Ecological, Physiological and Biochemical Adaptation in Helminth: Trends in Evolution of Anthelminthic Chemical Agents

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Abstract This review discusses the landmark anthelminthic substances – traditional medicine components, different categories of pluripotential synthetic and naturally occurring compounds. Much attention is paid to the sections devoted to recent discoveries (Emodepside, Monepantel, Derquantel, Tribendimidine) and to some promising works. The review is also focused on some aspects of molecular mechanisms of action of anthelminthic substances and of helminth adaptation to anthelminthic substances, and on alternative worming treatment options. Based on the systemic analysis of particular features of the chemical structure of anthelminthic substances, the hypothesis on the viability of the targeted search for such compounds among the derivatives of conditionally progenitor cyclic hydrocarbons – benzene, indene, naphthalene, 1H-cyclopenth[a]-naphthalene, anthracene and phenanthrene – by alternating absolutely unsaturated and saturated structures, including heterocyclic analogues containing nitrogen, oxygen and sulfur and different substitutes and functional groups, was voiced.

Keywords Anthelmintic Substances, Folk Medicine, Non-Organic and Organic Anthelminthic Substances, Avermectins, Emodepside, Monepantel, Derquantel, Tribendimidine, Biological Methods of Helminthoses Control

1. Introduction

It is well-known that humans occupy a certain niche in the ecosystem and, standing at the top of the food chain, they interact constantly with environmental pathogenic micro- and macro-organisms. Human evolution involved fighting different diseases, including helminthoses. Even now helminthoses are still dangerous parasitoses of humans, animals and plants. Chemotherapy and prevention are of high priority in control of these diseases.

The entire variety of anthelminthic drugs available on the market (both single- and multi- multicomponent), with narrow to broad activity ranges, are based on compounds belonging to a limited set of relatively safe and highly efficient active ingredients (substances) [1,2]. Anthelminthic substances are synthetic non-organic and organic or natural compounds. In the latter case, compounds are largely the products of secondary bacterial, fungal and plant metabolism and may be used both in native and in chemically modified form [3].

However, the intensive administration of anthelminthic preparations leads to development of resistance, which is one of the ways of biochemical adaptation of helminths to the first- and second-order environmental changes (the host and ecological niche occupied by the host, where certain stages of the complex-cycle helminth metamorphoses take place), which necessitates regular renewal of the range of chemical agents, among different measures.

This review is aiming to classify anthelmintic substances by their origin and to outline the prospects of search for new anthelminthic chemical formulas, besides alternative anthelminthic treatment methods.

2. Evolution in Chemotherapy of Helminthoses

2.1. Remedies of Traditional (Ethnic) Medicine

Traditional medicine has long tested many minerals, mushrooms, plants, animal tissues and biological substances of animal origin, e.g. snake and spider venom, milk [4], and also animals themselves (e.g. leeches, bees etc.) to make powders, infusions, ointments, extracts, mixtures etc. to treat various diseases [5], including helminthoses [6]. Anthelminthic (anti-helminthic) substances as agents against parasite worms were initially called vermis (from Latin vermus meaning worm, and fugere meaning to expel) [6].

Numerous folk remedies [7] were created and included into reference books of ancient and medieval philosophers
and healers. For instance, the Ancient Egyptian papyrus of Ebers (dated approx. 1550 B.C.) contains information on human snail fever and helminthes [6]. Hippocrates described some worms in his works (dated approx. 500 B.C.) and introduced the terms of *helminthos* and *ascaridos* (in Greek, the diseases caused by helminthes and ascarids, respectively) [8]. Ancient Roman physician Galen (approx. 129-200 A.C.), one of the founders of pharmacology, suggested the methods to make infusions and ointments (e.g. with plant extracts) called Galenic drugs; he also introduced the notion of active substances [9]. Avicenna’s Canon of Medicine (980-1037 A.C.) mention malaria and many helminths, e.g. *Dracunculus* [10]. These reference books abound in recommendations as to healing diseases caused by parasite worms, e.g. administration of wormseed sage in ascaridosis. The anthelminthic effect of the wormseed sage (*Artemisia cinerea*) is due to the natural compound of santonin. It is a sesquiterpenic lactone first extracted in 1830 by German pharmacist Kahler (known as "apotheker Kahler") and pharmaceutical student J.A. Alms from raw materials of Russian origin [11], and introduced into medical practice in 1838 [12]. However, it was not until 1963 that its chemical structure was established [13]. Many other plants (pomegranate, European aspen, male fern, tansy, certain chamomiles, tobacco, pumpkin, garlic) were found to possess anthelminthic properties [9, 14, 15]. For example, filixan for treatment of cestodiases is derived from the male fern root extract (*Dryopteris filix-mas*) [1]. Structural formulas of some anthelminthic vegetal substances are provided below:

