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(54) Title: DRUG FOR PARASITIC CONTROL OF ANIMALS

(57) Abstract

The invention concerns a drug for parasitic control of farm and domestic animals (pets) in the cases of cestodes, trematodoses, nematodoses and pests (ticks, mites and insects) invasions. The purpose of the invention presented is to develop a highly effective drug for parasitic control of animals, covering a wide spectrum of internal and external parasites. With the drug for antiparasitic control of animals, being a combination between praziquantel and avermectins, is achieved: an enhanced anthelminthic influence by praziquantel on the nematodes and by avermectins on the cestodes; a broadening of the antiparasitic spectrum, covering helminthoses: cestodes, nematodoses, trematodoses and arachnoenthomoses (pests) invasions with ticks, mites and insects; a good tolerability by the animals even in the cases of tenfold therapeutic dose.

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DRUG FOR PARASITIC CONTROL OF ANIMALS

TECHNIQUE FIELD

This invention concerns antiparasitic drug for farm and domestic animals in the cases of cestodes, trematodoses, nematodoses, as well as in the cases of pests (insect and acar) invasions.

PRECEDING STATE OF THE TECHNIQUE

The compound 2-(cyclohexylcarbonyl)-1,2,3,6,7-11b-hexahydro-4H-pyrazino[2,1-a] isoquinolin-4-one, [MERCK INDEX, Eleventh edition, Merck & Co., Inc., Rahway, N.J., USA, 1989] has a INN (International Nonproprietary Name) praziquantel (PQ). It is applied in the veterinary practice as an antiparasitic drug with anticestodal and antitrematodal action. This substance however is known as not efficient against nematodes and external parasites (pests), [ROBERSON, E.L. - Anticestodal and Antitrematodal Drug, in: Veterinary Pharmacology and Therapeutics, 6th Ed., by N.A. Booth and L.E. McDonald, Iowa State University Press, Ames, Iowa, 50010, USA, 1989, 923-949].

Avermectins, (AVM), as known, represent antibiotics with wide-spectrum antiparasitic activity, produced by Streptomycetes, [MERCK INDEX, 11th Edition, Merck & Co., Inc., Rahway, N.J., USA, 1989]. The highest antiparasitic effectiveness of them reveal the antibiotic fraction B_1 (B_{1A} and B_{1B}), [CAMPBELL, W.C., Ivermectin and Abamectin, Springer-Verlag, New York, 1989]. The avermectins are endectocides, i.e. they act both against internal and external parasites: as anthelminthics with antinematodal effect and as antiectoparasitics acting as insecticides and acaricides against mange mites and pasture ticks, and against blood-sucking insects. The ivermectins (22,23-dihydroavermectins) are hydroginated analogues of the avermectins and have also an analogous biological activity, [CAMPBELL, W.C., Ivermectin and Abamectin, Springer-Verlag, New York, 1989]. The name 'avermectins' in this description from here will be used for the natural avermectins, for the semisynthetic ivermectins and for the technical products containing avermectins and ivermectins as well. The disadvantage of avermectins is that they do not manifest any anticestodal and antitrematodal effects.

The mode of action of the anthelminthics boils down to the following:

- the drug ought to get and to cross the contact areas of the parasites (for the nematodes - the cuticle and through their alimentary canal - the intestinal epithelium, but for the cestodes - tegument) and to penetrate into their inside.

- the drug ought to cause heavy injuries in the internal structure of the parasites.

Several combined antiparasitic preparations in which the active substances mentioned are included as components are known, [WALKER, G. (comp. by) - Compendium Data Sheets for Veterinary Preparations, 1992/93, Datapharm Publ. Ltd., London, 1992], such as:

- praziquantel + pyrantel pamoate: with anticestodal, antitrematodal and antinematodal activity;

- praziquantel + pyrantel embonate + febantel: with anticestodal, antitrematodal and antinematodal activity;

- ivermectin + pyrantel: with antinematodal and antiectoparasitic activity.

