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THE BASIC APPROACHES TO PHARMACOTHERAPY OF HELMINTHIASES AND PROSPECTS OF PHYTOMEDICINES DEVELOPMENT FOR THEIR TREATMENT

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Key words: helminthosis; pharmacotherapy; phytotherapy; medicinal plant raw material

Parasitic infections are one of the most acute and urgent problems of modern global society. The fact that most cases of helminthiases of the digestive system falls on children of the preschool and early school age is of particular relevance. Pharmacotherapy of helminthoses of the digestive system involves the preparatory stage, causal treatment and elimination of complications of the past disease. It is important to observe the diet. Foreign treatment standards provide two stages of treatment: elimination of helminths (medicines based on mebendazole, albendazole, thiabendazole, niclozamine, praziquantel) and elimination of complications of the past disease. In addition, non-pharmacological treatment is recommended, it includes good nutrition and personal hygiene. The domestic market of antihelmintics is represented by drugs based on praziquantel, mebendazole, albendazole, piperazine, pyrantel, levamisole, and one drug in the form of medicinal plant raw material – tansy flowers. Most of these medicines are produced abroad (57.9%). The age limits vary from the 6th months to 14 years. The price proposals on antihelmintic medicines vary depending on the dose, type of a dosage form and producer. The folk medicine offers a variety of prescriptions for treating helminthoses based on medicinal plants. On the basis of the analysis of the folk medicine formulations 11 medicinal plants have been identified as promising for creation of the complex phytomedicine with the antihelmintic activity.

Nowadays, parasitic infections are one of the most acute and urgent problems of the society. According to the World Health Organization approximately 1.2 billion people are infected with parasitic infections each year.

According to the recent findings helminthosis affect all, without exception, age groups. However, children are significantly more likely to become infected with helminths due to the lack of high-grade hygienic skills, and some studies prove greater sensitivity of the child's body to development of helminthiases since penetration of eggs or cysts of worms in the human body does not lead to development of helminthosis in all cases [4, 5, 15].

The share of children helminthoses of the digestive system is 92.3% of the cases of enterobiosis, 71.1% – ascariasis, 61.5% – trichocephalosis and 66.2% – toxocariasis. Children of the preschool and primary school age are the most susceptible to helminth infections, children aged 2-10 years are the most susceptible to helminthosis [8, 15, 17].

Helminths are divided into roundworms (nematodes), tapeworms (cestodes) and flukes (trematodes). Potential routes of helminth infection include faecal-oral, direct contact and transmissive [6].

It is known that the larvae and eggs of helminths when in contact with the human body orally are exposed to enzymes and nonspecific protection factors, the gastric juice and local immunity of the intestines, and it usually causes their death. But when weakening of the body's defences larvae and eggs are able to penetrate into the intestine and grow to adult forms [8].

The clinical picture of the disease depends on many factors, including duration and intensity of helminthic infestations and the general condition of a patient. As a rule, the helminthiasis symptoms are nonspecific and varied. In many respects this diversity of clinical manifestations is associated with a huge list of potential pathogens: there are about 70 species of helminths in Ukraine of more than 250. Disorders of the hepatobiliary system and the gastrointestinal tract in general are the most often [8, 18].

The main phases of the clinical course of intestinal helminthoses are:

1. Acute. It manifests with common allergic and toxic reactions.
2. Latent. Usually it is not accompanied by clinical symptoms.
3. Chronic. Clinical manifestations are individual in nature.
4. Complications [6].