2.2. Inception of the Planned Chemotherapy

The idea of using chemical compounds to treat animals and humans was proposed by hermetists (in the 4th to 16th centuries), in particular, by iatrochemists (iatrochemistry, or therapeutic chemistry, from the Greek iatrós, meaning physician) who were engaged in drug search and preparation (16th/18th centuries), applying the chemical substances known at that time [16], mostly the derivatives of Hg, As, Sb, Cu, Zn, Fe, S. For instance, Glauber’s sault (Na₂SO₄·10H₂O) is still used in certain cases as a laxative, to expel intestinal worms [17].

The scientific foundations of chemotherapy of parasitoses (including helminthoses) were laid at the turn of the 20th century, as a result of establishment of the structural theory of organic and non-organic substances. P. Erlich, Nobel prize winner in 1908, having studied over 600 arsenic compounds, showed the possibility of targeted synthesis of drugs capable of influencing the infinitesimal organisms and proposed the term of ‘chemotherapy’. In 1910, as a result of his studies, the arsenic-containing drug of Atoxil [18] against trypanosomiasis (along with salvarsan fighting against syphilis) was put into clinical practice [19]. The beginning of use of suramin, a derivative of urea which can still be prescribed sometimes to patients with onchocercosis and sleeping dropsy (the limitations are due to its high toxicity), goes back to the same period (1916) [1]:

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**Santonin**

![Santonin](image)

**Artemisimin**

![Artemisimin](image)

**Cucurbitine**

![Cucurbitine](image)

**Ascaridol**

![Ascaridol](image)

**Thymol**

![Thymol](image)

**Carverol**

![Carverol](image)

**Arachinol**

![Arachinol](image)

**Nicotine**

![Nicotine](image)

**Anabasine**

![Anabasine](image)

**Acid residure**

![Acid residure](image)

**Pyrethins**

![Pyrethins](image)

**Spirit residure**

![Spirit residure](image)
Early in the 20th century, the simplest chlorine organic compounds, carbon tetrachloride CCl₄ (1921) and hexachloroethane C₆Cl₁₆ (1928), started to be used against *Fasciola hepatica* [1]. Due to their toxicity for mammals, they have been mostly cancelled. However, hexichol (paraxylene chloride derivative introduced in the USSR in 1964) remains in the list of anthelminthic substances in certain republics of the former USSR and in China (efficient against adult maritas) [20]:

Till the mid-20th century, non-organic compounds of arsenic (As), tin (Sn), stibium (Sb), fluor (F), hydrogen peroxide (H₂O₂), sulfur (S), oxygen O₂, metallic arsenates – arsenite aluminum and dyad metals (Ca, Cu, Zn, Sn), Fe (dyad and triad iron) were widely used as anthelminthic substances, despite the explosive growth in organic substances synthesis. For instance, against mature and immature helminthes, the efficient dose of copper acetoarsenite and calcium arsenate Ca₃(AsO₄)₂ for lambs came to 0.3-0.5 g/capita [21], and the dose of copper sulfate (CuSO₄·5H₂O) for buffalo calves, 112 mg/kg of live weight [22]. At present, non-organics are not used as anthelminthic substances, due to their high toxicity and emergence of more efficient organic substances, e.g. albendazole, phenbendazole, praziquantel etc., which are used against monieziasis of ruminant and other parasitoses [6]. However, certain organoelemental (e.g. organometallic) compounds (e.g. sodium thioacetarsamid and As³⁺ based melarsomin) are used in dogs’ heartworm disease (caused by *Dirofilaria immitis*) [23]. Structural formulas of certain arsenic and stibium-containing substances are provided below [24,25]:

