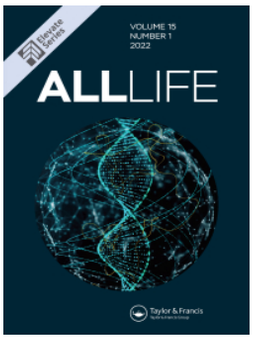

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REVIEW

Advances in schistosomiasis drug discovery based on natural products.

F. L. Mtemeli[a], J. Ndlovu[a], G. Mugumbate[b], T. Makwikwi[c] and R. Shoko[a]

[a]Department of Biology, School of Natural Sciences and Mathematics Chinhoyi University of Technology, Chinhoyi, Zimbabwe; [b]Department of Chemical Technology, Midlands State University, Gweru, Zimbabwe; [c]Department of Pharmaceutical Sciences, Tshwane University of Technology, Pretoria, South Africa

ABSTRACT

Schistosomiasis is a neglected tropical disease affecting over 250 million people worldwide. The disease is the second most prevalent neglected tropical disease after malaria. Treatment of schistosomiasis relies on the administration of praziquantel (also known as biltricide). Reliance on a single drug poses a threat to the public health system as the parasite may become resistant as shown by some laboratory findings. The possibility of the resistance rising to clinically significant levels has motivated the scientific community to search for new drug nominees. For a long time, natural products have always been a foundation for the identification of drug leads in the pharmaceutical industry. This paper reviews the progress made in the discovery of natural anti-schistosomal agents in the field of drug discovery. We focus mainly on natural products that have been tested on the schistosome parasite and exhibited potency. We also highlight applications of advanced techniques in drug discovery, with a major focus on computer-aided drug discovery methods. Specifically, we discuss structure-based drug discovery and ligand-based drug design approaches, with an emphasis on virtual screening.

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KEYWORDS
Schistosomiasis; praziquantel; schistosomicidal; virtual screening; natural products

Introduction

Schistosomiasis is a water-borne parasitic neglected tropical disease (NTD) and is endemic in the poverty-stricken parts of sub-Saharan Africa. Of the world's estimated 240 million cases of the disease in 2020, 90% of the cases were recorded in sub-Saharan Africa (Aula et al. 2021; Abe et al. 2020; Fuss et al. 2020). The distribution of the disease is influenced by the low-income status of the regions, characterised by poor sanitation, lack of effective health policies and generally poor living conditions (Onasanya et al. 2021). Africa, generally, depends on herbal medicines with over 80% of the populations, particularly in rural areas, depending on herbal medicines (Cam et al. 2005). It is, therefore, important to understand how these communities use traditional herbal medicines given the prevalence of schistosomiasis.

Schistosomiasis is caused by five species of schistosomes; *Schistosoma mansoni, Schistosoma intercalatum*, *Schistosoma japonicum*, *Schistosoma mekongi* and *Schistosoma haematobium*. *S. haematobium* causes urogenital schistosomiasis, whereas the other species cause intestinal schistosomiasis. Of the species, *S.man soni* and *S. haematobium* are the common species in Africa (Oyeyemi et al. 2020). Cercariae are subsequently shed by the vector snails into freshwater and penetrate the intact skin of humans who get in contact with contaminated water (Mbereko et al. 2020; Caffrey et al. 2019). After penetrating the human skin, the maturing larvae become adults that produce eggs in about 5–7 weeks. The eggs produced are usually released into the environment through faeces or urine to complete the lifecycle. However, in some cases, the eggs remain in host tissues where they induce inflammation and then die (Neves et al. 2015).

Over the past few years, natural products (NPs) and compounds derived from NPs are gaining popularity as a foundation for the development of new schistosomiasis drugs (Neves et al. 2015). The efficiency of novel compounds against schistosomes is well-defined using various approaches like prophylactic strategies, killing the adult parasite, the cercariae and schistosomula and suppressive tactics such as hindering worm egg-laying (Tekwu et al. 2017). Regardless of all the studies that

CONTACT R. Shoko shoko.ryman@gmail.com Department of Biology, School of Natural Sciences and Mathematics Chinhoyi University of Technology, Chinhoyi, Zimbabwe

This article has been corrected with minor changes. These changes do not impact the academic content of the article.

are underway, in the absence of a vaccine, the treatment of schistosomiasis depends solely on PZQ, which has been the drug of choice since the 1970s (Gönnert and Andrews 1977). The other two drugs oxamniquine and metrifonate ceased to be used clinically because of various reasons such as toxicity of metrifonate to humans and the selective effectiveness of oxamniquine on *S. mansoni* only (Cheuka et al. 2017).

