

Natural Bioactive Compounds against *Schistosomahaematobium* and *Schistosoma mansoni*

ABSTRACT

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Aim: This documentary review aimed to make a synthesis of bioactive plants or natural compounds on schistosomes. We carried out a review from 2000 to 2022, oriented towards the plants in order to search natural compounds bioactive on schistosomes which can be a great contribution for new drugs discovering.

Terms such as “schistosomiasis and medicinal plants”, “natural anti-schistosome compounds”, “phytochemical screening”, “bioactive compounds on schistosomes” were used for the online literature search through the following sites: PubMed; Google Scholar; ScienceDirect and Hinari.

Results: There are many plants already used for the traditional treatment of schistosomiasis. This review found nearly 72 families of plants belonging to 228 botanical species have been listed. Some of these have been studied in vitro / in vivo and preliminary results have shown their schistosomicidal properties. Moreover, the results of qualitative phytochemical screening and toxicity testing of these natural compounds provide hope for new drug discoveries.

Conclusion: Even if plants efficacy is proven, we need more in-depth investigations to determine their chemical components in order to minimize the undesirable effects and to guarantee their safety by assessing their toxicity.

18 **Keywords:** *Schistosomiasis; Schistosoma; Praziquantel; natural compounds; bioactive*

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1. INTRODUCTION

Schistosomiasis or bilharzia, also called “snail fever” is one of the most commonly encountered neglected tropical diseases (NTDs) with high prevalence very often, in low-income countries, especially among schools where hygiene conditions are quite precarious [1, 2]. It is a parasitic illness caused by flatworms of the trematode genus. Three species are generally implicated in human pathology. These include: *Schistosoma mansoni*, which is found in the large intestine, *Schistosoma japonicum* which has a preference for the small intestine and *Schistosoma haematobium* with the bladder environment as its preferred zone [3]. Schistosomiasis is the second endemic parasitosis worldwide after malaria [4, 5]. It affected 230 million people worldwide in 2020 with 80 to 90% of cases in Africa area. This parasitological disease linked both to fecal peril and to certain water activities such as fishing, swimming and agriculture [2], [6–8].

Prevention of schistosomiasis through mass chemotherapy, and therapy are the only alternative currently, as there is no known effective vaccine for large-scale use[9]. Some drugs such as metrifonate (introduced in 1960), Amoscanate and Oxamniquine have been used and abandoned either for their side effects, or for their low efficacy or for their hepatotoxicity [10, 11].

The management of schistosomiasis cases generally uses praziquantel (PZQ), the anthelmintic which is preferentially used to support schistosomiasis cases [12–14]. After nearly a century of research into schistosomiasis drugs, it was not until 1970 that PZQ was developed [15]. This anthelmintic, produced by Merck and used since 1970 [5] is known as Biltricide® [15,16]. It is the only drug approved by the world health organization (WHO) to treat schistosomiasis [17–19]. Its repeated and frequent use could induce cases of resistance or therapeutic failures [19–22]. Although effective, taking PZQ is often difficult in children with swallowing difficulties, while chewing is contraindicated according to recommendations [5]. This parasitic disease remains so far a heavy burden, with high prevalence especially for developing countries despite mass treatments as a preventive

measure [1], [12], [20], [23–26]. In rural areas, where living conditions are precarious, the use of PZQ is not systematic due to poverty[19]. People generally use plants to treat schistosomiasis [19], [27, 28]. Chemoprevention is an alternative to get away or to eradicate this NTD, but the cost of this operation constitutes a difficulty for its implementation [29, 30]. Also, the success of this operation must integrate vector control through the use of molluscicides as recommended by the WHO control strategy [31].

The search for new perspectives for the management or even the eradication of this parasitic disease is an imperative for the researchers. Moreover, one of the major challenges of the WHO is to eradicate schistosomiasis by the year 2030 in countries where this parasitosis remains endemic[32,33,34]. Indeed one of the WHO objectives in its traditional medicine strategy 2014-2023 is to promote traditional medicine which plays a complementarity role with conventional medicine [35]. For this purpose, research should be directed towards new horizons by involving the plant environment in the search for new medicines as an alternative to the current use of the treatment of schistosomiasis [36, 37]. A literature review will allow us to have an overview of some studies conducted on plants or natural bioactive substances that can be potential sources for the development of new drugs against schistosomiasis or others diseases[38]. Phytotherapy can be an effective, accessible and inexpensive solution to effectively control schistosomiasis in addition to water treatment and health education [39,40]. Some advocate that we could modify, or even create a new formulation of PZQ in order to make it more bioactive and bioavailable [41]. Developing a new generation of antischistosomal drugs is a necessity for searchers.