The combinations mentioned have a common disadvantage - they do not cover the whole spectrum of internal and external parasites - because the natural invasions are frequently mixed.

The purpose of the present invention is the developing of a highly effective drug for parasitic control of wide spectrum of internal and external parasites of animals.

TECHNICAL NATURE OF THE INVENTION

The present invention represents a drug for parasitic control of animals, containing 2-(cyclohexylcarbonyl)1,2,3,6,7-11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one and avermectins (equalized in terms of biological activity to B_{1A} fraction) in quantitative proportions from 10:1 to 50:1.

The combination of the active components such as praziquantel and avermectins (or their technical products containing avermectins) is suitable for the production of pharmaceuticals. The dosage form may contain the active substances mixed with the usual constituents, as indicated in the examples given. The drug formulation, according to the invention, may be applied orally and in some cases parenterally.

The advantages of this drug formulation are as follows:

- an enhanced anthelminthic effect of avermectins (ultrastructurally established) on the nematodes, obtained by means of praziquantel and the similar increased effect of praziquantel on the cestodes by means of avermectins as well;

- a broadening of the antiparasitic influence, in comparison with the combinations existing, covering the cases of helminthoses, nematodoses, trematodoses (three classes of internal parasites) as well as the cases of arachnoenthomoses (pests) - invasions with mites, ticks, insects (two classes of external parasites);
- tolerated by animals even in the cases of tenfold therapeutic dose.

DESCRIPTION OF THE TABLES, TABULATED DIAGRAMS AND FIGURES

Tabulated diagram 1

Damages of pattern parasites caused by praziquantel (PQ), avermectins (AVM) and combination between praziquantel and avermectins (PQ + AVM): examination in vitro.

Figure 1

Electron-microscopic photos of Ascaris suum after single application of PQ and of AVM

Figure 2

Electron-microscopic photos of Ascaris suum after a combined application of PQ + AVM

Figure 3

Electron-microscopic photos of Toxocara canis after single application of PQ and of AVM

Figure 4

Electron-microscopic photos of Toxocara canis after a combined application of PQ + AVM

Figure 5

Electron-microscopic photos of Moniezia expansa after single application of PQ and of AVM

Figure 6

Electron-microscopic photos of Moniezia expansa after a combined application of PQ + AVM

The following patterns give examples concerning the invention without restricting it:

Example 1:

Composition of a solid dosage form in %:	
Praziquantel	11.35
Abamectin (Avermectin B_1 - Avermectin $B_{1A} \geq 80\%$ Avermectin $B_{1B} \leq 20\%$)	1,13
Lactose	50.70
Wheaten starch	33.82
Polyvinylpyrolidone m.w. 25 000 (Kolidone K_{25})	3.00

The granulation should be performed in a whirlpool drier. The granules formed may be applied as a premix, or after a suitable processing with slipping, lubricating and disintegrating constituents, it may be tabletted or capsulated.

Example 2:

Praziquantel	11.65
Bulmectin (a technical product, in biological activity equalized to 0.416% avermectin B_{1A})	15.76
Lactose	34.21
Wheaten starch	29.98
Polyvinylpyrolidone m.w. 25 000 (Kolidone K_{25})	2.33
Sugar	6.07

The technological processing is as per Example 1.

Example 3:

Composition of a solid dosage form in %:	
Praziquantel	11.27
Ivermectin (22,23-dihydroavermectin B_1 - 22,23-dihydroavermectin $B_{1A} \geq 80\%$ 22,23-dihydroavermectin $B_{1B} \leq 20\%$)	0.23
Lactose	51.68
Wheaten starch	33.82
Polyvinylpyrolidone m.w. 25 000 (Kolidone K_{25})	3.00

The technological processing is as per Example 1.

Example 4:

Researches with pattern nematodes and a cestode, incubated in vitro in nutrient liquid with the addition of PQ and of AVM, single and in combinations of PQ + AVM in the course of 4 hours have been made. The results are shown in Table 1.