Chlorine, copper sulfate, and slack lime are still in the toolbox of veterinarians, cattle breeders and sanitary services for disinfection of reservoirs, stalls and other facilities. Studies are underway to create composite anthelminthic substances, e.g. albendazole and copper pectinate (II) (n = 20-30, molecular weight = 17,000-25,000 Da) [26]:

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2.3. Modern Anthelmintics

2.3.1. Phenothiazines and piperazines

The breakthrough in chemotherapy of helminthoses occurred in the 1940/1950’s, with introduction of synthetic organic chemicals – phenothiazine (1940; the first phenothiazine, methylene blue, was applied as fabric dye) [27] and piperazine (1953) [28] – in nematodosis treatment:

Veterinarians still administer them, e.g. piperazine and its salts (adipinate, sulfate, phosphate) and phenothiazine are used in fur-farming, pig farming and aviculture as ascaridosis treatment, and DEC, in nematodoses (toxocariasis, filariasis, etc.) [1].

2.3.2. Benzimidazoles and other heterocyclic anthelmintics

The 1960’s saw introduction of efficient pluripotential anthelminthic drugs — benzimidazoles (the most numerous substances), imidazole thiazoles and tetrahydropirimidines into the clinical practice, for treatment of intestinal and non-intestinal nematodoses as well as cestodiases:

Thiabendazole (1961), albendazole (since 1972, it has been released for treatment of animal and human echinococcosis) [29], levamisole (1966) [30] and pyrantel (1966) [31] were the first representatives of the named anthelminthic substances. Some of them are still in use (often as part of multi-component anthelmintic substances) [1, 2].

Other nitrogen-containing heterocyclic substances emerged in the 1970’s, the most important of which were pyrazine isochinolines, e.g. prasiquantel (biltricide, discovered in 1977) administered for treatment of cestodiases and trematodoses [32]. Prasiquantel showed excellent results and remains in the list of animal and human anti-schistosomiasis drugs [1,2,33]:

2.3.3. Salicylanilides

This important anthelmintic class was discovered when searching for biocide properties in phenol compounds (phenols, biphenols, tiophenols etc.) administered as antimicrobial and fungicide agents (the well-known example is carbolic acid) (Lister J.,1867). These were niclozamide (Hecht G. et al., 1960), tribromsalan (Boray J.C.et al., 1965), cloxanide (Boray J.C.
et al, 1965). More efficient substances were developed later: oxiclozanide (Broome A.W. et al., 1966), clozantel (Janssen M.A.C. et al., 1973) and rafoxanide (Mrozik H. et al., 1969), which are important in distomiasis control [47]:

2.3.4. Macrolides

The 1980's were the beginning of the era of natural avermectins (abamectin, doramectin) produced by soil bacteria *Streptomyces avermitilis*, and their pluripotential semi-synthetic derivatives (ivermectin, selamectin, etc.) against nematodes, insects and mites at very low doses (0.2-0.3 mg/kg) (Table 1) [34].