Making an accurate diagnosis followed by the proper treatment is possible only on the basis of the laboratory diagnosis data. Usually feces, urine, duodenal contents, bile, perianal and rectal mucus, and blood are examined. It is also important to study the status of the patient's immune system as the nature of the immune response is determined by morphological and biological characteristics of each species of helminth. In a specific immune response circulating antibodies of classes IgG, IgM, IgE and IgA are involved. The IgE index increases significantly since it is the exact antibody

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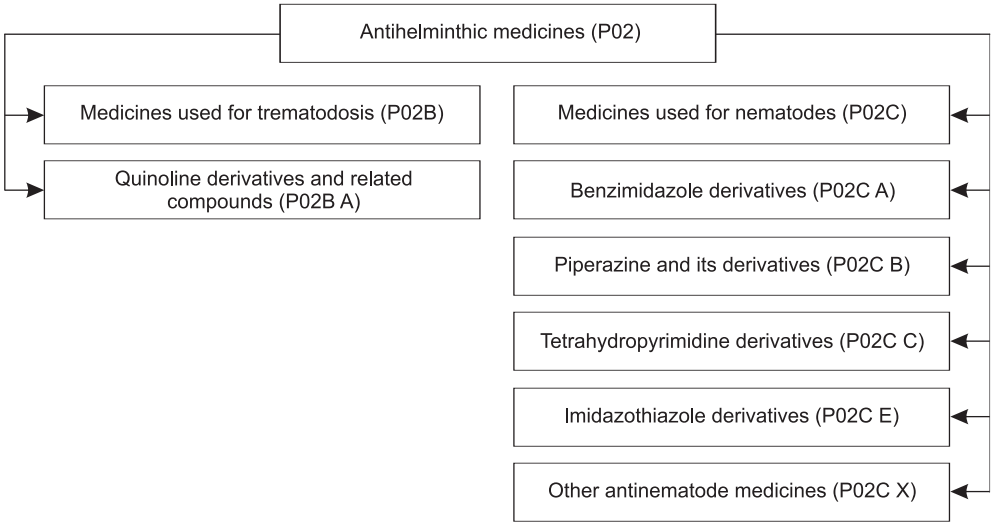

Fig. The ATC classification of anthelminthic medicines

class, which together with eosinophils is the main defence mechanism of human body from helminthic invasion [6, 8, 16].

Pharmacotherapy of helminthosis usually consists of the preparatory stage, causal treatment and correction of the consequences and complications of recent helminthosis. Often the preparatory stage requires intake of antihistamines. It is also important to follow the rules of a balanced diet, the diet No. 4 is recommended [6, 8].

Foreign experience in the treatment of helminthiases provides two goals of pharmacotherapy: elimination of helminths and elimination of the disease complications (anemia, metabolic disorders, etc.). The therapy with medicines (the level of evidence: B) on the basis of mebendazole, albendazole, thiabendazole, niclosamine, praziquantel is recommended. In addition, non-pharmacological treatment is recommended; it includes good nutrition and personal hygiene. It should be noted that any phytomedicines or herbal therapy as a whole are not mentioned in the US and British guidelines for helminth pharmacotherapy [19-21]. It is also indicated that the existing medicines can-

Table 1

Antihelminthic medicines

Medicinal substance	ATC-code	Name of the medicine	Manufacturer (country)	Age limits
Praziquantel	P02B A01	Biltricid®	Bayer Pharma (Gemany)	From 4 years
Mebendazole	P02B A01	Vermoxum	Gedeon Richter (Romania)	From 2 years
		Vermoxum®	Janssen – Cilag SpA (Italy)	From 2 years
Albendazole	P02B A03	Aldazol	Kiev Vitamin Plant (Ukraine)	From 3 years
		Zentel™	GlaxoSmithKline Export	From 3 years
		Angelmin	Agrofarm Ltd (Ukraine)	From 3 years
		Vorrmil	Mili Healthcare (The United Kingdom)	From 2 years
Piperazine	P02C B01	Piperazine adipate	CPP Lugansk JSC (Ukraine)	From 4 years
		Piperazine adipate-Darnitsa	Darnitsa PSC (Ukraine)	From 4 years
Pyrantel	P02C C01	Helmintox	Lab. Innotech International (France)	From 6 months
		Nemotsid™	IPCA (India)	From 6 months
		Pyrantel	Bravo Healthcare Ltd. (India)	From 6 years
		Pyrantel Polpharma	Medana Pharma S. A. (Poland)	From 6 months
		Pyrantel suspension	Kusum Healthcare (India)	From 6 months
		Pyrante; tablets	Kusum Healthcare (India)	From 6 years
		Pyrantel-VISHFA	Zhytomyr PF LLC (Ukraine)	From 6 months
Levamisole	P02C E01	Dekaris	Gedeon Richter	From 3 years
		Levamizole-Zdorovie	Zdorovye Co., Ltd (Ukraine)	From 14 years
Other medicines	P02C X10**	Tansy flowers	Lektravy JSC (Ukraine)	From 12 years

not be used in pregnant women, nursing mothers and children under the age of 2 years.

