

## Praziquantel: A Review

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### Abstract

Praziquantel is a synthetic heterocyclic broad-spectrum anthelmintic agent effective against parasitic schistosome species as well as most other trematodes and adult cestodes. This article aims to present a comprehensive overview of studies concerning the drug history, structure, dosage, pharmacokinetics, side effects, toxicity, mechanism of action and resistance of praziquantel.

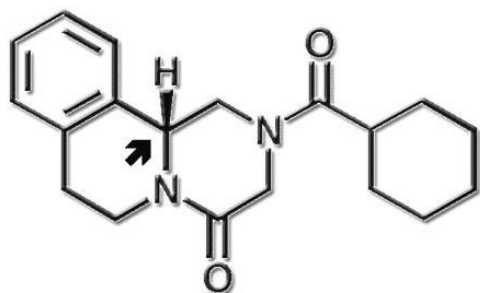
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### Praziquantel (PZQ) History and Structure

Systematic searching for schistosomicidal drugs began in the mid-1920s through the work of Kikuth and his colleagues [1-3]. Antimonials were the only available chemotherapeutic agents for schistosomiasis from the 1920s to the 1960s. Until the 1970's, treatment of schistosomiasis was nearly as dangerous as the disease itself. New drugs are more consistently effective, less toxic and applicable to oral rather than parenteral administration [4]. During the last decades, niridazole was supplanted by metrifonate for the treatment of infection with *S. haematobium* and by oxamniquine for *S. mansoni* but these newer agents have no activity against *S. japonicum* [5]. Praziquantel (PZQ) is a pyrazinoisoquinoline derivative (Figure 1). The drug name's etymology is p(y)razi(ne) chemical component + qu(inoline) chemical component + ant(h)el(mintic). PZQ was initially synthesized by E. Merck, Germany in the 1970s as potential tranquilizer [6]. Shortly, its anthelmintic properties were tested and proved at the laboratories of Bayer A.G., Germany [7,8]. Praziquantel possesses an asymmetric center in position 11b (arrowhead). The commercial preparation is a mixture of equal parts of levo and dextro-isomers. *In vivo* and *in vitro* studies showed that although the two isomers have the same toxicity, only the levo-isomer is responsible for the antischistosomal activity [9-12]. Half the currently-administered pill is hence unnecessary. A progressive step would be the commercial production of the active enantiomer alone which would reduce to half the amount of drug needed to achieve cure, reduce the tablet size, and allow doses to be increased without compromising safety [13]. Praziquantel was developed first for the veterinary market and then for the human market. Its curative efficacy against various plathyhelminths pathogenic to man was confirmed in testing during the 1970s. Early animal studies showed that the drug was about equally effective against *S. mansoni*, *S. haematobium*, *S. japonicum*,

*S. intercalatum* and *S. matthei* [14]. PZQ was first released by Bayer in 1979, after the mandatory toxicological tests and clinical trials had been completed [15]. Early multicentre trials of praziquantel antischistosomal activities have been carried out under the auspices of the World Health Organization using standard protocols. In Zambian children affected by *S. haematobium* there was only one treatment failure in 79 patients [16]. In Brazil, praziquantel cured 25 of 28 patients with *S. mansoni* infection [17], and in the Philippines 60 of 75 people affected by *S. japonicum* [18]. In all the above mentioned studies, cure was defined as complete cessation of excretion of viable eggs. *Schistosoma mekongi*, a virtually untreatable parasitic disease in Laos and other parts of South-east Asia also seemed amenable to treatment with praziquantel [19]. By using the recommended PZQ dosages the cure rates were: 75-85% for *S. haematobium*; 63-85% for *S. mansoni*; 80-90% for *S. japonicum*; 89% for *S. intercalatum* and 60-80% for double infections with *S. mansoni* and *S. haematobium* [20]. PZQ is now considered as the drug of choice for treatment of schistosomes and a major advance in the treatment of most trematode and cestode infections [20-24]. This pharmaceutical product is the first anthelmintic drug to fulfill the World Health Organization's requirements for population-based chemotherapy of a broad range of parasitic infections [25].

