Anti-opisthorchiasis activity of plants of the genus Achillea and genus Artemisia: research results in conditions in vitro and in vivo

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Anti-opisthorchiasis activity of the genus Achillea and the genus Artemisia plants: results of in vivo and in vitro research

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SUMMARY

Carried out screening pharmacological studies of plants of the genus Achillea (yarrow: Achillea millefolium L. - t. common, Achillea nobilis L. - t. noble) and Artemisia (wormwood: Artemisia absinthium L. - n. bitter, Artemisia vulgaris L. - n. ordinary, Artemisia gmelinii Web.ex Stechm - n. Gmelin, Artemisia dracunculus L. - n. Tarragon) of the family Asteraceae - Astrovye. The presence of a group of sesquiterpene lactones (as a potential carrier of anthelmintic activity against Opisthorchis felineus) in all studied plant objects was confirmed. The specific anti-opisthorchiasis activity of the fractions of sesquiterpene lactones of plants of the genera Yarrow and Wormwood has been studied using an in vitro model, and the most promising objects have been identified.

Key words: opisthorchiasis, Opisthorchis felineus, Achillea millefolium, Achillea nobilis Artemisia absinthium, Artemisia vulgaris, Artemisia gmelinii, Artemisia dracunculus sesquiterpene lactones, anti-opisthorchiasis activity, in vitro model, in vivo model.

RESUME

Pharmacological screening studies of Achillea plants (A. millefolium, A. nobilis) and Artemisia plants (A. absinthium, A. vulgaris, A. gmelinii, A. dracunculus) were carried out. The presence of sesquiterpene lactones group (as a potential carrier of anthelmintic activity against Opisthorchis felineus) in all studied plant objects was confirmed. In vitro the specific antiopisthorchiasis activity of the sesquiterpene lactones fractions from Achillea and Artemisia plants was studied, leader objects were revealed. Pronounced antiopisthorchiasis activity of A. millefolium and A. nobilis was confirmed by in vivo investigations using golden hamstersmales.

Keywords: opisthorchiasis Opisthorchis felineus, Achillea millefolium, Achillea nobilis, Artemisia absinthium, Artemisia vulgaris, Artemisia gmelinii, Artemisia dracunculus, sesquiterpene lactones, antiopisthorchiasis activity, in vitro model, in vivo model.

INTRODUCTION

Plants of the Asteraceae family are a source of a variety of biologically active compounds. Among them, the group of sesquiterpene lactones is of particular importance, whose effectiveness in the treatment of helminthic invasions has been proven by chemical and pharmacological studies [1]. The relevance of such studies does not raise doubts in the conditions of endemicity of opisthorchiasis in the territory of Central and Eastern Siberia. The spread of this invasion, the high prevalence of the population of different ages, significant economic damage (associated with an increase in temporary disability among the working population and children), in most cases, the need for inpatient treatment, make opisthorchiasis to be attributed to socially significant diseases [2]. The main feature of the development of opisthorchiasis is that pathogenesis captures one of the most important systems of the human body - the hepatobiliary system [3]. Opisthorchiasis invasion is often accompanied by hepatomegaly, cholangitis, fibrosis of the periportal system, cholecystitis, and other concomitant diseases [4]. In addition, opisthorchiasis is recognized as carcinogenic by the International Agency for Research on Cancer (IARC) and the World Health Organization (WHO).

a factor contributing to the development of bile duct cancer and cholangiocarcinoma [5].

The existing clinical protocols for the treatment of opisthorchiasis provide for the use of the only etiotropic drug praziquantel registered in the territory of the Russian Federation. It is characterized by a significant number of contraindications and side effects from the main body systems [6]. In addition, there are interruptions in the supply of this drug to the Russian pharmaceutical market [7]. In this regard, the search for new, safer and more affordable medicines for the consumer for the treatment of opisthorchiasis, including of plant origin, is urgent.

In this regard, the family Asteraceae (Asteraceae) is of interest, in which the rough cornflower has been studied most fully both chemically and pharmacologically.(Centaurea scabiosa L.) [8]. However, there is evidence that some representatives of the genera yarrow (i.e. common, i.e. noble) and wormwood (n. Bitter, n. Ordinary, n. Gmelin, n. Tarragon) are used in folk medicine as antiparasitic agents. According to the literature, they contain in the chemical composition a group of sesquiterpene lactones [9], which are known to exhibit anthelmintic activity againstOpisthorchis felineus [10, 11].