Antihelmintic medicines must meet the following requirements:

- high efficiency;
- a wide range of actions;
- the absence of the resorptive effect, the harmful effect on human organs and tissue;
- a rapid clearance from the body;
- the absence of cumulation.

Antihelmintic medicines should provide the ovicidal (destroy eggs), larvicidal (destroy larvae) and wormicidal (destroy adult worms) action [6, 17].

In order to study the prospects of developing new domestic medicines to treat helminthosis on the basis of the medicinal plant raw material the main groups of antihelminthic medicines of the officinal medicine, as well as the medicinal plant raw material used in the folk medicine were analyzed.

The analysis of medicines presented at the Ukrainian pharmaceutical market to treat helminthoses was conducted on the basis of the data given in the compendium on-line and the Reference book of medicines of Ukraine [7, 10].

The ATC classification of antihelminthic medicines is given in Figure.

The group of anthelminthic medicines includes 19 medicines (Table 1).

As it is seen from Table 1, 11 out of 19 medicines are manufactured abroad (57.9%), whereas only 8 drugs – in Ukraine (42.1%). However, only one drug (5.3%) is of the natural origin.

The age limits vary from 6 months to 14 years. Thus, the lowest age limit from 6 months is presented with 5 medicines (26.3%), from 2 years it is allowed to take 3 medicines (15.8%), from 3 years – 4 medicines (21%), from 4 years – 3 medicines (15.8%), from 6 years – 2 medicines (10.5%), from 12 years – 1 medicine (5.3%), from 14 years – 1 medicine (5.3%).

Price offers for these medicines vary (Table 2). The study was carried out based on the price at http://medbrowse.com.ua/ site database with price offers for Kharkiv and the Kharkiv region, including Internet pharmacies offers with delivery from other regions of Ukraine (as of 06.15.2016).

Table 2

Price offers on antihelminthic medicines

Name of the medicine	The number of price offers	The lowest price, UAH	The highest price, UAH
Aldazol	153	42.31	61.00
Angelmin	66	29.39	43.00
Biltritsid®	79	248.02	346.86
Vermoxum	239	30.73	108.58
Vormil	443	33.00	160.12
Gelmintoks	340	40.40	90.51
Dekaris	321	52.45	98.08
Zentel ™	274	29.97	59.04
Levamisole-Zdorovye	64	12.70	20.12
Nemozol	5	200.00	287.26
Tansy flowers	138	6.32	27.08
Piperazine adipate	55	3.81	6.13
Pyrantel	377	10.35	145.00

As can be seen from the above data, price offers have significant fluctuations. These fluctuations depend on the dose, the dosage form and the availability of several manufacturers. Further, more in-depth market research of antihelmintic drugs is planned in order to calculate the average cost of treatment.

The main side effects of the digestive system, the central nervous system and allergic reactions of some active substances of antihelmintic medicines are presented in Table 3 [18].

In the folk medicine there are a lot of prescriptions to treat the different types of worms. Based on the analysis of the folk medicine formulations 11 medicinal plants have been identified as promising for creation of the complex phytomedicine with the antihelmintic activity (Table 4) [1-3, 9, 11-15].