However, the lack of information or scientific data on these plants, compound extracts or chemical groups constitutes an obstacle for their use [30], [42–44].

2. MATERIAL AND METHODS

We carried out a systematic search for articles deadline from 2000 to 2022 with antischistosomal plants, extracts or chemical compounds through the following sites: PubMed (<https://pubmed.ncbi.nlm.nih.gov/>); Google Scholar (<https://scholar.google.com/>);

ScienceDirect (<https://www.sciencedirect.com/topics/social-sciences/research-article>) and Hinari (<https://www.emro.who.int/fr/information-resources/hinari/hinari.html>) Terms such as “schistosomiasis and medicinal plants”, “natural anti-schistosome compounds”, “phytochemical screening”, “bioactive compounds on schistosomes” were used for the online literature search. These search terms allowed us to have publications and an overview related to our research topic. The analysis of this documentation allowed us to identify plants and natural compounds active on schistosomes. We noted that *in vitro* and *in vivo* tests were carried out in purebred mice with the different extracts of plants belonging to several families according to the botanical nomenclature.

Our literature review focused on articles published from January 2001 to December 2022 and we sorted articles that best met our selection criteria. The documentation collection period is from September 2022 to April 2023. We also searched the libraries of the WHO and the West African Health Organization (WAHO) on plants with schistosomicidal properties.

The selected articles had to meet one of the following criteria: deal with plants or natural bioactive compounds effective on schistosomiasis; *in vitro* and *in vivo* tests on schistosomes involving natural substances; the phytochemical profile of plant extracts against schistosomiasis; toxicity testing of plant extracts effective against schistosomiasis. We proceeded to a full reading of each article in order to take stock of the research work already done and to establish the link with our research topic.

3. REVIEW

3.1. YEARS OF PUBLICATIONS

Between 2001 and 2022, more than two hundred articles were submitted to us based on the keywords and expressions used with the aim of taking stock of the existing plants repertory may possibly be explored in the search for bioactive substances on schistosomes.

Among the documentation proposed through our research, around one hundred articles met our selection criteria (see Figure 1).

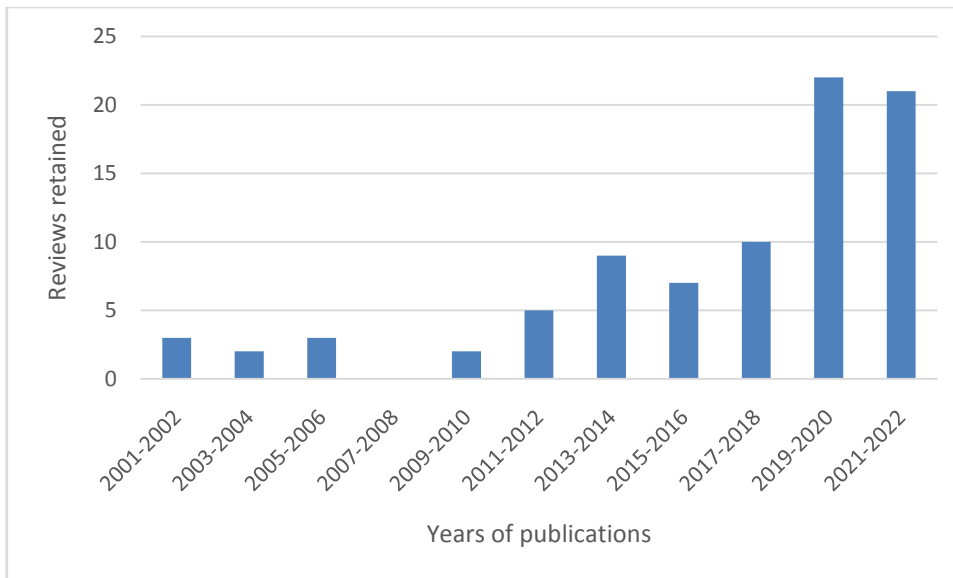


Fig.1. Number of publications exploited and interval of year of appearance

The highest rate of publication of the documentation was recorded between 2019 and 2020, followed by the last two years with a slight decline. This could be explained by a motivation of researchers in view of emergence of NTDs in recent years. It could be due to the funding allocated by WHO to researchers in achieving its considerable reduction objectives for burden of morbidity and mortality, or even eradication of NTDs by 2030[32, 33].