The primary mechanism of PZQ remains unknown. However, the drug acts on the tegument of mature worms only. It is hypothesised that PZQ interrupts calcium ion homeostasis in the parasite, which results in an uncontrolled influx of calcium ions causing muscle contraction and paralysis (Thomas and Timson 2020). The drug's easy administration, safety, tolerance, affordability and effectiveness against all five species of schistosomes have made its use advantageous (Chisango et al. 2019). The disadvantage of PZQ is that if a patient harbours parasites at various life stages, the patient will still show symptoms of the disease regardless of treatment (Caffrey et al. 2019). The reliance by the medical sector on a single drug for the treatment of schistosomiasis and the failure of existing measures to eliminate the disease has led to intensified efforts to find new anti-schistosomiasis drug leads (Mtemeli et al. 2021; Lombardo et al. 2019; Gouveia et al. 2018). Here, we review the progress that has been made in the development of new drugs used for treating schistosomiasis based on NPs.

The schistosomiasis drug discovery journey

Drugs have assumed critical roles in the prevention and treatment of several diseases, including schistosomiasis. The historical framework of the use of drugs in treating infections and alleviating symptoms goes back to ancient times (Lesser 2021). At present, traditional target-based and phenotype-based screening assays are frequently employed in drug discovery; predominantly for NTDs (Moreira-Filho et al. 2021).

The conventional process used in the discovery and development of an effective drug is expensive and time-consuming. The process usually consists of six main steps *viz*; disease selections, target hypothesis, lead identification, lead optimisation, preclinical trial and clinical trial (Kumar 2017). These steps were devised to ensure that drugs delivered to patients are safe and efficacious.

NPs have attracted interest for therapeutic use for a long time. In fact, 64% of all marketed drugs originate from NPs (Ferreira et al. 2018). Some of the NP-derived drugs that are trademark of today's pharmaceutical care include quinine, theophylline, penicillin G, morphine, paclitaxel, digoxin, vincristine, doxorubicin and cyclosporine *etc* (Cragg and Newman 2013; Shelar and Shirote 2011).

NPs are considered to be a significant foundation for drug discovery because they have diverse chemical components and biomedical activities (Süntar 2020). Also, NPs are exceptional in that they are often rich in stereogenic centres and cover portions of chemical space that is usually not occupied by a greater part of synthetic drugs and medications (Marxer et al. 2012).

The investigation of medicinal plants as an innovative strategy for the tentative control of schistosomiasis is one of the sustainable and encouraging research leads. Since schistosomiasis is one of the NTDs, the drug discovery channel is, by all means, underfunded (Lombardo et al. 2019). However, the academic research side has explored a great number of bioactive ingredients from plants with schistosomicidal properties; specifically, those used in traditional herbal medicine (Bergquist et al. 2017; Tung 2014). Some of the plants with anti-schistosomal activities that have been studied are discussed below.

Zingiber officinale

The anti-schistosomal activity of *Z. officinale* has been evaluated against *S. mansoni* and the potency of the plant has been demonstrated (Mostafa and Eid 2011; Sanderson et al. 2002). Successful *in vitro* studies of the anti-schistosomal activity of *Z. officinale* was done although the researchers observed no significant difference in treated and untreated mice for the *in vivo* experiments (Sanderson et al. 2002). Other studies revealed anti-schistosomal effects of *Z. officinale* with regards to the histopathological changes observed in the small intestines of infected mice (El-Sameih et al. 2017). A dramatic decrease in the number of granulomas and retracted granulomal development resulting in the majority of eggs being trapped within intestinal compartments not inducing an inflammatory response was observed (Aly and Mantawy 2013). Additionally, *Z.officinale* also facilitated the restoration of the appearance of normal hepatocytes and normal hepatic strand organisation by scavenging free radicals with its

strong antioxidant effect (Abd El Wahab et al. 2021). The treatment of *S. mansoni*-infected mice with aqueous ginger extract loaded on chitosan nanoparticles led to an apparent decrease in elevated liver peroxidation and improved liver function that reflects the antioxidant defence system (El-derbawy1 et al. 2019). At a maximum nontoxic dose of the extract, the cytotoxicity assay showed that treated Vero cells did not display any morphological differences when compared to the control, at the value of 250 µl/ml (El-Nour et al. 2021). Another study observed the significant synergistic effect of ginger-derived nanoparticles when used in combination with PZQ or mefloquine (Abd El Wahab et al. 2021).

