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Development and application of anthelminthic drugs in China

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ABSTRACT

China was once a country plagued by parasitic diseases. At the beginning of the founding of the People's Republic of China, nearly 80% of the population suffered from parasitic diseases because of poverty and poor sanitary conditions. After nearly 70 years of development, China has made remarkable achievements in the prevention and control of parasitic diseases, and the prevalence of parasitic diseases has been greatly reduced. In addition to organizational leadership from the government and various preventive measures, drug treatment and drug research & development are important and irreplaceable links in prevention and control work. Since the 1950s, China has begun to introduce, produce and imitate antiparasitic drugs from abroad, such as santonin, benzimidazole, and praziquantel. Chinese scientists have also contributed to the optimization of production techniques, improvements in drug formulation, the application in the clinic and the mechanisms of actions of generic drugs. At the same time, China has independently developed tribendimidine (TrBD, a broad spectrum anthelminthic), and its anthelminthic spectrum has been comprehensively studied. It is active against almost 20 parasites, is especially superior to benzimidazoles against *Necator americanus,* and surpasses the effectiveness of praziquantel against *Clonorchis sinensis.* In the treatment of tapeworm disease, the traditional Chinese medicines pumpkin seeds and betel nuts have good curative effects for taeniasis. Chinese scientists have explored the action modes and clinical administration methods of pumpkin seeds and betel nuts, which is still the main clinical regimen for the disease. This paper reviews the history and progress of the study of anthelmintics in intestinal helminth infections since the founding of the People's Republic of China and aiming to support clinicians and drug researchers in China and other countries.

1. Introduction

In the process of preventing and controlling intestinal helminthiasis in China, drug R&D and clinical use play an important and irreplaceable role. Chinese pharmaceutical researchers have made substantial efforts to prevent and control helminthic infections. Before the 1970s, santonin, neem bark, Rangoon creeper, Chenopodium oil, hexylresorcinol, tetrachloroethylene, chloroform-castor oil, 1-bromo-2-naphthol and bephenium were the most frequently used drugs for the treatment of intestinal nematode infections. However, almost all of these drugs are no longer used in clinic because of the narrow antiparasitic spectrum, poor effectiveness and significant adverse reactions (Xiao, 2009). Although piperazine has been widely used in China, it is mainly used for the treatment of Ascaris infection. Since the 1960s–mid-1970s, pyrantel, levamisole, albendazole and mebendazole (later listed in essential drugs by the WHO) were developed abroad successively. These drugs were then copied in China in the 1970s (Nanjing Pharmaceutical Factory, 1977; Shanghai Institute of Pharmaceutical Technical Information Station, 1973; Wang, 1982) and were put into production after pharmacological and toxicological tests, followed by clinical treatment of intestinal helminth infections. While copying generic drugs, Chinese scientists also independently developed new drugs. Scientists screened an abundance of new chemical structures on animal models by modifying the known active structures or separating active components from traditional Chinese medicines. Tribendimidine (TrBD), the first broad-spectrum new drug for anti-intestinal nematodes, already has independent intellectual property rights in China and new drug certificates and production licenses issued by State Food and Drug Administration (SFDA) in 2004 (Xiao et al., 2005). Currently, TrBD is produced by Shandong Xinhua Pharmaceutical Limited.

Traditional Chinese medicine (TCM) is also used in the treatment of intestinal helminth infection, especially taeniasis. Semen Arecae, Omphalia (dried sclerotia of *Omphalia lapidescens* Schroet), Rhizoma Dryopteris Crassirhizomae, Pericarpium Granati, pumpkin seeds and the extract from the radical bud of Herba Agrimoniae were used for the treatment of taeniasis very early in China (Zhang, 1990). It was also

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reported that agrimophol extracted from agrimony has a significant effect against tapeworm, even better than those of clinical drugs such as Yomesan (niclosamide) and Bitin (dichloro bisphenol) in animal experiments (Feng, 1978; Pharmacology Laboratory of Shenyang Province, 1974). A combination of pumpkin seeds and arecoline is still widely used in the clinic (Li et al., 2013; Long et al., 2014).

In addition to traditional drugs, the synthetic drugs currently used in the clinic are niclosamide and praziquantel. Bitin and quinacrine have also been used for taeniasis but have not been widely used clinically (Liang, 1953).

This paper reviews the clinical application and R&D of anthelminthic drugs in China since the founding of the People's Republic of China, aiming to inspire researchers and clinicians in China and other countries.

2. Santonin and "Bao Ta Tang"

From the 1950s to 1970s, as one of the most common formulations for children, "Bao Ta Tang" was widely used for mass deworming in schools and kindergartens. This unique drug dosage form once played a dramatic role in protecting children from intestinal helminth infections, and people around and over the age of 50 can still recall its use.

The active ingredient of "Bao Ta Tang", santonin, has a colourless crystalline or white powdery appearance and is extracted from *Artemisia cina*. Santonin was initially prepared as a tablet and was later prepared as a colourful conical-shaped candy with a sweet fragrance and taste by adding sucrose, dry protein, spice, pigment and acetic acid because ascariasis mainly occurred in children. "Bao Ta" is the Chinese pronunciation of pagoda in temples, because of its conical shape same as the pagoda and "Tang" means candy. "Bao Ta Tang" means a pagoda shaped candy. Children loved it as much as they loved ordinary sweets, so people named the "santonin" drug formulation as "Bao Ta Tang" vividly. In the early days of the founding of People's Republic of China (PRC), as the registration and supervision system of drug brands had not yet been built, "Bao Ta Tang" was used as a drug and drug brand name by more than a dozen pharmaceutical factories in China (Wang, 2008).