3.2. SCHISTOSOMICIDAL PLANTS

The plant environment is increasingly explored in search of new alternatives in the search for solutions against schistosomiasis which has become a real challenge in the response to NTDs [45].

This approach is in line with the objectives of the WHO in its program for NTDs eradication by 2030 [33].

The documentary review allowed us to know that there are a lot of schistosomicidal plants belonging to different botanical families. This plant environment is a potential source of natural substances as an alternative which can contribute to the development of new antischistosomal drugs, and which will strengthen the capacity to treat this parasitosis on a global scale [46]. The plant material listed is the result of ethnobotanical surveys that have

made it possible to inventory plants used in traditional medicine and with anthelmintic potential in general and antischistosomal particularly [47, 48]. The listed plants belong to 72 families containing a total of 229 botanical species (see tables 1 and 2). The majority of plants have been listed through ethnobotanical surveys [48], on the shelves of the WAHO [47] and the WHO libraries.

Table1. The different families of plants encountered in the literature

Botanic family	Botanic family	Botanic family
<i>Agavaceae</i> [21,47]	<i>Cannabinaceae</i> [58]	<i>Ochnaceae</i> [48]
<i>Amaranthaceae</i> [21, 22,30]	<i>Ebenaceae</i> [10,27]	<i>Olacaceae</i> [46]
<i>Amaryllidaceae</i> [3, 36]	<i>Euphorbiaceae</i> [30,47,74]	<i>Papaveraceae</i> [54]
<i>Anacardiaceae</i> [27,36]	<i>Fabaceae</i> [9,48,60]	<i>Sterculiaceae</i> [44]
<i>Annonaceae</i> [30,47,48]	<i>Liliaceae</i> [63]	<i>Phyllanthaceae</i> [21]
<i>Apiaceae</i> [17]	<i>Asteroidae</i> [79]	<i>Phytolaccaceae</i> [3]
<i>Apocynaceae</i> [3,27,36]	<i>Hypericaceae</i> [47]	<i>Pinaceae</i> [21]
<i>Asclepiadaceae</i> [36,46]	<i>Bombacaceae</i> [44]	<i>Piperaceae</i> [17]
<i>Asparagaceae</i> [27,30,36]	<i>Hypoxidaceae</i> [44]	<i>Poaceae</i> [43,48]
<i>Asphodelaceae</i> [27]	<i>Lamiaceae</i> [18,30,43]	<i>Polygalaceae</i> [27,30]
Botanic family	Botanic family	Botanic family
<i>Asteraceae</i> [3,22,30]	<i>Leguminosae</i> [44]	<i>Punicaceae</i> [36]
<i>Bignoniaceae</i> [27,43]	<i>Loganiaceae</i> [48]	<i>Renonculaceae</i> [36]
<i>Boraginaceae</i> [27,43]	<i>Caesalpiniaceae</i> [50]	<i>Rhamnaceae</i> [18,22]
<i>Balanitaceae</i> [30]	<i>Myrsinaceae</i> [50]	<i>Rosaceae</i> [3,13,44]
<i>Burseraceae</i> [75]	<i>Lythraceae</i> [3,21]	<i>Rubiaceae</i> [43,47]
<i>Capparaceae</i> [36,43]	<i>Malpighiaceae</i> [36]	<i>Rutaceae</i> [10,22,71]
<i>Caricaceae</i> [21]	<i>Malvaceae</i> [43]	<i>Sapindaceae</i> [57]
<i>Celastraceae</i> [27,43,48]	<i>Primulaceae</i> [50]	<i>Chrysobalantaceae</i> [50]
<i>Clusiaceae</i> [48,56]	<i>Meliaceae</i> [3,10,30]	<i>Flacourtiaceae</i> [50]
<i>Cochlospermaceae</i> [47]	<i>Pedaliaceae</i> [44]	<i>Nympheaceae</i> [50]
<i>Combretaceae</i> [27,30,36]	<i>Moraceae</i> [48]	<i>Solanaceae</i> [53]
<i>Cucubitateae</i> [22,36,48]	<i>Moringaceae</i> [43,68]	<i>Verbenaceae</i> [21,43,4]
<i>Ancistrocladaceae</i> [44]	<i>Myrtaceae</i> [46,53,82]	<i>Zingiberaceae</i> [3,67,78]
<i>Dipterocarpaceae</i> [48]		<i>Zygophyllaceae</i> [36,48]