This article is devoted to the results of screening studies of anthelmintic activity of so common and so noble, wormwood, p. Ordinary, p. Gmelin and p. Tarragon in relation to Opisthorchis felineus.

MATERIALS AND METHODS

Research objects: Achillea millefolium L. (common yarrow), Achillea nobilis L. (yarrow), Artemisia absinthium L. (bitter wormwood), Artemisia vulgaris L. (common wormwood), Artemisia gmelinii Web. ex Stechm. (wormwood gmelin),Artemisia dracunculus L. (tarragon wormwood), family Asteraceae.

The aboveground part of the studied plants was collected in natural habitat in the phase of mass flowering [12] in various regions of Russia during 2016: A. millefolium, A. absinthium, A. vulgaris, A. gmelinii, A. dracunculus - in the Tomsk region (near the city of Tomsk); A. nobilis - in the Republic of Bashkortostan (in the vicinity of Sterlitamak). The plant material was driedair-shadow method and ground to a particle size of 2–4 mm.

Fractions of sesquiterpene lactones for pharmacological studies under conditions in vitrowere obtained by the method of K.S. Rybalko [13]. For this, the crushed aerial part of the studied plants was extracted three times with purified water when heated to 85–90 -C at a raw-extractant ratio of 1:10 (the duration of each extraction was 60 min). The resulting extracts were separated from the raw material by filtration and combined. Then, chloroform extraction was obtained from the combined aqueous extract by liquid-phase extraction: 1 part of the concentrated aqueous extract and 2 parts of chloroform were placed in a separating funnel. Extraction was carried out by sharp shaking of the separating funnel. After stratification of the resulting emulsion, the chloroform layer was separated, filtered through a paper filter with anhydrous sodium sulfate, and the extraction was repeated twice. The obtained chloroform extracts were combined,

Extractive complexes of the studied plants for pharmacological studies under conditions in vivo was obtained by the method of bismaceration [14] using purified water and 70% ethyl alcohol as extractants.

To obtain aqueous extracts, the crushed aerial part of the studied plants was extracted three times with purified water when heated to 85–90 -C and a raw-extractant ratio of 1:10 (the duration of each extraction was 60 min). The resulting aqueous extracts were separated from the raw material by filtration and combined. The solvent was removed from the extracts in a rotary evaporator at reduced pressure (at a temperature of 50–60 -C).

To obtain ethanol extracts, the crushed aerial part of the studied plants was extracted three times with 70% ethyl alcohol when heated to 78–80 -C and a raw-extractant ratio of 1:10 (the duration of each extraction was 60 min). The resulting ethanol extracts were separated from the feed by filtration and combined. The solvent was removed from the extracts in a rotary evaporator at reduced pressure (at a temperature of 40–50 -C).

To detect the group of sesquiterpene lactones in fractions of so common and so noble, as well as wormwood, p. Ordinary, p. Gmelin and p. Tarragon, we used the method of IR spectroscopy. IR spectra were recorded on a Nicolet 5700 spectrometer (INTERTECH Corp., USA) in chloroform.

Reproduction of the experimental opisthorchiasis model in vitro was carried out according to generally accepted technique [15]. For this, viable maritas were isolated from the dissected organs of the hepatobiliary system of golden hamsters infected with opisthorchiasis.Opisthorchis felineus. In sterile Petri dishes with a diameter3.5 cm were placed 3 ml of RPMI 1640 medium, 50 μg / ml solution of benzylpenicillin sodium salt, 50 U / ml solution of streptomycin, 80 μg / ml solution of hemin. Five viable maritas were placed in each Petri dish with a nutrient medium, solutions of antibiotics and hemin.Opisthorchis felineus. Then, samples of fractions were added to the cups. sesquiterpene lactones of the studied plants at doses of 100, 300 and 600 μg / ml. Solutions of antibiotics and hemin were prepared using saline sodium chloride solution. Solutions of sesquiterpene lactone fractions - on dimethyl sulfoxide. A solution of praziquantel at a concentration of 50 μg / ml (in physiological sodium chloride solution) was used as a reference drug.

