

## Review

# Medicinal plants and their bioactive constituents: A review of bioactivity against *Schistosoma mansoni*

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Accepted 9 May, 2013

Schistosomiasis is a neglected disease that affects approximately 200 million people worldwide. In order to reduce the parasite prevalence, further researches aiming new treatment methods is necessary. Once infected by *Schistosoma mansoni*, one can have no symptoms in the acute phase, however, chronic phase is characterized by marked egg-induced hepatic granulomatous inflammation. To prevent the disease, the main prophylactic method is environmental sanitation which decreases the entrance of eggs into water bodies. In addition to fighting the snail, treatment of population is important. Currently, for treatment of schistosomiasis, the most used drugs are Praziquantel (PZQ) and Oxamniquine, whereas PZQ is the drug of choice. Each drug has a specific mechanism of action aimed at the elimination of the parasite. However, any parasite treatment based on the use of a single drug poses serious concerns regarding the onset of resistance. The search for new therapeutic agents derived from medicinal plants for schistosomiasis has progressed significantly in the last decade. The aim of this paper is to provide an updated survey on medicinal plants that have significant therapeutic effects in animal models of schistosomiasis. A considerable number of herbal constituents with schistosomicidal effect have been well characterized and may be good candidates for prospective studies and investigations that may result in clinical usage.

**Key words:** *Schistosoma mansoni*, schistosomicidal, medicinal plants.

## INTRODUCTION

Parasitic diseases represent a serious public health problem in many parts of the world, particularly in many developing countries, reflecting the social and economic situation of these countries (Urbani et al., 2003). Considered as a neglected disease by the World Health Organization (WHO), schistosomiasis is the second most prevalent tropical disease. Its endemic in approximately 70 countries and it affects approximately 200 million people

worldwide. Also, it is estimated that 779 million are at risk of contracting this infection (Steinmann et al., 2006). The disease is chronic and insidious, with few reports of diagnosis in early stages. Its evolution can lead to the development of clinical forms, making men and women disabled in their most productive ages. To reduce the occurrence of parasitic infection, it is necessary to search for new treatment methods (Engels et al., 2002).

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Schistosomiasis is caused by digenetic trematodes, belonging to the genus *Schistosoma*. Out of five species of *Schistosoma* that parasitize humans, the most relevant are *Schistosoma mansoni* (Sambon, 1907), *Schistosoma haematobium* (Bilharz, 1852) and *Schistosoma japonicum* (Katsurada, 1904) (Paraense, 1975). They cause intestinal (*S. mansoni* and *S. japonicum*) and urinary schistosomiasis (*S. haematobium*).

In Brazil, schistosomiasis is caused by *S. mansoni* and holds a serious public health problem, extending over 19 states. In the Southeast and Northeast, there are areas of intense transmission, from Maranhao to Espirito Santo and Minas Gerais, while in the North and South, there are only isolated focus (Coura and Amaral, 2004; Teles, 2005). According to Katz and Peixoto (2000), more than 8 million people are infected, while another 30 million are at risk of infection. This endemic is associated with poverty and low economic development, and the use of contaminated surface waters for agriculture, household work and/or recreation.

By conducting a literature review of the medicines described in this paper, it will be possible to evaluate the potential of new drugs with greater therapeutic effect based on the understanding of action mechanism in existing drugs. Thus, many natural organic compounds have been described due to their potential schistosomicidal effects. Despite the great interest in natural products for treatment of parasites, Brazilian drug companies still face some problems such as the need for large industry efforts to meet national guidelines imposed by the National Policy on Medicinal Plants and Herbal Medicines (Ferreira, 1998).

There are great difficulties on the treatment of schistosomiasis due to the complexity of the parasite life cycle and the existence of resistant strains of *S. mansoni* to PZQ. This affects, currently a large number of medicinal plants whose therapeutic potential and their mechanisms of action have been studied in a variety of animal models. These reviews provided useful information for development of new drugs for schistosomiasis. Thus, this review aims to gather studies on medicinal plants, their extracts or their constituents with schistosomicidal effects in animal models, and their possible mechanisms of action.