As mentioned above, santonin is extracted from *A. cina*, a cold-tolerant native perennial semishrub in the Arctic Circle (Wang, 2008). The special characteristics of the climate are suitable for the growth of *A. cina* and make this plant unique in the former Soviet Union. *A. cina* also survived outside of the Arctic Circle under a suitable environmental condition and with well-managed artificial cultivation by botanists in the former Soviet Union, but with a low survival rate (Wang, 2008).

From 1950 to 1951, the early days of the People's Republic of China, the raw materials for the production of santonin in China were all imported from the former Soviet Union. In 1952, as an aid project from the former Soviet Union, China introduced the seeds of the wild native plant *A. cina*. The Ministry of Agriculture, Ministry of Chemical Industry, Ministry of Health and Ministry of Public Security jointly issued a document for implementing a series of measures to introduce and cultivate *A. cina*. Twenty grams of seeds from the former Soviet Union was transported and delivered to four state-owned farms in Hohhot, Datong, Xi 'an and Weifang for trial planting under the protection of public security personnel. By the end of 1954, due to the environmental temperature, sunshine, natural climate, fertilizer constituents, soil properties, daily management, ambient conditions, etc., the cultivation of the plant failed in three state-owned farms in Hohhot, Datong, Xi 'an, and only succeeded in a farm in Weifang. Since 1954, the Weifang farm has become the only plantation base for the extraction of raw materials for santonin in China. By the late 1950s, the planting area in Weifang farm expanded to 8640 mu, the average yearly output of *A. cina* flowers and leaves was nearly 150,000 kg, and the seed yield was approximately 3100 kg, which not only supplied the domestic production of santonin at more than a dozen national pharmaceutical enterprises but was also exported in small amounts.

In September 1982, with the development of the medical market and the introduction of new drugs from abroad, increasingly more drugs for deworming were on the Chinese market. The Ministry of Health and State Pharmaceutical Administration announced the withdrawal of 127 drugs and formulations including santonin due to safety concerns and better alternatives. Thus, the "Bao Ta Tang" became a historical brand that was gradually forgotten by most people. The production and cultivation of *A. cina* that was introduced from the former Soviet Union were stopped in Chinese land.

After santonin was discontinued from use, other "Bao Ta Tang" of anthelminthic drugs, including piperazine phosphate and levamisole, were developed successively (Levamisole hydrochloride work group, 1984; Gu, 1965). However, they are not nearly as widely used as the santonin "Bao Ta Tang".

3. Benzimidazoles

Albendazole (ABZ) is one of the most commonly used drugs against intestinal helminths in China. In recent years, the dosage forms of albendazole used clinically in China are tablet, capsule, granule, oral solution, dry syrup, etc. (Chinese Pharmacopoeia Commission, 2015). There are 361 Chinese patents related to ABZ. Of these, 256 applications were for invention, and 81 inventions were authorized. From 1999 to 2017, the application numbers were generally on the rise due to the innovation of chemical synthesis methods for albendazole active pharmaceutical ingredients (APIs) or the active metabolites of abendazole sulfoxide (ABZSX), the improvement of the physical and chemical properties of API of ABZ, the new dosage forms, combination drug therapy that enhanced the curative effect and new formulations for livestock. And the number of patents each year is increasing (Fig. 1). Patents related to human parasitic diseases were mainly related to the improvement of dosage forms and synthesis methods of APIs and ABZSX. Since the mid-1970s–mid-1980s, researchers found that mebendazole and albendazole have therapeutic effects on echinococcosis. In 1980s, the world health organization (WHO) conducted two multicenter clinical trials of ABZ and MBZ for the treatment of echinococcosis, further confirming the efficacy of these two drugs for echinococcosis (Davis et al., 1986, 1989). However, the bioavailability of benzimidazoles is poor, in which albendazole has better bioavailability than mebendazole. Even though, only about one-third of patients experience complete remission or cure; an additional 30–50% of treated patients develop some evidence of a therapeutic response when administered with ABZ (Horton, 1997). Therefore, since the 1990s, Chinese patents on albendazole dosage forms have been devoted to the improvement of bioavailability. With the ABZ "dosage form" as the key word, 43 issued patents and 13 authorized patents were retrieved for Chinese patent. Among them, the two patented formulations of ABZ are

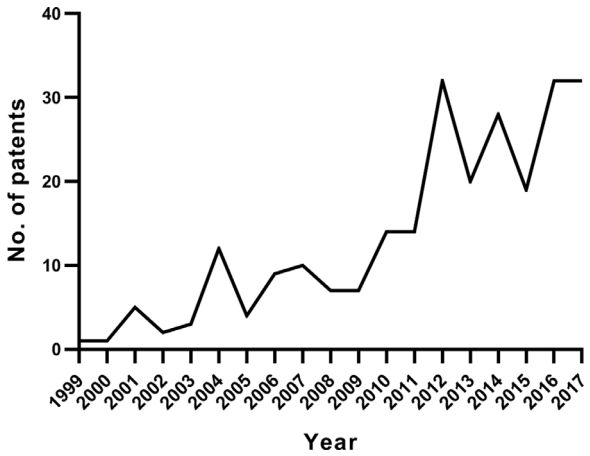

Fig. 1. Number of issued patent applications related to ABZ from 1999 to 2017.

used in the clinic for the treatment of echinococcosis: ABZ oral emulsion was marketed in China in September 2003, and ABZ-liposome is used as a hospital preparation only in one hospital and not licensed by the SFDA.

