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Anti-Schistosomal Activity of Medicinal Plants: Mini Review

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Abstract: Schistosomiasis is a parasitic disease caused by the Schistosoma genus' parasites, and several complications associated with this pathology can lead to death. Indeed, *Schistosoma mansoni* and *Schistosoma haematobium* are the major species responsible for this disease, spreading particularly in Africa. While synthetic drugs used to treat Schistosomiasis are often not effective and represent major side effects. In this context, many research teams are currently focusing on identifying natural secondary metabolites with anti-schistosomal properties. Therefore, this work highlighted an overview of some medicinal plants' anti-schistosomal activity and their bioactive compounds.

Keywords: Schistosomiasis; medicinal plants; bioactive compounds; anti-schistosomal activity.

1. Introduction

Schistosomiasis is a tropical disease caused by worms of the genus *Schistosoma*, affecting between 230 and 250 million worldwide [1]. It is transmitted by freshwater mollusks, which act as intermediate hosts [2]. This infection remains a major public health problem in developing countries. The two major species that caused human Schistosomiasis are *S. mansoni* and S. *haematobium*, responsible for intestinal and urinary Schistosomiasis, respectively, spread out mainly in Africa [3].

Praziquantel (PZQ) and oxamniquine are the classic treatments for human schistosomiasis [4]. However, these drugs have limitations; they cause frequent treatment failures, high rates of reinfection [5], and, in some cases, specific resistance against praziquantel [6]. In addition to treating the infected individuals, snail control with molluscicides (Niclosamide, sodium pentachlorophenate, and tributyltin oxide) has been mandatory to reduce the risk of schistosomiasis transmission in endemic areas [7]. However, it presents major risks for the environment and human health.

It is necessary to find effective treatments, less expensive, and with little undesirable effects in this context. Moreover, phytotherapy is a promising alternative in managing parasitic

diseases [8, 9], notably bilharziasis. Indeed, several studies have evaluated anti-schistosomal power using medicinal plants and their bioactive compound [10, 11].

2. Overviews on Schistosomiasis

Bilharziasis is a parasitic disease caused by trematode worms of the genus *Schistosoma*. It exists in 75 to 76 countries, mainly in Africa, Asia, and South America [12], and can also occur in non-endemic areas. Generally, five *Schistosoma* species can infect man, including *Schistosoma haematobium*, *Schistosoma mansoni*, *Schistosoma japonicum*, *Schistosoma mekongi*, and *Schistosoma intercalatum* [13]. The schistosome has several development stages, including worm, egg, miracidium, schistosomula, sporocyst, and cercaria [14]. The male and female genitals are located face-to-face and allow almost permanent copulation [15]. Adult worms have a lifespan varying from 5 to 32 years, but the average duration of laying varies from 3 to 12 years [16]. Its development cycle is dixene, but it includes an intermediate host (mollusk). The asexual phase of the parasite's reproduction occurs, and a definitive host in which the sexual part of this reproduction occurs [17, 18]. The disease transmission depends on close contact between humans, the parasite, the intermediate host, and surface water as well as other important factors such as climate, socio-economic level, and population density.

3. Anti-Schistosomal Activity of Medicinal Plants

Given that Schistosomiasis remains a global challenge, especially in sub-Saharan Africa, it affects the world's most impoverished populations and subsequently causes significant morbidity and mortality worldwide. Moreover, the existing treatment does not kill immature schistosomes. It has serious adverse effects, and also, the developed resistance limits its effectiveness (infections, therefore, cannot be treated effectively) [19, 20]. It is, therefore, urgently needed to develop alternative drugs for patients. Several studies have reported anthelmintic activities and evaluated the schistosomicidal properties of medicinal plant extracts. These studies showed promising results with efficacy effects against all Schistosoma species and on the parasitic host, giving hope to save the lives of millions of people worldwide. Furthermore, several extracts from the medicinal plant were tested against *Schistosoma* (Table 1). These species include *Plectranthus tenuiflorus*, *Ocimum americanum*, *Bridelia micrantha*, *Peganum harmal*, *Allium sativum*, *Clerodendrum umbellatum*, *Mitracarpus frigidus*, *Rauwolfia vomitoria*, *Cleome droserifolia*, and *Punica granatum* [21-46].