Petri dishes with samples were incubated at 37 -C in an atmosphere of carbon dioxide (5%). Evaluation of the viability of the opisthorchis marita was carried out after 24, 48 and 72 hours of exposure according to the value of their motor activity, assessed visually under a microscope with a twenty-fold magnification. At the same time, the movements of the oral sucker, the movements of the body for flexion / twisting, as well as the peristalsis of the internal organs were noted (Table 1).

Table 1

Scale for assessing motor activity marit Opisthorchis felineus

Assessment of motor activity marit Opisthorchis felineus, points	Interpretation of motor activity scores marit Opisthorchis felineus
3	normal physical activity
2	reduced physical activity
1	very weak physical activity, visible only with a microscope magnification of 20x
0	lack of motor activity or death: recorded in the absence of movement within 2 minutes of observation through a 20x microscope

Experimental opisthorchiasis model reproduced in vivo on golden male hamstersweighing 40–45 g according to the generally accepted method [16]. For this purpose, opisthorchus metacercariae were isolated from infected fish, mainly dace and roach, by digestion in artificial gastric juice. Opisthorchis felineus. The invasion of animals was carried out by intragastric administrationviable metacercariae in the amount of 50 copies. in 0.5 ml of isotonic sodium chloride solution. The experimental animals were kept in a vivarium under natural light conditions on a standard diet with free access to food and water.

On the 30th day of invasion, the fact of the development of experimental opisthorchiasis was confirmed by the detection of a significant number of opisthorchiasis in the organs of the hepatobiliary system (liver, gallbladder) of several animals. Opisthorchis felineus.

The anti-opisthorchiasis effect of dry extracts of so common and so noble, p. Bitter, p. Ordinary, p. Gmelin and p. Tarragon, obtained in 70% ethanol and purified water, was evaluated on 75 infected animals, the weight of which on the 30th day invasion increased to 90-110 g.

The experimental animals were divided into 15 groups: group No. 1 (intact) - healthy animals; group No. 2 (control) - animals with opisthorchiasis. Group No. 3 - animals with opisthorchiasis who received a reference drug - praziquantel in the form of a suspension of 1% starch mucus at a dose of 20 mg / kg of animal weight 2 times a day for 1 day [17].

Groups No. 4-5 - animals with opisthorchiasis treated with dry extracts of yarrow

ordinary 70% ethanol and purified water, respectively.

Groups 6–7 - animals with opisthorchiasis who received dry extracts of yarrow in 70% ethanol and purified water, respectively.

Groups No. 8-9 - animals with opisthorchiasis who received dry extracts of wormwood in 70% ethanol and purified water, respectively.

Groups No. 10-11 - animals with opisthorchiasis who received dry extracts of wormwood in 70% ethanol and purified water, respectively.

Groups 12-13 - animals with opisthorchiasis, who received dry extracts of wormwood gmelin in 70% ethanol and purified water, respectively.

Groups No. 14-15 - animals with opisthorchiasis who received dry extracts of tarragon wormwood in 70% ethanol and purified water, respectively

These extracts were administered at a dose of 2.0 g / kg as a suspension on 1% starch mucus three times a day for five days.

All studied samples were injected intragastrically through a metal probe; the latency period after the end of the course of treatment was 14 days. After this period, the animals were removed from the experiment by asphyxiation with carbon dioxide, the liver was removed, and the opisthorchiasis marits were counted in the organs of the hepatobiliary system (the intensity-efficiency coefficient was calculated, which is a criterion for anti-opisthorchiasis activity) [16]:

where K is the average number of maritas O. felineus in the control group;O - the average number of marits of opisthorchus in the experimental group.

RESULTS

From the above-ground part of the so-called ordinary and so-noble, p. Bitter, p. Ordinary, p. Gmelin, p. Tarragon by the method of K.S. Rybalko isolated fractions of sesquiterpene lactones. The characteristics of the appearance and yield of fractions are presented in table. 2.

table 2

Characteristics of the appearance and yield of fractions of sesquiterpene lactones, obtained from the above-ground part of the so-called ordinary, etc., noble, n. bitter, n. ordinary, n. gmelin, tarragon