Table 2. Directory of botanical families and species bioactive on schistosomes

Agavaceae family	Asteraceae family	Ebenaceae family
<i>Agave americana</i>	<i>Ageratum conyzoides</i>	<i>Eucleadivinorum</i>
<i>Agave lophantha</i>	<i>Ageratum conyzoides</i> L	<i>Eucleanatalensis</i>
<i>Asclepiassinaica</i>	<i>Ambrosiamaritima</i>	Euphorbiaceae family
<i>Asiminatriloba</i>	<i>Arteisiaannua</i>	<i>Alchorneacordifolia</i> ,
<i>Solanum nigrum</i>	<i>Artemisia absinthium</i>	<i>Antidesmavenosum</i>
<i>Solanum nigrum</i> (L)	<i>Artemisia afra</i>	<i>Euphorbiamauritanica</i>
Amaranthaceae family	<i>Baccharisdracunculifolia</i>	<i>Euphorbiapeploides</i> (A)
<i>Chenopodium album</i> (L)	<i>Baccharis trimera</i>	<i>Euphorbiaroyleana</i>
<i>Dysphaniaambrosioides</i>	<i>Berkheyaspeciosa</i>	<i>Euphorbiatirucalli</i> (L)
Amaryllidaceae family	<i>dracunculifolia</i> DC	<i>Jatropha curcas</i>
<i>Allium cepa</i>	<i>Echinopskebericho</i>	Fabaceae family
<i>Allium cepa</i> (L)	<i>Taraxacum officinale</i>	<i>Abrus precatorius</i>
<i>Allium sativum</i>	<i>Vernonia amygdalina</i>	<i>Abrus precatorius</i> (L)
<i>Allium sativum</i> (L)	<i>Vernonia colorata</i>	<i>Acacia nilotica</i>
Anacardiaceae family	<i>Vernonia shirensis</i>	<i>Acacia polyacantha</i>
<i>Lanneabarteri</i>	Bigoniaceae family	<i>Albizia adianthifolia</i>
<i>Lanneachimperi</i>	<i>Kigeliaaethiopum</i>	<i>Albizia antuneziana</i>
<i>Mangiferaindica</i>	Boraginaceae family	<i>Albizia versicolor</i>
<i>Orozoapulcherrima</i>	<i>Alkanna orientalis</i>	<i>Bauhinia reticulata</i>
<i>Schinopsisbrasiliensis</i>	Balanitaceae family	<i>Bauhinia variegata</i> L
<i>Scierocaryabirrea</i>	<i>Balanites aegyptiaca</i>	<i>Bobgunniamadagascarien</i>
<i>Searsialongipes</i>	Burseraceae family	<i>Cassia petersiana</i>
Annonaceae family	<i>Commiphoramolmol</i>	<i>Cassia sieberiana</i>
<i>Annona senegalensis</i>	Capparaceae family	<i>Cratylia mollis</i>
<i>Anonidiummannii</i>	<i>Cleomedroserifolia</i>	<i>Dichrostachys cinerea</i> (L)
<i>Asiminatriloba</i>	Caricaceae family	<i>Emilia javanica</i>
<i>Xylopiiathiopica</i>	<i>Caricapapaya</i> (L)	<i>Eminiapoladenia</i>
<i>Xylopioochrantha</i>	<i>Caricapapya</i>	<i>Eriosemagriseum</i>
Apiaceae family	Celastraceae family	<i>Erythrinaabyssinica</i>
<i>Apiumgraveolens</i> (L)	<i>Maytenus senegalensis</i>	<i>Erythrina senegalensis</i>
<i>Coriandrum</i> sativum	Clusiaceae family	<i>Isobertiniaangolensis</i>
<i>Foeniculumvulgare</i>	<i>Garcinia huilensis</i>	<i>Piliostigmathonningii</i>
Apocynaceae family	Cochlospermaceae family	<i>Pterocarpus angolensis</i>
<i>Alstonia boonei</i>	<i>Cochlospermumtinctorium</i>	<i>Pterodonpubescens</i>
<i>Calotropisprocera</i>	Combretaceae family	<i>Rhynchosia</i> insignis
<i>Cryptostegiagrandiflora</i>	<i>Anogeissusleiocarpus</i>	<i>Tetrapleuratetraptera</i>