3.1. Anti-schistosomal effects of plant extracts.

The anti-schistosomal effect medicinal plants depend on several factors, including medicinal plants tested, used methods, and strains tested. Table 1 summarizes the results of different reported studies in the literature on the anti-schistosomal effects of medicinal plant products. Osman and colleagues showed that *Peganum harmala* seeds exhibit a mortality rate of 100% during the first half-hour of exposure for all the extracts used at different concentrations [34]. Otherwise, stem and root bark and fruit rind and placenta of *Punica granatum* tannins revealed an effective *in vitro* activity on the miracidia of *Schistosoma mansoni*, which exhibited a cytotoxic effect of 50% at the concentration of 0.39 ppm [33]. In another study, the methanolic extract of *Plectranthus tenuiflorus* showed moderate anti-cercaria and anti-schistosomula activities with IC_{50} values of 12.29 and 17.39 mg/100 mL, respectively.

Table 1. Anti-schistosomal effects of some medicinal plants.

Family	Species	Extract	*In vivo/In vitro*	Larvae species	Effect	References
Agavaceae	*Agave lophantha*	Ethanol extract	*In vitro*	Worms of *Schistosoma mansoni*	LC_{50}=8.2 ppm	[21]
Amaranthaceae	*Chenopodium ambrosioides*	Hydro-alcoholic extract	*In vitro*	Cercariae	Increased mortality of cercariae	[40]
			In vitro	Adult worms	Increased mortality of adult worms	[40]
			In vivo	Swiss mice infected with cercariae of *S. mansoni*	Reduced the eggs in feces and liver	[40]
Amaryllidaceae	*Allium sativum*	Methanolic extracts	*In vitro*	*Schistosoma mansoni* worms	High anti-schistosomal activity	[22]
			In vivo	*Schistosoma mansoni* worms	A reduction of 27.6% and 21.7% in worm burden in the groups having received *Allium sativum*	[22]
Anacardiaceae	*Lannea schimperi*	Methanolic stem bark extracts	*In vitro*	Cercariae	100% of the mortality was observed at 2 mg/mL	[41]
		Methanolic stem bark extracts	*In vitro*	Adult *Schistosoma mansoni*	Exhibited 100% activity against adult worms at the dose range of 1 to 2 mg/ml after 48 hours of exposure	[41]
		Methanolic stem bark extracts	*In vitro*	Schistosomula	Significant activity against Schistosomula	[41]
	Searsia longipes	Methanolic stem bark extracts	*In vitro*	Cercariae	100 % mortality was observed at the concentration range of 1 to 2 mg/mL	[41]
			In vitro	Schistosomula	Significant activity against Schistosomula	[41]
				Adult *Schistosoma mansoni*	Exhibited 100% activity against adult worms at the dose range of 0.5 to 2 mg/mL after 48 hours of exposure	[41]
	Ozoroa pulcherrima Schweinf	Methanolic extracts of root parts	*In vitro*	Adult worms of *Schistosoma mansoni*	Significant reduction	[42]
			In vitro	Cercariae	Most active on cercariae with an LC_{50} of 20.65 µg/mL after 30 minutes	[42]
	Ozoroa pulcherrima Schweinf	Roots methanolic extract	*In vivo*	Liver injury induced by *Schistosoma mansoni* in mice	Significant reduction of worm burden and ova count in the feces, Liver and intestine	[43]
Apocynaceae	*Rauwolfia vomitoria*	Ethanol extract of stem bark	*In vitro*	*Schistosoma mansoni*, Cercariae	LC_{50}=207.4 μg/mL in 1 hour	[23]
		Ethanol extract of the root	*In vitro*	*Schistosoma mansoni*, Cercariae	LC_{50}=1430 μg/mL in 1 hour	[23]
		Ethanol extract	*In vivo*	*Schistosoma mansoni*, Adult worms	All adult worms exposed to the concentrations range of 250–1000 μg/mL for both plant parts	[23]