3.1. New dosage forms for benzimidazoles

Benzimidazoles (BZs) are effective against intestinal nematodes but have poor efficacy in the treatment of systemic parasitic diseases such as echinococcosis. The WHO recommends ABZ and mebendazole (MBZ) at high doses (15–20 mg/kg per day for ABZ and 50 mg/kg per day for MBZ) (Eckert et al., 2001) and for a long duration (6 months–2 years; commonly, some patients require lifelong medication) in the administration of echinococcosis due to their low solubility and poor bioavailability (Hemphill et al., 2014). Therefore, the improvement of the dosage forms of benzimidazoles tends to involve the improvement of the aforementioned properties, increasing the solubility and bioavailability of ABZ or MBZ. There are nearly ten patents for the improvement of dosage forms for human parasitic diseases, but only two new dosage forms, ABZ emulsion and ABZ liposomes, have been successfully applied in clinical practice.

3.1.1. ABZ oral emulsion

Because taking BZs with oily food may increase bioavailability and improve efficacy, Xiao et al. made a new drug formulation by emulsifying ABZ with 30% soybean oil (ABZE-30) and evaluated its activities against *Echinococcus granulosus* and *Echinococcus multilocularis* in mice, compared with ABZ suspension in 1% tragacanth (ABZ suspension) (Xiao et al., 2002). ABZE-30 resulted in higher circulating plasma concentrations of the major bioactive metabolite, ABZSX, and produced higher concentrations of ABZ in the hydatid cyst wall after oral administration. Mice that received ABZSX (100 mg/kg per day for 14 days) exhibited a 45% reduction in the weight of their hydatid cysts relative to control mice when the drug was administered to mice 4 months post-infection. However, there was no significant difference between the ABZ suspension group and the control group. When treated with the same dose of ABZE-30, the hydatid cyst weight was reduced by 81% ($P < 0.05$).

In a clinical trial, the effect of ABZE-30 on hepatic cystic echinococcosis was better than those of the current drugs with stable and reliable curative effects and mild adverse reactions (Chai et al., 2001). For patients treated with albendazole emulsion at a daily dose of 10 mg/kg and 12.5 mg/kg, the average cure rate, therapeutic response rate and ineffective rate were 74.5%, 99.1% and 0.9%, respectively, and the average long-term (1 year after drug withdrawal) rates were 83.1%, 89.3% and 0.6%, respectively. In the other two clinical trials, with the ABZ tablet as the control, the ABZE short-term and long-term cure rates were 70–74.63% and 73.33–75% and significantly different from those of the ABZ tablet, in which the short-term and long-term cure rates were only 33.33–47.01% and 40–75% (Wei, 2016; Gulishayila, 2015).

3.1.2. ABZ liposome (ABZ-L)

ABZ-L was prepared by a neutralized method containing ABZ, lecithin, sodium benzoate, antioxidant and physiological saline, etc. The ABZ distribution in mice measured by ^{3}H-labelled radioisotope tracer showed a strong liver-targeting effect after peritoneal injection with ABZ-L, suggesting that the new formulation had the potential for clinical treatment of liver echinococcosis (Wei et al., 2002; Wen et al., 1996).

In a clinical evaluation (Ke et al., 2002), the patients were divided into 3 groups. Group A was orally administered ABZ-L alone at 10 mg/kg per day for 3–6 months continuously, and the other two groups accepted surgery (Group B) and PAIR (puncture, aspiration, injection, re-aspiration) (Group C), with each treatment combined with the administration of ABZ-L starting at 7 days before surgery until one month after surgery. Sixteen of 35 (45.7%) cases were considered cured in Group A, 9 of 35 (25.7%) were considered effective (main symptoms were significantly alleviated, and the diameter of the hydatid cyst was reduced by 2 cm or the number of cysts decreased by more than 2, or calcification in the hydatid lesion was observed), 6 of 35 (17.1%) were considered partially effective (clinical symptoms and signs were relieved or relatively stable and the hydatid cyst or mass did not obviously increase), 4 of 35 (11.5%) were considered non-effective, and the total effective rate was 88.57%. One to three years of follow-up for Group B and Group C were carried out, and no recurrence was found during that time. The follow-up period for the drug group ranged from 3 to 36 months; most of the patients had no obvious adverse reactions after long-term medication, and the incidence of adverse effect was 11.32%, mainly consisting of transient gastrointestinal reactions including diarrhoea, nausea, upset stomach and aminotransferase abnormality, All of the symptoms disappeared later and none of the subjects terminated the treatment for drug side effects. In the trial, ABZ-L demonstrated a promising effect for the treatment of human echinococcosis with high tolerability with a relatively slight side-effect or toxicity. In another clinical observation of ABZ-L for treating complex liver alveolar echinococcosis, ABZ-L also demonstrated safety and efficacy (Li et al., 2010).

3.1.3. Other new dosage forms of benzimidazoles used in human parasitic diseases

There are additional authorized patents (including invalid patents) for new drug formulation of BZs for human parasitic diseases that have not been applied clinically. Some patent applications have been made public but are still in the audit stage, mainly for the treatment of hydatid disease and the improvement of children's medication compliance.

The new dosage forms associated with echinococcosis treatment were aimed at increasing the solubility and bioavailability of BZs, including BZ oil suspension, soft capsule, freeze-dried powder of ABZ liposomes, ABZ clathrate and ABZ chitosan microspheres.

The MBZ soft capsule contains oleic acid as a dispersive phase, which increases the bioavailability of the drug, especially the content of the drug in the cyst wall and fluid of *E. granulosus*, and tends to be distributed in the target organs, such as the liver, lung and kidney (Liu et al., 2014).

