesterolemic properties of various flavonoids (dihydroquercetin, anthocyanidins, rutin, hyperoside, etc.) [2, 3, 4, 8, 13]. According to the literature, saponins and lignans contained in plants such as schisandra chinensis, gynostemma five-leafed, ginseng also have a beneficial effect on the heart muscle and are able to effectively regulate vascular tone [12].

Purpose of the study: conducting screening studies to study antiaggregatory andanticoagulant activity of some types of medicinal plant materials to identify promising sources for the prevention and treatment of disorders of the hemostasis system.

MATERIALS AND RESEARCH METHODS

raw materials of the Samarkand immortelle and annual wormwood - from wild species in the Kyrgyz Republic, pomegranate leaves - from cultivated species in the Republic of Azerbaijan, papaya leaves - from introduced plants in the Republic of Bashkortostan and from wild species in India, fenugreek seeds - from cultivated plants to the territory of Egypt in 2019–2020. Shoots of plants of the genus Crataegus L. were harvested during the flowering period, fruits - during the fruiting period from 10–15 year old trees. Flowers of the Samarkand immortelle, wormwood herb, five-leaved gynostemma herb, Schisandra chinensis leaves were harvested during the flowering period. Papaya leaves, pomegranate leaves, fruits and stems of Schisandra chinensis, fenugreek seeds were harvested during the fruiting period of the plant.

To study the antiaggregatory and anticoagulant activity, aqueous extracts were obtained from the studied types of plant raw materials, which were prepared in a ratio of 1:10; for this, the raw materials were crushed to a particle size of 3 mm. Decoctions were obtained from fruits, stems and seeds; infusions were prepared from shoots, herbs and leaves according to the method of the State Pharmacopoeia of the IV edition [1].

Experiments to determine anticoagulant and antiaggregatory activity under conditions were performed in vitro on the blood of healthy male donors aged 18-24 years old [7]. The total number of donors was 25. Blood sampling for the study of compounds in relation to the hemostasis system was carried out from the cubital vein using BD Vacutainer® vacuum blood sampling systems (Becton Dickinson and Company, USA). As a stabilizer for venous

blood was used 3.8% sodium citrate solution in a ratio of 9: 1. All tests were performed on platelet-rich and platelet-depleted plasma. Samples of platelet-rich plasma were obtained by centrifuging citrated blood at 1000 rpm for 10 minutes, platelet-free plasma at 3000 rpm for 20 minutes. An OPN-3.02 centrifuge (OJSC TNK DASTAN, Kyrgyzstan) [5] was used in the work.

The study of the effect on platelet aggregation was carried out according to the Born method [9] on an AT-02 aggregometer (NPF Medtech, Russia). Adenosine diphosphate (ADP) at a concentration of 20 μg / ml and collagen at a concentration of 5 mg / ml produced by Tekhnologiya-Standard (Russia) were used as inducers of aggregation. In the experiment, the maximum amplitude of aggregation, the rate of aggregation, the time to reach the maximum amplitude, and disaggregation in the presence of the studied compounds during platelet aggregation were evaluated. In collagen-induced platelet aggregation, the latency period was assessed, during which phospholipase C is activated (which leads to the formation of secondary messengers, as a result of which the secretion of platelet granules and the synthesis of thromboxane A2 develop).

Determination of anticoagulant activity was carried out by generally recognized clotting tests on an optical two-channel automated blood coagulation analyzer ASKa 2-01- "Astra" (NPTs "Astra", Russia). The parameters of activated partial thromboplastin time (APTT), prothrombin time (PT) and fibrinogen concentration according to A. Clauss were studied. We used reagents produced by "Technology-Standard" (Barnaul, Russia).

To assess the pharmacological activity, the investigated aqueous extracts were introduced into the blood plasma at the rate of 5% of the volume of the reaction mixture. The reference drugs used were: 2-acetyloxybenzoic acid (Acetylsalicylic acid, Shandong Xinhua Pharmaceutical Factory Co., LTD, China); "Heparin sodium" (JSC "Sintez", Russia). The antiaggregatory activity of the reference drug, acetylsalicylic acid, is presented for a concentration of 2 - 10^{-3} M / l, anticoagulant activity of sodium heparin - for a concentration of 5 - 10^{-4} g / ml [10].