Family	Species	Extract	*In vivo/In vitro*	Larvae species	Effect	References
Asteraceae	*Ajania nubigena,*	Luteolin	*In vitro*	*Schistosoma mansoni*	IC_{50}=5.8 µg/mL	[24]
		Linalool oxide acetate (1)	*In vitro*	*Schistosoma mansoni*	IC_{50}=36.9 µg/mL	[24]
		Luteolin	*In vitro*	*Schistosoma mansoni*, Schistosomula	IC_{50}=13.3 µg/mL	[24]
		Luteolin	*In vitro*	*Schistosoma mansoni*	Activity anti schistosomal	[24]
	Ageratum conyzoides	Essential oil	*In vitro*	Worms of *Schistosoma mansoni*	Interesting dose-dependent reduction in the number of eggs of *S. mansoni*	[25]
	Baccharis trimera	Dichloromethane extract (DE)	*In vitro*	Adults of *Schistosoma mansoni*	Able to inhibit 100% of the oviposition in females.	[26]
		Aqueous fraction (AF)	*In vitro*	Adults of *Schistosoma mansoni*	Able to inhibit 100% of the oviposition in females.	[26]
		Aqueous fraction (AF)	*In vivo*	Juvenile worms	Female worm total burden reductions of 75%	[26]
		Dichloromethane extract (DE)	*In vivo*	Juvenile worms	Female worm total burden reductions of 68%	[26]
		Dichloromethane extract (DE)	*In vivo*	Adults of *Schistosoma mansoni*	Schistosomicidal effects	[26]
		Aqueous fraction (AF)	*In vivo*	Adults of *Schistosoma mansoni*	Schistosomicidal effects	[26]
	Juglans nigra	Methanolic extracts	*In vivo*	*Schistosoma mansoni* worms	Moderate anti-schistosomal activity	[22]
	Tanacetum vulgare	Methanolic extracts	*In vivo*	*Schistosoma mansoni* worms	Moderate anti-schistosomal activity	[22]
Caricaceae	*Carica papaya*	Methanol extracts	*In vitro*	miracidia	CL_{50}=3.4 mg/L	[44]
		Ethanol extracts	*In vitro*	miracidia	CL_{50}=15.4 mg/L	[44]
		Butanol extracts	*In vitro*	miracidia	CL_{50}=8.1 mg/L	[44]
		Methanol extracts	*In vitro*	Cercariae of *S. mansoni*	LC_{90}=13.5 mg/L	[44]
		Ethanol extracts	*In vitro*	Cercariae of *S. manson*	LC_{90}=80.5 mg/L	[44]
		Butanol extracts	*In vitro*	Cercariae of *S. manson*	LC_{90}=18.5 mg/L	[44]
		Methanol extracts	*In vivo*	Cercariae of *S. manson*	The mortality (92%)	[44]
		Ethanol extracts	*In vivo*	Cercariae of *S. manson*	The mortality (40%)	[44]
		Butanol extracts	*In vivo*	Cercariae of *S. manson*	The mortality (70%)	[44]
Cleomaceae	*Cleome droserifolia*	Alcoholic extract	*In vivo*	Infected mice with *Schistosoma mansoni*	CD extract resulted in a weak reduction in worm	[27]
Dryopteridaceae	*Dryopteris filixmas*	Methanolic extracts	*In vivo*	*Schistosoma mansoni* worms	Low anti-schistosomal activity	[22]
Fabaceae	*Eriosema griseum*	Hydroalcohol extract	*In vitro*	Schistosomula, *Schistosoma mansoni*	Activity antischistosomal	[28]
Lauraceae	*Cinnamomum camphora*		*In vivo*	Cercaria of *Schistosoma japonicium*	CL_{50}=0.07 mg/L	[29]
Lamiaceae	*Ocimum americanum*	Hexane - OAH	*In vitro*	*Schistosoma mansoni*	Low worm reduction percentage	[30]
	Plectranthu stenuiflorus	Methanolic extract	*In vivo*	*Schistosoma mansoni*	IC_{50}=17.39 mg/100 mL	[31]