Table 3

The main side effects of some antihelmintic medicines

Side effects	Medicines of					
	Piperazine	Mebendazole	Levamisole	Pyrantel	Praziquantel	Albendazole
Nausea	+	+	+	+	+	+
Vomiting	+	+	+	+	+	+
Pain in the epigastrium	+	+	+	+	+	+
Diarrhea	+	+	+	+		+
Allergy	+	+	+	+		+
Dizziness	+		+	+	+	+
Headache	+	+	+	+	+	+
Impaired hepatic function		+		+	+	+
Fever			+		+	
Drowsiness				+	+	+

Table 4

The medicinal plant raw material with the antihelmintic activity

The medicinal plant raw material, its Latin name	The main groups of active substances	Pharmacological activity	The mechanism of action on helminths	Regulatory documents
1	2	3	4	5
Tansy flowers *Flores Tanaceti vulgaris*	Steroids (β-sitosterol, campesterol, cholesterol), terpenoids (α-amyrin, β-amyrin, sesquiterpene lactones), essential oil (β-thujone, camphor, α-pinene, borneol)	Antihelmintic, carminative, antispasmodic; stimulates peristalsis, etc.	Paralyzes the central nervous system of the helminth causing its death	Herbal Medicines, 3rd ed. / J.Barnes, L.A.Anderson, J.D.Phillipson. – London, Chicago: Pharmaceutical Press, 2007. – P. 572-573
Artemisia Cina flowers *Flores Artemisii cini*	Santonin essential oil (cineole, d, 1-a-pinene, terpinene, and 1-terpineol, terpinenol, etc.), a sesquiterpene alcohol – sesquiartemisol, betaine, choline, bitter substances and dyes, acetic and malic acid	Antihelmintic, antibacterial, anti-inflammatory, analgesic, irritating and distracting in rheumatism and neuralgia, etc.	Causes convulsive contraction of nematode muscles, as a result they lose their ability to be fixed to the intestinal wall	Государственная фармакопея СССР. – 11-е изд. – М.: Медицина, 1987. – Вып. 1. – 1990. Вып. 2
Pumpkin seeds *Semen Cucurbitae*	Fatty oil, squalene, phytosterols (spinasterol, avenasterol, ergosterol), fatty acids (linoleic, oleic)	Antihelmintic, anti-androgenic, anti-inflammatory; an inhibitor of 5α-reductase, etc.	Changes the motor activity of the helminth, at first causing relaxation, and then the contraction of muscles	WHO monographs on selected medicinal plants. – Vol. 4. – Italy: Salerno-Paestum, 2005. – P. 83-91
Onion bulbs *Bulbus Allii Cepae*	Alliin derivatives, essential oils, vitamins C, B_1, carotenoids, sugars	In diarrhea and intestinal atony; reduces platelet aggregation; enhances fibrinolysis; antiseptic, etc.	–	WHO monographs on selected medicinal plants. – Vol. 1. – Geneva: WHO, 1999. – P. 5-15
Onion sativum (garlic) bulb *Bulbus Alii sativi*	Sulphur-containing substances, sulphates (allicin, vinyldithiin, sulphides)	Bactericidal, bacteriostatic, antithrombotic, hypoglycemic, lipid-lowering, antihypertensive, diaphoretic, expectorant, antineoplastic	The antibiotic action, including that for helminths; allicin can modify the thiol groups in proteins, and it leads to inactivation / activation of different regulatory proteins that are responsible for intracellular signalling, cell-cell communication and cell division	WHO monographs on selected medicinal plants. – Vol. 1. – Geneva: WHO, 1999. – P. 16-32