The research results were processed using the statistical package Statistica 10.0 (StatSoft Inc, USA). The normal distribution of the actual data was checked using the Shapiro-Wilk test. It was revealed that the type of distribution of the obtained data differs from the normal one, therefore, in further work, nonparametric methods were used. Data are presented as median, 25th and 75th percentiles. Analysis of variance was performed using the Kruskal-Wallis test. The critical level of significance p for statistical tests was taken equal to 0.05.

RESULTS OF THE STUDY

The data obtained from the study of the anticoagulant activity of the studied types of raw materials and the reference drug, which was heparin, are presented in table. 1.

Table 1

Influence of the studied types of raw materials on the parameters of the plasma hemostasis link, Me (0.25-0.75)

No.	Substance code	APTV,% to control	PV,% to control	Fibrinogen,% k control
1	BK fruits	+ 7.2 (5.2-9.3)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
2	Fruits of BA	+ 4.7 (3.3-6.1)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
3	BM fruits	+ 7.3 (6.9-8.5)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
4	Shoots BM	+ 5.2 (3.6-8.1)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
5	Shoots BK	+ 5.3 (4.8-6.9)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
6	BA shoots	+ 3.7 (2.6-6.4) †	0.0 (0.0-0.0)	0.0 (0.0-0.0)
7	Stems LK	+ 4.4 (3.6-5.7)	0.0 (0.0-0.0)	0.0 (0.0-0.0)

No.	Substance code	APTV,% to control	PV,% to control	Fibrinogen,% k control
eight	LK fruits	+ 5.2 (4.6-8.3)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
nine	Leaves LK	+ 3.7 (3.1-4.5) *	0.0 (0.0-0.0)	0.0 (0.0-0.0)
ten	Grass GP	+ 2.3 (1.7-3.8) *	0.0 (0.0-0.0)	0.0 (0.0-0.0)
eleven	BP fruits	+ 7.1 (6.3-9.7)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
12	Shoots BP	+ 5.2 (4.9-6.4)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
13	Grass BS	+ 4.2 (3.1-6.5)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
fourteen	Grass PO	+ 3.8 (3.2-5.5) *	0.0 (0.0-0.0)	0.0 (0.0-0.0)
15	Leaves P (dick)	+ 5.3 (4.9-7.6)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
16	Leaves P (intr)	+ 4.1 (3.6-6.2)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
17	BPen fruits	+ 3.8 (2.1-5.6) *	0.0 (0.0-0.0)	0.0 (0.0-0.0)
eighteen	BSl fruits	+ 4.1 (3.7-5.3)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
19	BKr fruits	+ 4.8 (3.7-6.1)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
twenty	Seeds Page	+ 5.1 (3.6-6.2)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
21	Leaves G	+ 4.3 (3.4-6.8)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
22	Heparin sodium	+ 20.3 (19.7-21.4)	0.0 (0.0-0.0)	0.0 (0.0-0.0)

Note: * p> 0.05 - in comparison with the control; compounds vs sodium heparin at p ≤ 0.05; n = 6.

According to the data obtained, none of the studied objects showed anticoagulant activity comparable in effect to the reference drug. However, the studied samples had an effect of varying severity on the plasma component of the hemostasis system, manifested by a change in the index of the internal blood coagulation pathway - lengthening of APTT, but these samples in the studied concentration did not affect the index of fibrinogen and PT concentration. Analyzing the data obtained, we can talk about a tendency towards the manifestation of anticoagulant activity of some of the studied species, especially for fruits of blood-red hawthorn (+7.2), fruits of softish hawthorn (+7.3), fruits of riverine hawthorn (+7.1) ...

Indicators of antiaggregatory activity of the studied types of raw materials and the reference drug, which was acetylsalicylic acid, are presented in table. 2.

table 2

Influence of the studied types of medicinal plant materials on indicators of platelet aggregation, Me (0.25-0.75)