Family	Species	Extract	*In vivo/In vitro*	Larvae species	Effect	References
			In vivo	Anti-cercaria	IC_{50}=12.29 mg/100 mL	[31]
			In vivo	Anti-miracidium	IC_{50}=24.37 mg/100 mL	[31]
Liliaceae	*Asparagus stipularis Forssk*	Asparagalin A,	*In vitro*	Strain *Schistosom amansoni*	Significant activity	[32]
Lythraceae	*Punicagranatum tannins*	Ethanol extract	*In vivo*	Miracidia of *Schistosom amansoni*	Concentration as low as 0.39 ppm	[33]
Myrtaceae	*Syzygium aromaticum*	Methanolic extracts	*In vivo*	*Schistosoma mansoni* worms	High anti-schistosomal activity	[22]
	Callistemon citrinus	Aqueous extract	*In vivo*	Infected mice with *S. mansoni*	Significant decrease in worm burden and tissue egg load together	[45]
Nitrariaceae	*Peganum harmala*		*In vitro*	Cercaria	250 ppm up to 1000 ppm showed a 100% mortality rate during the first half an hour of exposure	[34]
Phyllanthhaceae	*Bridelia micranth*	Water extract-BMW	*In vitro*	*Schistosoma mansoni*	Low worm reduction percentage	[30]
Pinaceae	*Pinus canariensis*	Ethanol extract	*In vitro*	Worms of *Schistosoma mansoni*	LC_{50}=12.8 ppm	[21]
Punicaceae	*Melaleuca armillaris*	Essential oil	*In vivo*	*Schistosoma mansoni*	Both treatments significantly ameliorated the disturbing levels of GSH and MDA in infected mice	[35]
	Punica granatum	Peels and leaves extracts	*In vitro*	*Schistosoma mansoni worms*	100% death rate, 24 hours	[36]
	Punica granatum	peels and leaves extracts	*In vitro*	*Schistosoma mansoni*	100% death rate, 24 hours	[36]
Rubiaceae	*Mitracarpus frigidus*	Methanolic extract	*In vivo*	Cercariae	Reduced total worm count	[37]
			In vitro	Cercariae	Schistosomicidal activity	[37]
Rutaceae	*Zanthoxylum. leprieurii*	1-Hydroxy-3-methoxy-N-methylacridone	*In vitro*	Activity against cercariae *Schistosoma mansoni*	LC_{50}=78.78 µg/mL	[38]
		Arborinine (3)	*In vitro*	Activity against cercariae *Schistosoma mansoni*	LC_{50}=6.98 µg/mL	[38]
Sapindaceae	*Dodonaea viscosa*	Aerial plant part (leaves) extracts	*In vivo*	Mice infected with *S. mansoni*	Reduces the number of eggs in hepatic tissues	[46]
Simaroubaceae	*Eurycoma longifolia*	Longilactone (1)	*In vitro*	*Schistosoma Japonicum*	Antischistosomal effect at a concentration of 200 mg/mL.	[39]
Solanaceae	*Solanum elaeagnifolium*	Ethanol extract	*In vitro*	Worms of *Schistosoma mansoni*	LC_{50}=6.0 ppm	[21]
Verbenaceae	*Clerodendrum umbellatum*	Leaves aqueous extract	*In vivo*	*Schistosoma mansoni* (mice model)	In an important reduction in faecal egg output by 75.49% and 85.14% for 80 mg/kg and 160 mg/kg	[10]

In parallel, the anti-miracidium activity of this extract was important (IC_{50}=24.37 mg/100 mL) [31]. Waiganjo and coworkers have shown that *Ocimuma mericanum* and *Bridelia micrantha* extracts had anti-schistosomal activity, as indicated by the high worm reduction [30].