The electron-microscopic examinations of the parasites treated in vitro in the way mentioned show damages of the structures that explain to some extent the compatibility and the enhanced antiparasitic activity of the combination PQ + AVM.

PQ, as known, is not active as an antinematodal remedy, [ROBERSON, E.L. - Anticestodal and Antinematodal Drugs, in: Veterinary Pharmacology and Therapeutics, 6th Ed., by N.A. Booth and L.E. McDonald, Iowa State University Press, Ames, Iowa, 50010, USA, 1988,928-949], in fact is not completely indifferent with respect to the nematodes examined. It affects, applied single, the integrity of their cuticle and of the intestinal wall, (Tables 1, Tabulated diagram 1, Fig. 1 and 3), although it does not give rise to death of the parasites.

The AVM, in the cases of single application lead to serious damages in the structure of the cuticle and the intestinal epithelium of both nematodes (Table 1, Fig. 1 and 3).

The injuries caused to both pattern parasites by the combination PQ+AVM are the heaviest - in the cuticle (unsticking, pocket-formation, tearing), in the intestinal epithelium (vesical structures formation among the microvilli, formation of myelinic structures, vacuolization and necroses), in the cases of Toxocara canis - with

damages also in the hypoderma and the basal membrane; in the cases of Ascaris suum - with more necrotic alterations (Table 1, Tabulated diagram 1, Fig. 2 and 4). The stronger injuries in the structures of the nematodes examined by the combination of PQ + AVM could be explained by the influence of the PQ which creates an invasion atrium for the easier penetration of the AVM into the organisms of the parasites and its stronger effect respectively.

Analogous effects with respect to the AVM were achieved during the experiments carried out with the cestode Moniezia expansa. AVM, as known, do not have any anticestodal activity, [ROBERSON, E.L. - Anticestodal and Antitrematodal Drugs, in: Veterinary Pharmacology and Therapeutics, 6th Ed., by N.A. Booth and L.E. McDonald, Iowa State University Press, Ames, Iowa, 50010, USA, 1988, 928-949], in the electron-microscopic examinations in vitro do not manifest indifference to the cestodes either. They cause some not great alterations to the moniezial tegument; in the microvilli, in the basal and muscular layer (erosions, even small necrotic zones), (Table 1, Tabulated diagram 1, Fig. 5). The injuries by PQ are stronger (Table 1, Tabulated diagram 1, Fig. 5). The strongest damages in the structures of the cestode are caused by the combination PQ + AVM. A decrease of the number of microvilli, erosions and necroses in the basal layer predominate in these cases and, also a reduction of heterochromatine and injuries of the nucleus of the tegumental cells (Table 1, Tabulated diagram 1, Fig. 6). The explanation of the stronger and more widespread injuries in the structure of the cestodes by the combination PQ + AVM caused should be in the supplementary influence of the AVM that facilitates the penetration of PQ into the organism of cestodes and increases their alterations.

DAMAGES OF PATTERN PARASITES CAUSED BY PRAZIQUANTEL (PQ), AVERMECTINS (AVM) AND COMBINATION OF PRAZIQUANTEL + AVERMECTINS (PQ + AVM) - INVESTIGATIONS IN VITRO

TABLE No1

NEMATODES / DAMAGES	ASCARIS SUUM			TOXOCARA CANIS			MONIEZIA EXPANSA			CESTODES / DAMAGES
	PQ	AVM	PQ+AVM	PQ	AVM	PQ+AVM	PQ	AVM	PQ+AVM	
1. C U T I C L E										T E G U M E N T
										1.M I C R O V I L L I
- unsticking	+	++	+++	+	+	++				
- pocket formulation	+	++	+++	+	+	++				-decreasing of the numbers
- tearing	–	–	++	–	+	++	++	+	+++	- erosion on the surface
2. BASAL MEMBRANE							+	+	++	-vesiculation
-densification and folding	–	–	–	–	+	+++				2.DISTAL CYTOPLASMIC LAYER
3. H Y P O D E R M A										
- vacuolation	–	+	+	+	++	+++	–	–	++	- lack of cellular organelles
- fracturing	–	–	–	–	++	+++				
- necrosis	–	+	+++	–	++	+++				3.BASAL LAYER
4 INTESTINAL EPITELIUM										-folding and densification of the basal membrane
- microvilli vesiculation	+	+	++	+	+	++	++	+	++	
- formulation of myelining structures	+	+	++	+	+	++				4.MUSCULAR LAYER
- vacuolation	–	+	++	–	–	–	++	+	+++	-necrosis
- necrosis	–	–	+++	–	–	–				5. TEGUMENTAL CELLS
							–	–	+++	- reduction of heterochromatine and alteration of the nucleus
							–	–	+++	
TOTAL NUMB. OF DAMAGES	4	9	21	5	12	22	8	5	18	TOTAL NUMB. OF DAMAGES

