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The Use of Brazilian Medicinal Plants to Combat *Schistosoma mansoni*

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1. Introduction

Human schistosomiasis, which is caused by trematodes of the genus *Schistosoma*, is considered one of the most prevalent and debilitating neglected diseases in tropical and subtropical areas, being endemic to approximately 76 countries and territories and affecting more than 207 million people worldwide. About 800 million people live in infection risk areas and 280,000 die every year due to this disease (Engels et al., 2002, Steinmann et al., 2006).

There are six main species of *Schistosoma* that can infect humans: *S. mansoni*, *S. hematobium*, *S. japonicum*, *S. intercalatum*, *S. mekongi* and *S. malayensis*. Among these, only *S. mansoni* is found in Brazil.

S. mansoni schistosomiasis was probably brought to Brazil by the Atlantic slave trade. Afterwards, migration flows spread the disease from the shore to the interior of the country, including areas containing its intermediate hosts, planorbides of the genus *Biomphalaria* (Paraense, 1986, Coura & Amaral, 2004). According to Paraense (1966, 1981), ten species and one subspecies of *Biomphalaria* can be found in the country, three of them being natural intermediate hosts (*B. glabrata*, *B. tenagophila*, *B. straminea*) and two having already been experimentally infected (*B. amazonica* and *B. peregrina*).

The life cycle of *S. mansoni* consists of an asexual reproduction stage in the intermediate hosts and a sexual reproduction stage in the definite ones. Under favourable conditions, it lasts 80 days (Katz & Almeida, 2003, Ministério da Saúde, 2005).

Nowadays, there are 25 million people living in endemic areas in Brazil, and 4 to 6 million are infected. It is the most affected country in the Americas (Lambertucci, 2010, World Health Organization [WHO], 2010). According to data provided by Brazil's Ministry of Health, there are cases of the disease in 19 states, from Rio Grande do Norte to Bahia and in the interior of Espírito Santo and Minas Gerais (Ministério da Saúde, 2005). Figure 1 shows the distribution of *S. mansoni* schistosomiasis in Brazil.

A major problem in countries where schistosomiasis is endemic is the control of the disease. In this regard, isolated or combined measures could be taken, such as the control of the intermediate hosts using molluscicides, improvement of basic sanitation and water supply conditions, sanitary education of exposed populations, individual or mass treatment in

high-prevalence areas, individual protection against the penetration of cercariae, and development of a vaccine (Coura & Amaral 2004).

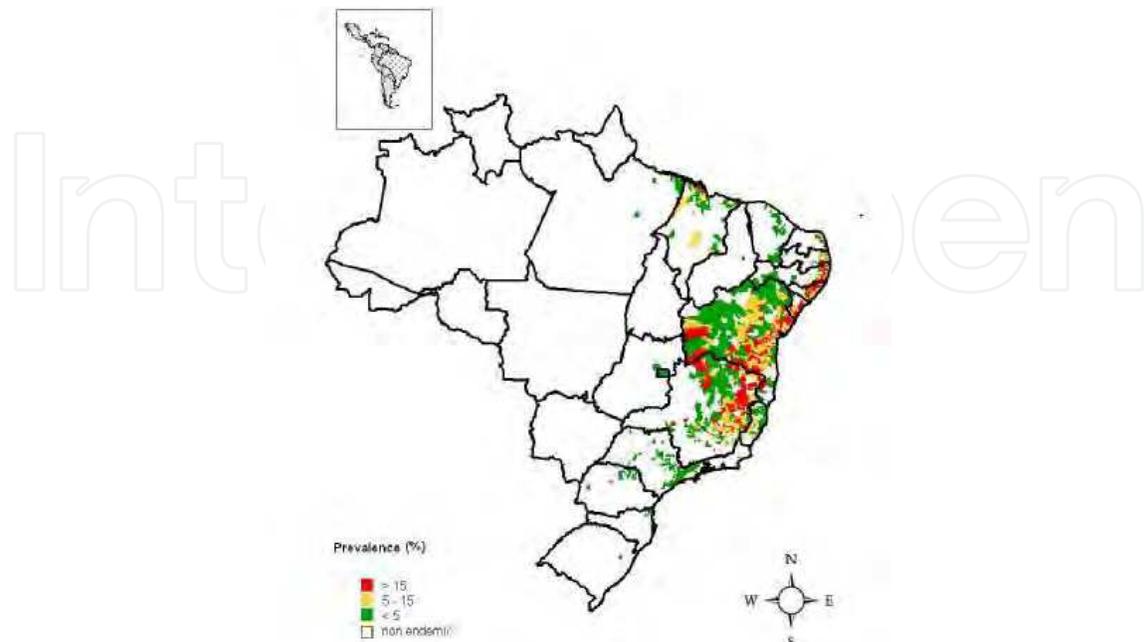


Fig. 1. Distribution of *S. mansoni* schistosomiasis in Brazil. Source: Ministério da Saúde (2005).

However, such control measures have many drawbacks: the wide dissemination of the intermediate hosts, their defence mechanisms against molluscicides, as well as the high costs and low efficiency of that sort of control, the high costs associated with the implementation of adequate sanitary and water supply conditions and the intense contact of rural population with contaminated fresh water, the long time needed for sanitary education, individual or mass treatments can be effective in reducing the morbidity, but they do not prevent reinfections, and patients can develop tolerance and resistance to them, individual protection is unlikely, except for specific groups of exposed people, finally, at the present moment there is no effective vaccine in the treatment for schistosomiasis (Coura & Amaral, 2004).

Despite the fact that the distribution of schistosomiasis has changed along the time, the number of infected people or people at risk of infection has not changed. Not even the efforts carried out for more than a century to control schistosomiasis by means of schistosomicidal drugs have prevented it from being one of the most prevalent diseases in the world (King, 2009). Albeit all the research conducted so far, there are no effective vaccines against parasitic diseases. Therefore, medication treatment is still the most efficient method (Date *et al.*, 2007).

The treatment for *S. mansoni* schistosomiasis is based on the use of praziquantel, a low-cost anthelmintic highly effective against all *Schistosoma* species that may cause infection in humans. Despite its benefits, some deficiencies have been reported. As a result, it is necessary to develop new effective schistosomicidal drugs.

Regarding *S. mansoni* schistosomiasis, the World Health Organisation (WHO) points out the need for permanent research on the development of a vaccine (WHO, 1998). Furthermore, current drugs need to be improved, or new ones should be developed. Nevertheless, the

cost for developing safe and effective drugs is extremely high, which leads to a dim perspective on the introduction of new schistosomicides (Cioli et al., 1995). As a result, research with medicinal plants constitutes a very viable alternative.

In this scenario, several studies and researches on natural bioactive products extracted from plants and used against schistosomiasis have been carried out in the search for a new medicine that can replace praziquantel or complement it (Xiao & Catto, 1989, Molgaard et al., 2001, Mahmoud et al., 2002, Mohamed et al., 2005, Shaohong et al., 2005, Penido et al., 2008, Moraes et al., 2010).

Taking into account the great variety of plants that haven't yet been therapeutically studied to combat *S. mansoni* schistosomiasis, in recent years our research group started a multidisciplinary project to perform *in vitro* screening of extracts from native and exotic plants commonly cultivated in Brazil.

2. Chemotherapy against schistosomiasis

It is believed that the use of chemotherapy against schistosomiasis started with Christopherson (1918), who reported a successful treatment for the urinary form of the disease (caused by *S. haematobium*) with tartar emetic. After that, several other antimony compounds were introduced for clinical use (Cioli et al., 1995, Parise-Filho & Silveira, 2001), and they were the most used medicines until the Second World War (Brindley, 1994). However, despite having been the basis of the treatment for schistosomiasis for around 50 years and having been effective against *S. mansoni*, *S. haematobium* and *S. japonicum*, the clinical use of antimony compounds was suspended on account of their severe side and toxic effects and patients' low tolerance to them (Cunha, 1982, Cioli et al., 1995, Silva, 1997, Cioli, 1998, Novaes et al., 1999).

Before antimony compounds fell into disuse, researches carried out in the 1920's showed activity of emetine and 2,3-dehydroemetine, which were used in the treatment for amoebiasis, against *S. japonicum*. Although emetine has shown a relatively good efficiency, the concentrations needed for activity against *S. japonicum* were two times higher than the required in the treatment for amoebiasis, reaching the toxicity limit. On the other hand, 2,3-dehydroemetine, in spite of being less toxic and having light side effects in comparison with emetine, fell into disuse because of its complicated administration (Blanc & Nosny, 1968, Cioli et al., 1995).

After the Second World War, new drugs were produced, and they were less toxic, more active, free from metals and orally administered (Cunha, 1982, Cioli et al., 1995). Lucanthone (1-[[2-(diethylamino)ethyl]amino]-4-methyl-9H-thioxanthen-9-one), or Miracil D, described for the first time in 1932, was the first orally administered schistosomicidal drug introduced in medical practice, being effective against both *S. mansoni* and *S. haematobium*. Its side effects were usually limited to nausea and vomiting, but severe effects on the heart and central nervous system were later reported (Kikuth & Gonnert, 1948).

In 1955, an organophosphate insecticide (2,2,2-trichloro-1-hydroxyethyl dimethyl phosphonate) was introduced under the general name trichlorphon (Lorenz et al., 1955), later changed to metrifonate. Then, in 1962, the possibility of extending its use to helminths came into consideration, and preliminary studies in humans provided evidence of therapeutic activity against schistosomiasis, ancylostomiasis, ascariasis, trichuriasis and onchocerciasis (Cerf et al., 1962, Davis & Bailey, 1969, Salazar et al., 1969). However, this compound has only proven effective in the treatment for urinary schistosomiasis (Jewsbury

et al., 1977). Therefore, at the present day metrifonate (Bilarcil) is still used in such treatment, but it has to be administered in three doses, and that is its main drawback (Korte et al., 1986, WHO, 1993, Cioli et al., 1995, Berge et al., 2011).

At the beginning of the 1960's, it was reported that a broad-spectrum antimicrobial called nitrofurantoin, along its derivatives, had shown schistosomicide activity, more specifically, anti-*S. japonicum* effect. Nonetheless, its suboptimal activity, high toxicity, and carcinogenic and mutagenic effects led to its use being stopped, and the same happened to its derivatives, some of which didn't even come to be used in the treatment for human schistosomiasis (Werbel, 1970, Robinson et al., 1970, Hulbert et al., 1973).

A very important moment in the therapeutics of schistosomiasis came after the introduction of niridazole (1-(5-nitro-2-thiazolyl)imidazolidin-2-one) in 1964 (Lambert & Stauffer, 1964) and hycanthone (1-N-b-diethyl-amino-ethyl-amino-4-(hydroxymethyl)-9-thioxanthone) in 1965 (Rosi et al., 1965). Niridazole (Ambilhar) showed low activity against *S. japonicum*, moderate activity against *S. mansoni* and very high activity against *S. haematobium*, whereas hycanthone (Etrenol), the main metabolite of lucanthone, proved effective against *S. mansoni*, *S. haematobium* and *S. rodhaini*. However, these drugs had some issues, such as the number of doses and various severe side effects (high toxicity in the central nervous system, kidneys and liver, in addition to mutagenic, carcinogenic and teratogenic effects). Furthermore, they were not considered safe enough for being used in large scale in endemic regions. Consequently, they were no longer used in the medication therapy of schistosomiasis (Fontanilles, 1969, Cioli et al., 1995).

