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Anti-Parasitic Activity of Sesquiterpene Lactones *Tanacetum Pseudoachillea*

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Abstract Studies have shown that the high antiparasitic activity of Tanacetum pseudoachillea is due to the presence of sesquiterpene lactones of tanahine, tanacin, tanapsin, tachyllin and tavulin. For these lactones, a more pronounced anthelmintic effect against nematodes is characteristic than cestodes and a certain antilamblious activity. The plant Tanacetum pseudoachillea can be considered as a promising source for the development of new antiparasitic agents.

Keywords Tanacetum pseudoachillea, Sesquiterpene lactones, Antiparasitic activity

1. Introduction

Natural sesquiterpenic lactones have multifaceted biological activity [1]. Of considerable interest is the study of the antiparasitic activity of sesquiterpene lactones, since a number of effective anthelmintic (santonin, gelenin) and antimalarial (artemisinin and its derivatives) agents have already been identified [2,3]. Tanacetum pseudoachillea C. Winkl. (tansy yarrow), growing in Central Asia, is one of the promising sources of sesquiterpenic lactones. It was previously shown that Tanacetum pseudoachillea has anthelmintic properties [4].

The aim of the study of this work was to determine the antiparasitic (anthelmintic and antiprotozoal) activity of the activity of individual sesquiterpene lactones of tanahine, tanacin, tanapsin, tachyllin and tavulin isolated from tansy yarrow.

Materials and methods. For research, sesquiterpene lactones tanahine, tanacin, tanapsin, tachyllin and tavulin were isolated according to the known method [5] from the aerial part of Tanacetum pseudoachillea.

Anthelmintic (anti-cestodose and anti-nematodosis) activity was studied in comparison with santonin on white outbred male mice weighing 18-20 g. An experimental model of cestodosis - hymenolepidosis was caused by infection of each animal at the rate of 200 invasive eggs Hymenolepis nana orally, the model of nematodosis from each animal aspurulosis the calculation of 100 invasive eggs of Aspiculuris tetraptera is also orally (mouse aspiculurosis is an adequate model of enterobiosis) [6].

The studied lactones were injected into animals with an intragastric atraumatic probe at a dose of 20 mg / kg in the form of an aqueous emulsion with apricot gum. Control animals that received an adequate amount of only an aqueous emulsion of apricot gum.

In mice with hymenolepidosis, the test substances were administered on the 10th day after infection (the imaginal stage of H. nana development) once a day for 5 days. On the 14th day after infection, the animals were slaughtered under light ether anesthesia, a small section of the small intestine 10 cm long was removed, it was opened and counted cestodes attached to the wall of the small intestine.

In mice with apiculurosis, lactones were started on the 10th day after infection once a day for 5 days. On the 4th day after the end of the administration of lactones, the results were evaluated by extracting and counting mature nematodes from a 10 cm long section of the colon.

Antiprotozoal activity was studied in experiments with experimental giardiasis using white outbred mice of both sexes weighing 13-15 g. To reproduce the experimental model, animals were infected orally with a suspension containing cysts and trophozoites of Giardia muris 5 × 103 in 0.5 ml [6]. A suspension was prepared from the contents of the small intestine of spontaneously infected mice (Roberts-Thomson, Mitchell, 1978). The studied lactones were injected into mice with a special atraumatic probe into the stomach in the form of an aqueous emulsion with gum arabic at the rate of 20 mg / kg on the 5th day after infection for the next 5 days. All experiments were carried out in accordance with the requirements of the "European Convention for the Protection of Vertebrate Animals Used for Experiments or for Other Scientific Purposes" (Strasbourg, 1986). After treatment, the mice were sacrificed under mild ether anesthesia by cervical dislocation and 10 cm of the small intestine were taken, starting from the gastroduodenal articulation, from each animal. Each segment was opened in the longitudinal direction in 5 ml