ABZ clathrate is made of ABZ coated with beta-cyclodextrin and mixed with a fixed amount of extenders, disintegrating agents and a malacia agent. The formulation enhanced the solubility of ABZ and improved its bioavailability in vivo (Ren et al., 2018).

ABZ chitosan microspheres are composed of ABZ and chitosan. ABZ and chitosan were dissolved in dilute acetic acid solution to form the aqueous phase, and a surface-active agent was dissolved in oily liquid to form the oil phase. The volume ratio of the aqueous phase to the oil phase was 1:2–1:8. Then, the aqueous phase was added into the oil phase and stirred to obtain the emulsion. The crosslinking hardener was added to the emulsion and stirred. Then, it was centrifugally separated, washed with petroleum ether and dried after the microspheres were cross-linked and solidified; that is, the ABZ chitosan microspheres were obtained. The drug formulation has a uniform size distribution and high encapsulation efficiency with a simple preparation method. The bioavailability of ABZ chitosan microspheres is 500% of ABZ Tablets in rat, and the time of drug release reaches 48 h in the body, which increases drug exposure (Wang and Peng, 2012).

3.2. The improvement of the ABZ synthesis method

Since 1975 when Gyurik and colleagues published the synthesis method of ABZ (Gyurik and Theodorides, 1975), many synthetic routes have been reported. In 1988, Zhang Changli summarized the ABZ synthetic routes in diagram form (Zhang, 1988). In general, there are four routes for the synthesis of ABZ. The starting materials are 2-nitro-

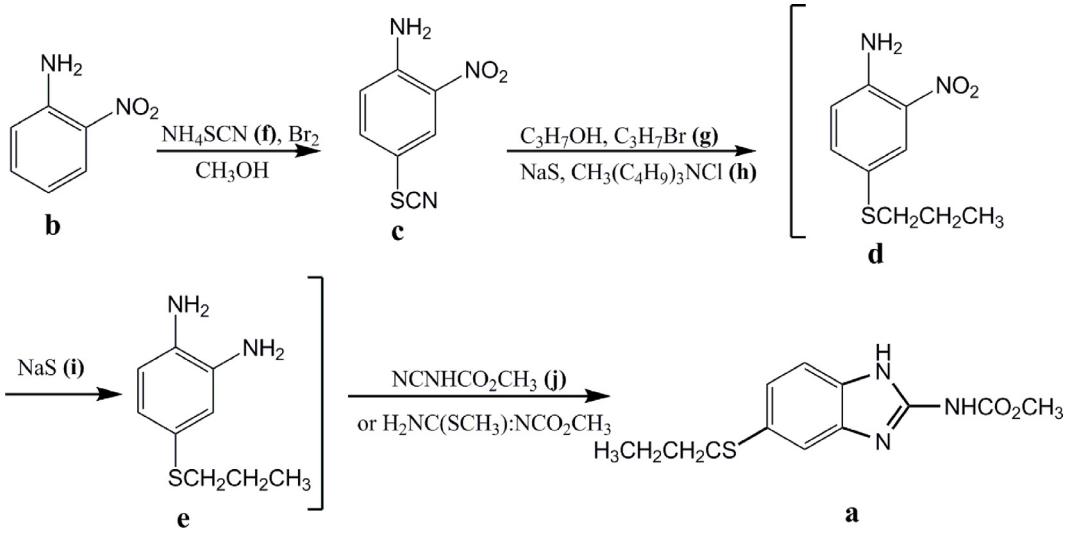

Fig. 2. The "one-pot method" synthesis route of ABZ.

5-chloro-*N*-acetanilide, *o*-nitroaniline, carbendazim and *o*-phenylenediamine. However, the production of API in China is mainly based on the route in the American patent US 4152522. That is, *o*-nitroaniline (**b**) as the starting material reacts with ammonium thiocyanate (**f**) in the presence of bromine or chlorine in low molecular weight alcohol to form 2-nitro-4-thiocyanatoaniline (**c**), followed by a reaction with brominated propane (**g**) in a sodium cyanide solution with methyltributylammonium chloride (**h**) or tetrabutylammonium bromide as the phase transfer catalyst to produce (2-nitro-4-propylthio)aniline (**d**), which is reduced by sodium sulfide (**i**) or sodium sulfhydrate and cyclized with methyl cyanocarbamate (**j**) to generate ABZ (**a**).

The main improvement to the synthesis route in industrial production in China is that (1) in the process of preparing (2-nitro-4-propylthio)aniline, NaS or sodium hydroxide is used instead of sodium cyanide, and (2) the intermediate (2-nitro-4-propylthio)aniline is difficult to separate, and the other intermediate 4-propylthio-*o*-phenylenediamine is not stable, so these two intermediates are not separated from the reaction system, which is called the "one-pot method" synthesis route (Fig. 2).

There are still some problems in the industrialized production route: (1) lot of sodium sulfide and methyl cyanocarbamate used in the synthesis process produce a large amount of waste water, resulting in the problem of environmental pollution; and (2) the impurities of products synthesized by the "one pot method" are difficult to refine. Therefore, various research institutions and pharmaceutical companies have made many explorations on the synthetic method (Liu et al., 2010). The improvement was mainly focused on the selection of reagents or catalysts for the second and third steps of the synthetic route, which aim to be environmentally friendly, improve production rate and optimize product quality. For example, in the condensation reaction, polyethylene glycols (PEGs) were selected as the phase-transfer catalyst, with sodium hydroxide solution instead of sodium cyanide or sodium sulfide solution, and the zinc chloride complex separation method was applied to obtain a complex of 2-nitro- 4-propylthioaniline zinc chloride. Then, compound **d** was obtained by destroying the complex and dissolving zinc chloride with alkali solution. In the reduction step, hydrazine hydrate was used as a reducing agent. In addition, methyl o-methylisourea carboxylate was used as the ring-closing agent in the last step. The total product yield of the route in the patent can reach 64.2%, with advantages such as high purity of product, low production cost, clean and safe industrial process as well as being easy to industrialize. In addition, it has been reported that using carbendazim as the starting material can reduce reaction steps and improve product quality (Zhu, 1990).