At the end of the 1960's, a series of 2-aminomethyl-tetra-hydroquinoline derivatives with schistosomicidal activity were described, the most promising being 2-N-isopropylaminomethyl-7-nitro-1,2,3,4-tetrahydroquinoline, named UK-3883. The hydroxylation of the 6-methyl group by *Aspergillus sclerotiorum* generated UK-4271, later called oxamniquine (Mansil/Vansil) and described for the first time by Richards and Foster in 1969 (Cioli et al., 1993, 1995).

Preclinical assays showed the schistosomicide potential of oxamniquine against *S. mansoni*, especially males (Foster & Cheetham, 1973).

Clinical assays carried out in Brazil with an orally administered single dose of 15 to 20 mg/kg have shown cure rates up to 90%, as well as good tolerance by patients. These results allowed oxamniquine to be extensively used, and it was included in Brazilian programmes for the control of *S. mansoni* schistosomiasis (Almeida-Machado, 1982, Foster, 1987, Cioli et al., 1993).

Further studies indicated some disadvantages in the use of oxamniquine, though. Since this drug has no cell specificity, which results in undesired peripheral toxicity, there are some side effects on the central nervous system (Davis, 1993, Soyez et al., 1996). It was also observed that oxamniquine showed low activity in the period between the 3rd and the 9th week of infection, which coincided with the egg production stage (Jordan et al., 1993, Frézard & Melo, 1997). Moreover, there were reports of patients infected with *S. mansoni* who were resistant to the treatment (Cioli et al., 1992).

At the beginning of the 1970's, pyrazinoisoquinoline derivatives were tested as antiparasitic drugs (Andrews, 1981). After many compounds were synthesised, 2-cyclohexylcarbonyl-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline-4-one, first called EMBAY-8440 and then praziquantel (Biltricide/Cysticide/Cesol/Distocid/Pyquiton), was considered the most promising (Cioli et al., 1995). Discovered in 1975 (Andrews et al., 1983, Day et al.,

1992), this drug was initially used against cestodes and limited to veterinary cases (Thomas & Gonnert, 1975).

The first studies with animals infected with *Schistosoma* sp. were performed in 1977, when schistosomicidal activity was detected (Gonnert & Andrews, 1977) and attention was drawn to the large variety of possibilities offered by worms of that genus. Further studies reported activity of praziquantel against *S. haematobium*, *S. japonicum*, *S. intercalatum* and *S. matheei*, other species of trematodes (*Opisthorchis sinensis*, *O. viverrini*, *Paragonimus* spp., *Fasciolopsis buski*, *Heterophyes heterophyes* and *Metagonimus yokogawai*) and cestodes (*Taenia solium*, *T. saginata*, *Hymenolepis nana*, *H. diminuta*, *Diphyllobotrium latum* and *D. pacificum*) (Webbe & James, 1977, Wegner, 1984, Bouree, 1991, Utzinger et al., 2003, Shuhua, 2005, Jeziorski & Greenberg, 2006, Shaohong et al., 2005).

Preclinical assays have also proven the efficiency of praziquantel in the treatment for 5-6-week infections, but failures were reported in cases of 1 to 5-week infections (Gonnert & Andrews, 1977, Webbe, 1977, Xiao et al., 1985, Sabah et al., 1986).

The first clinical studies took place in 1978 in cooperation with WHO, in endemic regions for *S. mansoni*, *S. haematobium*, *S. japonicum* and *S. intercalatum* (Katz et al., 1979, Davis et al., 1979, Ishizaki et al., 1979). In 1984, cure rates of 75% to 85% were reported for *S. haematobium*, 63% to 85% for *S. mansoni*, 80% to 90% for *S. japonicum*, 89% for *S. intercalatum*, and 60% to 80% for simultaneous infections with *S. mansoni* and *S. haematobium* (Wegner, 1984). It was also found out that praziquantel was well tolerated by patients of all ages with different clinical forms of schistosomiasis (Frohberg, 1984, Bassily et al., 1985), having light side effects on them (Cioli et al., 1995). Other studies indicated low toxicity and no mutagenic risks (Frohberg, 1984, Kramers et al., 1991).

Those screenings clearly established praziquantel as the drug of choice in the treatment for schistosomiasis (Cioli & Pica-Mattocchia, 2002). In addition, it was the first anthelmintic to fulfil the requirements of WHO (Silva et al., 2005).

After the development of praziquantel, there was little progress in the therapeutics of *S. mansoni* schistosomiasis.

In 1976, Striebel described the use of amoscanate (4-isothiocyanato-4'-nitrodiphenylamine) against helminthic diseases. At that time its wide activity range was confirmed, as it was used against most *Schistosoma* species, filariae and gastrointestinal nematodes (Bueding et al., 1976). Amoscanate was tested in humans infected with *S. japonicum*, and the cure rates were as high as 92%. However, this drug fell into disuse in view of hepatotoxicity (Hubei Nithiocyaninam Coodination Research Group, 1980, Cioli et al., 1995).

Also in 1976, a dithiolethione derivative called oltipraz (Barrau et al., 1977), active against *S. mansoni*, *S. intercalatum* and *S. haematobium* (Leroy et al., 1978, Gentilini et al., 1980, Katz et al., 1984), was synthesised. Preclinical assays confirmed the elimination of *S. mansoni* (Bueding et al., 1982), and clinical assays showed cure rates between 80% and 95% for this species. Photo-onycholysis was the most severe side effect observed, leading to the suspension of the drug in 1984 (Cioli et al., 1995).

Still in 1976, Nelson and Pellegrino (1976) described the schistosomicidal activity of alkylaminoalkanethio-sulfuric acids for the first time. Preclinical assays with *S. mansoni* provided evidence of preferential activity against adult females (Penido et al., 1999), but so far no clinical assays have been carried out.

In 1978, screening of benzodiazepine derivatives showed that some of the compounds of this group have strong schistosomicidal activity, in particular (+)-5-(*o*-chlorophenyl)-1,3-dihydro-3-methyl-7-nitro-2H-1,4-benzodiazepine-2-one, which was named Ro 11-3128

(Stohler, 1978). Preclinical studies proved it to be effective against *S. mansoni* and *S. haematobium* (Brickle & Andrews, 1995) and clinical studies confirmed its schistosomicidal activity, but some side effects, including strong sedative effect, have discouraged its development (Pax et al., 1978, Baard et al., 1979).

In the 1980's, derivatives of artemisinin (which is extracted from *Artemisia annua*) were used as anti-*Schistosoma* sp. for the first time by the Chinese, who demonstrated that the administration of this compound in animals experimentally infected with *S. japonicum* reduced their worm burden (Chen et al., 1980).

Such derivatives, which include arteether, artemisone and artelinic acid, among others, have been extensively used in the control of malaria. They are generically known as artemisinins and were developed in the 1970's (Krishna et al., 2008).

In 1982, it was shown that larval stages of *S. japonicum* were susceptible to artemisinins (Le et al., 1982). Further studies confirmed the schistosomicidal activity of both artesunate and artemether, the latter reaching cure rates of 99% (Le et al., 1983, Le et al., 1982). In 1984, such derivatives were proved effective against juvenile stages of *Schistosoma* sp., when treatments carried out with praziquantel fail, thus both artemether and artesunate are potential prophylactic drugs for schistosomiasis (Yue et al., 1984, Lu et al., 2010). Other studies extended the activity of artemisinin derivatives to other *Schistosoma* sp. that infect humans. In particular, assays carried out in Brazil in 1991 showed reduction of parasite burden in mice infected with *S. mansoni* and treated with artemether (Araújo et al., 1991). Since then, outstanding progress has been made in the study of anti-*Schistosoma* sp. activity, especially with artemether and artesunate (Cioli & Pica-Mattocchia, 2002, Xiao et al., 2000, Lu et al., 2010).

Clinical assays with artemether have already been carried out in Ivory Coast (Africa) and have shown less incidence of infections caused by *S. mansoni* and *S. japonicum* (Utzinger et al., 2003, Xiao et al., 2000). In regard to toxicity, it was proved by clinical tests that artemisinins are well tolerated when administered orally (Notprasert et al., 2002).

In some regions of the globe endemic areas for malaria and schistosomiasis overlap, and it is suggested that in such regions the use of artemisinin, intending to treat malaria cases, can reduce the morbidity rate of endemic schistosomiasis (Lescano et al., 2004).

After the first studies on the schistosomicidal activity of artemisinins, another drug had its anti-*Schistosoma* sp. activity researched, namely cyclosporin A, whose anthelmintic activity was discovered by Bueding et al. in 1981. Reduction in the number of worms and suppression of granuloma formation were noted in mice infected with *S. mansoni*, as well as prophylactic effect against this worm (Bout et al., 1986).

In 1984, a series of acridine derivatives showed schistosomicidal activity. *In vivo* studies demonstrated their efficiency against *S. mansoni*, *S. japonicum* and *S. haematobium* (Stohler & Montanova, 1984). Assays carried out in primates showed cure of the host with the use of some of these derivatives, RO 15-5458/000 being one of them (Coelho & Pererira, 1991). It is a fact that acridine derivatives are an important class of compounds for the development of new drugs with anticonvulsant, antidepressant, analgesic, anti-inflammatory, antiplatelet, antimalarial, antimicrobial, antifungal, vasodilator, antitumour, antiviral, and anti-*Schistosoma* sp. activity (Rollas & Kuçukguzel, 2007).

The most recent researches on new compounds or drugs with schistosomicidal activity have been carried out with: a) inhibitors of cysteine protease, such as K11777, considered a powerful schistosomicide that reduces the pathogenesis of experimental schistosomiasis (Abdulla et al., 2007), b) RNAi, in the attempt to develop drugs or compounds that act as

enzyme silencers, e.g., the compound 4-phenyl-1,2,5-oxadiazole-3-carbonitrile-2-oxide, or furoxan, which acts on thioredoxin-glutathione reductase from *S. mansoni* (Kuntz et al., 2007, Sayed et al., 2008), c) trioxolanes or secondary ozonides (1, 2, 4-trioxolanes), which comprehend a class of synthetic endoperoxides that are cheap, easily synthesised, and similar to artemisinins, having activity on experimental infections with *S. mansoni* and *S. japonicum* (Caffrey, 2007, Xiao et al., 2007), d) mefloquine (antimalarial), which showed schistosomicidal activity against young and adult *S. mansoni* worms (Van Nassauw et al., 2008, Keiser et al., 2009), e) arachidonic acid, which showed schistosomicidal properties against *S. mansoni* and *S. haematobium* (El Ridi et al., 2010), and f) miltefosine (anti-leishmania), which reduced the parasite burden of mice infected with *S. mansoni* (Eissa et al., 2011). At the present moment there are no clinical assays with these compounds.

Research with medicinal plants has gained prominence in recent years. According to WHO, this sort of research should be encouraged because traditional knowledge on biodiversity products is an important tool in the development of new pharmaceutical products intended to combat diseases that affect people in developing countries (WHO, 2002).

Table 1 shows the drugs or compounds used up to this point in the treatment for human schistosomiasis.