<i>Diplorynchuscondlocarpoum</i>	<i>Combretumangustifolium</i>	Liliaceae family
<i>Landolphia kirkii</i>	<i>Combretumglutinosum</i>	Allium sativum L
<i>Neriumoleander</i>	<i>Combretummucronatum</i>	Asteroidae family
		<i>Artemisia afra</i>
<i>Neriumoleander (L)</i>	<i>Combretummucronatum</i>	<i>Artemisia annua</i>
<i>Picralimanitida</i>	<i>Combretumsp</i>	Hypericaceae family
<i>Rauwolfia vomitoria</i>	<i>Terminalia mollis</i>	<i>Harunganamadagascariensis</i>
Asclepiadaceae family	Cucubitateae family	Bombacaceae family
<i>Pergulariatomentosa</i>	<i>Cucurbitapepo</i>	<i>Adansoniadigitata</i>
Asparagaceae family	<i>Cucurbitapepo L</i>	Hypoxidaceae family
<i>Asparagus stipularis (R)</i>	Cucurbitaceae family	<i>Hypoxishemerocallidae</i>
<i>Furcraeaselloa</i>	<i>Momordicacharantia</i>	Lamiaceae family
<i>Furcraeaselloa (L)</i>	Ancistrocladaceae family	<i>Coleuskilimandscharica</i>
<i>Ledebouriaovatifolia</i>	<i>Ancistrocladuskorupensis</i>	<i>Ocimumamericanum</i>
<i>Scillanatalensis</i>	Dipterocarpaceae family	<i>Origanummajorana</i>
Asphodelaceae family	<i>Monoteskatangensis</i>	<i>Plectranthusneochilus</i>
<i>Aloe vera</i>	<i>Monoteskerstingii</i>	<i>Plectranthustenuiflorus</i>
	Cannabinae family	<i>Tetradenia riparia</i>
	<i>Nigella sativa</i>	
Lamiaceae family	Myrtaceae family	Rutaceae family
<i>Coleuskilimandscharica</i>	<i>Melaleucaarmillaris</i>	<i>Cissusquadrangularis (L)</i>
<i>Ocimumamericanum</i>	<i>Melaleucaleucadendron</i>	<i>Citrus limon (L)</i>
<i>Origanummajorana</i>	<i>Pimenta racemosa</i>	<i>Citrus reticulata</i>
<i>Plectranthusneochilus</i>	<i>Syzygium aromaticum</i>	<i>Citrus sinensis (L)</i>
<i>Plectranthustenuiflorus</i>	<i>Syzygium guineense</i>	<i>Pilocarpusmicrophyllus</i>
<i>Tetradenia riparia</i>	Ochnaceae family	<i>Zanthoxylumleprierii</i>
Leguminosae family	<i>Ochnaschweinfurthiana</i>	<i>Zanthoxylumnaranjillo</i>
<i>Cassia senna</i>	Olacaceae family	Sapindaceae family
Loganiaceae family	<i>Olaxsubscorpioidea</i>	<i>Dodonaeviscosa</i>
<i>Buddleia lindleyana</i>	<i>Ximenia americana</i>	<i>Paulina pinnata</i>
<i>Strychnos inocua</i>	Papaveraceae family	Chrysobalanaceae family
<i>Strychnos spinosa</i>	<i>Fumariaofficinalis</i>	<i>Licaniatomentosa</i>
<i>Strychnos stuhlmannii</i>	Sterculiaceae family	Flacourtiaceae family
Caesalpiniaceae family	<i>Cola nitida</i>	<i>Flacourtiaindica</i>
<i>Azeliaquanzensis</i>	Phyllanthaceae family	Nymphaeaceae family
Myrsinaceae family	<i>Phyllanthus muellerianus</i>	<i>Nymphaemicrantha</i>
<i>Maesalanceolata</i>	<i>Phyllanthus niruri</i>	Solanaceae family
Lythraceae family	<i>Phyllantusamarus</i>	<i>Brugmansiamunamensis</i>
<i>Punicagranatum</i>	Phyllantaceae family	<i>Solanum elaeagnifolium</i>
Malpighiaceae family	<i>Hymenocardiaacida</i>	<i>Solanum incanum (L)</i>
<i>Flabellariapaniculata</i>	Phytolaccaceae family	<i>Solanum lycocarpum</i>
<i>Malvaceae</i>		