3.3. Synthesis route and pharmacodynamic study of ABZSX

Pharmacokinetic studies showed that ABZ was rapidly converted into albendazole sulfoxide (ABZSX) and sulfone (ABZSN) in the liver after being absorbed by the gastrointestinal tract. The content of ABZ is quite low, so it is speculated that the metabolites are the main active component of anti-parasitic activity (Marriner et al., 1986). Rats experimentally infected with *Clonorchis sinensis* metacercaria were treated with ABZ and its metabolites, ABZSX and ABZSN, for 7 consecutive days by gavage at the same dosage of 10 mg/kg per day and sacrificed 7 days post-treatment to observe the effects of the three compounds (Zhou et al., 1994). The average number of worms recovered from the ABZ, ABZSX and ABZSN groups were 0.4 ± 0.7, 0.2 ± 0.4 and 1.8 ± 10.4, respectively. Compared with the control group (14.5 ± 60), the former two had apparent significant differences, but the latter did not. However, all of them inhibited the ovulation of the worm, and the egg reduction rates of the ABZ, ABZSX and ABZSN groups were 92%, 91% and 73.6%, respectively.

Experiments with mice infected with *E. granulosus* have also shown that half the dose of ABZSX can achieve the same effect as ABZ, while no apparent effect of ABZSN was noted in the experimental therapy (Huang and Hu, 1995; Xiao et al., 1990). Therefore, Chinese scientists have explored the synthesis of ABZSX and its derivatives. Patents and papers published the synthetic routes, and a series of derivatives were synthesized and screened (Huang and Hu, 1995; Yuan et al., 2007; Zhu et al., 2008).

4. Antiparasitic action of aminophenamidine compounds and TrBD

Amidantel (*N*-(4-[(1-(dimethylamino)-ethylidene)-amino]-phenyl)-2-methoxyacetamide hydrochloride (BAY d 8815) synthesized by Wollweber in 1979 (Rim et al., 1980; Thomas, 1979; Wollweber et al., 1979), is a typical aminophenamidine (Fig. 3a). In animal experiments, amidantel had significant effects on *Ancylostoma caninum, Uncinaria stenocephala, Toxocara canis, Toxascaris leonina, Nippostrongylus muris, Strongyloides ratti* and *Litomosoides carinii*. The compound had low toxicity and did show teratogenicity or mutagenicity. The results of the clinical trial confirmed that it was very effective against *Ancylostoma duodenale, Necator americanus* and *Ascaris lumbricoides* (Rim et al., 1980).

In 1983, Chinese scientists synthesised amidantel and its derivatives and pursued detailed structure-activity relationship studies. The structure of amidantel was modified by substituting the amide group with

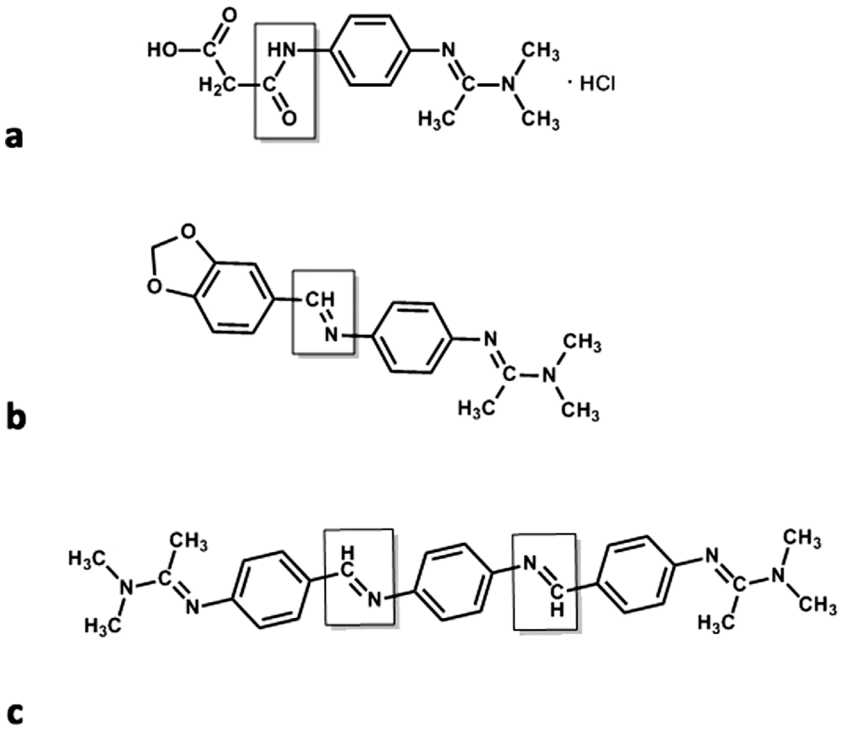

Fig. 3. (a) Amidantel (Bay d 8815), (*N*-4-1-(dimethyl-amino) ethylidene-amino-phenyl-2- methoxy-acetamide hydrochloride); (b) AH 85012, (*N*'-[4-(3,4-dioxomethylene benzylideneamino)phenyl-*N,N*-dimethyl acetamidine; (c) Tribendimidine (TrBD), (*N,N*′-bis[4′-(1-dimethyl amino ethylidene amino)phenyl]-1,4-phenylene-dimethylidyne amine.

the Schiff base group (Fig. 3), and many compounds with better activity against helminths than that of amidantel were found, especially AH85012 (Fig. 3b) (Qin et al., 1993) and TrBD (Fig. 3c) (Yao et al., 1996b). Eventually, TrBD was selected and put into further drug development pipelines. Since it was found to be irritating to the stomach in dogs, the enteric tablet was developed (Yao et al., 1996a).