YEAR	DRUG/COMPOUND	SPECIES
1918-1927	Tartar Emetic - Antimony Compounds	<i>S. mansoni</i> , <i>S. haematobium</i> , <i>S. japonicum</i>
1920	Emetine and 2,3-dehydroemetine	<i>S. japonicum</i>
1932	Lucanthone	<i>S. mansoni</i> , <i>S. haematobium</i>
1955	Metrifonate	<i>S. haematobium</i>
1964	Niridazole	<i>S. haematobium</i> , <i>S. mansoni</i> , <i>S. japonicum</i>
1965	Hycanthone	<i>S. mansoni</i> , <i>S. haematobium</i> , <i>S. rodhaini</i>
1969	Oxamniquine	<i>S. mansoni</i>
1975	Praziquantel	<i>S. mansoni</i> , <i>S. japonicum</i> , <i>S. haematobium</i> , <i>S. intercalatum</i> , <i>S. mekongi</i>
1976	Amoscanate	<i>S. mansoni</i> , <i>S. japonicum</i>
1976	Oltipraz	<i>S. mansoni</i> , <i>S. haematobium</i> , <i>S. intercalatum</i>
1978	Benzodiazepines	<i>S. mansoni</i> , <i>S. haematobium</i>
1980	Artemisinin Derivatives	<i>S. mansoni</i> , <i>S. japonicum</i> , <i>S. Haematobium</i>

Table 1. Drugs and compounds with schistosomicidal activity that have already been tested in humans. Sources: Cioli et al., 1995, Ribeiro-dos-Santos et al., 2006.

3. Development of tolerance and resistance of *Schistosoma mansoni* to schistosomicidal drugs

In the last 30 years the treatment for schistosomiasis has improved significantly in view of the introduction of praziquantel. Its oral administration in the dose of 40 to 60 mg/kg is efficient in reducing the morbidity, but the results of treatments with this drug have been less promising than expected. The reason is that cases of tolerance and resistance to the treatment for schistosomiasis have been reported for both oxamniquine and praziquantel (Parise-Filho & Silveira, 2001).

Different strains of *S. mansoni* have been found susceptible to treatment, whether they come from the same region or from various individuals within the same community (Parise-Filho & Silverira, 2001).

It has been known since the 1950's that different strains of *S. mansoni* show different responses to treatments carried out with the same medication (Katz, 2008). At that time it was proved that the strain from Egypt was less susceptible to the treatment with Miracil D than the strain from Liberia (Gonnert & Vogel, 1955).

The first cases of resistance to schistosomicidal drugs were actually reported by Katz et al. in 1973 in Brazil, and were related to oxamniquine and hycanthone. In 1978, strains tolerant and resistant to the treatment with praziquantel and oxamniquine were found in Brazil, Egypt, Kenya and Senegal (Dias et al., 1978, Stelma et al., 1995).

In 1987, Kinoti suggested that *S. mansoni* could develop resistance to therapeutic doses of some drugs. At the time, the large variation of susceptibility to drugs among parasites, even among those from the same region, was already known. Studies conducted in Kenya, where the required doses of oxamniquine are higher than in Brazil, suggested the existence of tolerant worms even before the extensive use of chemotherapeutic drugs with schistosomicidal properties (Coles et al., 1987).

In 1994, Fallon and Doenhoff provided an experimental demonstration that subtherapeutic doses of praziquantel, over many generations of parasites, resulted in worms less sensitive to the drug. Such resistance was in fact reported for the first time in Egypt and northern Senegal in 1995, when praziquantel was used in an attempt to control an epidemic of *S. mansoni* schistosomiasis (Fallon et al., 1995, Ismail et al., 1996).

There has been much debate on the possibility of praziquantel becoming less effective due to its potential to generate resistance. Regarding what happened in Senegal, where the cure rates were low (between 18% and 39%, whilst the normal rates are 70% to 90%) (Cioli 2000, Grysseels et al., 2001), some authors suggest that the cure rates were aberrant (Doenhoff et al., 2009). Explanations for such rates included: Rapid reinfections after the treatment, presence of immature forms of the parasite during the treatment, and no prior exposition of the immunological system of the population to *Schistosoma* sp. (Cioli 2000, Grysseels et al., 2001, Harnett & Kusel, 1986, Brindley & Sher, 1987, Doenhoff et al., 1987, Modha et al., 1990). Some authors, however, point out that, since the cure rates in Senegaleses were atypically lower than expected, suspicions of a development of tolerance and resistance to treatment in that region can not be ignored (Danso-Appiah & de Vlas, 2002). Other authors consider that resistance becomes a problem when chemotherapy is massively used aiming to eradicate the disease only by medication, especially when cure rates do not reach 100%. The key in the process is the percentage of surviving worms that will contribute to the resistance of the next generation (Ismail et al., 1999, Liang et al., 2001), because such resistance would favour low cure rates and rapid reinfections after the treatment (Stelma et al., 1995).

Somehow, the extensive use of praziquantel has increased the concern for the development of *Schistosoma* sp. resistant to treatment (Fallon & Doenhoff, 1994). Since there are few other options regarding the treatment for schistosomiasis (Doenhoff et al., 2009), in particular for *S. mansoni* schistosomiasis, it is necessary to search for alternative drugs.

The use of medicinal plants can be a very useful therapeutic alternative because the treatment is efficient and has low operational costs. Furthermore, such plants are easily found in Brazil, a country with a wide variety of native flora (Matos, 1994).

4. Researches with medicinal plants to combat schistosomiasis

Medicinal plants have been one of the most ancient forms of medicinal practice of humankind, having been used in the treatment of many diseases (Akerlele, 1993). Based on information gathered along centuries, popular observations on the use and efficiency of medicinal plants have contributed significantly to the disclosure of their therapeutic properties (Maciel et al., 2002, WHO, 2003).

It is estimated that only 17% of all the plants in the world have been studied in one way or another regarding their medicinal use, in most cases, no deep analyses were carried out on their phytochemical and pharmacological properties. Many species are used empirically, with no scientific support on their efficiency and safety. These data show the enormous potential of plants for the discovery of new phytotherapeutic drugs (Cragg et al., 1999, Cordell & Colvard, 2005, Hamburger et al., 1991, Hostettmann, et al., 2003, Guerra, et al., 1999).

Medicinal plants and their derivatives were the basis of drug therapeutics until the middle of the 20th century, when chemical synthesis, initiated at the end of the 19th century, reached a new development stage (Silva & Carvalho, 2004).

In the first half of the 20th century, studies with natural products were temporarily put aside on account of the emergence of new synthetic drugs, obtained from microorganisms that in most cases had no practical use in view of their high toxicity (Devienne et al., 2004). Furthermore, side effects caused by the use of those medicines were more and more frequently. There was no advantage in providing a fast and efficient treatment for a disease and then making another disease appear. Drugs had to be efficient and safe at the same time, as well as affordable (Oliveira & Akisue, 2000).

In fact, there was a revolution in therapeutics at that moment, which led to the development of researches in the pharmacochemical industry with the purpose of synthesising active ingredients with less toxicity. Nevertheless, it did not take too long until the production of new drugs from totally synthetic substances stopped, in view of the high costs involved in their research and development (Devienne et al., 2004).

It should be mentioned that the development of a new drug involves a complex process that may cost around 100 to 360 million dollars over a period of 10 to 12 years, representing about 15% of the income of the pharmaceutical industry (Rates, 2001). On the other hand, the development of researches with medicinal plants has much lower costs (Ferreira, 2001). Other estimates show that the world market of pharmaceutical products generates 320 billion dollars per year, of which 20 billion come from active substances derived from medicinal plants (Robbers et al., 1996). These facts have been promoting the interest in medicinal plants and the search for prototypes for the production of new drugs.

A big limiting factor, though, is that most plants under use have not been described in official codes - pharmacopeia -, and there are not even studies on them. In order to

introduce the use of medicinal plants in small production centres and prescription pharmacies, there must be investments in the elaboration of related official documents (Toledo et al., 2003). In this regard, the Brazilian government approved the National Policy for Medicinal Plants and Phytotherapeutic Drugs (PNPMF) by decree n. 5,813 of June 22th, 2006. This policy is an essential part of public policies for health, environment, and social and economic development, and is very important for the implementation of actions capable of promoting improvements in the life quality of Brazilian people (Ministério da Saúde, 2009).

The Brazilian flora consists of about 100,000 species, but only 8% of them had their chemical composition studied. In addition, many active ingredients are still unknown, and it is estimated that only 1,100 species have been examined regarding their therapeutic properties (Anthony et al., 2005, Reis et al., 2007, Varanda, 2006).

According to Rodrigues and West (1995), the study of medicinal plants in tropical countries is very interesting because such species have 3 to 4 times more chemical compounds than plants found in temperate zones.

From the pharmacological viewpoint, it is absolutely necessary that the activities of ingredients or substances isolated from plants be evaluated in preclinical assays. Experimental models are used in the analysis of antiparasitic, anti-inflammatory, antimicrobial, analgesic, antitumour and anticonvulsant effects, among others, as well as in toxicologic evaluation (acute and chronic toxicity), primary and cumulative dermal irritation, ocular irritation, cutaneous sensitivity, and phototoxicity. The development of such studies allows us to reach the end of the multidisciplinary cycle in the research with medicinal plants (Foglio et al., 2006).

According to Githori et al. (2006), plants with antiparasitic activity usually contain saponins, alkaloids, non-protein amino acids, tannins, polyphenols, lignins, terpenes, lactones, glycosides, and phenolic compounds. As a result, many species can be candidates for thorough studies concerning this function. Table 2 describes some species of medicinal plants with confirmed schistosomicidal activities.

Among the several medicinal plants cultivated in Brazil, in this chapter we will focus on four species that for decades have been submitted to biological and pharmacological studies, in view of the fact that their active ingredients have proven effective to combat many diseases. In recent years our research group started a multidisciplinary project intending to carry out *in vitro* screenings of extracts and fractions from these plants against experimental infections in *S. mansoni*. The best results were found for *Artemisia annua*, *Baccharis trimera*, *Cordia verbenacea* and *Phyllanthus amarus*.