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of physiological saline, placed on ice for 10 min, and mixed on a vortex mixer to disconnect trophozoites from the mucosa. The intestinal contents were washed with isotonic solution (0.85%) of sodium chloride (NaCl) by repeated centrifugation (3 min × 1500 rpm) until a clear supernatant was formed, which was carefully removed by pipetting. A flotation solution (saturated (30%) sucrose solution (18–20℃)) was added to the remaining faecal sediment with a volume 3–4 times larger than the faecal volume with vigorous stirring. The tubes were centrifuged at 1500 rpm for 5 minutes. After a 10-15 minute exposure, the surface film of the flotant (supernatant) was carefully removed with a 0.1 ml pipette dispenser and transferred to a test tube with an isotonic sodium chloride solution (1 ml). The procedure is repeated at least 3 times. Using a hemocytometer, the total number of trophozoites and lamblia cysts was counted in suspension. The effectiveness of the studied lactones was judged by calculating the average number of vegetative forms and lamblia cysts per animal.

The effectiveness of sesquiterpene lactones was determined by calculating the average number of detected parasites and intensity efficiency (IE), to calculate which the average number of parasites in opened animals in the experimental and control groups was compared and determined (in%) by the formula: IE = 100 (K-O) / K, where K is the average number of helminths in the control group; O-average number of helminths in the experimental group [6].

The results obtained were processed by the method of variation statistics using the Student t-test.

2. Results and Discussion

Previous phytochemical studies showed that sesquiterpene lactones tanahine (2), tanacin (3), tanapsin (4), tachyllin (5) and tavulin (6), isolated from the aerial part of Tanacetum pseudoachillea, belong to two structural skeletons types: germacranolides (2, 3, 6) and evdesmanolides (4, 5) (Fig. 1).

These sesquiterpene lactones have the following pharmacophore functional fragments in their structure: methylene lactone cycle (2-6);, unsaturated ester ketone group (3-5) and epoxy group (3), due to which they can attach sulfhydryl groups of enzymes at neutral pH, thereby blocking the vital enzyme systems of parasitic organisms [7].

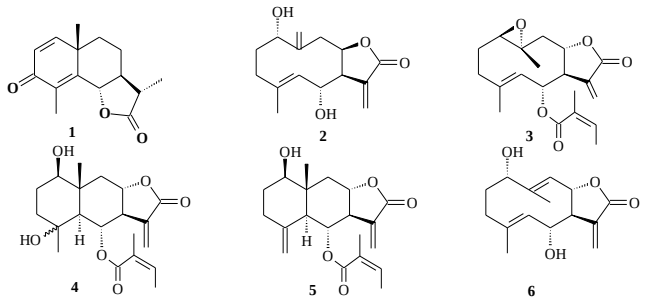

Figure 1. Structures of sesquiterpene lactones *Tanacetum pseudoachillea*

Studies have shown that the lactones used in the experiments (2-6) showed pronounced anthelmintic activity (both antimenolepidosis and antispasculosis). At the same time, a certain difference was revealed in the manifestation of the anthelmintic action of sesquiterpene lactones depending on the presence (or absence) of one or another reactive alkylating functional groups in their structures (table 1).

Table 1. Anticestodose and antinematode activity of sesquiterpene lactones *Tanacetum pseudoachillea* (M±m; n=10)

Test compound	*Hymenolepis nana*		*Aspiculuris tetraptera*	
	The number of detected parasites after opening, ind.	Intensity, IE (%)	The number of detected parasites after opening, ind.	Intensity, IE (%)
control	17,3±1,9	-	52,8±6,0	-
santonin (1)	4,8±0,8*	72,2	4,7±1,3*	91,1
tanahin (2)	6,4±0,7*	63,0	15,4±1,7*	70,8
tanacin (3)	5,5±2,3*	68,2	12,2±1,6*	76,9
tanapsin (4)	6,1±0,7*	64,7	12,3±2,0*	76,7
tachyllinus (5)	6,3±0,9*	63,5	13,9±2,0*	73,6
tavulin (6)	8,0±1,4*	53,7	18,9±2,1*	64,2

Note. * - Reliable to control (confidence level accepted at p<0,05)

Among lactones of the germacrane type (2, 3, 6), isolated from tansy of yarrow, the highest activity was tanacin (3). Its IE for Hymenolepis nana was 68.2%, and for Aspiculuris tetraptera 76.9%.