For some parasitic diseases, TrBD is more effective than ABZ, MBZ and pyrantel. In hamsters infected with *N. americanus* and treated orally with TrBD, the minimum effective dose necessary to cure infection was 150 mg/kg or 50 mg/kg daily for 2 consecutive days. A worm burden reduction of 99.7% was observed when a single oral dose of 100 mg/kg of TrBD was administered to hamsters infected with *N. americanus*. However, when treated with pyrantel, amidantel and MBZ, the minimum effective dosages were 250 mg/kg per day for 2 days, 100 mg/kg per day for 2 days and 500 mg/kg per day for 3 days, respectively. A slightly lower worm burden reduction (i.e., 97.4%) was observed when infected hamsters were given oral ABZ at a single dose of 150 mg/kg (Ren et al., 1987, 1988).

According to the phase II and III clinical comparative observations, the cure rates of the two groups, 300 mg of TrBD or 400 mg of ABZ, on ascariasis were 98.3% (115/117) and 98.9% (91/92), respectively (Xiao et al., 2004, 2005). These results indicated that the efficacy of TrBD against *A. lumbricoides* infections at a single oral dose of 300 mg is similar to that of ABZ at a somewhat higher dose of 400 mg. However, the therapeutic effect of TrBD on hookworm infection was much better than that of ABZ, especially in *N. americanus* infections. TrBD completed phase IV clinical trials in 2004 and was approved by SFDA as an anthelminthic for clinical application for the treatment of ancylostomiasis and ascariasis (Zhang et al., 2008). However, as described in the comprehensive and detailed articles reviewed by Xiao et al. (2005, 2013) the spectrum of antiparasitic TrBD goes far beyond that. TrBD showed potential activities against at least 20 species of human parasites, such as *Amoebotaenia cuneata, A. caninum, A. duodenale*, ***Davainea proglottina, Enterobius vermicularis, N. americanus, N. brasiliensis, Syphacia mesocricetus, Trichuris trichiura, Toxocara canis, Echinostoma caproni, S. ratti, Trichinella spiralis, Hymenolepis microstoma, Ancylostoma ceylanicum, Heligmosomoides bakeri, Opisthorchis viverrin,* and *Clonorchis sinensis.*

However, Moser et al. (2017) presented the first published data on the efficacy of tribendimidine against soil-transmitted helminth infections outside Asia, acquired in the framework of a randomised trial in two countries—Tanzania and Côte d'Ivoire. Against hookworm, Moser suggested their results confirmed the high ERRs of tribendimidine monotherapy reported by studies from China, while cure rates were lower than in previous studies, but in line with findings from Steinmann and colleagues (Steinmann et al., 2008). What we should notice is that, in the clinical trial reported by Xiao et al., the two species of hookworm were specifically identified. Hookworm species-specific diagnoses based on hatching eggs and morphological examination of third-stage larvae (L3) revealed *N. americanus* mono-infections, *A. duodenale* mono-infections and mixed hookworm species infection. The observed cure rate against *N. americanus* mono-infections was considerably higher than that observed against *A. duodenale* (94.9% versus 78.6%) (Xiao et al., 2013), which was consistent with previous experiments in lab (Keiser, 2013 and Ren et al., 1987). In some areas of China, people have undergone long-term mass deworming administration, and all of them were treated with albendazole tablet, which has a good effect on *A. duodenum* and a lower efficacy against *N. americanus*. Therefore, at present, the dominant species of hookworm infection in most areas of China is *N. americanus*, while it used to be *A. duodenale.*

Praziquantel (Embay 8440) is the outstanding member of the class of tetrahydroisoquinolines discovered jointly by E. Merch and Bayer AG, Germany (Seubert et al., 1977). The drug is known for its excellent broad-spectrum anthelminthic activity for trematodes and cestodes in both humans and domestic animals and is especially effective on adult worms in parasitifers (Ali, 2006). In China, praziquantel (PZQ) is the first choice in the treatment of clonorchiasis sinensis, and the recommended treatment regimen is 75–90 mg/kg, 120–150 mg/kg and 150–180 mg/kg of total dosage divided 2 times a day and for two days in accordance with mild, moderate and severe infections of patients, respectively (Yang and Wu, 2004). The large dosage makes it difficult for patients to finish the course of treatment or take the full dose. Therefore, local hospitals often reduce the dose in treatment; it is difficult to obtain the ideal cure rate. A randomized open-label trial was performed in Qiyang, Hunan, China to assess the efficacy and safety of TrBD and MBZ in patients with a co-infection of *Clonorchis sinensis* and

other helminths, with praziquantel (PZQ) at a dose of 75 mg/kg bw as a control (Qian et al., 2013). The results from the first treatment showed that the cure rates of single-dose TrBD and PZQ against *C. sinensis* were 50% and 56.8%, respectively; the single dose of 400 mg TrBD showed similar efficacy against *C. sinensis* as praziquantel at a dose of 75 mg/kg divided into four doses within 2 days with fewer adverse events. In another open-label clinical trial (Xu et al., 2014). single-dose TrBD achieved a cure rate of 44%, whereas cure rates of 58% and 56% were obtained for TrBD and PZQ administered for 3 days, respectively. The follow-up clinical trials in southeast Asia have further confirmed the efficacy of TrBD on *Opisthorchis viverrini* infection (Meister et al., 2019; Sayasone et al., 2018, 2016; Duthaler et al., 2016). Therefore, in the treatment of *clonorchiasis sinensis* and *Opisthorchis viverrini* infection, TrBD should be a promising alternative to praziquantel, especially for those co-infected with *C. sinensis, A. caninum and* other intestinal nematodes.