Scientific Name	Used Part of the Plant	Extract/Compound	Species	Observations	References
<i>Abrus precatorius</i>	Stem and Roots	Aqueous Extract	<i>S. mansoni</i>	<i>In Vitro</i> Test - Schistosomulum	Molgaard et al., 2001
<i>Ozoroa insignis</i>	Leaves and Bark of the Roots	Aqueous Extract	<i>S. mansoni</i>	<i>In Vitro</i> Test - Schistosomulum	Molgaard et al., 2001
<i>Elephantorrhiza goetzei</i>	Barks of the Stem	Aqueous Extract	<i>S. mansoni</i>	<i>In Vitro</i> Test - Schistosomulum	Molgaard et al., 2001

Scientific Name	Used Part of the Plant	Extract/Compound	Species	Observations	References
<i>Commiphora molmol</i>	Stem	Myrrh	<i>S. mansoni</i> e <i>S. haematobium</i>	–	Sheir et al., 2001, El Baz et al., 2003, Barakat et al., 2005
<i>Nigella sativa</i>	Seeds	Oil, Aqueous, Ethanolic and Chloroform Extracts	<i>S. mansoni</i>	<i>In Vivo</i> Test with Egyptian strain (Oil), <i>In Vitro</i> Test with Miracidia, Cercariae and Adults (Extracts)	Mahmoud et al., 2002, Mohamed et al., 2005, El-Shenawy et al., 2008
<i>Allium sativum</i>	Crushed Scale Leaves	Aqueous Extract, Dry Crude Extract	<i>S. mansoni</i>	Egyptian strain, <i>In Vivo</i> Test	Riad et al., 2007, Mantawy et al., 2011
<i>Clerodendrum umbellatum</i>	Leaves	Aqueous Extract	<i>S. mansoni</i>	Cameroonian strain, <i>In Vivo</i> Test	Jatsa et al., 2009
<i>Curcuma longa</i>	–	Curcumin	<i>S. mansoni</i>	LE strain,	Magalhães et al., 2009
<i>Zanthoxylum naranjillo</i>	Leaves	Fraction of Ethyl Acetate	<i>S. mansoni</i>	<i>In Vitro</i> Test	Braguine et al., 2009
<i>Dryopteris</i> sp.	Rhizome	Phloroglucinol	<i>S. mansoni</i>	LE strain	Magalhães et al., 2010
<i>Piper tuberculatum</i>	Inflorescence	Piplartine	<i>S. mansoni</i>	BH strain, <i>In Vitro</i> Test	Moraes et al., 2010
<i>Baccharis dracunculifolia</i>	Leaves	Essential Oil	<i>S. mansoni</i>	Native of Brazil, LE strain, <i>In Vitro</i> Tests	Parreira et al., 2010
<i>Cratylia mollis</i>	Seeds	Cramoll 1,4	<i>S. mansoni</i>	Native of Brazil, BH strain, <i>In Vivo</i> Test	Melo et al., 2011
<i>Zingiber officinale</i>	Rhizome	Aqueous Extract	<i>S. mansoni</i>	<i>In Vivo</i> Test	Mostafa et al., 2011
<i>Ageratum conyzoides</i> L.	Leaves	Essential Oil	<i>S. mansoni</i>	LE strain, <i>In Vitro</i> Test	Melo et al., 2011
<i>Allium cepa</i>	Scale Leaves	Dry Crude Extract	<i>S. mansoni</i>	Egyptian strain, <i>In Vivo</i> Test	Mantawy et al., 2011

Table 2. Medicinal plants with attested schistosomicidal activity.

4.1 Bioassays – *In vitro* tests

Given the global interest in exploring anthelmintic activities of plants and their products, there is a growing interest in finding the best way to evaluate their bioactivity. Time and financial costs involved in tests require the screening techniques to be sensitive, preferably low-cost and reproducible (Jackson & Coop, 2000).

In general, plants contain a large number of secondary metabolites, which can act individually or in combination to produce direct or indirect effects on the parasites. Accordingly, the first screening stage should reduce the number of substances for the following stage, which consists of the discovery of active compounds, a complex and expensive process. That stage is important because the understanding of the nature of the active compounds, their action mode and their targets in the parasites is what will determine its applicability (Jackson & Coop, 2000, Athanasiadou et al., 2001, Athanasiadou & Kyriazakis, 2004).

In vitro assays are used for screening. *In vitro* tests are a primary screening, considering that a large number of plants can be examined to demonstrate their potential effect (Cabaret et al., 2002, Athanasiadou & Kyriazakis, 2004, Ketzis et al., 2006).

During an *in vitro* test for helminths, the parameter analysed is the viability of adult worms. Motility, oviposition, tegument changes, changes in internal organs, mating, and especially the mortality of such worms can all be observed.

4.2 *In vitro* tests with Brazilian medicinal plants to combat *S. mansoni* schistosomiasis

The plants used in the assays were cultivated and collected at the Experimental Field of the Chemical, Biological and Agricultural Pluridisciplinary Research Centre (CPQBA) - Unicamp - Campinas (-22°54'20"/-47°03'39") - São Paulo - Brazil. In order to obtain the extracts, fractions and isolated compounds the aerial parts of the plants were used. In order to carry out the *in vitro* tests, mated males and females of *S. mansoni* were used. They were kept in RPMI-1640 medium, along with penicillin/streptomycin, in a CO₂ oven at 5% and temperature of 37°C. The results of these tests showed schistosomicidal activity in the samples during the observation period, which lasted 72 hours.

4.2.1 *Artemisia annua* L.

(Allegretti, S. M., 2011)

Artemisia annua L (Asteraceae), known as Artemisia or Qinghaosu, is indigenous to China and has been used for centuries in Chinese medicine in the treatment for fever crisis (Figure 2). This species was introduced and naturalised in several countries in Europe, northern and central Asia, India, Australia, northern Africa, and South and North Americas (Klayman, 1993, WHO, 2006).

Artemisinin and its derivatives are compounds with low toxicity, no mutagenic effects, and good tolerance, being a primary option in antimalarian therapy in many tropical and subtropical countries, such as China, Thailand, Cambodia, Laos, Vietnam, Brazil, Zaire, Gabon, Madagascar, Ghana, among others (Guo et al., 1998, Xiao, 2002, Jiraungkoorskul et al., 2006). Such compounds have also shown schistosomicidal activity (Jiraungkoorskul et al., 2006, Shaohong et al., 2006, Mitsui et al., 2008).

Our research group has compared the activity of artemisinin and artesunic acid in adult couples of the BH strain of *S. mansoni*, native of Belo Horizonte (-19°55'15"/-43°56'16"), Minas Gerais, Brazil, by means of *in vitro* tests. Twenty-two hours after the addition of the two compounds, death was observed in all concentrations tested. Three replications of the experiment were carried out for each concentration. Worms of negative control groups, i.e., with no addition of compounds or drugs, stayed alive until the end of the experiment. Table 3 shows the mortality of worms within the observation period.

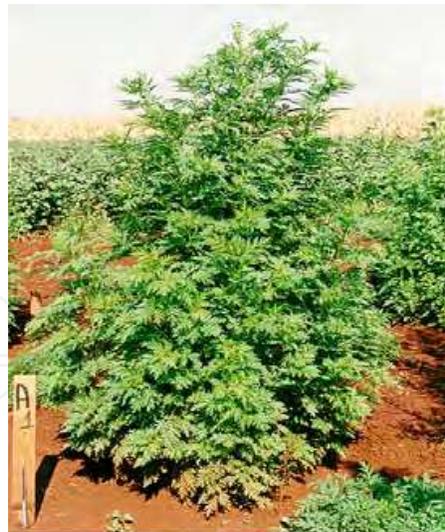


Fig. 2. *Artemisia annua* L. cultivated in the Experimental Field of CPQBA - Unicamp, 2011.

	Time when the mortality rate reached 100%		
	C1(1500µg/mL)	C2 (1000µg/mL)	C3(500µg/mL)
Artesunic acid	5 th hour	5 th hour	22 nd hour
Artemisinin	20 th hour	20 th hour	22 nd hour
Praziquantel	20 th hour	20 th hour	22 nd hour

Table 3. Activity of artesunic acid, artemisinin and praziquantel in relation to the mortality of *S. mansoni*. Concentrations: C1 = 1500µg/mL, C2 = 1000µg/mL, C3 = 500µg/mL.

It has already been proven that both artemisinin and artesunic acid act in different ways on strains of *S. mansoni*, such as LE, Liberian and Puerto Rico. Tests comparing strains of *S. mansoni* with artesunic acid are still rare in the literature, but in *in vivo* studies we notice that different strains respond differently to the treatment.

All these strains showed differences in the percentage of worm distribution in the hepatic portal system, mortality and oogram change (Araújo et al. 1999, Utzinger et al., 2002, Lu et al., 2004, 2006). Such differences between strains of *S.mansoni* in the vertebrate host are considered a manifestation of the genotypic expression of the trematode (Yoshioka et al. 2002). For the comparison between the activity of artesunic acid and artemisinin against the BH and SJ strains of *S. mansoni* (the latter being native of São José dos Campos, -23°10'46"/-45°53'13", São Paulo, Brazil), experiments in Swiss mice were carried out with further treatments on different days, i.e., on the 30th and 45th days after the infection. Concentrations of 300 and 500 mg/kg were orally administered, divided along five consecutive days. Fifteen days after the administration of the last concentration, the reduction rates of the BH strain worms in the hepatic portal system of mice were compared with negative control group (not treated), and the result was 49% of worm reduction for artesunic acid (with 300 and 500 mg/kg) in treatment carried out after 30 days of infection. However, no reduction was found for artemisinin in neither concentration, tested under the same conditions. In treatments carried out after 45 days of infection, there was worm reduction of 41% with the use of artesunic acid, 500 mg/kg, but no reduction was found in the group treated with artemisinin in the same concentration and on the same day.

In regard to the same strain, eggs eliminated in the feces were reduced at even 100% with the use of artesunic acid, 300 mg/kg, administered after 30 days of infection, but no similar results were found in similar treatments with artemisinin. Oviposition reduction of 100% was also observed with artesunic acid, in treatment carried out on the 45th day of infection in both concentrations, whereas artemisinin reached 81% of oviposition reduction on the same day, in the 300mg/kg concentration.

Better results were achieved with the SJ strain concerning worm reduction: maximum of 49% in treatments with 500 mg/kg of artesunic acid, administered after 30 days of infection, and 30% with artemisinin, in the same concentration and period. In treatments carried out after 45 days of infection worm reduction reached 76% with 300 mg/kg of artesunic acid, whereas no reduction was found with the use of artemisinin in the same period in either concentration.

Regarding oviposition, 500 mg/kg of artesunic acid provided a reduction of 99% when administered after 30 days of infection, whilst the same concentration of artemisinin provided a reduction of 89% in the same period. In treatments carried out with 500 mg/kg of artesunic acid after 45 dias, the reduction rate reached 98%, but no reduction was found in treatments with artemisinin.

These results showed that artesunic acid had better activity regarding the parameters in question (worm and oviposition reduction) for both strains under study. In addition, the use of artesunic acid showed no significant difference between these parameters in treatments carried on the 30th and 45th days of infection for both strains. Regarding artemisinin, we could observe that the SJ strain of *S. mansoni* showed higher worm and oviposition reduction rates than the BH strain, particularly in treatments after 30 days of infection, which demonstrates the difference between the strains in what refers to treatment response.

4.2.2 *Baccharis trimera* (Less) DC.

(Oliveira, R. N., 2011)

Baccharis trimera (Less) DC. (Figure 3) is a plant native of South and Southeast Brazil, also found in Argentina, Bolivia, Paraguay and Uruguay (Bona et al., 2005, Lorenzi & Matos 2002). This species belongs to the family Asteraceae, which includes around 1,100 genera and 25,000 species distributed worldwide (Moreira et al., 2003). Plants of this family are extensively studied regarding their chemical composition and biological activity because of their outstanding allelopathic, anti-inflammatory, antimutagenic and antimicrobial effects. Some of these species have even made possible the development of new drugs and insecticides, among other products (Verdi et al., 2005).

The genus *Baccharis* has more than 500 species widely distributed in Brazil, Colombia, Chile, Argentina and Mexico (Lorenzi & Matos, 2002). The phytochemistry of this genus has been studied since the beginning of the last century, and so far more than 150 compounds have been isolated and identified (Abad et al., 1999). Flavonoids and terpenoids, such as monoterpenes, sesquiterpenes, diterpenes and triterpenes, are the most frequent compounds (Moreira et al., 2003, Verdi et al., 2005).