(+) - occasional focal alterations; (++) - frequent focal alterations; (+++) - frequent massive damages.

Tabulated diagram 1

Damages of pattern parasites caused by praziquantel (PQ), avermectins (AVM) and combination between praziquantel and avermectins (PQ + AVM): examinations in vitro

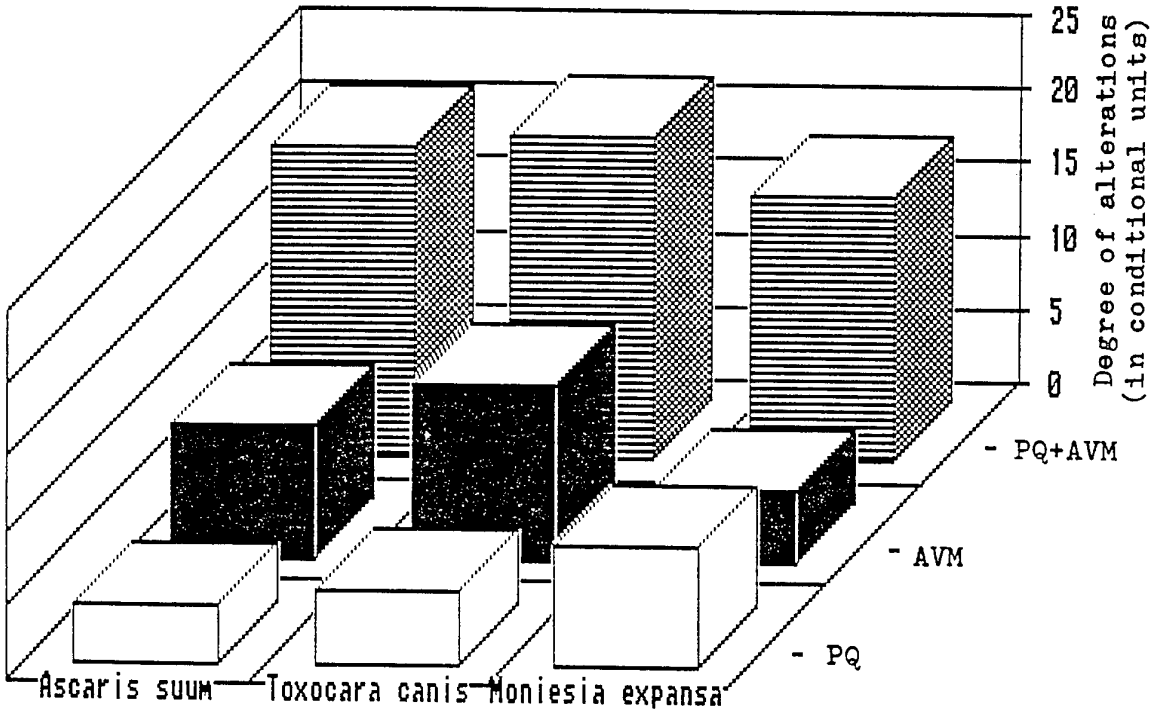
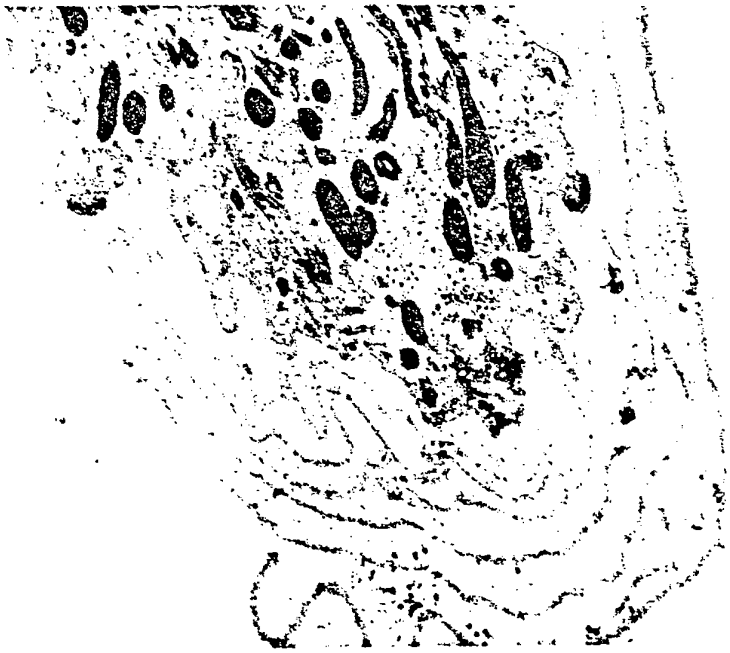
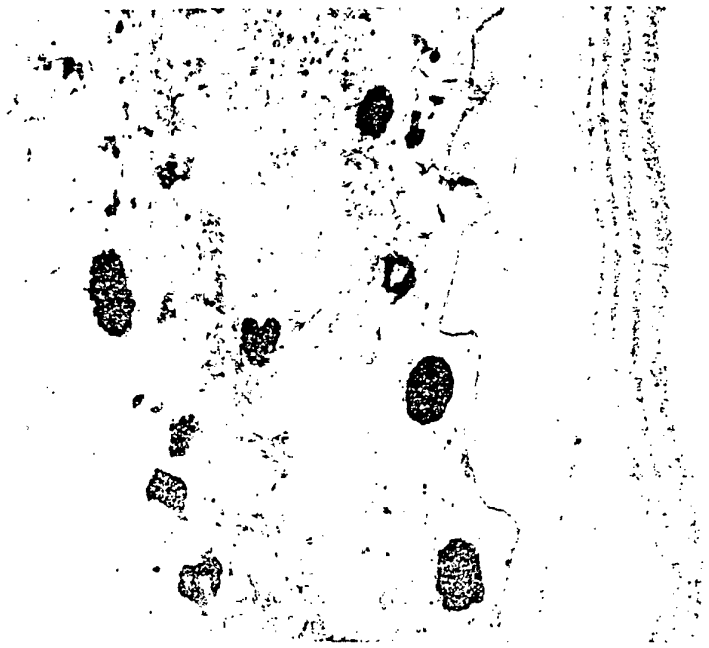


Figure 1

Electron-microscopic photos of Ascaris suum after single application of PQ and of AVM



PQ



AVM

Figure 2

Electron-microscopic photos of Ascaris suum after a combined application of PQ + AVM