<i>Brachychiton rupestris</i>	<i>Phytolacca dodecandra</i>	<i>Solanum nigrum</i>
<i>Sida pilosa</i>	Pinaceae family	<i>Solanum solamargine (F)</i>
Primulaceae family	<i>Pinus canariensis</i>	<i>Solanum tuberosum</i>
Anagallis arvensis L	Piperaceae family	Verbenaceae family
Meliaceae family	<i>Piper nigrum</i>	<i>Cleomedroserifolia</i>
<i>Azadirachta indica</i>	<i>Piper tuberculatum</i>	<i>Clerodendrum umbellatum</i>
<i>Khayagrandidifoliola</i>	Poaceae family	<i>Stachytarpheta cayennensis</i>
<i>Khayanyasica</i>	<i>Cymbopogon densiflorus</i>	Zingiberaceae family
<i>Khaya senegalensis,</i>	<i>Imperata cylindrica (L)</i>	<i>Aframomum alboviolaceum</i>
<i>Swietenia mahogani</i>	Polygalaceae family	<i>Curcuma longa</i>
<i>Trichilamon adelpha</i>	<i>Securidaca longipedunculata</i>	<i>Curcuma longa (L)</i>
Pedaliaceae	<i>Eriogonum umbellatum</i>	<i>Zingiber officinale</i>
Harpagophytum procumbens	Punicaceae family	Zygophyllaceae family
Moraceae family	<i>Prunicagranatum</i>	<i>Balanites aegyptiaca</i>
<i>Chlorophora excelsa</i>	Renonculaceae family	<i>Balanites aegyptiaca (L)</i>
<i>Ficus carica</i>	<i>Nigella sativa</i>	<i>Fagonia mollis Delile</i>
Moringaceae family	<i>Pulsatilla chinensis</i>	Rubiaceae family
<i>Moringa oleifera</i>	Rhamnaceae family	<i>Craterispermum caudatum</i>
Myrtaceae family	<i>Ziziphus spina-christi</i>	<i>Crossopteryx febrifuga</i>
<i>Callistemon umbellatum</i>	<i>Ziziphus spina-christi (L)</i>	<i>Gardenia jovis-tonantis</i>
<i>Callistemon rigidus</i>	<i>Zizyphus mauritiana</i>	<i>Mitracarpus frigidus</i>
<i>Callistemon speciosus</i>	Rosaceae family	<i>Mitragynastipulosa</i>
<i>Cadabaglandulosa</i>	<i>Malus domestica</i>	<i>Morinda lucida</i>
<i>Cajanus cajan (L)</i>		<i>Nauclea latifolia</i>
<i>Callistemon citrinus</i>		<i>Pavetta owariensis</i>
<i>Callistemon viminalis</i>		<i>Permacoce verticillata</i>
<i>Callistemon viridiflorus (L)</i>		
<i>Eucalyptus citriodora</i>		
<i>Eucalyptus rostrata</i>		
<i>Eucalyptus species</i>		
<i>Eugenia edulis</i>		
<i>Melaleuca styphelioides</i>		

3.3. PREPARATION OF PLANT MATERIAL

In search of plant extracts bioactive on schistosomiasis, the researchers proceeded to collect plants that had been previously identified by botanist experts. All harvested plants were fully dried in the shade for at least two weeks before being sprayed for the various extractions with different solvents. Virtually all plant parts have been used to search for

bioactive substances on schistosomes: leaves, barks, roots, fruits, stems, branches, bulbs, pods, rhizomes, or even the whole plant.

The solvents used for the different extractions were: distilled water, hydro-alcohol, ethanol, methanol (in varying percentages), acetone, chloroform, ethyl-acetate, acetonitrile, ether, methane, olive oil and hexane [49].