The name *Baccharis* (*Bakkharis*) comes from Greek and is an old denomination for some shrub-like plants (Kissmann & Groth, 1999). This plant is popularly known as carqueja and its most distinct characteristic is the presence of cladophylls, which replace leaves as the main photosynthetic organs of the plant, as there are no leaves or they are extremely reduced, with limited physiological function (Barroso, 1976). Carqueja was first used in folk

medicine in Brazil by Correa in 1931, who described the use of the infusion of its aerial parts in the treatment for female sterility and male impotence (Lorenzi & Matos, 2002). Nowadays *B. trimera* is mostly consumed in teas, being extensively used in folk medicine on account of its diuretic properties and in the treatment for gastrointestinal and hepatic diseases, as well as for angina, poor blood circulation, diabetes and inflammatory processes (Corrêa, 1984, Moreira et al., 2003, Souza et al., 1991).

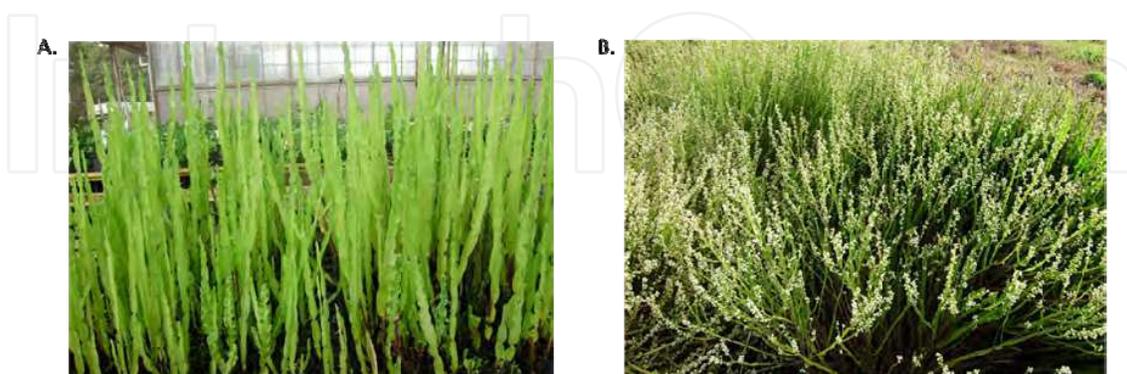


Fig. 3. *Baccharis trimera* (Less) DC. **A.** Seedling, **B.** Inflorescence. Source: Experimental Field of CPQBA- Unicamp, 2011.

From the species *B. trimera* a series of flavonoids have already been isolated, including eupatorin, eupatrin, cirsimaritin, rutin, cirsiolol, genkwanin, eriodictyol, kaempferol, quercetin, luteolin, nepetin, apigenin e hispidulin, 5-OH- 6,7,3,4-OMe flavone, 5,6-OH-7,3',4'-OMe flavone and 5,7,3,4-OH-3-O-rhamnosyl-glycosyl flavone (Borella et al., 2006, Soicke et al., 1987, Verdi et al., 2005).

Several biological studies were conducted intending to confirm the pharmacological properties of *B. trimera*. For instance, the decoction of this plant showed antimicrobial activity (bacteriostatic and bactericidal) in both Gram-positive and Gram-negative bacteria through *in vitro* assays, supporting its use as antiseptic and disinfectant (Avancini et al., 2000).

Among the studies conducted so far we can point out the works carried out with the aqueous extract from *B. trimera*. This extract showed activity on the reduction of gastric lesions induced by stress in mice (Gamberini et al., 1991), on the relaxation of the intestinal smooth musculature in rats (Torres et al., 2003), on the reduction of the blood glucose level in mice, indicating a potential antidiabetic activity (Oliveira et al., 2005), in addition to anti-inflammatory and immunomodulatory effects (Paul et al., 2009).

Hydroalcoholic extract showed antioxidant activity through *in vitro* and *in vivo* tests in neutrophils of mice (Pádua et al., 2010). Another *in vitro* test with the same extract showed antiparasitic activity against amastigote and promastigote forms of *Leishmania* (*L. amazoniensis*) and epimastigote forms of *Trypanosoma cruzi* (Luize et al., 2005).

It was also reported that the methanolic extract from *B. trimera* showed antimutagenic activity through *in vitro* assays (Nakasugi & Komai, 1998).

The molluscicidal activity in *Biomphalaria glabrata* (Pulmonata: Planorbidea) was studied from a diterpenic lactone and a flavone isolated from *B. trimera* (Santos-Filho et al., 1980).

The compound neoclerodane diterpene showed inhibitory action on metalloproteases present in the venom of *Bothrops* sp., which demonstrates the antihemorrhagic, antiproteolytic, antimyotoxic and antiedematogenic properties of *B. trimera* (Januário et al., 2004).

Polyphenolic compounds isolated from *B. trimera*, *B. crispa* and *B. usterii* by means of aqueous extract showed anti-inflammatory and antioxidant activities (Simões, et al., 2005). In addition to the studies mentioned here, other biological activities *B. trimera* have been demonstrated, as shortly shown in Table 4.

Activity	Extract/ Compound	References
Molluscicidal	Diterpene Lactone and Flavone	Santos-Filho et al., 1980
Antimutagenic	Methanolic Extract	Nakasugi & Komai, 1998
Disinfectant and Antiseptic	Decoction	Avancini et al., 2000
Antiproteolytic, Antihemorrhagic	Chloroform: Methanol	Januário et al., 2004
Antiparasitic, Antiulcer, Antioxidant, Hepatorenal	Hydroalcoholic Extract	Dias et al., 2009, Grance et al., 2009, Luize et al., 2005, Pádua et al., 2010
Hypoglycemic, Anti-inflammatory, Immunomodulatory, Genotoxicity, Antigenotoxicity	Aqueous Extract	Barbosa-Filho et al., 2005, Leite et al., 2007, Paul et al., 2009, Rodrigues et al., 2009

Table 4. Major biological activities of *Baccharis trimera* described in the literature.

Among the several biological activities of *B. trimera* mentioned in the literature, we can highlight its anti-inflammatory and hepatorenal activities, which raised the interest of our research group in studying this plant in the treatment for *S. mansoni* schistosomiasis because granulomatous inflammatory responses, the main pathology of the disease, affect many organs, especially the liver. Therefore, we have been carrying out screening of raw extracts and fractions from this plant by *in vitro* assays.

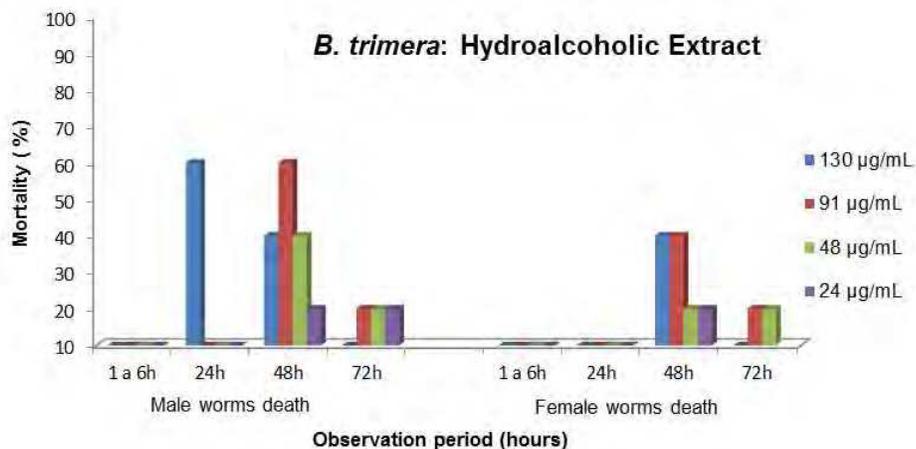
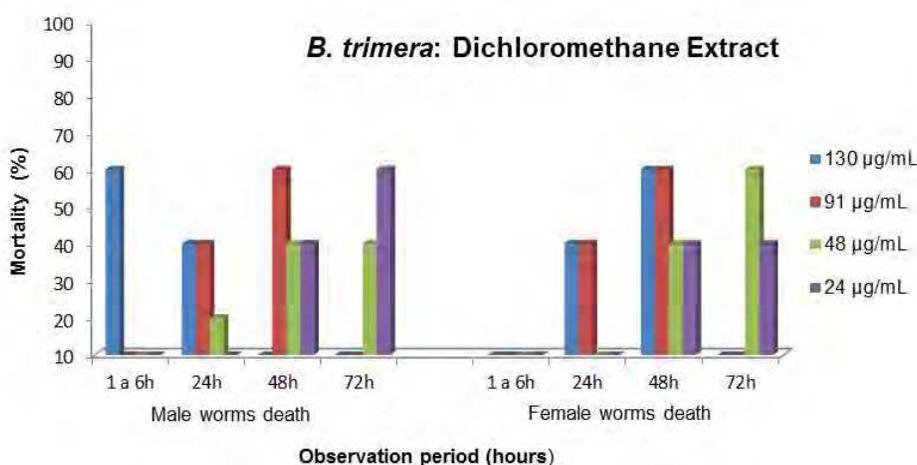
Crude dichloromethane and hydroalcoholic extracts were used so that the schistosomicidal activity of *B. trimera* on the BH strain of *S. mansoni* could be evaluated. Different concentrations - C1 = 130µg/mL, C2 = 91µg/mL, C3 = 48µg/mL and C4 = 24µg/mL - of the extracts were tested on couples of adult worms, five replications being performed for each concentration. At the end of the experiment, i.e., 72 hours later, the following mortality rates were observed:

	Dichloromethane Extract	Hydroalcoholic Extract	Praziquantel	Control
C1 (130 µg/mL)	100%	70%	100%	-
C2 (91 µg/mL)	100%	70%	100%	-
C3 (48 µg/mL)	100%	50%	70%	-
C4 (24µg/mL)	90%	30%	60%	-

Table 5. Evaluation of the mortality of couples of *Schistosoma mansoni* submitted to different concentrations of *Baccharis trimera*. Control: Negative Control Group, with no addition of any extract or drug for 72 hours.

Considering these results, we conclude that the dichloromethane extract showed better activity in comparison with the hydroalcoholic one and that male specimens of *S. mansoni* were more susceptible to the activity of the former. Therefore, it can be accepted that *B. trimera* has active compounds against the BH strain of *S. mansoni*.

The effect of the observation period on the mortality of the worms was also analysed. The crude dichloromethane extract proved to be more effective, as the concentrations C1 (130µg/mL) and C2 (91µg/mL) caused the death of 100% of the worms in an observation period of 48 hours (Figure 4).