<table>
<thead>
<tr>
<th>Substance</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothetical elementary structure:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“avermectin type” lacton nucleus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milbemycins, e.g. A₃, A₄</td>
<td>OH, H</td>
<td>-</td>
<td>H</td>
<td>Two homologues:</td>
<td>single bond</td>
</tr>
<tr>
<td>(native)</td>
<td></td>
<td></td>
<td></td>
<td>CH⁻, C₃H⁻</td>
<td>Respectively</td>
</tr>
<tr>
<td>Oxim milbemycin A₃/A₄ (semi-synthetic)</td>
<td>=NOH</td>
<td>the same</td>
<td>the same</td>
<td>the same</td>
<td>the same</td>
</tr>
<tr>
<td>Nemadectin (native)</td>
<td>OH, H</td>
<td>the same</td>
<td>the same</td>
<td>One homologue:</td>
<td>22-H,23-hydrox</td>
</tr>
<tr>
<td>(semi-synthetic)</td>
<td></td>
<td></td>
<td></td>
<td>isopenten-2-il-2</td>
<td>i-derivative</td>
</tr>
<tr>
<td>Moxidectin (semi-synthetic)</td>
<td>OH, H</td>
<td>the same</td>
<td>the same</td>
<td>the same</td>
<td>23-methoxym</td>
</tr>
<tr>
<td>(semi-synthetic)</td>
<td></td>
<td></td>
<td></td>
<td>(=NOCH₃)</td>
<td></td>
</tr>
<tr>
<td>Abamectin (native)</td>
<td>OH, H</td>
<td>OH</td>
<td>4(-L-oleandrosyl)-</td>
<td>Two homologues:</td>
<td>double bond</td>
</tr>
<tr>
<td>(semi-synthetic)</td>
<td></td>
<td></td>
<td>-L-oleandrozyl residual</td>
<td>sec-butyl,</td>
<td>iso-propyl</td>
</tr>
<tr>
<td>Emamectin (semi-synthetic)</td>
<td>the same</td>
<td>the same</td>
<td>the same</td>
<td>the same</td>
<td>the same</td>
</tr>
<tr>
<td>Eprinomectin (semi-synthetic)</td>
<td>the same</td>
<td>the same</td>
<td>the same</td>
<td>the same</td>
<td>the same</td>
</tr>
<tr>
<td>Ivermectin (semi-synthetic)</td>
<td>the same</td>
<td>OH</td>
<td>the same</td>
<td>the same</td>
<td>single bond</td>
</tr>
<tr>
<td>Doramectin (native, in specific conditions)</td>
<td>the same</td>
<td>OH</td>
<td>the same</td>
<td>One homologue:</td>
<td>double bond</td>
</tr>
<tr>
<td>Selamectin</td>
<td>=NOH</td>
<td>OH</td>
<td>NONE:</td>
<td>the same</td>
<td>single bond</td>
</tr>
<tr>
<td>(4-O-desoleandroxy-5-deoxi-5-hydroxyli min-22,23-dihydrodoramectin) – deglycosylized semi-synthetic doramectin analogue</td>
<td></td>
<td></td>
<td>The residual of one oleanandrose molecule (hydrolyzed di-saccharide 1,4-glycoside bond)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Several years prior to introduction of avermectins, representatives of another sub-group of 16-membered macrolides, milbemycins produced by actinomycetes *S. hygroscopicus* (*Ssp. aureolacrimosus*) as a mixture of compounds, were discovered. They are characterized by an absence of di-saccharine lateral chain at the C(13) position and by a presence of methyl (milbemycin A3), ethyl (milbemycin A4), isopropyl (milbemycin D) and secondary butyl (13-desoxy-22,23-dihydroavermectin B1a) groups as well as a saturated 22,23-connection (as with ivermectin) (1972) [35]. Semi-synthetic 5-oximins of A3 and A4 milbemycins are used as pesticides. Late in the 1980’s, nemadectins, congeneric with milbemycins, from *S. hygroscopicus* (*Ssp.noncyanogenus*) with a hydroxyl group at C(23), unsaturated hydrocarbon radical at C(25) and, like with milbemycins, without a di-saccharine lateral chain at C(13), were discovered. Nemadectin is a raw material for deriving moxidectin (the active substance of the veterinary drug cidecetin for treatment and prevention of endoectoparasitoses: psoroptic scab, dictyocaulosis, intestinal strongylatosis, pediculation, oestrosis, hypodermosis [35]) (Table 1).

Anti-parasitic effect is typical of all 16-membered macrolides having a structural nucleus with double bonds at 4,6,10 positions of the hypothetic parent saturated 16-membered lacton butadecenolide (8,10,14 positions, respectively, according to the adopted nomenclature of avermectins/milbemicyns), fragments of 1-oxahydrinden-5 and spiroacetal 1,7-dioxaspyro[5.5]undecan (or undecen-4) type and 7α-OH-group, which we conventionally called the "avermectin lactone nucleus". The substituents at positions of 5, 13, 22, 23 and 25 macrolides just modulate the anti-parasite activity: one way or another, all of them show sufficient biological activity and found practical application. Therefore, avermectins / milbemycins are a suitable raw material for deriving new substances through their chemical modification, and when some particular substrate is selected, preference is given to the already available effective producing strain. This thesis is confirmed by introduction of semi-synthetic ivermectin (1979) [36, 37], doramectin (1993) [34], eprinomectin (1998) [38], selamectin (2000) [34]. Introduction of other newly discovered substances is expected [39, 40].