## LIFE CYCLE OF THE PARASITE

*S. mansoni* is one of the species that cause schistosomiasis; and there are three species of intermediate hosts: *Biomphalaria glabrata*, *Biomphalaria straminea*, and *Biomphalaria tenagophila*. Adult *S. mansoni* live in the bloodstream. Their eggs pass out of the host with the faeces. In contact with water, free-swimming miracidia emerge from the egg and penetrate the soft tissues of the snail host. Within the snails, miracidia immediately differentiate into sporocysts and, as they migrate through the snail tissues, give rise to

cercariae. Cercariae are shed from the snails and are infective to humans by direct penetration of the skin (Abath et al., 2006) (Figure 1).

## IMMUNOPATHOLOGY

*S. mansoni* parasites are digenetic trematode platyhelminths that inhabit the mesenteric veins of humans and other mammals. Although the majority of people infected with these parasites have no or mild symptoms, a small proportion of them develop severe disorders such as the hepatosplenic and the cardiopulmonary chronic forms of the infection and less frequently, neuroschistosomiasis (Ferrari et al., 2008).

In the course of an infection, the immune response progresses through at least three phases (Pearce and MacDonald, 2002). In the first 3 to 5 weeks, during which the host is exposed to migrating immature parasites, the dominant response is T helper 1 (TH1)-like. As the parasites mature, mate and begin to produce eggs at weeks 5 to 6, the response alters markedly; the TH1 component decreases and this is associated with the emergence of a strong TH2 response. This response is induced primarily by egg antigens (Pearce and MacDonald, 2002).

Many of the eggs traverse the gut tissue and are excreted with the feces, but a significant number get lodged downstream in the liver where they eventually die. The host reacts to eggs and egg products by inducing a Th2-mediated immune response which may lead to granulomatous inflammation and pathological tissue remodeling and fibrosis. It is not clear if particular egg components are critical for the extravasation of the eggs from the blood vessels. Since freshly laid immature eggs are not yet believed to secrete proteins, one could hypothesize that the egg shell is involved in this process. More clearly however, the eggs' secretory proteins (ES) which are formed in the sub-shell area upon maturation and secreted into the egg's environment induce a major immune response of the host that appears to be leading to Th2 polarization (Meevissen et al., 2012). According to these authors, to other components of the egg, such as the hatching fluid and most of the so-called soluble egg antigens (SEA), the host will most likely be exposed only when eggs die and fall apart in host tissues (Meevissen et al., 2012).

## CONTROL AND PREVENTION

Until the 70s, combating schistosomiasis aimed first and foremost to the control of transmission, mainly aimed at reduction of populations of mollusks. According to the Ministry of Health (Brazil, 2008), since the 80s, after the arrival of more effective, safe and inexpensive drugs, the main goal has become the morbidity control, with

chemotherapy. According to WHO (1993), chemotherapy is the main alternative to reduce disease morbidity in endemic areas, as well as treating individual cases. However, the current strategy is to join together chemotherapy control to preventive measures such as health education and sanitation, besides the control of intermediate hosts, through the use of molluscicides, biological control and changes in the aquatic environment (Ministry of Health, 2008).

The disease control in Brazil is put at a disadvantage by: high dissemination of intermediate hosts, high costs for implementation of sanitation and optimal treated water supply, difficulties for individual protection. Thus, there is an enduring intense contact with natural waters providing re-infection. Another problem is the long time needed for results showed by health education adherence of communities to control programs (Coura and Amaral, 2004).