5. Niclosamide therapy for taeniasis

Although the most widespread use of the niclosamide Yomesan today is as a molluscicide, it has been used for clinical treatment of taeniasis since the early 1960s (Andrews, 1985; Donckaster et al., 1961; Tietze, 1960) and United States began to use this drug for taeniasis in the 1970s (Perera et al., 1970). Imitation niclosamide was also synthesized at the beginning of the 1970s in China and used for cestodiasis and taeniasis (Zhang, 1979).

The trade name of niclosamide is 'Mie Tao Ling', pronounced in PINYIN in China, meaning killing tapeworms quickly, effectively and specifically. The oral dosage is 2 g/day on each of 5–7 successive days and produces a 90% or more cure rate. The tablets should be crushed or chewed before swallowing and can be taken once or two times at an interval of 1 h The dosages for patients with 30 kg body weight (bw) are 1 g daily and 1.5 g for 30–50 kg bw (Xue and Xu, 2002; Yang and Wu, 2004).

When niclosamide was used to expel *Taenia solium*, the dosage described above was lethal to the worm but ineffective against eggs. Therefore, 1–2 h after medication, an appropriate laxative must be administered before the worm body is digested to remove the undigested dead segments from the intestine and avoid the release of hatching eggs that cause cysticercosis. The administration of a laxative before digestion of the worm body is an effective method for determining *Taenia* spp. according to the morphology of the cephalomere, and more importantly, can avoid incomplete anthelminthic treatment (Sun, 1985). Magnesium sulfate is often used clinically as a laxative. However, there are also reports that indicate there is no significant increase in efficacy when magnesium sulfate is used (Xu et al., 1979).

More importantly, niclosamide is considered a safe anti-tapeworm drug because it is only absorbed in the intestine but also has no effect on *Cysticercus cellulosae* (Garcia and Del, 2005), which makes it suitable for administration in patients with brain cysticercosis and ocular cysticercosis.

6. Praziquantel therapy for taeniasis

The medication regimen in the treatment of taeniasis is 10–30 mg/kg praziquantel, followed by taking 0.5 g/kg magnesium sulfate two hours later (Rao and Chen, 1990; Wang and Fang, 2008). Mirabilite is a traditional Chinese medicine that is often used as laxative (Wang and Fang, 2008).

In the early 1980s, imitation praziquantel was successfully produced in China for the treatment of schistosomiasis. Later, the pharmacological efficacy of praziquantel was extensively explored, but it was mostly targeted at schistosomiasis, which is a serious disease that has attracted overwhelming attention from government, parasitologists and medicinal chemists in China. Praziquantel used in clinical treatment is a racemic mixture, i.e., equal amounts of levo-praziquantel (R-PZQ) and dextro-praziquantel (S-PZQ) (Andrews, 1985). After discovering that *R*-praziquantel (levo-praziquantel) was the main active enantiomer, the chemistry and pharmacological action of enantiomers on *Schistosomiasis japonica, Schistosomiasis mansoni*, and *Clonorchis sinensis* were studied (Liu et al., 1986, 1993; Quan et al., 1988; Xiao and Catto, 1989), and the synthesis methods of R-praziquantel were also developed (Yue and Luo, 2013; Zhou, 1988). In particular, the biosynthetic route could avoid the production of large amounts of phosphorus waste liquor and reduce the environmental burden (Qian, 2012).

7. Pumpkin seed and areca combination therapy for taeniasis

Since ancient times, there has been an assortment of effective treatment methods for taeniasis. In classical Chinese traditional medical books, cestode (including Taenia and Bothriocephalus) is called White Worm or Cun White Worm, in which the Cun is a unit of length of approximately 3.33 cm today, maybe smaller length in ancient China. In Chinese classical medical textbooks (described below), the morphology of worms and symptoms of the diseases are described in detail, and the source of infection and methods of prevention are also precisely understood.

Some classical medical books, such as Jin Kui Yao lue (Medical Treasure of Golden Chamber), Zhu Bing Yuan Hou Lun (General Treatise on the Cause and Symptoms of Diseases) and Shen Ji Fang Xuan (General Collection for Holy Relief), documented that Taeniasis was related to eating raw beef, pork and fish. Because of the long history of knowledge of cestodes in traditional Chinese medicine, many effective herbs are present in medical practice, and up to dozens of recorded. A variety of books, including Ben Jing (Herb Classic), Ming Yi Bie Lu (Supplementary Records of Famous Physicians), Qian Jin Yao Fang (Gold Essential Formula for Emergency), Wai Tai Mi Yao Fang (Medical Arcane Essentials from the Imperial Library) and Ben Cao Gang Mu (Compendium of Materia Medica), recorded many anti-cestode medicines. Langya (a type of Rosaceae plant), Omphalia (dried sclerotium of a fungi of Tricholomataceae, *Omphalia lapidescens* Schroet), areca, pomegranate peel, pumpkin seeds, hawthorn, etc. have been confirmed with significant activities against cestodes by experiments in recent years (Zhang, 1998). Among them, the combination of pumpkin seed and areca is most widely used, which comes from the prescription of 'Qu Tao Tang' (Cestode-expelling Decoction). The constituents of 'Qu Tao Tang' (Cestode-expelling Decoction) are very simple, 60–120 g fresh pumpkin seeds and 30–60 g areca. Areca is ground with a pestle, soaked for a few hours in 400 ml of water, decocted to 100 ml, and filtered, and the debris of the decoction are discarded. The treatment procedure consists of two steps: first, chewing up fresh pumpkin seeds or taking the powder form of it ground in advance and then drinking the decoction of areca 2 h later. Worm bodies would be discharged along with diarrhoea 4–5 h later after, and 10 g Xuan Ming Fen (Natrii Sulfas Exsiccatus), the main component is anhydrous sodium sulfate Na_2SO_4 and used as a laxative, mixed with water is taken afterwards.