In the early 1980s, PZQ was not inexpensive in countries where schistosomiasis and other concerned helminthoses were endemic. In 1983, Korea Institute of Science and Technology and Shin Poong Pharmaceutical Company successfully developed a method for synthesizing praziquantel. The new method differed from the Bayer-E. Merck process in a critical step, adopting a cyclization reaction that used concentrated hydrochloric acid in the last stage of synthesis, while the Bayer-E. Merck method required high pressure catalytic hydrogenation at high temperature. The new method was significantly less expensive, with important implications for production costs. Shin Poong took the opportunity to pursue an aggressive strategy, using its low cost structure to erode the monopoly on praziquantel that Bayer enjoyed in the early 1980s. In 1987, the Egyptian International Pharmaceutical



**Figure 1:** Praziquantel, 2-(cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline-4-one.

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Industries Co. (EIPICO), started formulation of PZQ in Egypt under license from Shin Poong. This was soon followed by other producers in various countries [26]. Today, Korea and China produce much of the raw materials associated with praziquantel, and the cost of production has dropped significantly. A 600 mg tablet that cost \$1 in 1980 now costs just over 7 cents, making the possibility of widespread treatment even more realistic [27]. Several brands and generic formats of PZQ are now on the market, with some products of unclear origin; it is advisable to select reputed production or wholesale companies complying with international quality control procedures [28,29]. In 2001, Sulaiman et al. [30] collected thirty-four praziquantel samples from different manufacturers at the user level in different countries and subjected it to quantitative analysis of the active ingredient, purity, disintegration and dissolution, according to established pharmacopoeia standards. The results were generally quite reassuring, since generic and brand products were equally able to meet such standards. Two of the samples (from a single manufacturer), however, did not contain any praziquantel at all.

### PZQ Dosage

The recommended dose is 40-60 mg/kg body weight, the lower amount being generally used for *S. mansoni* and *S. haematobium*, while the higher dose (generally split into two administrations a few hours apart) is especially recommended for Asian schistosomes (*S. japonicum* and *S. mekongi*) [31]. Besides the high cure rate, praziquantel decreases the worm burden and egg production in those who are not cured. Patients who continue to shed viable eggs should be re-treated with the same dose; the second treatment is usually successful [32].

### PZQ Pharmacokinetics, side effects and toxicity

PZQ is absorbed well; absorption is 75-100% of an oral dose in experimental animals and humans [33]. Measurable amounts appear in the blood as early as 15 min after dosing [34], and peak levels occur after 1-2 h [35]. Co-administration of chloroquine and pre-administration of carbamazepine and phenytoin may reduce the bioavailability of PZQ [36,37]. On the other hand, co-administration of cimetidine and food may increase the bioavailability of PZQ [38,39]. PZQ is metabolized by the liver, and its (inactive) metabolites are excreted in urine and feces. It has been shown that the drug undergoes extensive metabolism by cytochrome P450; therefore, the systemic bioavailability of praziquantel is low and variable despite its almost complete gastrointestinal absorption [40]. Plasma half-life generally ranges between 1 and 3h. Elimination of more than 80% is completed after 24 h [41]. Excretion is predominantly as metabolites and parent drug. In humans about 80% of a dose is excreted in urine. PZQ and its principal metabolites are found in human milk at levels about 25-30% of those in maternal plasma [42].

PZQ has few side effects but no adverse reactions on hepatic, renal, hematopoietic or other body functions. PZQ safety and efficacy have ensured its widespread use. Its side effects are transient observed in 30-60% of patients and disappear within 24 h. The most commonly reported side effects are headache, nausea, anorexia, vomiting, abdominal pain, epigastric pain, diarrhea with or without blood and/or mucus, lassitude, fever, myalgia, dizziness, sleeplessness, sleepiness, and more rarely a skin rash with edema [43-45]. It seems that some of these reactions are likely to be due to dying schistosomes and to the release of their products and/or the host body's response to them. Thus the most severe side effects are encountered mainly in high intensity areas [46].

The toxicity of praziquantel in animals was found to be very low, both in acute and long-term experiments [47]. No genotoxic risks could be demonstrated from various mutagenicity studies in bacterial, yeast,

Drosophila and mammalian systems [48,49]. A review of all possibly skeptical data concluded that the few observations which suggested accumulation of potentially mutagenic metabolites may have been anomalies among a massive amount of evidence indicating PZQ is a safe drug [50]. Although PZQ is presumed to be safe in pregnant and lactating animals, its administration to pregnant women has been avoided in general practice [51]. Recently, after a review of two decades of clinical experience with PZQ and the results of an extensive risk-benefit analysis, it has been recommended that, in areas where schistosomiasis is endemic, all pregnant and lactating women should be considered high-risk and treated with PZQ [52,53].