Continuation of the Table 4

1	2	3	4	5
Male fern rhizome *Rhizomatis Dryopteris Filicis-maris*	Floroglucides (aspidinol, baspidin), filix acid, tannins, triterpenoids, vitamins, higher aliphatic alcohols, higher fatty acids and their esters	Antihelmintic, antibiotic	Muscle poison. It causes paralysis of the muscles of the helminth and disturbes its fixation to the intestinal wall	Dryopteris filix-mas (L.) Schott is an accepted name. The Plant List (2010). Version 1. Published on the Internet; http://www.theplantlist.org/. Royal Botanic Gardens, Kew and Missouri Botanical Garden (2010)
Aspen bark *Cortex Populi tremulae*	Simple phenols, phenolic glycosides, benzoic acid derivatives, coumarin derivatives, quinic and cinnamic acids, flavonoids, catechins, macro- and microelements, fatty acids, vitamins	Antihelmintic (opisthorchiasis), anti-inflammatory, antimicrobial, antitussive, choleretic	Penetrates through the cuticle of the helminth, causing its death	–
Clove buds *Gemmae Eugenii aromaticae*	Essential oil, mono- and sesquiterpenoids, flavonoids, tannins, steroids	Antiparasitic, antiseptic, tonic, carminative; stimulates digestion	–	–
Elecampane rhizome and roots *Rhizomatis cum radicibus Inuli helenii*	Inulin, mucus, terpenoids (β-sitosterol, stigmasterol), essential oil (alantolactone, azulene)	Antihelmintic, sedative; affects the blood glucose level; bactericidal, fungicidal, muscle relaxant	Causes spasmodic muscular action of helminths	Herbal Medicines, 3rd ed. / J.Barnes, L.A.Anderson, J.D.Phillipson. – London, Chicago: Pharmaceutical Press, 2007. – P. 240-242
Ginger rhizome *Rhizoma Zingiberi officinalis*	Zingiberene, starch, camphene, linalool, gingerine, phellandrene	Analgesic, anti-inflammatory, wound healing, antispasmodic, antibacterial, antihelmintic, a mild laxative	–	Herbal Medicines, 3rd ed. / J.Barnes, L.A.Anderson, J.D.Phillipson. – London, Chicago: Pharmaceutical Press, 2007. – P. 293-208
Saussure purple loosestrife herb *Herba Saussureae salicifoliae*	Tannins, sesquiterpene lactones (yanerin, cynaropicrin), flavonoids (apigenin, quercetin), coumarin (esculetin), alkaloids (sossyurin)	Antihelmintic, antitumor, antibacterial	Destroys the integrity of the outer cell membrane of the helminth and causes its death	–

The pharmaceutical company Mili Healthcare (the United Kingdom) proposed the medicine Votmil Phyto, which is composed of kamala (*Mallotus philippinensis*), false black pepper (*Embelia ribes*), flame of the forest (*Butea frondosa*), golden shower tree (*Cassia fistula*), nut grass (*Cuperus rotundum*), babchi (*Psoralia corylifolia*), celery (*Apium graveolens*), gardenia (*Gardenia gummifera*), caraway (*Carum carvi*), wrigthia (*Holarrhena antidysenterica*), pomegranate (*Punica granatum*), turmeric (*Curcuma longa*), emblic (*Emblica officinalis*). Of them 9 medicinal plants (kamala, false black pepper, golden shower tree, babchi, celery, gardenia, caraway, wrigthia) have antihelmintic properties. The most of the plants presented are not typical for Ukraine, and it makes impossible to use them as the medicinal plant raw material for developing domestic herbal medicines with the antihelmintic activity.

Therefore, it can be concluded about the relevance of development of medicines based on the medicinal plant raw material for treating helminthoses. These medicines should provide the complex antihelmintic action, have low toxicity, good tolerability, and do not cause allergic reactions. Creation of herbal medicines to treat helminthoses is of particular current interest in pediatrics since most medicines of the synthetic origin have many side effects, contraindications for use in children.

CONCLUSIONS

1. The characteristics of helminth infections of the digestive system as one of the most common diseases in the world are presented. The main approaches to the pharmacotherapy of helminthoses, including foreign recommendations, and the basic requirements for antihelmintic medicines have been studied.

2. The range of antihelmintic medicines represented at the domestic pharmaceutical market has been analyzed. It has been determined that medicines of the synthetic origin (94.7%) and of foreign production (57.9%) dominate. The age limits of this group of medicines vary from the 6th months to 14 years. The price proposals on antihelmintic medicines have been also studied.

3. The basic groups of active substances, their pharmacological effects and the mechanism of action of medicinal plants commonly occurring in the folk medicine formulations on helminths have been studied.