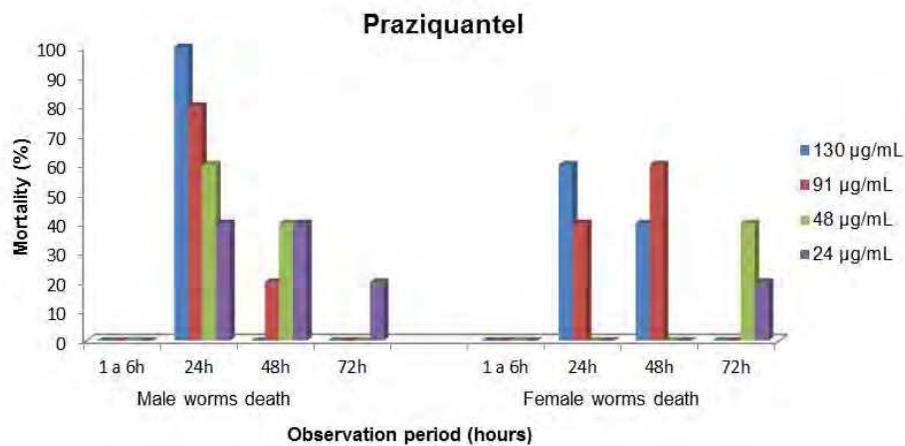


Fig. 4. Activity of the crude dichloromethane and hydroalcoholic extracts from *Baccharis trimera* and praziquantel on the viability of male and female *Schistosoma mansoni* worms in relation to the observation period of 72 hours.

4.2.3 *Cordia verbenacea* DC.

(Frezza, T.F., 2011)

Cordia verbenacea DC (also referred to as *Cordia salicina*, *Cordia curassavica*, *Cordia cylindristachia*, *Lithocardium fresenii*, *Lithocardium salicinum* and *Lithocardium verbaceum*) is a medicinal plant native of Brazil, commonly known as maggy plant (*erva-baleeira* or *salicina* in Brazilian Portuguese). It belongs to the family Boraginaceae, widely distributed along the Brazilian shore, but found mainly from the shore of São Paulo to Santa Catarina (Carvalho et al., 2004). Species of the genus *Cordia* are found in tropical and subtropical regions in Asia, southern Africa, Australia, Guyana and South America in general (Ficarra et al., 1995). Figure 5 shows a specimen of *C. verbenacea*.

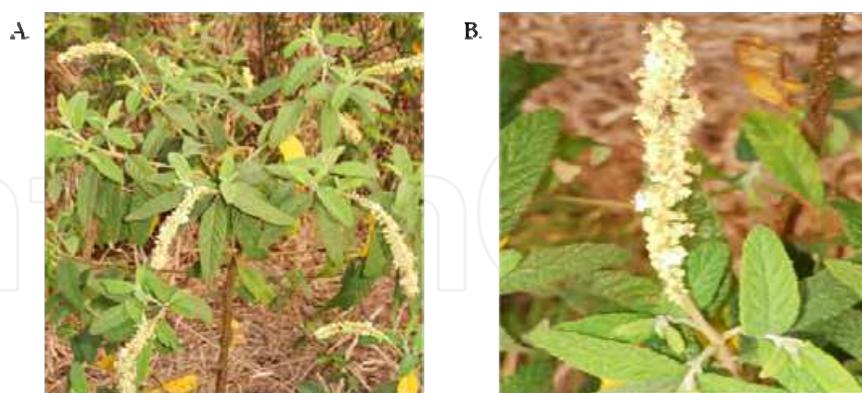


Fig. 5. *Cordia verbenacea*. **A.** Leaves, **B.** Inflorescence. Source: Experimental Field of CPQBA - Unicamp, 2011.

Several compounds are found in the aerial parts of *C. verbenacea*, including tannins, flavonoids and essential oils. Such parts have been used in folk medicine in the form of alcoholic extracts and infusions in view of their antiulcer, antimicrobial, anti-inflammatory and antirheumatic activities, as well as their tonic and analgesic properties (Carvalho et al., 2004, Passos et al., 2007). Since a variety of chemical groups found in extracts from *C.*

verbenacea allegedly have biological activities, this plant is an important material for pharmaceutical investigation (Michielin et al., 2009). In recent years, the activities of different extracts from *C. verbenacea* have been extensively discussed.

Preclinical studies have shown that the hydroalcoholic extract from *C. verbenacea* has anti-inflammatory activity, either by oral or topical administration, and protects the gastric mucosa (Sertie et al., 2005, Roldão et al., 2008). It also has antioxidant activity (Michielin et al., 2011) and inhibits the growth of Gram-positive and Gram-negative bacteria (Meccia et al., 2009, Michielin et al., 2009).

Its essential oil has antimicrobial activity along with inhibitory activity against the growth of some Gram-positive bacteria in *in vitro* cultures (Carvalho et al., 2004), as well as antiallergic activity (Passos et al., 2007) and larvicidal activity against *Aedes aegypti* (Santos et al., 2006). The bioguided isolation of this oil led to the identification of other two active compounds with anti-inflammatory activity, namely alpha-humulene and trans-caryophyllene (Passos et al., 2007).

The anti-inflammatory activity of the essential oil made it possible to develop the first Brazilian phytodrug, Acheflan, an anti-inflammatory drug of topical use.

Different activities have also been reported for other extracts, such as the methanolic extract, which presents effects on oedema formation and reduction of myotoxicity induced by the venom of *Bothrops jararacussu* (Ticli et al., 2005), and the dichloromethane extract, which has shown antiedematogenic activity in *in vivo* assays (Bayeux et al., 2002). The antiparasitic activity of methanolic extracts from *C. verbenacea* has already been tested against *Leishmania* sp. (Braga et al., 2006) and is currently studied by our research group against *S. mansoni*. *C. verbenacea* was chosen by our research group for *in vitro* studies because of its anti-inflammatory properties.

Table 6 provides a summary of the actions of extracts or compounds from *C. verbenacea*.

Activity	Extract/ Compound	Reference
Anti-inflammatory, Protection of the Gastric Mucosa, Antiulcer, Antioxidant, Antimicrobial	Hydroalcoholic Extract	Sertié et al., 1990, Sertié et al., 2005, Passos et al., 2007, Roldão et al., 2008, Meccia et al., 2009, Michielin et al., 2009, Michielin et al., 2011
Anti-inflammatory, Antimicrobial, Antiallergic, Larvicidal	Essential Oil	De-Carvalho et al., 2004, Santos et al., 2006, Passos et al., 2007
Reduction of Myotoxicity, Antiparasitic (<i>Leishmania</i> sp.)	Methanolic Extract	Ticli et al., 2005, Braga et al., 2007
Antiedematogenic	Dichloromethane Extract	Bayeux et al., 2002

Table 6. Major biological activities of *Cordia verbenacea* described in the literature.

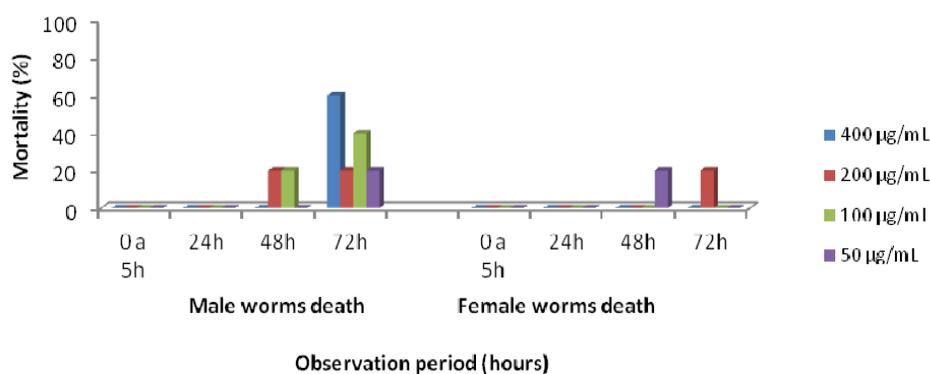
The aqueous fraction, organic fraction (obtained from the ethanolic extract) and essential oil were used for the analysis of the *in vitro* schistosomicidal activity of *C. verbenacea* against the BH strain of *S. mansoni*. Different concentrations of the extracts were tested against couples of adult worms, with five replications carried out for each concentration. At the end of the experiment (72 hours), the following mortality rates were observed:

	Essential Oil	Aqueous Fraction	Organic Fraction	Praziquantel	Control
C1 (400 µg/mL)	30%	30%	100%	100%	-
C2 (200 µg/mL)	30%	30%	100%	100%	-
C3 (100 µg/mL)	30%	20%	90%	90%	-
C4 (50 µg/mL)	20%	10%	60%	90%	-

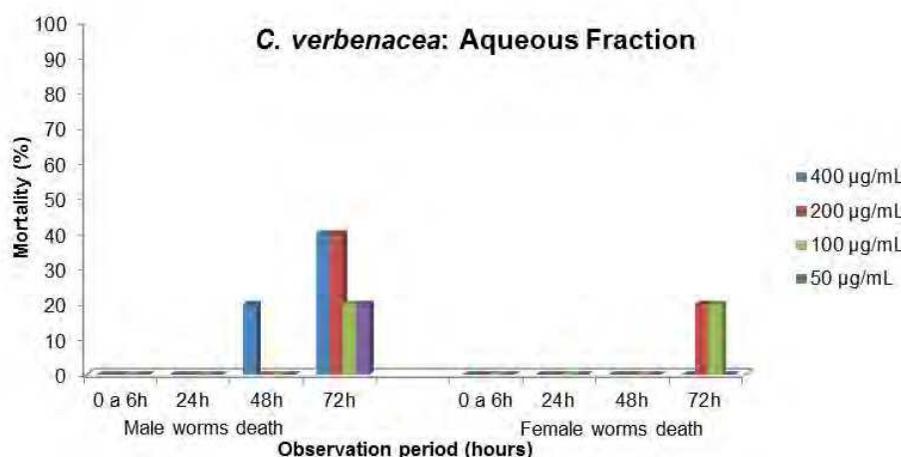
Table 7. Evaluation of the mortality of couples of *Schistosoma mansoni* submitted to different concentrations of *C. verbenacea*. Control: Negative Group Control, with no addition of any extract or drug for 72 hours.

The effect of the observation period on the mortality of the worms was also analysed. We consider that the best extract from *C. verbenacea* was the one that in 24 hours was able to eliminate more worms with higher concentrations (Figure 6).