2.3.4.1. Biological Activities of Avermectins

The diversity of avermectins’ properties (in addition to anthelminthic, insecticidal and acaricidal activities) arouses interest in searchers [41]. Ivermectin blocks CANCER1-dependent growth in cells of benign and malignant tumors (type II neurofibromatosis, ovarian carcinoma etc.) resulting from inactivation of p21-protein-dependent kinase (CANCER1) [42, 43]. Inhibition of the yellow fever virus replication [44] and sporogony in *Plasmodium falciparum* and *Anopheles gambiae* by ivermectin has been recently discovered [45]; the anti-TB effect of avermectins was also established [46]. In light of these discoveries, obtaining and study of biological properties of new semi-synthetic derivatives of 16-membered lactones seems to be promising in search for new medicinal substances of different pharmacological groups.

2.3.5. Other Substances

Besides the above basic anthelminthic classes, numerous substances of different chemical origin were obtained: e.g. hygromycin (aminoglycoside antibiotic and anthelminthic agent produced by *Streptomyces hygroscopicus*) [48], and organophosphoric drugs (metriphonate, citioate, etc.) [1], application of which is limited by low efficiency or significant side effects [6].

2.4. Modes of Action

Availability of a broad range of anthelminthic agents is due to the variety of hosts, helminths, development of their drugs resistance and some other factors. The processes, in which the anthelminthic substance is involved from its getting into a patient’s body to producing the treatment effect, can be consolidated into two groups. The first includes physico-chemical and chemical interaction of the substance with environmental factors (pH, temperature, enzymes etc.) when it moves to the helminth’s location in the host’s body (Fig. 1), with the respective biochemical and physiological consequences. For instance,
non-fermentative and fermentative changes are possible, as in case of dichlophos that is capable of spontaneous transformation in water solutions into a more active dichlorvos that interacts with the nicotinic receptor (nACHR) (14), or nitazoxanide that quickly (in approx. 6 minutes) turns, in the blood plasma under enzyme impact, into active metabolites of tizoxanide and glucoronide tizoxanide that inhibit pyruvate ferredoxine oxidoreductase and thus undermine the helminth’s energy metabolism [49].

The second group includes the processes that ensure the anthelminthic agent transportation to target cells via investments (cuticle, tegument) or internal cavities (oral, pharyngeal and intestinal cavities) of the helminth and interaction with these cells (see Fig. 1).

![Figure 1. Pattern of anthelminthic substance delivery to a helminth in the body and interaction with the target cell.](image)

By the nature of their interaction with the targeted cell, all anthelminthic agents can be divided into: quick-acting (2-4 hours, they inhibit ionotropic receptors) and slow-acting (1-4 days, they influence metabolic processes) [50] (Fig. 2). Substances included in the first group act as nACHR agonists (imidazol thiazoles, tetrahydropirimidines, pyrazine isochinolines, amino acetonitril derivatives etc.) and antagonists (phenothiazine, spiroindoles), allosteric modulators of GABA_A-receptor and glutamate dependent chloride channels (GluCls) (16-membered macrolides — avermectins and milbemycins), GABA-ergic receptor (piperazine) agonists, Ca^{2+}-channel activators (praziquantel) and Ca^{2+}-dependent K^{+}-channel SLO-1 activators (emodepside). Slow-acting ß4-tubulin ligands (benzimidazoles) interfere with its polymerization and the microtubular apparatus formation, which leads to degenerative changes and other metabolic disorders in a nematode’s intestinal cells and cuticle. Other drugs of this group are SH-group containing substances (melarsomin); ChE1 [carbamates, organophosphoric substances (metronphonate), diphenyl substances (biphenium, nitrozocanate and amoscanate); cyclo- and lipoxygenases (e.g. DEC that interferes with arachidonic acid metabolism and blocks prostaglandin formation in the host, which leads to capillary constriction and occlusion to microfilaria; it increases microfilaria phagocytosis by vascular walls, lymphocytes and granulocytes; in addition, its effect is obviously related to the inducible NO-syntase); chitinases (in particular, clozantel that also has protonic ionophoric activity that is synergic with chitinase inhibition); pyruvate ferredoxin oxidoreductase (nitazoxanide) [50, 51].
2.5. Efficacy

The helminthosis chemoprevention and chemotherapy cost efficiency largely depends on correctness and appropriateness of methods used combined with efficiency of anthelminthic agents and with allowance for the helminth development cycle, particular features of the host, climate etc. For instance, mebendazole and thiabendazole act on trichinella intestinal forms, but not on incapsulated forms [33, 51].