3.4. ANTISCHISTOSOMAL ACTIVITY OF NATURAL SUBSTANCES

We noticed that there is a varied range of plants with antischistosomal and antimolluscicidal properties [47], [50] and therefore, the ability to neutralize the parasite [51].

All the strains of schistosomes used for the different tests were acquired through research institutions, and *S. mansoni* has been the subject of most studies unlike other species of schistosomes [52, 53]. Obtaining cercariae for *in vitro* and *in vivo* testing required collection of intermediate host snails that were maintained and infected for their excretion of cercariae in many laboratories such as the Schistosome Biological Supply Center (SBSC), Theodor Bilharz Resaech Institute (TBRI), Gisa, Egypt; in Medical Parasitology Department, Faculty of Medicine, Menoufia University, Giza, Egypt.

3.5. IN VITRO STUDY OF THE ANTISCHISTOSOMAL ACTIVITY OF PLANTS

Several researchers have carried out work on the *in vitro* anti schistosome activity of plants. Most authors focused on one or at most three plants and priority was given to *in vitro* tests. *In vivo* testing remained a challenge [54]. Others, on the other hand, have shown the effectiveness of natural substances by taking these two aspects into account [52], [55].

For most authors *in vitro* activity was evaluated in the culture RPMI-1640 medium. This medium has been used either in combination with serum or with antibiotics such as Gentamicin, Streptomycin, Penicillin and many others as supplements [56]. All *in vitro* tests were incubated for 24 or 48 hours at 37°C with 5% of CO₂. The concentrations of the different extracts tested were between 62.25µg/ml and 500µg/ml in search of lethal

concentrations of the extract. The lethal concentrations that we observed varied between 125µg/ml to 500µg/ml [57]. Those concentrations below 125µg/ml had a reduced activity on the parasites because they let perceive the mobility of certain parasites with microscopy [57].

The *in vitro* test was the most common and all results were promising, as they all showed efficacy of crude plant extracts on at least one stage of the parasite and even on the intermediate host snail [52], [54], [58].

The antischistosomal activity of a plant extracts may be linked to a chemical substance or to a combination of chemical groups which should be identified [59, 60].

According to many authors, the lethal dose LC₅₀ (the dose of the plant substance at which 50% of the parasites die) can vary according to the part of the plant used for the same incubation period: *Pterocarpus angolensis* DC; LC₅₀ (T=1 hour): leaves 102mg/mL; stem 51.3 mg/mL and bark 33.8mg/mL [53]. Also, the effectiveness of the active substance may depend on the solvent used: *Calotropis procera* (at 25mg/mL): the ethanolic extract caused the death of all adult forms of *S.mansoni* in ½ hour while the aqueous extract didn't become effective until 4 hours later [61, 62] ; *Clerodendrum umbellatum*: LC₅₀ of the aqueous extract= 805.21µg/mL against 343.10 µg/mL for the methanolic extract [28].

3.6. *IN VIVO* STUDY OF THE ANTISCHISTOSOMAL ACTIVITY OF PLANTS

As far as *in vivo* tests are concerned, some research conducted has shown some shortcomings in their effectiveness. Some natural compounds with high *in vitro* mortality, on the other hand, exhibited low mortality rates in mice [57]. This is the case of *Allicin* which has been tested *in vitro* and *in vivo* [52]. Others, on the other hand have given interesting results *in vitro* and *in vivo* [63].

Many authors have carried out *in vivo* tests by taking PZQ as control. In the majority of cases for the results obtained, this drug had the greatest parasiticidal activity, compared to the different crude extracts [64–70]. Furthermore, it could also be noted that there was no statistically significant difference between PZQ and other plant extracts in terms of efficacy

on schistosomes [71]. Many studies have shown that PZQ, in combination with plant extracts gave very good results in the treatment of schistosomiasis [62], [72]. Others, on the other hand, had as a control group infected and untreated mice in comparison with infected mice and treated with crude plant extracts to research the lethal activity of the extract [52].