C. verbenacea: Essential Oil



C. verbenacea: Aqueous Fraction



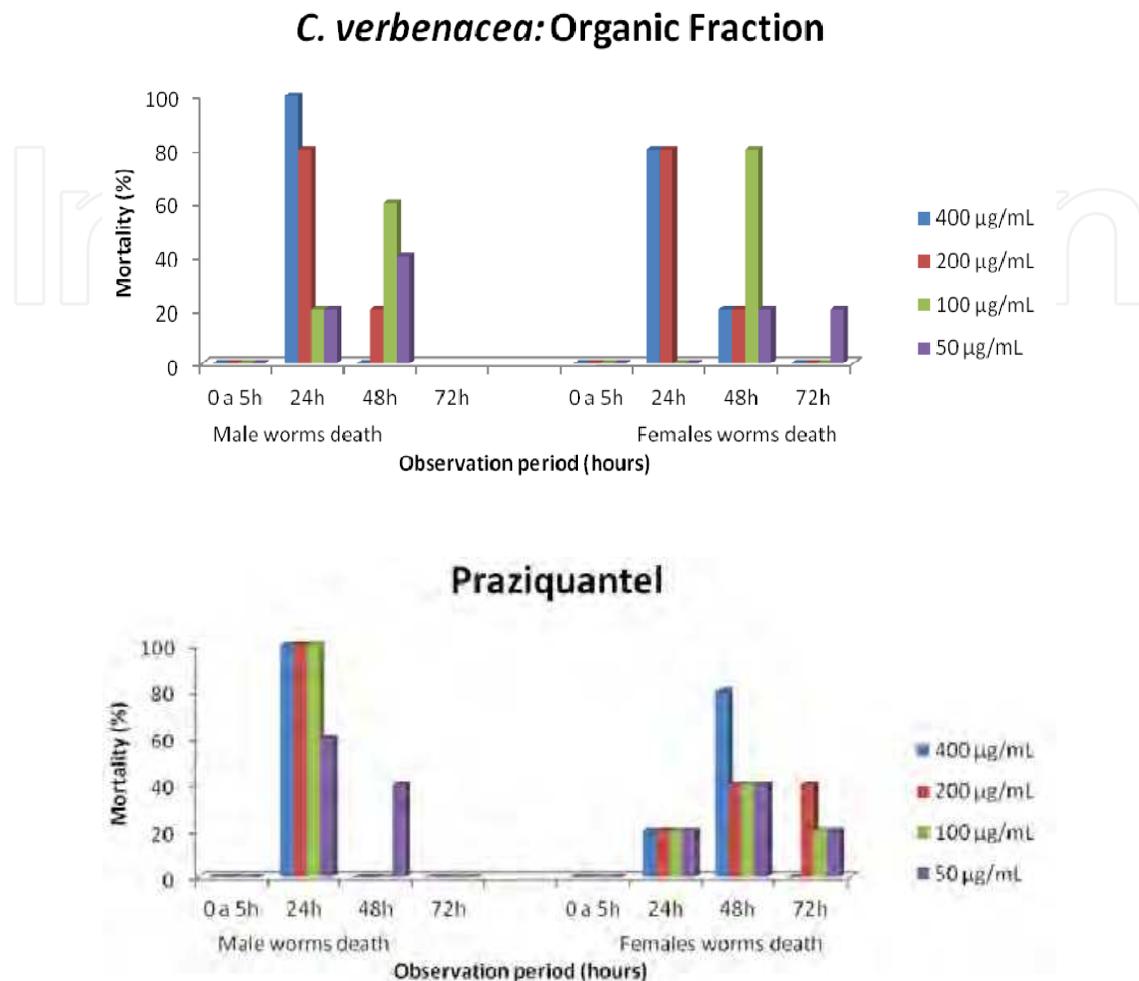


Fig. 6. Activity of the aqueous fraction, essential oil and organic fraction from *Cordia verbenacea* and praziquantel on the viability of male and female *Schistosoma mansoni* worms in relation to the observation period of 72 hours.

4.2.4 *Phyllanthus amarus* L.

(Oliveira, C.N.F., 2011)

Phyllanthus amarus belongs to the family Euphorbiaceae (Calixto et al., 1998), which comprises 317 genera and 8,000 species, grouped into 49 tribes and 5 subfamilies (Torres et al., 2003). Plants belonging to the genus *Phyllanthus* are widely distributed in most tropical and subtropical countries (in both hemispheres) and include between 550 and 750 species. It is believed that there are about 200 species of this genus distributed throughout the Americas, being mostly found in Caribe and Brazil (Calixto et al., 1998, Torres et al., 2003). The name *Phyllanthus* comes from Greek, *phyllon* meaning 'leaf' and *anthos* meaning 'flower', a reference to the flowers produced in branches, resembling compound flowers (Figure 7) (Torres et al., 2003).

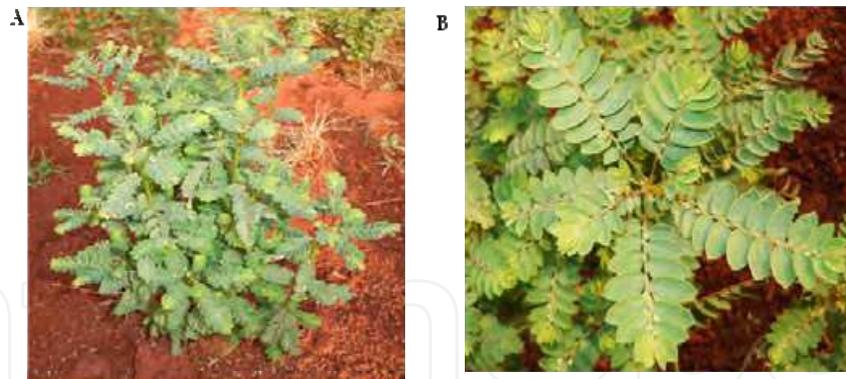


Fig. 7. **A** – Specimen of *Phyllanthus amarus*, **B**. Amplified image. Source: Experimental Field of CPQBA – Unicamp, 2011.

In Brazil, plants of the genus *Phyllanthus* are popularly known as stone-breaker (*quebra-pedra*, *arrebenta-pedra* or *erva-pombinha* in Brazilian Portuguese) and are recognised in folk medicine in Brazil and other countries for their diuretic properties. They are used in the treatment for kidney and bladder disorders, helping in the passage of renal calculi, and also act on intestinal infections, diabetes and hepatitis B (Calixto et al., 1998, Jain et al., 2003, Khatoon et al., 2006, Rajakannan et al., 2003, Torres et al., 2003).

A large variety of species of plants belonging to this genus have been phytochemically and pharmacologically investigated and many molecules have been isolated and identified. Among all the species studied, *P. amarus* has been given special attention. Although many of its compounds are chemically known, the properties of most of these compounds remain unknown. Some pharmacological activities of *P. amarus* have already been confirmed by scientific studies, such as: (1) treatment for hepatitis B, by suppression of the replication of the virus (Thyagarajan et al., 1988), (2) hepatoprotective effect against actions of paracetamol, carbon tetrachloride (CCl₄), galactosamine and alcohol (Krithika et al., 2009, Pramyothin et al., 2007) – phyllanthin and hypophyllanthin, which are lignans present in *P. amarus*, are described as having hepatocyte-protective action against carbon tetrachloride (Khatoon et al., 2006), (3) aqueous extracts from *P. amarus* have shown a strong inhibitory action against hepatic carcinoma (Rajeshkumar & Kuttan, 2000), (4) possible antispasmodic effects of the extract on the smooth musculature have been reported because they contribute to the effects on the renal calculi (Kassuya et al., 2003), (5) antibacterial activity of the ethanolic extract (Kloucek et al., 2005), (6) potential anti-inflammatory activity of both the hexane extract and the chemical fraction rich in lignans, obtained from the leaves of *P. amarus*. The anti-inflammatory activity of lignans was evaluated and it was noticed that nirantin is the most active substance of this fraction. Moreover, an analgesic effect has also been reported (Kassuya et al., 2005, Kassuya et al., 2006), (7) inhibition of gastric lesions with the use of the methanolic extract from *P. amarus* (Raphael & Kuttan, 2003), (8) *in vitro* and *in vivo* inhibition of the replication of the human immunodeficiency virus (HIV) (Notka et al., 2004), (9) hypoglycemic activity, useful in the treatment for diabetes mellitus, with the methanolic extract (Raphael et al., 2002), (10) antiplasmodial activity, demonstrated by the use of the aqueous extract from the leaves and stem of the plant against *Plasmodium berghei* (Dapper et al., 2007), (11) studies on the radioprotective properties of polyphenols (tannins and flavonoids) isolated from *P. amarus* and described by Londhe et al (2009) showed that of all the tested compounds ellagitannin had the best activity, (12) potential antioxidant activity of the aqueous extract in rats (Karuna et al., 2009).

Considering the studies carried out so far, briefly presented in Table 8, the interest for plants of the genus *Phyllanthus* has increased significantly, particularly in regard to their therapeutic potential against many diseases. Many reasons have contributed to this interest, including: their wide distribution in many tropical and subtropical countries, the large number of species in this genus, their extensive therapeutic use in folk medicine, and the great variety of secondary metabolites present in these plants (Calixto et al., 1998).

Activity	Extract/ Compound	Reference
Inhibition of gastric lesions; Hypoglycemic	Methanolic Extract	Raphael & Kuttan, 2003; Raphael et al., 2002
Hepatoprotective	Crude Extract; Phyllantin	Pramyothin et al., 2007; Krithika et al., 2009
Protection of the hepatocytes against carbon tetrachloride (CCl ₄)	Phyllantin and Hipophyllantin, which are lignans present in the plant	Khatoon et al., 2006
Inhibition of hepatic carcinoma; Supression of the replication of the virus of hepatitis B; Hepatoprotective; Antisplasmoidal (<i>Plasmodium berghei</i>); Antioxidant	Aqueous Extract	Rajeshkumar & Kuttan, 2000; Thyagarajan et al., 1988; Pramyothin et al., 2007; Dapper et al., 2007 ; Karuna et al., 2009
<i>In vitro</i> and <i>in vivo</i> inhibitory effect of HIV; Antibacterial	Ethanollic Extract	Notka et al., 2004; Kloucek et al., 2005
Anti-inflammatory; Analgesic	Hexane Extract and Chemical Fraction rich in lignans, obtained from the leaves of <i>P. amarus</i>	Kassuya et al., 2005; Kassuya et al., 2006
Radioprotective Properties	Ellagitannin, isolated compound	Londhe et al., 2009

Table 8. Major biological activities of *Phyllanthus amarus* described in the literature.

There have been no reports of studies on *P. amarus* applied to the treatment for *S. mansoni* schistosomiasis. Nevertheless, records of anti-inflammatory and hepatoprotective activities of this plant have been found, which has led to the selection of the plant for this study, as the main pathology of schistosomiasis is the granulomatous inflammatory response.

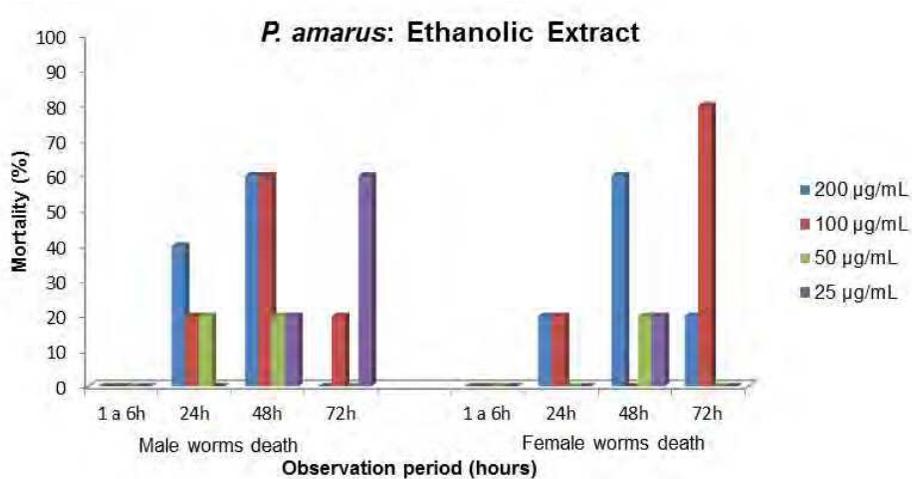
An *in vitro* study with the ethanolic extract and fractions obtained from *P. amarus* was carried out so that the schistosomicidal effect of this plant against the BH strain of *S. mansoni* could be verified. Four concentrations - C1 = 200µg/mL, C2 = 100µg/mL, C3 = 50µg/mL e C4 = 25µg/mL - of the extracts were tested against couples of adult worms, with five replications carried out for each concentration. At the end of the experiment (72 hours), the mortalities observed are the ones indicated in Table 9.