Efficiency comparison for anthelminthic agents of different generations suggests that introduction of new substances was accompanied with the dose reduction and reached the bottom in avermectins [52] (Fig. 3).

2.5.1. Helminth Adaptation and Drug Resistance

Intensive administration of anthelminthic agents is not only accompanied with some adverse biochemical consequences for a patient (negative adverse effects) but also leads to appearance and establishment of the biocide-resistant forms in helminth population. This fact was noted by P. Erlich as early as in the beginning of the 20th century, and resistance to frequently used anthelminthic substances is now registered universally [52-63].

The resistance develops as a result of helminth adaptation to anthelminthic effects. While interacting with the target, it
initiates a cascade of physical, chemical and biochemical events (in addition to those related to the expression of anthelminthic effects) that involve intracellular effectors at different levels (up to the genetic apparatus and its functional activity), and therefore, in addition to the initial target, a modified target may appear and be reproduced (see Fig. 2). Reduction in expression of receptor proteins or its subunits (nAChR agonists), increased P-glycoprotein expression ([54] and multiple resistance proteins (GluCl allosteric modulators), single nucleotide polymorphism (b-tubuline ligands) play an important part in resistance development [50, 61]. In particular, it was experimentally shown in C. elegans nematodes that simultaneous mutation ofavr-14, avr-15 and glc-1 genes encoding GluCl -subunits is the reason for significant resistance to ivermectin, due to the reduction in affinity of the substance to the chlorine ion channel. On the contrary, mutation of any two genes of the channel either does not lead to resistance or does lead to an insignificant one [62].

Resistance formation may be accelerated by incorrect anthelminthic agent administration [52-55] (Table 2).

2.6. New Anthelminthic Agents

Resistance onset in pathogenes encourages the search for new anthelminthic agents with a different action mechanism and/or the one typical of the already existing substances (but more efficient) [64-66]. For instance, in 2000/2010 emodepside, monepantel, derquantel (veterinary science), as well as tribendimidin and nitazoxanid (medicine) emerged (Table 2).

Emodepside represents a N-methyl derivative of a 24-membered cyclooctadepsipeptide – the product of Mycelia sterilia fungus fermentation, first extracted from the microbial flora of Japanese camellia leaves by Japanese scientists in 1990 [67]. It is efficient against nematodes in the gastro-intestinal tract and lungs and microfilaria resistant to benzimidazoles, 16-membered macrolides and cholinergic agonists. It is included into newly created drugs recommended for feline and canine nematodosis treatment [68-70].

Structural formulas of substances developed in 2000/2010:

Table 2. Certain most important anthelminthic substances for human and animal helminthosis treatment

<table>
<thead>
<tr>
<th>Pathogenic group (pathology)</th>
<th>Drug, anthelminthic class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nematodes</td>
<td>Avermectins and milbemicyns, monepantel*, emodepside*, tribendimidin*, derquantel*, benzimidazoles, morantel, pyrantel, levamizole, clozantel (and halogenized salicylanilides), piperazin</td>
</tr>
<tr>
<td>Intestinal nematodes</td>
<td>Diethylcarbamazine, suramine, ivermectin</td>
</tr>
<tr>
<td>Tissue nematodes (filariasis)</td>
<td>Triclabendazol (against all forms), praziquantel, clorsulon, clozantel (and halogenized salicylanilides), oxoizoxamide, albendazole (against adult forms)</td>
</tr>
<tr>
<td>Trematodoses of different localization</td>
<td>Antimonates, metriphonate, oxamnichin, praziquantel</td>
</tr>
<tr>
<td>Common liver flukes (fasciolasis)</td>
<td>Triclabendazol (against all forms), praziquantel, clorsulon, clozantel (and halogenized salicylanilides), oxoizoxamide, albendazole (against adult forms)</td>
</tr>
<tr>
<td>Blood flukes (schistosomiasi)</td>
<td>Antimonates, metriphonate, oxamnichin, praziquantel</td>
</tr>
<tr>
<td>Lung and intestinal flukes</td>
<td>Praziquantel, triclabendazol, niclozamide (alternative), albendazole (alternative)</td>
</tr>
<tr>
<td>Cestodiasis</td>
<td>Benzimidazoles, praziquantel, niclozamide</td>
</tr>
</tbody>
</table>