Another important aspect is that most people infected by schistosomiasis remain asymptomatic. The clinical stage corresponds to development of parasite in the host and varies depending on location, intensity of parasitism, the response capacity of an individual, and the treatment (Coura and Amaral, 2004)

## TREATMENT

Therapy against schistosomiasis began with tartar emetic, a trivalent antimonial highly toxic compound, but its side effects have led to the searching on metal-free drugs (Katz and Coelho, 2008). As alternatives drugs, have emerged Lucanthone and Hycanthone, obtained by the action of fungus *Aspergillus sclerotiorum* on Lucanthone (Simoes, 2009). According to these authors, another alternative was the Niridazol, which acts on the three species of *Schistosoma* that parasitize human: *S. mansoni*, *S. japonicum* and *S. haematobium*. However, as they cause serious side effects, they were not considered safe enough to be used in large scale in treating schistosomiasis (Simoes, 2009). The next steps for treatment of schistosomiasis came with Oxamniquine and Praziquantel (Simoes, 2009).

## PRAZIQUANTEL

PZQ is a synthetic derivative of isoquinoline Pyrazine (Figure 2), is currently the drug of choice, according to the WHO for treatment of schistosomiasis in large scale being effective against the five species of *Schistosoma* (Doenhoff et al., 2002). In general, the PZQ has low toxicity and is eliminated through urine and feces after 24 h (Cioli and Pica-Mattocchia, 2003). PZQ has some effect on the parasite, such as muscle contraction, metabolic abnormalities and tegument damage (Pax et al., 1978; Becker et al., 1980; Fetterer et al., 1980; Mehlhorn et al., 1981; Lima et al., 1994a; Ribeiro et al., 1998; Oliveira et

al., 2006). In relation to these effects, clinical efficacy of the drug is best observed with the action on the tegument of *S. mansoni*. Twenty-four hours after administration of PZQ by oral route, the tegument is wholly destroyed with intense infiltrated granulocytes, Eosinophils, invading the parasite's inner tissue (Katz, 2005).

PZQ has two major effects: (i) stimulation of motor activity by calcium influx from external sources causing spasms and paralysis of the muscles, (ii) damage to the tegument, shown by formation of vacuoles and vesicles. Furthermore, PZQ acts synergistically with the host immune response, since it depends on antibody productions. The damage to the tegument along the body of the worm impairs its functioning and also destroys the defense system, facilitating the attack of the host immune system (Th2) with increased levels IL- 5, IL-10 and IL-13 (Reda et al., 2011; Joseph et al., 2004).

It is believed that most of these mechanisms of action of PZQ are dependent processes of  $Ca^{+}$  (Cioli et al., 1995), since *in vitro* experiments performed in culture medium free of  $Ca^{++}$  showed blocking responses and depend on this ion (Pax et al., 1978; Wolde Mussie et al., 1982; Xiao et al., 1984). It is suggested that PZQ acts by inhibiting the calcium channel as well (Greenberg, 2005), since, due to interference in those channels of the parasite, it is possible to obtain a significant result on the level of inhibition of the schistosomicidal activity of PZQ (Pica-Mattocchia et al., 2007). Oliveira et al. (2006) have demonstrated that PZQ is also capable of inhibiting the activity of adults' worms' excretory *S. mansoni* and this can be recovered depending on the concentration of the drug after its withdrawal.

The resistance of *S. mansoni* to Praziquantel has been reported in Egypt where the drug has been used extensively over 10 years (Doenhoff et al., 2000; El-Banhawey et al., 2007; El-Ansary et al., 2007). There are some reports on the possibility of resistance of some strains of *Schistosoma* to Praziquantel in the field (Fallon et al., 1995; Mandour et al., 1990), and in laboratory (Couto et al., 2010; 2011).

## OXAMNIQUINE

OXA is a tetrahydroquinoline semisynthetic and became available for treatment of Schistosomiasis in the 70s. Recently, it was widely used in mass treatment, reaching approximately 13 million people in South America and Africa (Fenwick et al., 2003). Currently, OXA has not been manufactured in Brazil and it has been replaced by PZQ for treatment of Schistosomiasis, in public health campaigns as well as in clinics, due to its high efficiency and low cost of manufacturing by Oswaldo Cruz Foundation (FIOCRUZ). OXA has an anticholinergic effect which increases motility of the parasite and inhibits nucleic acid synthesis. It is most effective on the male parasite than on the female one. At therapeutic doses, it

shows greater sensitivity to *S. mansoni* and has no notable effect on other *Schistosoma* spp which parasitize human beings (Abdul-Ghani et al., 2009). Several authors have demonstrated the presence of strains resistant to OXA in Brazil. Drug resistance is therefore a more serious and complex issue than previously thought (Ferrari et al., 2003).