Anonidium mannii

The presence of alkaloids, phenols, polyphenols, saponins, tannins and steroids in *A. manni* has been demonstrated (Ngangoue et al. 2020). Two compounds from the plant, aristolactam A-II and piperolactam D, had good activity (IC_{50} of 10–20 µM) on adult *S. mansoni in vitro* and demonstrated effective inhibition of the recently discovered, Nicotinamide Adenine Dinucleotide catabolizing enzyme in *S. mansoni* (*Sm*NACE) (ToussiMatchi et al. 2020). Schistosomes are unable to produce Nicotinamide Adenine Dinucleotide (NAD) – a vital cellular metabolite. The parasites salvage NAD by using vitamins from the host. Interruption of the parasite's NAD salvage pathway adversely impacts both the mature and immature worms' metabolism, reproduction and survival (Schultz et al. 2020). Cytotoxicity tests were performed on Huh7 and A549 cells at the concentration of 100 µM and the cell viability of Huh7 cells was found to be ≈15% and 80% for A549 cells (ToussiMatchi et al. 2020).

Rauwolfia vomitoria

Ethanolic crude extracts of *R. vomitoria* stem bark and root have been shown to have moderate anti-schistosomal properties against the cercariae and adult worms of *S. mansoni*. In a study by Tekwu et al. (2017), the stem bark and root displayed half-maximal inhibitory concentration (IC_{50}) values of 77.5 and 112 µg/mL, respectively. Their results suggested that the stem bark is comparatively more toxic than the roots. Using this criterion, all the IC_{50} values that were defined in their study were much greater than 20 µg/mL. This indicates that both plant parts are not intensely cytotoxic and can be used in the treatment of schistosomiasis. HepG2 and Chang liver cells were assessed using the 3-(4,5-dimethylthiazol-2-yl)−2,5-diphenyl-2H-tetrazolium bromide (MTT) assay and the extracts were found to be safe at $IC_{50} > 20$ µg/mL (Tekwu et al. 2017).

Cucurbita pepo

Studies have shown that *Cucurbita pepo* seed oil is effective against *S. mansoni* schistosomula, juveniles and adults *in vitro* (Ammar et al. 2020; Beshay et al. 2019). The mortality rate of the worms, the effect on motility, morphological integument changes and *C.pepo* seed oil-induced DNA instability are indications that the seed oil is a promising anti-schistosomal product (Ammar et al. 2020). In older studies, the administration of the seed oil to treat *S. mansoni*-infected mice led to significant reductions in liver and intestinal egg burden, with a noteworthy increase in the percentage of dead eggs in the oogram pattern. The seed oil also led to an improved granuloma size, structure and fibrosis (Beshay et al. 2019).

Pulsatilla chinensis

It has been shown that Hederacolchiside A1 (HSA) found in the plant P. *chinensis* has anti-schistosomal properties (Kang et al. 2018). In tests done on mice infected with *S. japonicum*, female worm recovery and egg load in treated mice were reduced. The schistosomicidal activity of HSA against both juvenile and adult *S. japonicum* with a dose–response relationship was observed (Kang et al. 2018).

Artemisia annua

Since the 1980s, artemisinins, a family of sesquiterpene trioxane lactones, *A. annua* (sweet wormwood) derivatives, have shown to be anti-schistosomal agents (Neves et al. 2015). Artemisinins appear to be more effective on juvenile worms than adult worms (Liu et al. 2014). This may be due to artemisinins' mechanism of action on the schistosomes as the artemisinins react with the iron ions of haeme. The iron ions of haeme, are derived from haemoglobin digestion. Reactive oxygen species and chelates are produced in the process (Xiao et al. 2001). Several clinical studies

have commenced, repositioning artemisinins as schistosomicidal drugs (Panic et al. 2014; Liu et al. 2014).