Note: The superscript (*) marks the substances developed in 2000/2010.
The efficiency and the action spectrum of the substances administered for anthelmintic treatment depend on many factors: the host (including humans) and the helminth species (their anatomic, histological and physiologo-biochemical properties, e.g. presence of a tegument, body and organ temperature, individual differences); the lifecycle of a bio- or geo-helminth and pathogen localization in the intermediate or definitive host body; the host’s position in the ecosystem’s food chain, its nutrition and living features (climate, lifestyle etc.) [71, 118-120]; bioavailability, physical and chemical properties of the anthelmintic agent and its interaction with the target (receptors, enzymes and other endogenous metabolites and cellular elements) etc., which is (or must be) taken into account in the successful anthelmintic treatment protocol.

Emodepside inhibits muscles function (throat, body and organs involved in egg laying), by increasing conductance of Ca\(^{2+}\)-activated K\(^{-}\)-channels (SLO1) in pre- (obviously, to a greater extent) and post-synaptic cells of a nematode’s neuromuscular plexus [72] (Fig. 4). However, the sequence of events in this case needs to be specified. They also assume that [73], in addition to the above, the slow-acting signal mechanism (with participation of latrophilin-like pre-synapse and G\(_{q}\)-protein receptor) plays a minor part [72, 73].

Monepanthel (S-enantiomer, a synthetic product, was discovered in 2008 and admitted to the market in 2010) is a so-called amino-acetonitrile derivative (AADs) [74]. Its most active metabolite is sulphone monepanthel [75, 76], a pluripotential drug against larvae and adult gastro-intestinal helminths that are resistant to the common anthelmintic drugs, is efficient in low doses (2.5-3.5 mg/kg) [77]. The interaction of monepanthel with nemadof-specific nAChR Hco-MPTL-1 interferes this receptor function and paralyzes the helminth’s muscles [78, 79]. Derquantel is a semi-synthetic derivative of paragerquamide A found among natural spiroindoles produced by the mildew Penicillium paraherquei [80, 81]. Derquantel inhibits nAChR [82], is a pluripotential anthelmintic agent and is applied in combination with abamecine for treatment and control of different gastro-intestinal nematodoses (including cases of helminths resistance to other drugs), which points to the feasibility of search of anthelmintic agents among such compounds.

Tribendimidine is an aminophenyl dimidine derivative of amidantel that was first synthesized in China in 1980 [83] and was introduced into medical practice there in 2004 [84-86], it has anti-nematode effect. Tribendimine is included into the L-subtype of nAChR agonists with the same action mechanism as that of levamizole and pyrantel; so it is not prescribed in case of levamizole resistance. However, developers recommend administering tribendimidine instead of benzimidazoles or in combination with them, in case of resistance to the latter [87].

Out of anthelmintic drugs developed during the last decade, it is worth mentioning nitazoxanide [49, 88] — a salicylic acid derivative, in which, unlike with salicyl anilides, its residual is bound with the nitrothiazole fragment via an amide bond. As mentioned above, active metabolites of nitazoxanide inhibit pyruvat ferredoxine oxidoreductase (see also [89]). It has protozoacide, anthelmintic and anti-bacterial properties and is used in medicine [2]. By its efficiency, nitazoxanide is inferior to benzimidazoles, but it can be used against benzimidazole-resistant forms [89].

Work on chemical modification of known substances continues. In particular, benzimidazole derivatives, i.e. benzimidazolyl-chalcones (chalcones are flavonoids with an open pyran ring) [90], as well as 5-O-succinoyl avermectin and Gemaec on its basis [91-93] have been developed. These so-called horizontal developments are aimed at obtaining analogues with improved physical, chemical and pharmacological properties (e.g. reduction in residual quantities in milk after administration of drugs in the lactation period, etc.).