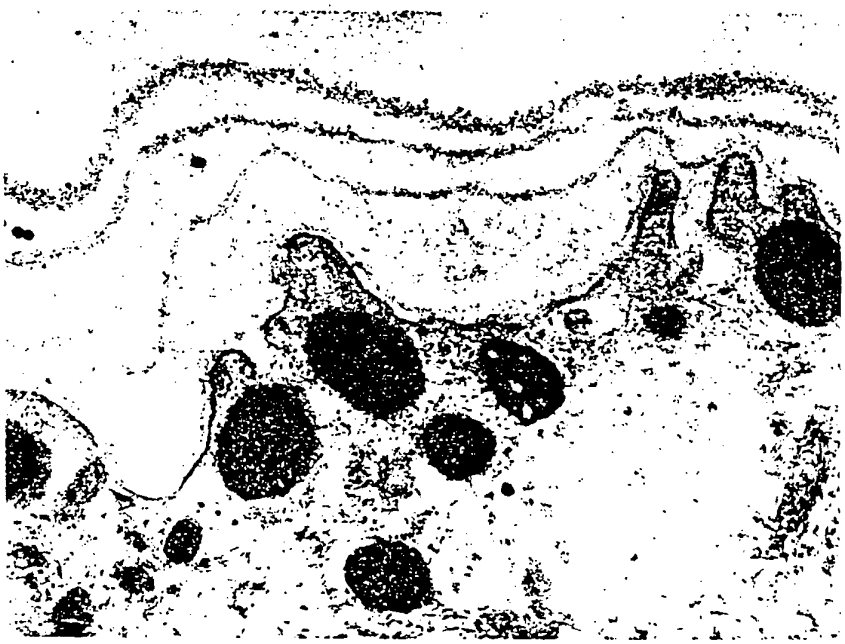


Figure 3

Electron-microscopic photos of Toxocara canis after single application of PQ and of AVM

PQ

AVM

Figure 4

Electron-microscopic photos of Toxocara canis after a combined application of PQ + AVM