The plant species from which selected fraction sesquiterpene lactones	Faction appearance sesquiterpene lactones	Sesquiterpene fraction yield lactones (in terms of for air-dry raw materials),%
Artemisia absinthium L.	dark brown viscous mass with a characteristic odor	0.72 ± 0.15
Artemisia vulgaris L.		0.53 ± 0.11
Artemisia gmelinii Web. ex Stechm.	brownish-green viscous mass with a characteristic odor	0.87 ± 0.10
Artemisia dracunculus L.		0.72 ± 0.19
Achillea millefolium L.	dark brown powder with a characteristic odor	0.62 ± 0.13
Achillea nobilis L.		0.44 ± 0.15

IR spectroscopy confirmed the presence of a group of sesquiterpene lactones in the fractions obtained by K.S. Rybalko from the studied species of yarrow and wormwood. The identification was carried out by the presence in the IR spectra of the analyzed fractions of characteristic absorption bands of the structural elements of sesquiterpene lactones: - the lactone cycle (1780-1760 cm^{-1}) and exocyclic methylene group (1765-1740 cm^{-1}) [13].

In conditions in vitro, the anthelmintic activity of the obtained fractions was studied in relation toisolated marit Opisthorchis felineus. The greatest anti-opisthorchiasis activity was shown by fraction of yarrow at a dose of 300 mcg / ml - within 24 hours of exposure there was a significant inhibition of the motor activity of marita opisthorchus, and after 72 hours - the death of 100% of opisthorchus in the group (Table 3). A less pronounced anthelmintic effect was shown by the fraction of sesquiterpene lactones isolated from gmelin wormwood. At a dose of 300 μg / ml, this fraction causes the death of only 20% of the opisthorchis in the group within 72 hours. Fractions

sesquiterpene lactones of wormwood, bitter and tarragon were shown in experiments in vitro moderate anti-opisthorchiasis activity in a dose 600 μg / ml.

Table 3

Results of determination of pro-opisthorchiasis activity of fractions sesquiterpene lactones so common and so on noble, p. bitter, p. ordinary, p. gmelin and p. tarragon in conditions in vitro

No.	Plant species, from which the fraction is isolated sesquiterpene lactones	Motor activity marit opisthorchiv (according to the scale)								
		24 hours			48 hours			72 hours		
	Dose, μg / ml	100	300	600	100	300	600	100	300	600
1	Achillea millefolium L.	3	1	1	3	2	0	3	1	0
		3	1	0	3	1	0	3	0	0
		3	1	0	3	1	0	3	0	0
		3	1	0	3	1	0	3	0	0
		2	1	0	1	1	0	0	0	0
	The average	2.8	1	0.2	2.6	1,2	0	2.4	0.2	0
2	Achillea nobilis L.	3	2	1	3	1	0	3	1	0
		3	2	1	3	1	0	3	1	0
		3	1	1	3	1	0	3	0	0
		3	1	1	2	1	0	1	0	0
		3	1	1	2	1	0	1	0	0
	The average	3	1.4	1	2.6	1	0	2.2	0,4	0
3	Artemisia absinthium L.	3	3	1	3	3	1	3	3	1
		3	3	1	3	3	1	3	3	1
		3	2	1	3	3	1	3	3	1
		3	1	1	3	2	1	3	3	1
		3	1	1	3	2	1	1	3	1
	The average	3	2	1	3	2.6	1	2.6	3	1
4	Artemisia vulgaris L.	3	3	1	3	3	1	3	3	1
		3	3	1	3	3	1	3	3	1
		3	3	1	3	3	1	3	3	1
		3	3	1	3	3	1	3	3	1
		3	2	1	3	2	1	3	2	1
	The average	3	2.8	1	3	2.8	1	3	2.8	1
5	Artemisia gmelinii Web. ex Stechm.	3	3	2	3	3	2	3	3	1
		3	3	2	3	3	2	3	3	1
		3	3	2	3	3	2	1	3	1
		3	3	1	3	3	1	1	3	0
		3	3	1	0	3	1	0	3	0
	The average	3	3	1.6	2.4	3	1.6	1.6	3	0.6
6	Artemisia dracunculus L.	3	3	2	3	3	2	3	3	2
		3	3	2	3	3	2	3	3	1
		3	3	2	3	3	1	3	3	1
		3	3	2	3	3	1	3	3	1
		3	3	1	3	3	1	3	3	1
	The average	3	3	1.8	3	3	1.4	3	3	1,2

7	Praziquantel (50 mcg / ml)	1 1 1 1 1	1 1 1 1 1	1 1 1 1 1
eight	Saline sodium chloride 0.9% (15 µl)	3 3 3 3 3	3 3 3 3 3	3 3 3 3 3
nine	DMSO (15 µl)	3 3 3 3 3	3 3 3 3 3	3 3 3 3 3
Note (scale for assessing motor activity marit Opisthorchis felineus):3 - normal physical activity; 2 - reduced physical activity; 1 - very weak physical activity, visible only with a microscope magnification of 20x; 0 - lack of motor activity or death: recorded in the absence of movement within 2 minutes of observation through a 20x microscope.				