### PZQ mechanism of action

*In vitro* and *in vivo* studies indicate that, while initially effective, effectiveness against schistosomes decreases until it reaches a minimum at 3-4 weeks post infection. Effectiveness then increases again until it is once again fully effective at 6-7 weeks [54]. Single-sex female infections are largely refractory to treatment and single-sex male infections moderately refractory, in comparison with bisexual infections. The fact that worms from unisexual infections are less sensitive than those from bisexual infections even under *in vitro* conditions, may suggest that the former worms are perhaps intrinsically less developed and possibly less sensitive [55].

Although PZQ-effect on worms is very dramatic, the drug's precise mechanism of action on adult worms is unknown. Most evidence implicates that tegument and muscles of susceptible parasites are targets of the action of praziquantel. Within seconds of exposure to the drug, adult schistosomes exhibit a rapid, sustained contraction of the worm's musculature [56], and vacuolization and disruption of the parasite tegument [57,58], an effect associated with the subsequent exposure of parasite antigens on the surface of the worm [59]. Both of these responses are thought to be linked to a praziquantel-dependent disruption of  $Ca^{2+}$  homeostasis [60,61].

$Ca^{2+}$  is an essential and versatile intracellular messenger. Normally low (submicromolar) levels of  $Ca^{2+}$  within the cytoplasm are interrupted by  $Ca^{2+}$  pulses that trigger  $Ca^{2+}$  dependent responses. Indeed, it can be argued that virtually all reactions in excitable cells are regulated either directly or indirectly by  $Ca^{2+}$  [62]. The effects of praziquantel on  $Ca^{2+}$  homeostasis is most probably due to a direct action of the drug on membrane permeability to  $Ca^{2+}$ . Early studies indicated that praziquantel is not acting as a  $Ca^{2+}$  ionophore [63]. On the other hand, it has been reported that praziquantel alters the structure of membrane bilayer phospholipids or membrane fluidity [64,65], which could result in changes in membrane permeability to  $Ca^{2+}$  or to indirect effects on membrane receptors and channels. Voltage-gated  $Ca^{2+}$  channels have been identified as candidate targets of praziquantel action.  $Ca^{2+}$  channels consist of a main pore-forming  $\alpha_1$  subunit that is modulated by auxiliary subunits such as  $\beta$  and  $\alpha_2\delta$ . When co-expressed with  $\alpha_1$  subunits,  $\beta$  subunits increase the gated current and exert dramatic effects on the biophysical properties of the channel. Schistosomes express two  $Ca^{2+}$  channel  $\beta$  subunit subtypes: a conventional subtype similar to  $\beta$  subunits found in other vertebrates and invertebrates; and a novel variant subtype with unusual structural and functional properties. The variant schistosome  $\beta$  subunit confers praziquantel sensitivity to an otherwise praziquantel-insensitive mammalian  $Ca^{2+}$  channel, implicating it as a mediator of praziquantel action. This may indicate that the variant  $Ca^{2+}$  channel  $\beta$  subunits that are unique to platyhelminths play an essential role in PZQ action [66-69]. However, schistosome isolates with reported reduction in praziquantel sensitivity

did not exhibit changes in primary structure of schistosome  $\beta$  subunits, nor did they show changes in expression levels of those subunits [70]. Thus, a reduction in praziquantel susceptibility in these strains apparently does not depend on altered structures or expression levels in the  $\text{Ca}^{2+}$  channel  $\beta$  subunits. It seems that there are many unanswered questions regarding schistosome  $\text{Ca}^{2+}$  channels and their role in praziquantel action.

As mentioned above, PZQ also induces alterations of parasite's muscle physiology/biochemistry. Worms exposed *in vitro* to  $1\mu\text{M}$  PZQ show almost an instantaneous and sustained contraction with a half-maximal effect time of 12 sec. This contraction results in paralysis of the parasite leading to the hepatic shift observed *in vivo* which is 95% complete within 5 min after a single oral dose for infected mice [57,58].