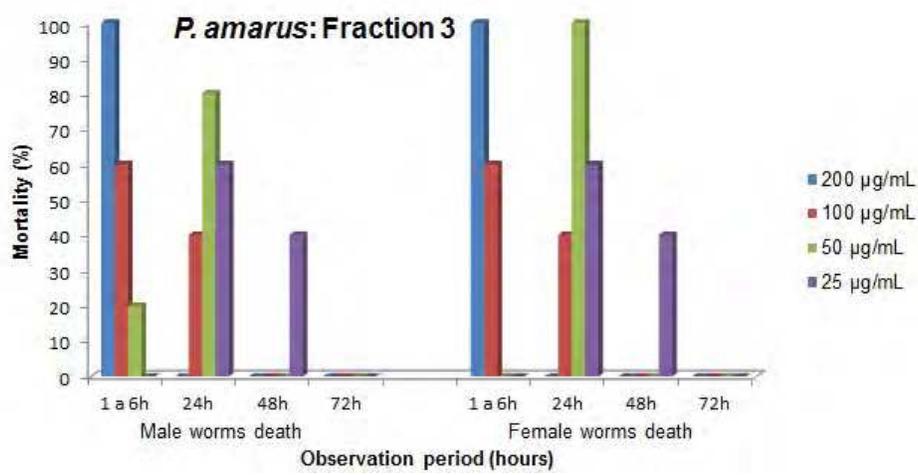
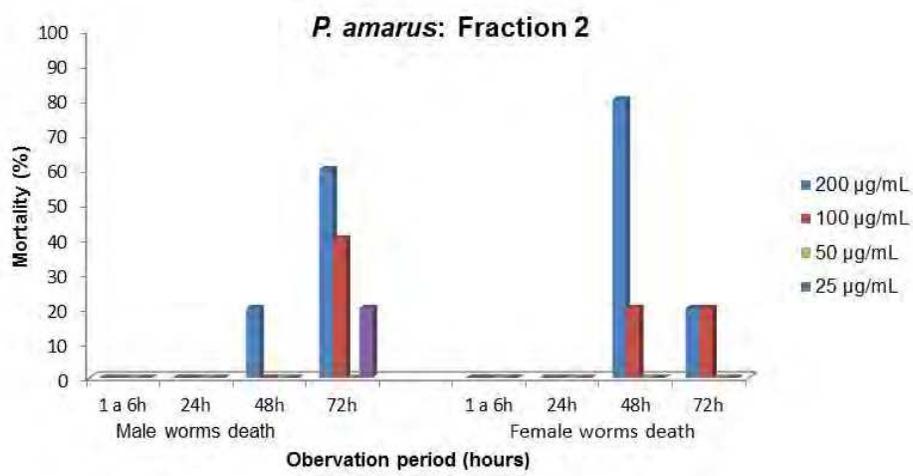
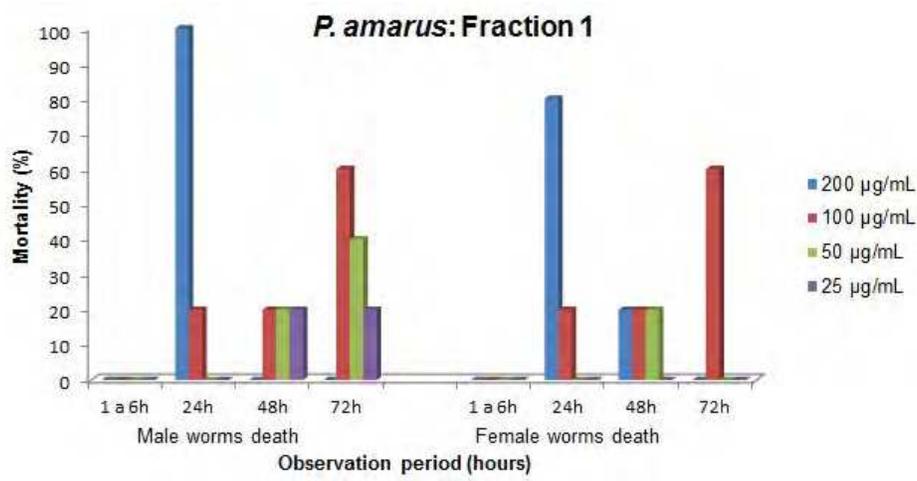
	Ethanollic Extract	Fraction 1	Fraction 2	Fraction 3	Fraction 4	Praziquantel	Control
C1 (200 µg/mL)	100%	100%	90%	100%	100%	100%	-
C2 (100 µg/mL)	100%	100%	40%	100%	90%	60%	-
C3 (50 µg/mL)	40%	40%	-	100%	30%	80%	-
C4 (25 µg/mL)	20%	20%	10%	100%	20%	60%	-

Table 9. Evaluation of the mortality of couples of *Schistosoma mansoni* submitted to different concentrations of *Phyllanthus amarus*. Control: Negative Group Control, with no addition of any extract or drug for 72 hours.

These results show that the fractions had better activity against the worms, taking into account the ones that managed to eliminate them more quickly.

The effect of the observation period on the mortality of the worms was also analysed. We consider that fractions 1 and 4 in C1 (200µg/mL) and fraction 3 in C1, C2 (100µg/mL) and C3 (50µg/mL) were more effective because after 24 hours of observation 100% of the worms were dead (Figure 8).





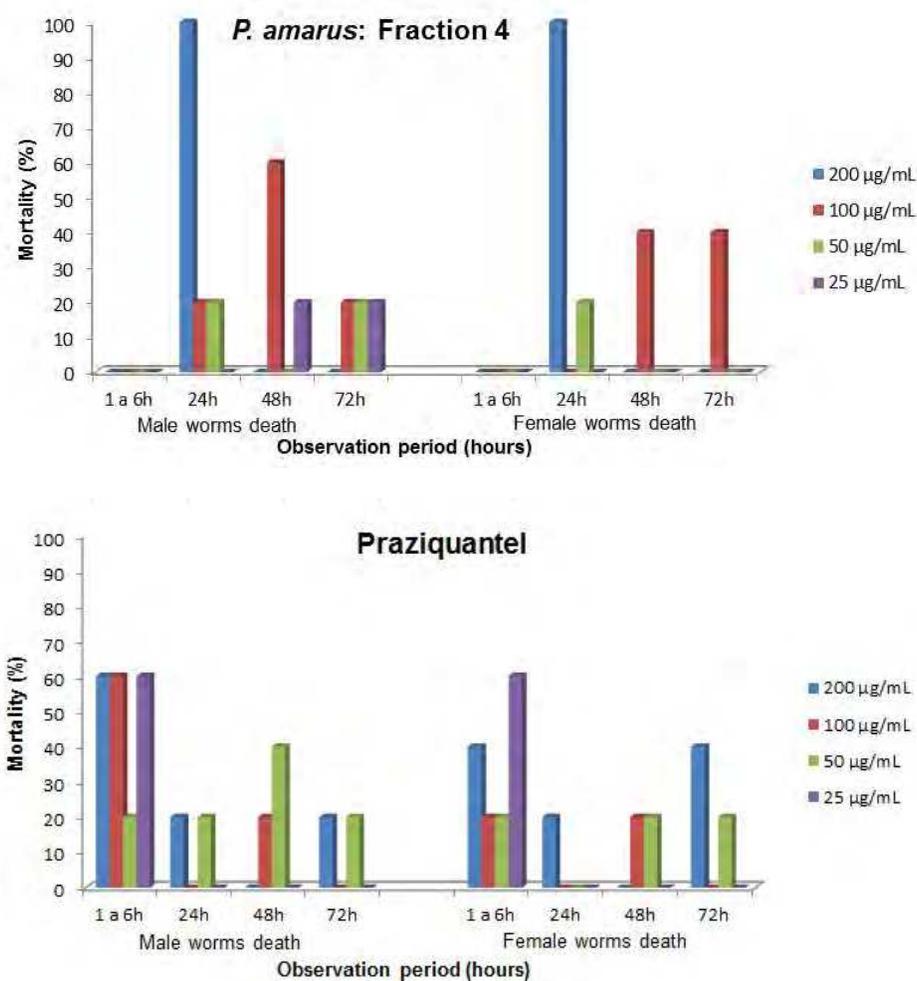


Fig. 8. Activity of the crude ethanolic extract and fractions 1, 2, 3 and 4 of *Phyllanthus amarus* and praziquantel on the viability of male and female *Schistosoma mansoni* worms in relation to the observation period of 72 hours.

As seen in the results of the *in vitro* tests, fraction 3 isolated from the crude ethanolic extract from *P. amarus* showed the best schistosomicidal activity.

5. Conclusion

We can conclude that the species of plants studied by our research group have schistosomicidal activity against *S. mansoni*. It is also worth pointing out that:

- The higher activity of artesunic acid in both *in vitro* and *in vivo* assays in comparison with artemisinin, with higher worm and oviposition reduction rates for both strains studied, which demonstrates that the different responses to the treatment by the two strains have not prevented the compound from working against them,
- *In vitro* assays with *B. trimera* showed better schistosomicidal activity for the crude dichloromethane extract, resulting in the mortality rate of 100% in the three concentrations tested, moreover, it was possible to notice that male *S. mansoni* worms were more susceptible to the action of this extract,

- The higher activity of the organic fraction from *C. verbenacea* in *in vitro* tests on the viability of the worms, killing a larger amount in less time in comparison with other extracts, also showing higher activity against male worms,
- The results of the *in vitro* tests carried out with *P. amarus*, which demonstrated that fraction 3 isolated from the crude ethanolic extract had better schistosomicidal activity because the mortality rate was 100% in all concentrations tested.

Considering the good results obtained so far, our research group will continue the chemical biomonitoring study by means of activity assays, aiming to isolate and identify fractions and compounds responsible for schistosomicidal activities shown by the medicinal plants under investigation.

6. Acknowledgements

The authors are thankful to the FAPESP and CAPES for financial support.

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Schistosomiasis

Edited by Prof. Mohammad Bagher Rokni

ISBN 978-953-307-852-6

Hard cover, 310 pages

Publisher InTech

Published online 13, January, 2012

Published in print edition January, 2012

In the wake of the invitation by InTech, this book was written by a number of prominent researchers in the field. It is set to present a compendium of all necessary and up-to-date data to all who are interested. Schistosomiasis or blood fluke disease, also known as Bilharziasis, is a parasitic disease caused by helminths from a genus of trematodes entitled Schistosoma. It is a snail-borne trematode infection. The disease is among the Neglected Tropical Diseases, catalogued by the Global Plan to combat Neglected Tropical Diseases, 2008-2015 and is considered by the World Health Organization (WHO) to be the second most socioeconomically devastating parasitic disease, next to malaria. WHO demonstrates that schistosomiasis affects at least 200 million people worldwide, more than 700 million people live in endemic areas, and more than 200.000 deaths are reported annually. It leads to the loss of about 4.5 million disability-adjusted life years (DALYs).

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