## MEDICINAL PLANTS

Natural products have been utilized by humans since ancient times, and the relief and cure of their diseases was the first purpose for using natural products in medicine. The history of the oriental and occidental civilizations is very rich in examples of the utilization of natural products in medicine and health care. Chinese traditional medicine is one of the most important examples of how natural products can be efficient in the treatment of diseases, and it points to the importance of scientific research on natural products concerning the discovery of new active chemical entities. The complexity, chemical diversity and biological properties of natural products always fascinated people, and during the last 200 years, this led to the discovery of important new drugs. In the last 30 years, the development of new bioassay techniques, biotechnology methods, bio-guided phytochemical studies, automated high throughput screening and high performance analytical methods, have introduced new concepts and possibilities of rational drug design and drug discovery (Viegas et al., 2006).

Out of estimated 100,000 species of plants cataloged in Brazil, only 8% had their chemical compounds studied, and it is estimated that only 1,100 species have been studied for therapeutic use (Reis et al., 2007). This great unknown diversity yet constitutes important source for searching new drugs (Anthony et al., 2005). Repeated chemotherapy on schistosomiasis has resulted in emerging resistant strains of *Schistosoma*. The development of such resistance has attracted the attention of many researchers. Many medicinal plants have been studied to investigate their potential schistosomicidal (Mostafa et al., 2011).

Tests with extracts from Chinese ancient medicinal plants have been successful in China (Xiao et al., 2000), such as artemisinin, used in the treatment of malaria by *Plasmodium falciparum*, extracted from leaves of *Artemisia annua*. Tests with artemisinin has proved effective against *S. japonicum*, *S. haematobium* and *S. mansoni* (Xiao et al., 2000; Utzinger et al., 2003; Yuanqing et al., 2001; Lescano et al., 2004). De Souza et al. (1991) have found moderate reduction of worms in hamsters infected with *S. mansoni* after treatment with artemethen, a derivative of artemisinin. Barth et al. (1997) found that *in vitro* tests on *S. mansoni* decreased motility of worms, inhibiting oviposition and high mortality of parasites when goyazensolide is used, a component

extracted from *Eremanthus goyazensis*, a plant of the Asteraceae family.

Biologically active compounds from *Millettia thonningii*, a legume found in Africa, showed cercaricidal and schistosomicidal actions, and was even observed as decrease in motility of miracidia of *S. mansoni* (Perrett et al., 1994; Lyddiard et al., 2002). Schistosomicidal activity of crude aqueous extract of ginger against *S. mansoni* was investigated by Mostafa et al. (2011) who observed that parasitic load and egg density in the liver and feces of mice treated with ginger were smaller than their counterparts. Males recovered from mice treated with ginger lost their normal architecture of surface, extended erosion beyond the tegument, besides numerous bubbles around tubers. Histopathological data have indicated a reduction in number and size of granulomatous inflammatory infiltration in the liver and intestine of treated mice compared to the untreated ones. The results suggest that ginger have schistosomicidal activity.