Also, PZQ induces an almost instantaneous vacuolization of the tegument of the susceptible parasites. The vacuolization occurs at the base of the syncytial layer. Vacuoles increase in size, protrude above the surface resulting in a final bursting of the blebs [71]. *In vivo* studies indicated that the degree of PZQ-induced damage was related to both the sex of the worms and to the developmental status of each individual worm. Male worms exhibited more extensive and longer lasting surface damage than females [59,72]. However, the level and extent of the changes increased as the worms became more developmentally advanced with adult worms showing extensive damage to the tegument and vacuolization and disruption of the subtegumental tissues. The possible correlation between the stage-dependent changes in susceptibility to praziquantel and age-related changes depend particularly in the phospholipid composition of the outer tegumental membrane [72]. The observed vacuolization of the parasite's tegument alone is not lethal; the immune mechanisms of the host may be responsible for the lethal effects [73]. These morphological alterations accompanied by an increased exposure of schistosome antigens at the parasite surface render it susceptible to the host immune system [59]. It seems that PZQ and the immune system work in synergy to eliminate schistosomes. Some of the drug exposed antigens have been identified and appear to be connected with the host immune response that is required for the complete activity of praziquantel [71,74,75]. It has been reported that PZQ treatment can have an immunizing effect by accelerating the development of the naturally acquired immune response toward whole parasite antigens [76]. Also, PZQ may induce anti-fecundity immunity in case of re-infection [77]. It was observed that in B cell-deficient mice the schistosomicide effect of PZQ is strongly reduced or completely abolished. The drug efficacy was completely restored by passive transfer of immune serum obtained from *S. mansoni* infected donor mice at the acute phase [78]. In immunologically intact mice, the efficacy of PZQ can be enhanced by the passive transfer of sera from rabbits immunized with *S. mansoni* adult worm antigens [79], or by vaccination with a preparation of worm membrane antigens [80]. This mechanism would result in enhanced killing of the worms through antibody-dependent cellular reactions [61]. Also, mice with severe T cell immunodeficiencies do not clear their schistosome infections when treated with praziquantel [81]. In contrast to the experimental studies, praziquantel was just as effective a treatment for schistosomiasis patients with HIV-1, even those with decreased CD4+ T cell counts, as it was for HIV-1 negative schistosomiasis patients [82,83]. Part of this may be due to the likelihood that infection with schistosomes preceded infection with HIV-1, based on the age prevalence curve for both pathogens. As a result, the antischistosome antibody responses critical for praziquantel efficacy may have developed prior to depletion of CD4+ T cell help that may be necessary for antibody production. Sera from both HIV-1 positive and negative schistosomiasis patients contained antibody

reactivities to antigens that have been proposed as important targets for praziquantel efficacy [84]. Severe undernutrition imposes a drop on the proliferative response of human stimulated lymphocytes [85], numbers of T CD4+ and T CD8+ cells are significantly reduced [86]. In murine hosts it was found that protein deficiency impairs the schistosomicidal action of PZQ [87], a similar effect may be found in humans.

Secondary effects of PZQ are inhibition of glucose uptake, lowering of glycogen levels and stimulation of lactate release [88,89].

Glutathione S-transferase (GST) isoenzymes appear to play a central role in the parasite detoxification system. Because the three-dimensional structure of GST has a "pocket" in which the molecule of the drug could fit, it has been suggested as a receptor for PZQ [90]. However, PZQ failure to affect the activity of GST is strong evidence against this hypothesis [91].

### PZQ Resistance

*Resistance* may be defined as an acquired reduction in drug sensitivity following therapy with the drug in question. *Tolerance* is an innate insusceptibility to a drug to which the population has not previously been exposed. Both resistance and tolerance are assumed to be genetically inherited [92]. There is a common supposition that *S. mansoni* has a capacity to develop resistance to therapeutic doses of a determined drug, especially when the parasitic population is under continuous pressure from schistosomicides [93,94]. Early low-level resistance will be difficult to detect, after which the typically rapid shift from 10% to 90% resistance will come as a surprise to many practitioners [95]. Because the drug treatment does select for drug-resistant worms [96], it is suggested that the major factor in avoiding the development of such resistance is the percentage of worms that do not encounter the anthelmintics, *i.e.* worms in refugia; these drug-sensitive parasites are the most important component of maintenance of a worm population that will remain susceptible to dewormers because it provides a pool of genes to dilute the resistant genes [97].