No.	LRS	Latent period,% to control	Maximum amplitude, % to control	Speed aggregation,% to control	Time achievement of MA, % to control	Disaggregation,% to control
1	BM fruits	+ 4.2 (3.2-5.7) #	- 16.3 (15.2-18.3) *	+ 4.7 (3.2-5.9), #	+ 15.3 (14.1-18.3) *, #	0.0 (0.0-0.0)
2	BK fruits	+ 7.8 (5.1–8.1) *, #	- 17.8 (14.2-19.3) *	- 10.4 (7.2-13.6) *	+ 14.1 (10.2-16.5) *	0.0 (0.0-0.0)
3	Fruits of BA	+ 8.3 (6.3-10.5) *, #	- 20.8 (16.3-23.1) **, #	- 31.2 (26.4–32.7) **, #	+ 7.2 (5.3-10.1) *	0.0 (0.0-0.0)
4	Shoots BM	+ 3.6 (2.1-5.8) #	- 18.3 (16.7-19.5) *, #	+ 2.9 (11.8-17.9) #	+ 16.5 (14.7-17.9) *, #	0.0 (0.0-0.0)

No.	LRS	Latent period,% to control	Maximum amplitude, % to control	Speed aggregation,% to control	Time achievement of MA, % to control	Disaggregation,% to control
5	Shoots BK	+ 3.5 (2.4-4.3) #	- 16.4 (13.9-19.5) *	- 18.1 (17.2-19.8) *, #	+ 23.4 (19.2-25.4) **, #	0.0 (0.0-0.0)
6	BA shoots	+ 4.1 (2.3–6.2), #	- 11.1 (8.9-12.6) *	- 2.3 (1.2-3.7) #	+ 12.3 (7.5-14.2) *	0.0 (0.0-0.0)
7	Stems LK	+ 5.1 (4.3–8.7) *, #	- 11.3 (9.5-13.2) *	+ 1.9 (0.7-2.5) #	- 11.4 (9.3-14.2) *, #	0.0 (0.0-0.0)
eight	LK fruits	+ 10.3 (7.1-12.6) *	- 17.3 (17.1–20.3) **, #	+ 15.3 (10.1-19.4) *, ##	- 15.4 (10.7-16.2) *, #	0.0 (0.0-0.0)
nine	Leaves LK	+ 6.4 (5.1-7.5) *, #	- 13.4 (12.1-15.8) *	+ 5.3 (3.5-7.1) *, #	- 10.3 (8.3-12.7) *, #	0.0 (0.0-0.0)
ten	Grass GP	+ 4.6 (3.1-6.2) #	- 14.4 (11.3-16.7) *	- 10.4 (8.3-12.1) *	+ 18.6 (14.9-21.3) *, #	0.0 (0.0-0.0)
eleven	Flowers BS	+ 3.7 (3.1-4.5), #	- 4.3 (3.2-5.7) **, #	+ 4.2 (3.1-5.8) #	+ 14.6 (13.2-17.5) *, #	0.0 (0.0-0.0)
12	BP fruits	+ 7.4 (5.3–8.2) *, #	- 18.1 (15.3-19.7) *	- 8.9 (6.1-11.7) *	+ 15.9 (12.4-17.5) *	0.0 (0.0-0.0)
13	Leaves P (Dick)	+ 4.3 (2.3–5.5) #	- 3.8 (2.3–6.1) *, #	- 1.2 (0.4–2.7) **, #	+ 7.1 (6.1-10.3) *	0.0 (0.0-0.0)
fourteen	Leaves P (intr)	+ 3.6 (2.1-5.8) #	- 3.3 (2.7-5.8) *, #	- 3.1 (1.7-4.2) **, #,	+ 6.5 (4.7-8.9) *	0.0 (0.0-0.0)
15	Shoots BP	+ 3.2 (2.7-5.1) #	- 15.9 (13.2-17.4) *	- 17.9 (16.1-19.3) *, #	+ 21.6 (18.9-24.3) **, #	0.0 (0.0-0.0)
16	Grass PO	+ 4.3 (2.4–6.1) #	- 3.1 (1.9-4.7) *, #	- 2.4 (1.3-3.6) #	+ 6.3 (4.5–8.9) *	0.0 (0.0-0.0)
17	BPen fruits	+ 4.1 (3.8–5.3) #	- 6.7 (5.2-8.3) **	- 9.3 (8.3-12.6) *	+ 9.7 (7.5-13.2) *, #	0.0 (0.0-0.0)
eighteen	BSl fruits	+ 6.7 (5.8-7.9) *, #	- 3.1 (2.1-4.5) #	- 4.9 (3.3-7.9) *, #	+ 7.1 (5.3–8.1) *	0.0 (0.0-0.0)
19	BKr fruits	+ 7.8 (5.4-9.6) *, #	- 9.6 (7.5-12.3) *	- 14.1 (10.3-15.9) **	+ 14.2 (8.3-17.1) *	0.0 (0.0-0.0)
twenty	Seeds Page	+ 3.7 (2.3–5.4) #	- 4.2 (3.6-7.1) *, #	- 3.4 (2.5-5.7) #	+ 6.2 (4.9-9.1) *	0.0 (0.0-0.0)
21	Leaves G	+ 5.2 (4.1-6.9) *, #	- 3.7 (2.5-4.9) #	- 4.7 (2.6-5.9) *, #	+ 6.9 (4.3-8.2) *	0.0 (0.0-0.0)
22	Acetylsali-cylinder acid	- 2.1 (1.1-2.6)	- 13.7 (10.8-16.4) *	- 10.5 (7.6-12.3) *	+ 10.5 (8.7-13.4) *	0.0 (0.0-0.0)