Feng Lanzhou observed the pharmacological effects of water extract of pumpkin seeds, water extract of betel nuts and a mixed solution of both on cestodes *in vitro* (Feng, 1956). With the water extract of pumpkin seeds, the middle and back segments of *Taenia saginata* became wider and thinner, and the middle of segment became sunken and paralyzed. However, the head and mature segment still moved freely. The effect of betel nut water extract on tapeworms mainly acted in the front part of the worm. The worm was quickly paralyzed from head to tail with a mixture of betel nut and pumpkin seed water extract.

8. Challenges with current helminth control drugs in China

In the World Health Organization's Essential Drugs List, ABZ, MBZ, pyrantel and levamisole are the drugs used to control soil-transmitted

helminth infections, which have been used for more than 30 years (Kobayashi et al., 2006). A single oral dose of ABZ, MBZ and pyrantel had good curative effects on ascaris infection but poor curative effects on whipworm infection (Zheng et al., 2009). The curative rates of a single oral dose of ABZ, MBZ and pyrantel for hookworm infection were 72%, 15% and 31%, respectively, while the curative effect of levamisole on these nematodes was poor or unstable (Keiser and Utzinger, 2008). Therefore, it is necessary to evaluate the efficacy of current drug regimens on a large scale with to the goal of improving treatment regimens. Hookworms are the most harmful soil-transmitted nematodes. In the third national survey of important human parasitic diseases in China, the composition of the population infected with hookworms *A. duodenale, N. americanus* and co-infection with the two species accounted for 14.38%, 77.45% and 8.17%, respectively. The result is different from that in the first and second surveys. Studies have shown that *A. duodenale* is more sensitive to ABZ than *N. americanus*. After repeated deworming treatments over the years, *N. americanus* has become the dominant species. Therefore, the measures and therapeutic schedules for the prevention and control of ancylostomiasis should be adjusted according to the composition of hookworm species to achieve the best therapeutic effect in the future. TrBD has a good effect on both species of hookworm, especially for *N. americanus*. Therefore, it is necessary to promote the application of TrBD in the treatment of intestinal nematode infections.

The pumpkin-betel nut method commonly used in clinical practice for repelling tapeworm in China is cumbersome in site use and has not yet been developed as medicine. The development of compound medicines also has certain difficulties. First, the sources of natural medicines and components of medicinal plants are very complicated, and quality control is difficult to meet SFDA requirements. Second, pumpkin seeds have not yet been included in the Chinese Pharmacopoeia. To develop the compound medicine of pumpkin seeds and arecoline, it is necessary to first develop and declare pumpkin seeds as a new type of TCM and obtain approval from the SFDA.

Parasitic diseases are neglected diseases. The prevention and control of parasitic diseases in our country has been given attention by the government, and great progress has been made. However, the research and development of parasitic drugs in China, including anthelminthic drugs, are at a standstill. Drug treatment is an important link in prevention and control work. In the long run, the lack of follow-up drug support may be detrimental to the further development of parasitic disease prevention and control work. The current commonly used drugs have been used for more than 30 years. Although there are few reports of resistance in the treatment of human parasitic diseases, there have been many reports on resistance in the prevention and treatment of animal parasitic diseases. Because of the low market returns of new drugs for parasitic diseases, the research and development of antiparasitic drugs need the support of special government policies. At the same time, it calls for new research and development mechanisms for drugs of neglected tropical diseases, such as Public-Private Partnerships (PPPs), to promote the research and development (R&D) of drugs for parasitic and other neglected tropical diseases.

In addition to the insufficient investment in the research and development of antiparasitic drugs, few enterprises are willing to engage in the production of such drugs due to the low market returns. For example, according to the Complete Collection of Chinese Pharmaceutical API Enterprises and Products (2014 edition), there are 15 ABZ API manufacturers. But as we have learned, only a few enterprises are actually engaged in the production of ABZ API and the preparations.

On October 8, the General Office of the CPC Central Committee and the General Office of the State Council jointly issued the Opinions on Deepening the Reform of Examination and Approval System to Encourage the Innovation of Drugs and Medical Devices (hereinafter referred to as "Opinions") (http://www.gov.cn/zhengce/content/2015-08/18/content_10101.htm). Currently, SFDA is conducting generic drug consistency evaluation according to the “Opinions” (State Food and Drug Administration, 2016). That is to say, a series of comparative tests should be carried out on quality and efficacy between the approved generic drugs and reference drugs, which is generally the drugs invented and produced by some pharmaceutical company abroad. For example, the quality of praziquantel produced in China must be compared with and consistent with that of the original product, Biltricide and Cesol manufactureed by E. Merck. The consistency evaluation of generic drugs may involve great expense, and antiparasitic drugs with low market returns can hardly arouse the investment willingness of pharmaceutical companies. It is likely that many of the scarce antiparasitic drugs will be abandoned. Therefore, privilege policies and investment from the government are also urgently needed.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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