Many authors recommend better exploring the *in vivo* activity of plant extracts that have shown conclusive results *in vivo* [54], [73–76]. Others still advocate conducting studies on the biology of intermediate hosts and considering breaking the chain of transmission of schistosomiasis [77]. Also, it would be interesting to conduct more in-depth studies on plants that have shown their effectiveness on schistosomes using a variety of solvents at concentrations. In addition, the schistosomicidal activity of a plant or a bioactive substance is undoubtedly linked to a chemical substance or group that is important to identify, isolate and quantity; which also makes it possible to better understand the mechanism of action of these plants or bioactive substance [78, 79].

It should also be noted that some authors have carried out *in vitro* / *in vivo* tests on mice, with other drug groups such as antimalarial drugs [15]. Some molecules have shown higher mortality rates on adults than cercariae: Arthemeter at 300mg/kg/day for 2 days caused the death of 85.4-98.3% of *S. mansoni* adults and 70% cercariae. Others, on the other hand, were less effective on adult forms: Chlorambucil at 25 mg/kg for 5 days caused the death of 22.7% of adults against 75.8% of cercariae [37].

3.7. PHYTOCHEMICAL SCREENING

We noticed that the compounds of the natural substances were detected qualitatively. Among plants with potential schistosomicidal activity, their active ingredients are mostly unknown. The technic of spectrophotometry through gas chromatography for the detection of chemical compounds of crude extracts was used [51], [71], [80–82].

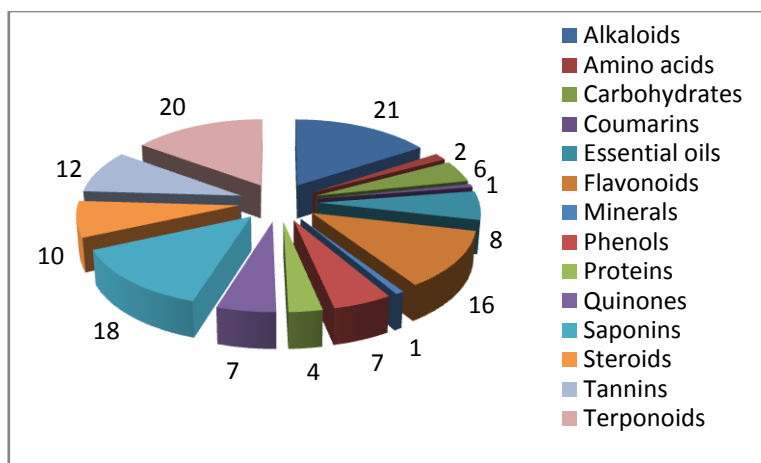


Fig. 2. Proportion in percentages of chemical compounds

It should be noted that some chemical groups are more present than others in terms of percentage as we notice at the **figure 2**. We have alkaloids and terpenoids groups with almost equal proportion, followed by flavonoids and saponins groups with the same trends. The chemical compounds present in high proportion could be explained by the fact that some authors have sought them especially [51], [71], [80–82]. These include alkaloids, flavonoids, saponins, tannins, terpenoids, steroids and quinones.

Indeed, plants are a huge source of chemical compound belonging to several chemical groups with a lot of medicinal properties such as anti-oxidant, anti-inflammatory, antimicrobial etc. [83].

3.8. CYTOTOXICITY TESTS

The search for bioactive substances in the plant environment must also take into account their harmful effects or their toxicity. The toxicity test is also an essential step in the process of researching new drugs in general. **We can note that many authors have demonstrated the non-toxicity of plant extracts on “Vero cells” through different types of active extracts at varying concentrations.** There are similarities between toxicity test and *in vivo* test. The toxicity test is also carried out in RPMI-1640 medium, supplemented with fetal bovine serum and/or antibiotics. The extracts to be tested are brought into contact with the “Vero cells”.

Incubation is also done with 5% CO₂ at 37°C for 24 to 48 hours [55]. Several studies have shown promising results as the toxicity of the herbal extracts used was extremely low or non-existent [84]. Others, however, have shown their effectiveness, but their toxicity remains to be investigated

4. CONCLUSION

According to many studies, plants could be an alternative in the treatment of schistosomiasis. Several plants are already used by traditional healers, but very few have been analyzed in the laboratory.

Many schistosomicidal plants have been cited in the literature. However, we can note that among the multitude of schistosomicide plants, more appropriate tests are required through clinical trials in order to determine the most effective.

It is also necessary to study the phytochemical profiles in a qualitative and quantitative approach of these natural compounds for the implementation of new molecules against schistosomiasis through clinical research trials.

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