Note: The latency period is presented for platelet aggregation induced by collagen,other parameters for ADP-induced platelet aggregation.

* - p ≤ 0.05, ** - p ≤ 0.001 - in comparison with the control; # - p ≤ 0.05,

- p ≤ 0.001 - in comparison with acetylsalicylic acid; n = 4.

According to the data obtained, all the studied types of raw materials reduce the maximum amplitude, which indicates their effect on platelet aggregation, however, they increase the latent period of platelet aggregation, in contrast to the reference drug.

Aqueous extracts of leaves and stems Schisandra chinensis, Gynostemma pentaphyllum herbs, escapes Crataegus almaatensis showed results comparable to the reference drug, andsome of them exceeded the activity indicators of the reference drug - acetylsalicylic acid - fruits Crataegus submollis on 19%, fruits Crataegus sanguinea - on 30%, shoots Crataegus submollis - on 34%, shoots Crataegus sanguinea - on 20%, fruits Crataegus rivularis - on 32%, shootsCrataegus rivularis - on 16%, fruits Schisandra chinensis - on 26%. The greatest antiaggregatory activity was shown by a decoction of fruitsCrataegus almaatensis, exceeding the effect of the reference drugby 52%. Most of the studied types of plant materials influenced the rate of aggregation

platelets, significantly reducing it in comparison with acetylsalicylic acid. Thus, the efficiency of water extracts from raw materials such as fruitsCrataegus pennsylvanica, Crataegus rivularis fruits, Gynostemma pentaphyllum herb and Crataegus sanguinea fruits are comparable to the drug comparisons. The fruits exceed it in strengthCrataegus almaatensis, shoots of Crataegus sanguinea, shoots of Crataegus rivularis and fruits of Crataegus macracantha. An interesting fact is thatsome investigated types of raw materials, reducing the maximum amplitude, increase the rate of aggregation (fruits and shoots Crataegus submollis, shoots and stems of Schisandra chinensis). Estimating the time reaching the maximum amplitude, we can say that shoots act at the level with the comparison drug Crataegus almaatensis and the fruits of Crataegus pennsylvanica, while the fruits andescapes Crataegus submollis, fruits and shoots of Crataegus sanguinea, Gynostemma pentaphyllum herb,flowers Helichrysum maracandicum, fruits and shoots of Crataegus rivularis, fruits of Crataegus macracantha.

Some patterns are leaves Carica papaya, Helichrysum maracandicum flowers, Artemisia annua herb, Punica granatum leaves, Trigonella foenum-graecum seeds - in the concentration usedshowed weak antiplatelet properties, inferior in their effect to the reference drug.

DISCUSSION AND CONCLUSIONS

Based on the screening pharmacological studies carried out to identify promising types of medicinal plant materials with anti-coagulant and antiaggregatory activity, the following conclusions can be drawn:

1. It was found that all studied species in the studied concentration have only a tendency to manifest anticoagulant activity.
2. Antiaggregation properties were revealed in all studied samples to one degree or another.
3. Identified promising types of raw materials for further more in-depth pharmacological and pharmacognostic studies.

Thus, as a result of experimental screening studies, the following types of medicinal plant raw materials were identified, exhibiting antiaggregatory and anticoagulant activity - all studied species of the genus Crataegus, Gynostemma pentaphyllum herb, all studied raw materials Schisandra chinensis.

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