3. Prospects in the Development of Substances

3.1. Screening Methods

Virtual and experimental Screening of known synthetic compounds and metabolites of land and marine organisms, mostly bacteria, fungi, plants but also, possibly, noxious animals (spider toxins or toad bufotoxin having cardiotonic effect), as well as semi-synthetic and synthetic analogues of the last compounds is still of critical significance. Their chemical nature can be different: mono- and polycyclic (condensed and non-condensed, or poly-phenyl) aromatic (e.g. poly-atom phenols — plant tannins) and heterocyclic (e.g. fervenulin) compounds, flavonoids, alkaloids, lactones, terpenoids, peptides etc. Numerous articles on deriving such substances with anthelmintic properties have been recently published, namely: fungichromine B (28-membered polylene macrolide produced by actinomyeete Streptomyces albogriseolus HA10002, it is efficient against tubercular nematodes) [104], fervenline (103), nafuredine (produced by Aspergilluss niger FT-0554) [105], bacterial protein Cry5B (Bacillus thuringiensis) [106], cysteine protease of the pipeapple, papaya, other plants [107], ross alcaloids
3.2. Some Considerations for Synthetic Search

The search for synthetic anthelminthic substances among the derivatives of conditionally parent hydrocarbons, such as benzene, indene, naphthalene, 1H-cyclopent[a]-naphtalene and phenanthrene, by modifying the structure, from absolutely unsaturated to saturated forms, including heterocyclic forms containing N, O, and S atoms, different substituents and functional groups, seems promising. This can be illustrated by classical anthelminthic agents, such as biphenyl, biphenium, and recently discovered substances of monepanthel and tribendimin that contain two and three benzene residuals, respectively.

Different saturated and unsaturated cys-hydrindan derivatives (including conditionally heterocyclic analogues, e.g. benzimidazoles) in the form of the CD-fragment of aglycons of cardiac steroids (see section 3.2.1), the divalent residual of cys-1-oxahydrinden-4,5 within 16-membered macrolide anthelminthic agents, the BC-fragment of the tricyclic 1H-cyclopent [a]-naphtalene (e.g. in the form of santonin containing the condensed 5-membered lactone ring) are hypothetically attractive. In this connection 8,14-[115], 9,10- and 9,11 -secosteroids, e.g. analogues of Torgov seco-diketone, vitamin D$_2$ [116], 6,7- secoecdysteroids and others may also be promising.

3.3. Alternative Methods for the Helminthosis Control

Biological treatment methods destroying helminth eggs applicable for pastures (nematophagous fungus *Duddingtonia flagrans*) [94], reservoirs (ascomycete *Caryospora callicarpa* YMF1.01026) [95], gastro-intestinal tract (nematophagous fungus *Pochonia chlamydospora*) [96], immune system reinforcement [97], selection of helminth-resistant breeds and lines should be regarded as alternative approaches to helminthoses control in animals. With discovery of so-called pattern recognition receptors (PRR) that are capable of specific interaction with nematode and flatworm antigens in the inherent and adaptive immune system of mammals, there are prospects to develop vaccines based on resistant helminth tissues [98]. Filariasis treatment using agents acting on *Wolbachia pipiens* bacteria (cytoplasm symbiont of nematodes) [99], e.g. tetracycline antibiotics such as doxicycline [100] and others, may also be used as a helminthoses prevention and treatment method [101]. It is noteworthy that endo-symbionts were found in more than 90 % of studied nematodes [50, 102].

4. Conclusion

Chemotherapy is central in fighting animal and human helminthoses. Pathogen resistance to known anthelminthic substances necessitates their constant renewal.

A new substance development, be it designing a new compound or identification of properties of any existing compounds, is a time-consuming and expensive process. Application of the diversification (different types of compounds) and the focused (related compounds) screenings, software-based evaluation of anthelmintic activity in silico [117], chemical and genetic trials on model small animals (nematodes *Artemia salina*, *Caenorhabditis elegans*, etc.) are intended to accelerate introduction of new substances [50, 118]. Further knowledge in molecular action mechanisms of anthelminthic agents and in resistance development would improve planning of helminthoses control protocols.

In our opinion based on codification of known substances by chemical structure, the target search among the derivatives of conditionally parent hydrocarbons – benzene, indene, naphthalene, 1H-cyclopent[a]-naphtalene, anthracene and phenanthrene by structure variation from unsaturated to saturated forms, including their heterocyclic analogues containing nitrogen, oxygen, sulfur, different substituents and functional groups, may be promising.
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