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ОСНОВНІ ПІДХОДИ ДО ФАРМАКОТЕРАПІЇ ГЕЛЬМІНТОЗІВ ТА ПЕРСПЕКТИВИ РОЗРОБКИ ФІТОПРЕПАРАТІВ ДЛЯ ЇХ ЛІКУВАННЯ

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Ключові слова: гельмінтози; фармакотерапія; фітотерапія; лікарська рослинна сировина

Паразитарні інфекції є однією з найбільш гострих і актуальних проблем сучасного світового суспільства. Про особливу актуальність проблеми свідчить той факт, що більшість випадків захворювання на гельмінтози системи травлення припадає на дітей дошкільного та молодшого шкільного віку. Фармакотерапія гельмінтозів системи травлення передбачає підготовчий етап, етіотропне лікування та усунення ускладнень перенесеного захворювання. При цьому важливо дотримуватися дієти. Зарубіжні стандарти лікування передбачають два етапи лікування: знищення гельмінтів (препарати на основі мебендазолу, альбендазолу, тіабендазолу, ніклозаміну, празіквантелу) та усунення ускладнень перенесеного захворювання. Додатково рекомендується нефармакологічне лікування, яке полягає в забезпеченні повноцінного харчування і дотриманні правил особистої гігієни. Вітчизняний ринок протигельмінтних препаратів представлений лікарськими препаратами на основі празіквантелу, мебендазолу, альбендазолу, піперазину, пірантелу, левамізолу і одним препаратом у вигляді лікарської рослинної сировини – квіток пижмо. Більшість препаратів цієї групи виробляється за кордоном (57,9%). Вікові обмеження варіюють від 6 міс. до 14 років. Цінові пропозиції на протигельмінтні препарати коливаються в залежності від дозування, виду лікарської форми і виробника. Народна медицина пропонує безліч рецептів для боротьби з гельмінтозами на основі лікарської рослинної сировини. На підставі проведеного аналізу прописів народної медицини визначено 11 лікарських рослин, які є перспективними для створення комплексного фітопрепарату з протигельмінтною активністю.

ОСНОВНЫЕ ПОДХОДЫ К ФАРМАКОТЕРАПИИ ГЕЛЬМИНТОЗОВ И ПЕРСПЕКТИВЫ РАЗРАБОТКИ ФИТОПРЕПАРАТОВ ДЛЯ ИХ ЛЕЧЕНИЯ

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Ключевые слова: гельминтозы; фармакотерапия; фитотерапия; лекарственное растительное сырье

Паразитарные инфекции являются одной из наиболее острых и актуальных проблем современного мирового общества. Особую актуальность проблемы подчеркивает тот факт, что большинство случаев заболевания гельминтозами системы пищеварения припадает на детей дошкольного и младшего школьного возраста. Фармакотерапия гельминтозов системы пищеварения предусматривает подготовительный этап, этиотропное лечение и устранение осложнений перенесенного заболевания. При этом важно соблюдать диету. Зарубежные стандарты лечения предусматривают два этапа лечения: уничтожение гельминтов (препараты на основе мебендазола, альбендазола, тиабендазола, никлозамина, празиквантела) и устранение осложнений перенесенного заболевания. Дополнительно рекомендуется нефармакологическое лечение, которое заключается в обеспечении полноценного питания и соблюдении правил личной гигиены. Отечественный рынок противогельминтных препаратов представлен лекарственными препаратами на основе празиквантела, мебендазола, альбендазола, пиперазина, пирантела, левамизола и одним препаратом в виде лекарственного растительного сырья – цветками пижмы. Большинство препаратов данной группы производится за рубежом (57,9%). Возрастные ограничения варьируют от 6 мес. до 14 лет. Ценовые предложения на противогельминтные препараты колеблются в зависимости от дозировки, вида лекарственной формы и производителя. Народная медицина предлагает множество рецептов для борьбы с гельминтозами на основе лекарственного растительного сырья. На основании проведенного анализа прописей народной медицины определено 11 лекарственных растений, которые являются перспективными для создания комплексного фитопрепарата с противогельминтной активностью.

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