In the 1970s and early 1980s, the drug hycanthonone was used as population-based treatment for *S. mansoni*. Experimental studies in animals indicated that 10-20% of worms survived therapy, and it was found that the progeny of these survivors were resistant to hycanthonone [45]. Resistance could also be induced by exposure of the 27- to 29-day-old parasite to hycanthonone, when schistosomes are developmentally insusceptible to the anthelmintic [98]. This procedure leads to drug resistance in subsequent generations in the developmentally drug-susceptible adult parasite [99]. The remarkable feature of hycanthonone resistance is that it occurred within a single generation and thus did not appear to be the result of selection by the drug, because all of the progeny of the schistosomes exposed to hycanthonone exhibited resistance and because no drug pressure was applied to the drug-sensitive stages of these parasites. After exposing immature *S. mansoni* in mice to hycanthonone, within a single generation, genomic rearrangements, detected as rRNA-encoding DNA restriction fragment length polymorphisms (RFLPs), accompanied the appearance of resistance in this model [100]. It was indicated that the resistance trait was heritable, autosomal recessive, inducible by drug exposure, and not intrinsic [101-103]. Hycanthonone and oxamniquine belong to the group of aminoalkyltoluenes, their mode of action is related to an anticholinergic effect which increases the parasite's motility [104,105]. Like praziquantel, the immune effector mechanisms can enhance the antischistosomal activity of hycanthonone and oxamniquine [74]. Also, hycanthonone and oxamniquine mechanism of action is related to inhibition of nucleic acids synthesis [106,107]. In the *S. mansoni* strains resistant to hycanthonone or oxamniquine,

the synthesis inhibition of nucleic acids after treatment is reversible, while in susceptible strains the inhibition is irreversible. The genetic mechanism linked to the acquisition of resistance against *S. mansoni* is probably due to a lack of a bioactivation process, perhaps owing to a specific enzyme that promotes the schistosomicide effect of the drug. There is probably one single autosomal recessive gene responsible for resistance against hycanthon and oxamniquine [101,102]. Cioli et al. [101] showed evidence that the related gene could be responsible for production of specific sulphotransferase that may be the drug activating enzyme. This may explain the findings of cross resistance related to those drugs in strains that have been initially isolated as resistant to only one of those two mentioned drugs [108]. *Schistosoma mansoni* isolates resistant to hycanthon/oxamniquine are susceptible to praziquantel [109]. Hycanthon was ultimately withdrawn for safety reasons before resistance became a clinically significant issue, but concern remained over the relative ease with which resistance occurred [95]. Oxamniquine is still in use mostly in Brazil, although it has been reported that human strains of *S. mansoni* have altered their susceptibility to the drug [110-113]. PZQ has been in use for more than 25 years [114], and concern is increasing that resistance has emerged in human schistosomes [13,92,103,115,116]. PZQ resistant strains of *S. mansoni* have been reported in Egypt [117-121], Senegal [122,123], and even in Brazil, where it is rarely used [113,124,125]. Yue et al. [126] failed to induce drug resistance in *S.japonicum* after exposure of infected mice to PZQ for several generations.

Fallon and Doenhoff succeeded to induce PZQ resistance in *S. mansoni* and demonstrated that *S. mansoni* subjected to drug pressure may develop resistance to schistosomicidal drugs over the course of relatively few passages [127]. Liang et al. [128] confirmed these results. Ismail et al. [117] used isolates of *S. mansoni* originally showing marked diminished susceptibility to PZQ, passaged them in mice and treated them with sub-curative doses of PZQ. The results showed that repeated passage of *S. mansoni* isolates in the laboratory did not render them more susceptible to PZQ [121]. Indeed, these resistant isolates showed less susceptibility to the drug than before, or at least they retained their original level of insusceptibility to PZQ. William et al. [129] tested the stability of six *S. mansoni* isolates derived from human infections not cured by three successive doses of PZQ and produced infections in mice that were significantly more difficult to cure than infections with control worms. They reported that only three of the six isolates retained their decreased response to praziquantel after multiple passages through the life-cycle in the absence of therapeutic pressure. They concluded that the stability of some of the isolates and the reversion of others indicates that the biological or genetic factors conferring decreased praziquantel response vary among the isolates [129]. In Egypt, there has been a striking change in the geographic distribution of the two species of *Schistosoma* (*S. haematobium* and *S. mansoni*) and their snail vectors since the construction of the High Dam at Aswan in 1968 [130-133]. This change was believed to be caused by less silt and variability in velocity and volume of water flow since construction of the dam, and has resulted in an increase in *S. mansoni* and concomitant decrease in *S. haematobium* prevalence [133]. As mentioned above, in 1987 formulation of PZQ in Egypt under a licensing agreement from Shin Poong was started. Before 1987, PZQ was being produced in Egypt under license from Bayer, but sold at a very high price. Shin Poong's licensee competition with Bayer's licensee in Egypt contributed to major reductions in the private market price for PZQ [26]. From 1988 onward, Egypt's Ministry of Health began providing praziquantel free of charge in its national schistosomiasis control program. Egypt adopted a strategy of population-based selective chemotherapy, with praziquantel