A survey conducted in South Africa showed three plants as potential antischistosomal agents for *S. haematobium*. They are: *Berheya speciosa* (Asteraceae), *Euclea natalensis* (Ebenaceae) and *Trichilia ematica* (Melicaceae) (Sparg et al., 2000). Extracts of *Phyllanthus amarus*, a Euphorbia, popularly known as jigsaw stone, stone breaks or dove herb was used as *in vivo* tests against *S. mansoni* BH strain in infected *Mus musculus*. It is commonly used to treat liver diseases and urogenital (Khatoon et al., 2006). However, when used on *S. mansoni*, *P. amarus* resulted in up to 63% reduction in the number of worms and ceased oviposition showing the schistosomicidal potential activity of the plant (Oliveira, 2008). The efficacy of *Balanites aegyptiaca* fruit mesocarp was compared to PZQ in mice infected with a Sudanese strain of *S. mansoni*. A significant reduction was observed on OPG (amount of eggs per gram of feces), on the load of eggs in the tissues and on the recovery of adult worms, in animals treated with the plant as well as in those treated with the drug (Koko et al., 2005).

Schistosomicidal properties of *Nigella sativa* seeds have been tested *in vitro* against miracidium, cercaria and adult worms of *S. mansoni*. The results indicate they have strong biocidal effect on all stages of parasite and also showed an inhibitory effect on the oviposition of female adult worms. Data have revealed that *N. sativa* induced oxidative stress on adult worms, indicated by a decrease in the activity of antioxidant superoxide dismutase enzymes, peroxidase and reductase glutathione enzymes, glucose metabolism, and hexokinase glucose-6-phosphatase (Mohamed et al., 2005).

*Eremanthus erythropappus* is a plant popularly known as Candela (Asteraceae), with high prevalence in the State of Minas Gerais. The essential oil extracted from the wood of *E. erythropappus* inhibits the active penetration of cercaria into the skin and thus was considered a schistosomicidal potentiality. This effect was related to the

was related to the presence of unsaturated sesquiterpene lactones. For the experiment were also chosen ethanolic extract, dichloromethane and Candeia's leaf hexane to evaluate their schistosomicidal activity *in vitro* experimental model. The damage caused by extracts on adult worms were irreversible, confirming the *in vitro* activity of Candeia's extracts in adult worm of *S. mansoni*, causing total paralysis on males and females (Almeida et al., 2012).

Jatsa et al. (2010) studied the evaluation of schistosomicidal activity *in vitro* from the aqueous extract of *Sida pilosa*. Infectivity rates showed that oral treatment with the extract of *S. pilosa* resulted in significant reduction in parasite burden and egg deposition.

*Harpagophytum procumbens*, commonly known as "Devil's claw" is a medicinal plant originally from Africa, specifically from Kalahari Desert, used by Indians in the form of infusion for treatment of rheumatic diseases, diabetes, atherosclerosis and malaria. The pharmacological properties of iridoid glycosides 0.5 to 3% are linked to antiinflammatory effects. Rodolpho et al. (2010) evaluated the inhibitory effect of crude extract of *H. procumbens* in removing eggs during infection by *S. mansoni*. After treatment, there was a significant reduction on eggs on group treated with 15 mg/kg of crude extract. In this sense, the treatment using *H. procumbens* may contribute to reduction of eggs during infection with *S. mansoni*, perhaps a possible alternative for treatment of schistosomiasis.

The extract of *Piper tuberculatum* was tested *in vitro* and acted efficiently on adult worms of *S. mansoni*, even when exposed to low concentrations. Male worms were more sensitive, while *in vivo* tests we observed with decrease in the number of first and second-stage eggs, indicating a decrease in oviposition (Simoes, 2009).

Piplartine is an amide found in several species of *Piper* (Piperaceae). This amide showed various biological activities such as antifungal and insecticidal and trypanocidal and leishmanicidal effects. The effect of piplartine isolated from *Piper tuberculatum* on schistosomula and on adult worms of *S. mansoni* was evaluated, and the results revealed that piplartine is an efficient compound against larvae and adult worms of *S. mansoni in vitro* (Moraes et al., 2011). In Mali (Niger), the demand for traditional medicine is a very common habit, not only because of its cultural importance, but also because most people cannot afford western medicines. Mali is considered the main area of transmission of *S. mansoni* and *S. haematobium* (Bah et al., 2006).