In conditions in vivo (on a model of experimental opisthorchiasis caused by Opisthorchis felineus)investigated the anthelmintic activity of extracts obtained from the aerial part of the so-called common and so noble, the bitter item, the ordinary item, the gmelin item and the tarragon item. The greatest anti-opisthorchiasis activity is possessed by extracts of yarrow, obtained using 70% ethanol and purified water as an extractant: the IE coefficient was 45.29 ± 8.15% and 43.58 ± 2.56%, respectively (Table 4). At the same time, 70% ethanol extract of yarrow showed a level of activity comparable to the reference drug praziquantel (IE praziquantel - 58.11 ± 13.43%). A less pronounced effect was demonstrated by 70% ethanol extracts of wormwood and P. bitter (IE coefficient 24.33 ± 7.69% and 24.35 ± 3.84%, respectively), accompanied by signs of toxic effects on experimental animals. The lowest anti-opisthorchiasis activity under conditionsin vivo have shown 70% ethanol extract of tarragon wormwood (IE = 20.48 ± 2.58%) and aqueous extract of wormwood (20.51 ± 2.56%).

Table 4

Results of a study of the anti-opisthorchiasis activity of extractive complexes
t. ordinary, etc. noble, n. bitter, n. ordinary,
P. gmelin and P. tarragon in conditions in vivo

Experimental group (test sample)	Qty animals, PCS.	Dose, g / kg (introduction scheme)	IE,%
Group # 1 (intact - healthy animals)	5	-	-
Group no. 2 (control - animals with opisthorchiasis)	ten	-	-
Group No. 3 (praziquantel)	5	0.02 g / kg (2 times a day - 1 day)	58.11 ± 13.43
Group No. 4 (70% ethanol extract Achillea millefolium)	5	2.0 g / kg (3 times a day - 5 days)	45.29 ± 8.15
Group No. 5 (aqueous extract Achillea millefolium)	5	2.0 g / kg (3 times a day - 5 days)	43.58 ± 2.56
Group No. 6 (70% ethanol extract Achillea nobilis)	5	2.0 g / kg (3 times a day - 5 days)	40.07 ± 2.95
Group No. 7 (aqueous extract Achillea nobilis)	5	2.0 g / kg (3 times a day - 5 days)	39.74 ± 3.85
Group No. 8 (70% ethanol extract Artemisia absinthium)	5	2.0 g / kg (3 times a day - 5 days)	21.35 ± 3.84
Group No. 9 (aqueous extract Artemisia absinthium)	5	2.0 g / kg (3 times a day - 5 days)	19.07 ± 5.12
Group No. 10 (70% ethanol extract Artemisia vulgaris)	5	2.0 g / kg (3 times a day - 5 days)	24.33 ± 7.69
Group No. 11 (aqueous extract Artemisia vulgaris)	5	2.0 g / kg (3 times a day - 5 days)	20.51 ± 2.56
Group No. 12 (70% ethanol extract Artemisia Gmelinii)	5	2.0 g / kg (3 times a day - 5 days)	21.79 ± 1.28
Group No. 13 (aqueous extract Artemisia Gmelinii)	5	2.0 g / kg (3 times a day - 5 days)	22.05 ± 4.27
Group No. 14 (70% ethanol extract Artemisia dracunculus)	5	2.0 g / kg (3 times a day - 5 days)	20.48 ± 2.58
Group No. 15 (aqueous extract Artemisia dracunculus)	5	2.0 g / kg (3 times a day - 5 days)	19.35 ± 3.84

DISCUSSION

Fractions isolated from the above-ground parts of the so-called common and so-noble, the bitter item, the ordinary item, the gmelin item and the tarragon item by the method of K.S. Rybalko, have similar physical properties and are characterized by yield values in the range of 0.5-1.0% (in terms of air-dry raw materials). Analysis of these fractions by IR spectroscopy confirmed the presence of a group of sesquiterpene lactones in them, on the basis of which it was assumed that the studied species have anti-opisthorchiasis activity againstOpisthorchis felineus. This

the hypothesis was confirmed by carrying out pharmacological tests under conditions in vitro and in vivo.