In contrast, the methanol extract of *Allium sativum* proved to be the most potent, *in vitro*, for anti-schistosomal activity against adults of *Schistosoma mansoni*. However, these effects were less effective *in vivo* [22]. The aqueous extract of *Clerodendrum umbellatum* leaves demonstrated anti-schistosomal activity *in vivo* on a *Schistosoma mansoni* using mice

as an animal model. The results showed that this extract resulted in an important reduction in fecal egg output by 75.49% and 85.14% at 80 mg/kg and 160 mg/kg of the extract, respectively [10]. This reduction was similar to that obtained in the group of mice treated with 100 mg/kg of praziquantel [10]. In another study, the stem bark and roots of *Rauwolfia vomitoria* were found to be active against cercariae and adult worms. Indeed, within 2 hours of exposure, all the cercariae were killed at concentrations ranging from 62.5 to 1000 µg/mL and from 250 to 1000 µg/mL, respectively [23]. Furthermore, all adult worms exposed to concentrations varied from 250 to 1000 µg/mL. For both plant parts, they died within 120 hours of incubation [23]. The effect of the crude extract of *Cleome droserifolia* leaves on mice experimentally infected with *Schistosoma mansoni* showed that this extract slightly reduced the worm burden (32.46%) and affected the viability of both mature and immature eggs [27]. On the other hand, the extract of peels and leaves of *Punica granatum* significantly affected adult *S. mansoni* worms and schistosomes, with a death rate of 100%, after 24 hours of exposure to plant extract [36].

3.2. Anti-schistosomal activity of plant essential oils.

Essential oils are volatile compounds known by their various biological effects, including anti-schistosomal activity [25, 35]. Interestingly, the essential oil of *Ageratum conyzoides* caused an interesting dose-dependent reduction in the number of eggs of *S. mansoni* [25]. In another study, the essential oil of the fresh leaves of *Melaleuca armillaris* rich in 1,8-cineole, terpinene-4-ol, and limonene was evaluated by Rizk et al. (2012) for its anti-schistosomal activity *in vivo*. Consequently, they found that this essential oil significantly ameliorated the disturbing levels of proteins, including natural antioxidant enzymes such as malondialdehyde and glutathione in infected mice [35].

3.3. Anti-schistosomal activity of plant bioactive compounds.

Several investigations have evaluated the anti-schistosomal activity of compounds derived from medicinal plants. Indeed, two compounds derived from *A. nubigena* (luteolin and (3R,6R)-linalool oxide acetate) showed anti-schistosomal activity against *S. mansoni* with IC_{50} range from 5.8 to 36.9 µg/mL [24].

Furthermore, the linalool-rich extracts from *Cinnamomum camphora* exhibited striking larvicidal and molluscicidal effects with LC_{50}=0.25 mg/L against *Oncomelania hupensis* and LC_{50}=0.07 mg/L against cercaria of *S. japonicium* [29]. Likewise, this bioactive compound significantly reduced the schistosomulum recovered from mouse skin after infection by challenge [29].

In contrast, Zondegoumba et al. (2019) evaluated the *in vitro* schistosomicidal property of two compounds (1-Hydroxy-3-methoxy-N-methylacridone and Arborinine) isolated from the fruits of *Zanthoxylum leprieurii*. The results showed that these two compounds exhibited remarkable cytotoxicity against cercariae with LC_{50} values of 78.78 and 6.98 µg/mL, respectively [38]. In another work, the administration of asparagaline A (isolated from the roots of *Asparagus stipularis*) has been shown to retard the worm growth [32]. Additionally, Longilactone isolated from *Eurycoma longifolia* leaves exhibited a significant anti-schistosomal effect at a concentration of 200 mg/mL [39].

4. Conclusions

Several medicinal plants have shown important anti-schistosomal activities. These effects are related to the presence of bioactive compounds such as flavonoids, alkaloids, phenolic acids, and terpenoids. In addition, the anti-schistosomal investigation of these molecules showed that they possess important activities with several targets. This review shows that medicinal plants are an important source for discovering anti-schistosomal drugs. However, further investigations concerning these bioactive compounds' toxicity and clinical trials are required to validate their therapeutic potential.

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Conflicts of Interest

The authors declare no conflict of interest.

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