provided only to infected persons, based on the results of individual diagnosis, and also provided for free [26,134]. Control of schistosomiasis in Egypt was the goal of an ambitious ten year program coordinated by the Egypt's Ministry of Health and the U.S. Agency for International Development, concluded in 1998 [135]. It is well documented that during the USAID/Government of Egypt's schistosomiasis research project (SRP), over a 10 year period, the Egyptian Ministry of Health and Population dispensed almost 30 million doses of PZQ [133]. Heavy use of PZQ continues to this day as it remains the drug of choice for treatment of schistosomiasis [136]. Therefore, if PZQ-resistance were to emerge, Egypt would be a likely place. Ismail et al. [117] reported that during a survey in some villages of the Nile Delta some cases remained infected in spite of the praziquantel three treatment regimens [118,119]. Several factors may be responsible for such result. Some of the infections resisted chemotherapy because of host factors, while others are attributable to the worms themselves. Pharmacokinetic parameters were the same in patients treated successfully after a single dose versus those not treated successfully following two or three doses, thus eliminating the possibility that poor cure rates among infected villagers was due to a decrease in PZQ bioavailability [119]. The *in vitro* action of the drug on schistosomes was related to its *in vivo* action confirming that these isolates were PZQ-resistant strains [120,137,138]. Interestingly, some of these PZQ-resistant isolates maintained in the laboratory for years reverted to a PZQ-sensitive phenotype when they were passaged in mice in the absence of PZQ pressure [129]. Moreover, after one decade of the first report of PZQ resistance in the Nile Delta [119,120], the same villages were investigated for the current sensitivity of *S. mansoni* infection to PZQ after 10 years of therapeutic pressure, testing the hypothesis that the number of drug failures would have increased as continued drug pressure selected for worms with diminished sensitivity to PZQ. The data showed that there has not been an increase of drug failure [139].

The construction of the Diama dam on the Senegal river basin in 1985, the Manantali dam in 1989 on the Bafing river, Mali and the resulting ecological changes have led to a massive outbreak of *Schistosoma mansoni* in Northern Senegal, associated with high intensity of infections, due to intense transmission [140,141]. When PZQ was used in an attempt to control the disease it gave cure rates of only 18-39% [122,123]. This may be explained by the presence of pre-treatment high intensity of infection, high probability of immature parasites and rapid reinfection [142,143]. However, antigen detection results after treatment confirmed that in most patients adult worms did persist after treatment [123]. Also, oxamniquine was found to be as effective as normal in the same population [144], and schistosome isolates obtained from naturally infected snails proved to have a decreased susceptibility to praziquantel in the laboratory [139,145,146]. However, still some investigators believe that laboratory tests have not provided convincing evidence for the presence or absence of a praziquantel resistant schistosome strain in Senegal, and that the observed low cure rates are largely the result of the specific epidemiological situation [143].

The reality of reports concerning PZQ-resistance is hard to establish because it is often difficult to distinguish between host factors and parasite factors when patients are not cured of schistosomiasis with normally effective doses. As regards the host factors, since the host immune system plays an active role in the process of killing PZQ damaged worms, normal parasites might survive treatment in immunocompromised hosts. Also, variability of host PZQ metabolism can also cause variability of efficacy [120]. Concerning the parasite factors, therapeutic failure may be attributed to the development of drug resistance by the worms or to early post treatment re-infection

[125,147]. Moreover, in areas of high transmission, the therapeutic failure may result when an infected host is treated sometime after being re-infected, because of the presence of migrating immature forms of the parasite which are experimentally proven to be PZQ-resistant [98,148,149]. Generally, a lack of standardized methods and reference material hamper *in vivo* and certainly *in vitro* detection of resistance in human helminths [29]. Up to now it is not possible to identify genetic resistance markers using reliable molecular techniques [125,150]. Therefore experimental *in vivo* chemotherapeutic research is indispensable in evaluating the susceptibility to schistomocides [113].

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