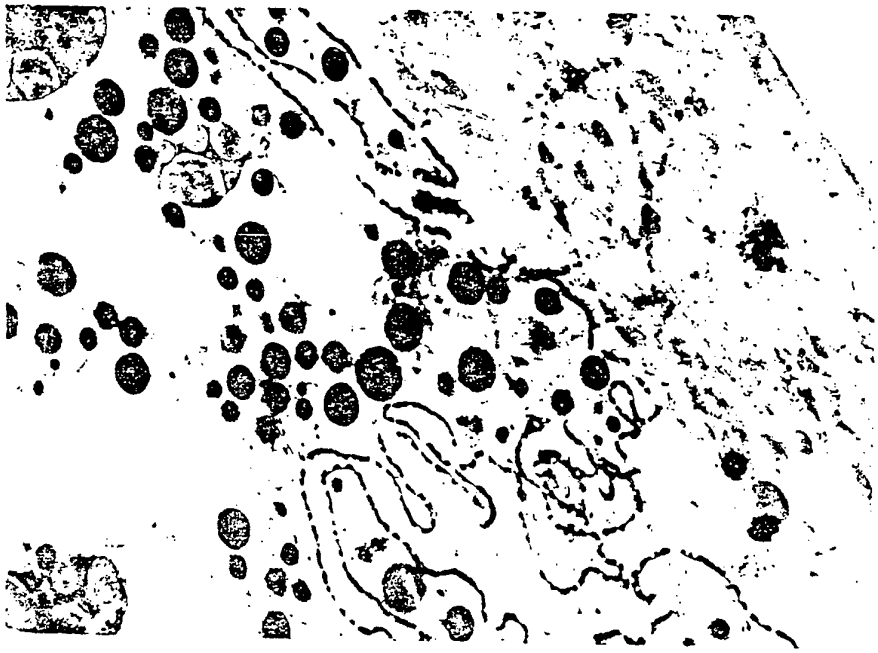


Figure 5

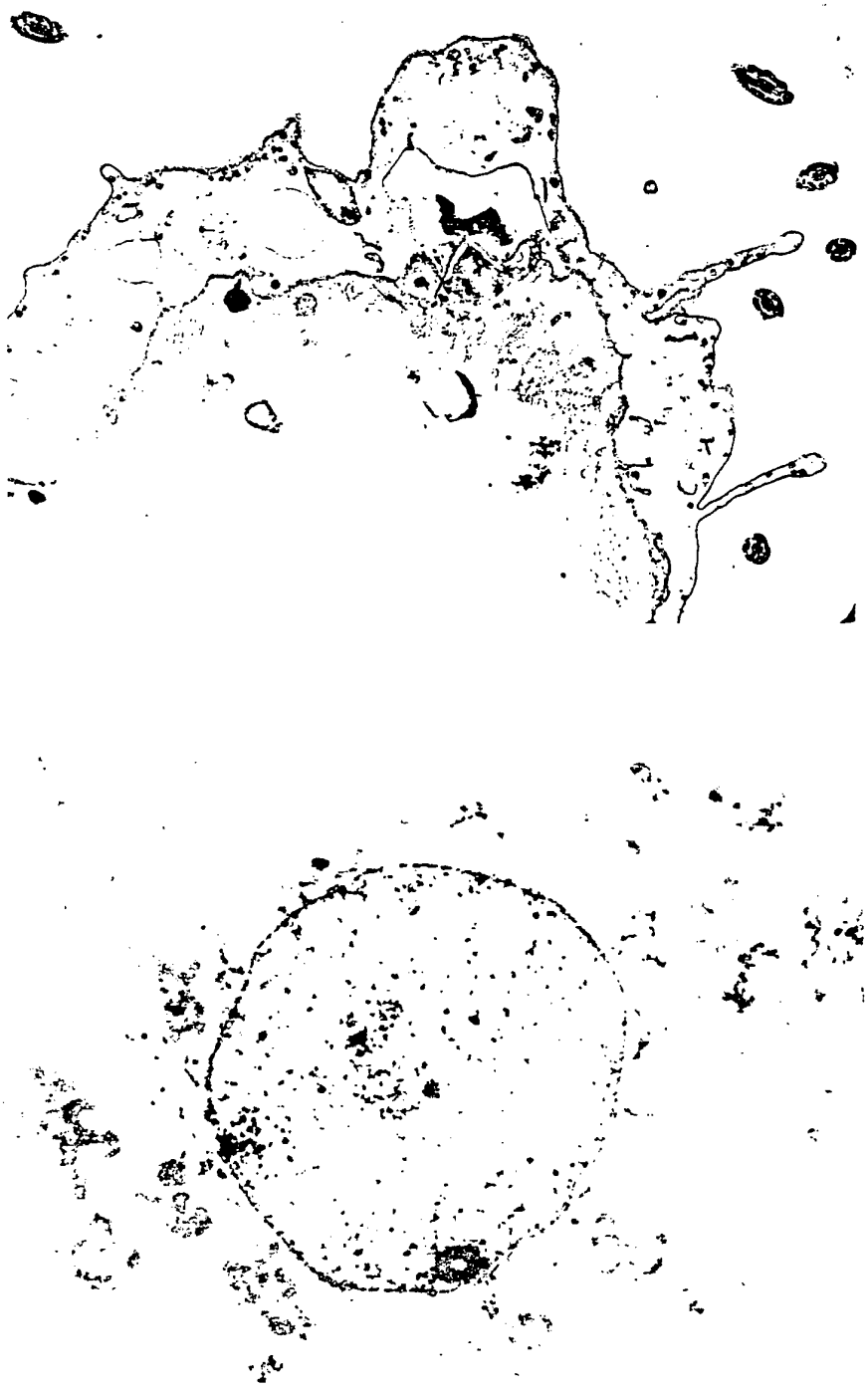
Electron-microscopic photos of Moniezia expansa after single application of PQ and of AVM

PQ

AVM

Figure 6

Electron-microscopic photos of Moniezia expansa after a combined application of PQ + AVM



PATENT CLAIMS

1. A drug for parasitic control of animals, characterized by its contents of 2-(cyclohexylcarbonyl)1,2,3,6,7,-11b-hexahydro-4H-pyrazinol[2,1-a]isoquinolin-4-one and avermectins (equalized in terms of biological activity to fraction B_{1A}) in quantitative proportions as follows: from 10:1 to 50:1.

2. A drug, according to the claim # 1, characterized by the fact that as avermectins the semisynthetic ivermectins are applied.

3. A drug, according to the claim # 1, characterized by the fact that as avermectins a technical product containing avermectins, equalized to fraction B_{1A} in biological activity is applied.