The higher activity of tanacin (3), in contrast to tanahine (2) and tavulin (6), is apparently due to the fact that it has two additional alkylating fragments in its structure: an epoxy group and unsaturated ester ketone group at C -6. Deprived of these structural elements, tanahine (2) and tavulin (6) showed IE in respect of Hymenolepis nana 63.0 and 53.7%, and in relation to Aspiculuris tetraptera 70.8 and 64.2%, respectively.

Among the studied lactones of tansy of the eudesman type (eudesmanolide), tanapsin (4) and tachyllin (5), which have rather similar structures, showed close and quite pronounced antimenolepidous and antiaspi-culurosis activity. Their IE against Hymenolepis nana was 64.7 and 63.5%, and against Aspiculuris tetraptera 76.7 and 73.6%, respectively.

An analysis of the data showed that the factor of the presence of an exocyclic methylene group in conjunction with the lactone carbonyl in sesquiterpene lactones (2-6) was of decisive importance in the manifestation of their pronounced antiparasitic activity, and the presence of additional alkylating functional groups (unsaturated ketone group ester and epoxy) enhanced their anthelmintic activity.

And, although the studied lactones (2-6) were somewhat inferior in activity to santonin (1), which, in contrast to them, was characterized by a highly reactive alkylating function (cyclohexadienone, unsaturated ketone group), nevertheless, we can speak of a pronounced anthelmintic action of the

studied sesquiterpenic lactones.

The experiments performed allowed us to identify in the studied sesquiterpene lactones and a certain antilablious activity. Among the studied lactones of the germacrane type: tanacin, tanahine and tavulin, the highest antilablious activity was detected in tanacin (IE = 62.6%). Tanahin and tavulin acted weaker. Their IE was 58.0 and 56.8%. As for the compounds belonging to the type of eudesman, it is noteworthy that the pronounced anti-labial activity in tachyllin and tanapsin is IE - 69.7 and 67.4%, respectively.

Table 2. Antilamblious activity of sesquiterpene lactones *Tanacetum pseudoachillea* (M±m, n=10)

Lactone name	Identified activity	
	The number of detected parasites after opening, ex.($x10^5$)	Intens Efficiency %
Tanacin	1170±131	62,6
Tanahin	1315±155	58,0
Tavulin	1354±164	56,8
Tahillin	949±100	69,7
Tanapsin	1020±127	67,4
Control	3134±277	-

Note. All the results in the table on the number of lamblia in the intestine after administration of the studied lactones to animals are significantly lower than the control values ($p<0,001$).

All the above data, deserving close attention by themselves, were nevertheless interesting from the standpoint of a definite regularity of the structure of their molecules and their manifestation of the lambliocidal action. Of course, a full analysis of the severity of the lambliocidal action of sesquiterpene lactones from the point of view of the structure of their carbohydrate skeleton due to the small number of compounds used in this work is not possible, however, the detected trend in this aspect can not be ignored. First of all, in the ranks of the studied lactones, it was noteworthy that the presence of the α, β-unsaturated acyl group in the molecule of sesquiterpene lactones slightly increases their antilamblious activity. This is clearly seen in the example of similar in chemical structure lactones from different studied series. Among germacranolides, tanacin acts more pronounced than tanahine and tavulin. Among the eudesmanolides, tachylline and tanapsin, which also have an acyl group in their structure, have a clearer effect. The data obtained open up the prospect of searching for sesquiterpenic lactones with high giardicidal activity.

Thus, the plant Tanacetum pseudoachillea can be considered as a promising source of the development of new effective antiparasitic agents based on the sesquiterpene lactones contained in it.

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