An ethnopharmacological survey was conducted in this area to assess the plants used against schistosomiasis among traditional healers. Fifty-five plants belonging to 30 families have been reported as schistosomicidal remedies, while nine combinations of plants were used for the urinary form of the disease. *Cissus quadrangularis* and *Stylosanthes erecta* plants were the primary and the most utilized plants used against schistosomiasis in Mali

(Bah et al., 2006). *Clerodendrum umbellatum* (Verbenaceae) is traditionally used in countries like Cameroon for treatment of many diseases, including intestinal helminthes. The leaves' aqueous extract of this plant was evaluated *in vivo* the schistosomicidal activity. These have shown schistosomicidal properties in doses of at least 80 mg/kg body weight (Jatsa et al., 2009).

*Biomphalaria alexandrina* were treated with dry powder leaves of *Solanum nigrum* and *Ambrosia maritima*. These two plants affect the parasite development in snails. Attenuated cercaria released from treated snails were used to infect male mice to evaluate their pathogenicity compared to control (cercaria from untreated mollusks). The average number of adult worms decreased compared to control. Amount of eggs in liver and intestine of mice infected with attenuated cercaria was significantly smaller due to low fecundity of worms developed from attenuated cercaria. The number and size of granulomatous reactions showed significant reduction in mice infected with attenuated cercaria (El-Ansary et al., 2003).

## PLANTS WITH MOLLUSCIDAL ACTIVITY

Many aquatic snails act as intermediate hosts for larval trematodes. The WHO has tested thousands of synthetic compounds for controlling this host. Although effective, molluscicidal showing the activity of some compounds has not proved entirely satisfactory (Singh et al., 2010). With growing awareness of environmental pollution, efforts have been made to discover molluscicidal products from plants. Common medicinal plants such as *Thevetia peruviana* (Family Apocynaceae), *Euphorbia hirta* and *Euphorbia pulcherima* (Family Euphorbiaceae), have strong molluscicidal activity on freshwater clams. The toxicological actions of *T. peruviana* may be due to the presence of apigenin-5-methyl ether (flavonoids) and triterpenoid glycosides, whereas a number of alkaloids (pseudo-akuammigine besides betulin, ursolic acid and beta-sitosterol), steroids, triterpenoids, diterpenoids, pulcherrol, beta-sitosterol, ellagic acid and beta-amyrin Hentriacontane are present in *E. hirta* and *E. pulcherima* (Singh et al., 2010).

The species originated in Madagascar *Euphorbia milii*, and are used in Brazil as an ornamental plant. It is also known as "Crown of Christ", "Two friends" and "Mattress bride." Studies about its muluscicida activity have been carried out and laboratory results showed effectiveness against *B. glabrata* *B. tenagophila*, *B. pfeifferi*, *B. straminea* and *Bulinus* spp. (Schall, 2010). Latex obtained from *Euphorbia splendens* demonstrated under laboratory and field conditions, that can it be used as a natural molluscicide (Lima et al., 2010).

*Tetrapleura tetraptera*, commonly known as Aridan (fruit), is usually found in lowland forest in tropical Africa. It is one of molluscicidal medicinal plants from Nigeria. All