According to the results of testing the activity of fractions under conditions in vitro, leader factions. They are samples of fractions of sesquiterpene lactones, so common, and so on. The activity of these fractions at a dose of 300 μg / ml is comparable to and significantly exceeds the activity of the fractions obtained from p. twice the dose and after at least 72 hours of exposure.

The difference in the activity of the same group of biologically active substances of different species of yarrow and wormwood may indicate that different classes of sesquiterpene lactones may have different values of anthelmintic activity. Thus, according to the literature, the group of sesquiterpene lactones of wormwood is mainly represented by the class of germacranolides, which are practically not characterized by anthelmintic activity against opisthorchiasis [18, 19]. The group of yarrow sesquiterpene lactones is still not exhaustively studied. However, according to the available literature data, it is mainly represented by the class of guayanolides [20, 21], for some representatives of which anti-opisthorchiasis activity has been described [1, 22].

To confirm the results of pharmacological tests obtained under conditions in vitro,additional screening studies of extractive complexes of the studied plant species were carried out under conditions in vivo. They confirmed a significant anti-opisthorchiasisthe activity of the so-called ordinary and so-called noble. At the same time, in the studied dose (2000 mg / kg), the extract of the aerial part of yarrow in 70% ethanol showed the greatest effect, which, taking into account the values of the relative deviation, is approximately comparable to the activity of the reference drug praziquantel. It should be noted that information on the fact that plants of the genus Yarrow have specific anti-opisthorchiasis activity in relation toOpisthorchis felineus have not been published before and were obtained for the first time.

Extracts from the aerial parts of g. Bitter, p. Ordinary, p. Gmelin, and p. Tarragon, obtained on purified water and 70% ethanol did not show in the experiment in vivo pronouncedanti-opisthorchiasis activity (which correlates with the test results in vitro). However onOn the second day of intragastric administration of samples of wormwood extracts to experimental animals (in accordance with the study design), signs of acute toxicity began to appear, expressed in decreased and impaired motor activity, limb tremor, decreased appetite, and anxiety. It should be noted that there were no signs of toxic effects on experimental animals with extracts of yarrow, in contrast to extracts of the studied species of wormwood.

Comparing the results of this work with previously published materials concerning the assessment of the anti-opisthorchiasis activity of another member of the family Asteraceae cornflowerrough, and the prospects for its use as a raw material for obtaining an anti-opisthorchiasis agent [23], the following conclusion can be drawn - the rough cornflower, in contrast to wormwood, has a more pronounced anti-opisthorchiasis activity, without showing toxic effects in a wide range of therapeutic doses, therefore it has a more acceptable ratio of effectiveness - safety, and unlike yarrow with comparable indicators of specific activity, it has a larger raw material base, since it is more common in Western Siberia and has a multiple of the plant biomass.

Thus, the results of comparative pharmacological tests make it possible to consider common yarrow, noble yarrow and rough cornflower as promising objects for study in order to create drugs for the treatment of opisthorchiasis.

CONCLUSIONS

1. As a result of experimental studies under conditions in vitro high indicators of anti-opisthorchiasis activity of sesquiterpene lactone fractions Achillea millefolium and Achillea nobilis per dose 300 mcg / ml, causing the death of all marita opisthorchus in the group within 72 hours of exposure.

2. In conditions in vivo, the pronounced anti-opisthorchiasis activity of ethanol and aqueous extracts Achillea millefolium and Achillea nobilis (IE: 45.29%; 43.58%; 40.07% and 39.74%, respectively). Similar extracts from aerial partsArtemisia absinthium, Artemisia vulgaris, Artemisia gmelinii, Artemisia dracunculus in vivoactivity (against the background of the noted toxic effects) did not show.

3. For the first time experimentally confirmed anti-opisthorchiasis properties Achillea millefolium and Achillea nobilis.

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