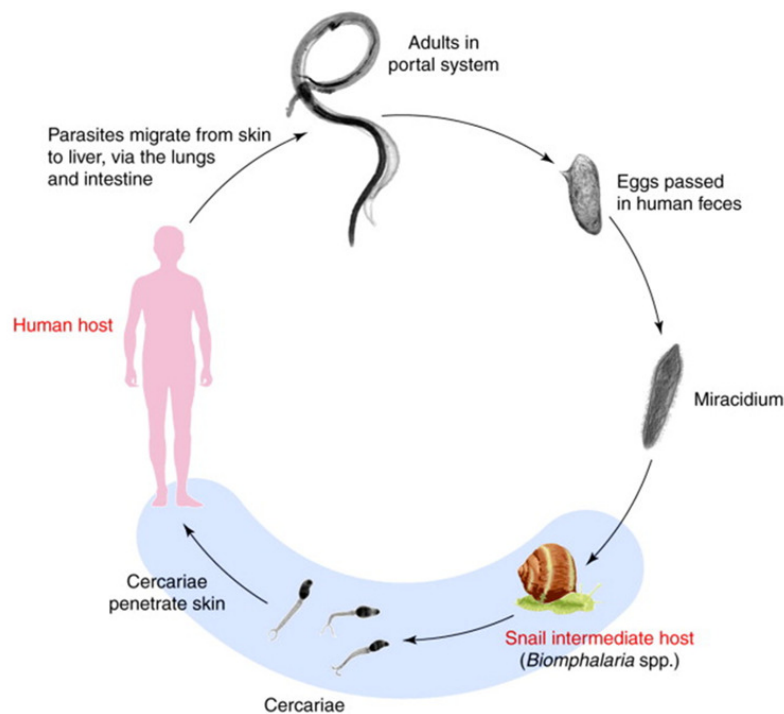


Figure 1. Schistosomiasis life cycle.

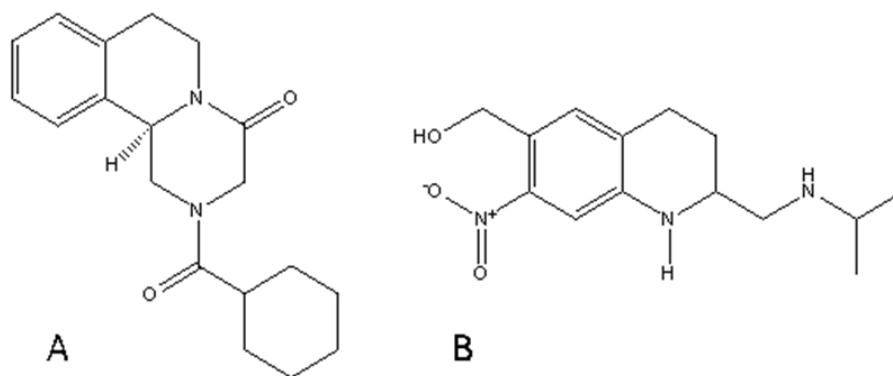


Figure 2. Chemical structures (A) Praziquantel, (B) Oxamniquine.

isolated compounds from the fruits or other parts were found to exhibit strong molluscicidal properties against the snail *B. glabrata* (Aladesanmi, 2006). Alcoholic extracts of six medicinal plants of Brazilian cerrado were assessed for their molluscicidal activity on *B. glabrata*. The bark extract of *Stryphnodendron polyphyllum*, which is rich in tannins, was the most promising plant with molluscicide compound (Bezerra et al., 2002). Antiprotozoal and molluscicidal activities were performed with ethanol extracts of plant species on the Brazilian side of the Paraná River. Extracts were obtained from the leaves of *Cayaponia podantha*, *Nectandra falcifolia*, *Castiglioni* and *Paullinia elegans*, as well as the aerial parts of *Helicteres gardneriana*, *Melochia arenosa*, all

belonging to the genera used in popular medicine. Regarding to molluscicidal activity, acute toxicity of *M. arenosa* in *B. glabrata* was lethal to 100% (Truitt et al., 2005).

## CONCLUSION

The information collected in this review of a large number of herbal extracts and constituents that have therapeutic effects in animal models of Schistosomiasis should be used in researching for new therapeutic agents originated from medicinal plants for this parasitic disease. The herbal constituents whose schistosomicidal effects have

been well characterized should be great candidates for further research that may result into clinical use. Some of these constituents with well-defined chemical structures may serve as samples and models for the synthesis of analogous drugs with greater efficacy and fewer side effects. However, despite these herbal preparations showing therapeutic potential in animal models, clinical science of most herbal extracts and mixtures is still limited. Therefore, herbal extracts and constituents with schistosomicidal effects demonstrated in this paper in animal models may serve as better assessments in preclinical studies and clinical trials.

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