In addition to the few studies discussed above, many other studies have been carried out on plants with schistosomicidal properties. Table 1 presents a summary of other plants that have shown potency against schistosomes.

Current drug nominees for schistosomiasis

Only a limited number of plant species traditionally used against *S. mansoni* have undergone scientific screening. Primarily, *in vitro* assessments were made on these plants and the most significant results were obtained from the *Abrus precatorius* L. subsp. *Africanus* v*erdc* root extract which, however, still needs to be further assessed *in vivo* and randomised clinical trials. The most progressive agents that have been tried for potential use in the treatment of schistosomiasis to date are the quinine analogues and artemisinin-based antimalarial drugs (Duarte Galhardo de Albuquerque et al. 2020). The trials were motivated mostly by their proven usefulness in treating malaria. The effective clinical trials by these agents give assurance for the use of NPs in this infectious disease (Cheuka et al. 2017). Some chemical structures of anti-schistosomal bioactive molecules are cardoldiene (18), 2-methyl cardoldiene (19) (both derived from *Anacardium occidentale)*, berberine (20) (derived from plants in the Berberidaceae family in the genus *Berberis*), furoxan (21), and artemether (22) (derived from *Artemisia annua*) shown in (Fig 1).

Nanoparticles and nanocarriers

Some researchers have discovered that nanoparticles such as nanoselenium and nanogold have therapeutic properties against intestinal disorders induced by *S. mansoni* (Adekiya et al. 2020 Dkhil et al. 2019). In these studies, the nanoparticles caused a reduction in the intensity of oxidative stress, changes in body weight, histological damage and the number of goblet cells in the jejunum. It was proposed that the therapeutic effects of nanoparticles are associated with their antioxidant activities (Dkhil et al. 2019). It was also revealed that the particular physical structure of nanoparticles, such as having large surface areas, permits the nanoparticles to interact with microorganisms (Ghosh et al. 2019). Their size gains them access to the cells. In another study that investigated the *in vitro* cytotoxicity and schistosomicidal activity of oleic acid-loaded nanocapsules, a 100% concentration-dependent mortality was observed from 200 µg/mL in 4 h of incubation and 50 µg/mL in 24 h (Nunes et al. 2021). Curcumin loaded gold-nanoparticles were tested on *S. mansoni in vivo* and displayed a synergistic anti-schistosomal effect when combined with PZQ. A 97.4% reduction of worm burden in the 3rd week was observed (Mokbel et al. 2020). The studies showed that the nanocapsules and curcumin loaded gold-nanoparticles led to severe damage to the tegument dorsal surface, making it a promising new treatment alternative.

Marine organisms

The potency of 13 macroalgae extracts from the Gracilaria, Dictyota and Laurencia genera was tested against *S. mansoni in vitro* (Stein et al. 2015). The extracts of *Dictyota dichotoma, Dictyota menstrualis, Dictyota mertensii, Plocamium brasiliense, Spyridia hypnoides, Gracilaria ornate, Chondria littoralis and Laurencia dendroidea* led to a100% mortality of adult worms at a concentration of 500 g/ml after 2 h. When the concentration was lowered to 100 g/ml and 100% mortality was observed after 24-72 h. In another trial, 45 crude extracts obtained from 37 species of Brazilian macroalgae were screened for schistosomicidal and molluscicidal activity *in vitro* on *S. mansoni*. Of the 37 species, 21 displayed schistosomicidal activity. Worm reproduction was notably inhibited by most of the species, as observed by egg counting (Stein et al. 2021). Given that there is a dearth of literature on the potential of marine organisms in schistosomiasis drug discovery, these few studies may generate increased interest to characterise more seaweeds.

Progress made in anti-schistosomal lead compound optimisation and development

Academic and pharmaceutical research groups working on drug discovery have made significant progress in identifying a range of novel leads, which still stand as the foundation for anti-schistosomal drug discovery (Bergquist et al. 2017). Many experiments have been done *in vitro* on larval, juvenile and adult *S. mansoni*. To date, more than 500 000 compounds have

Table 1. *In vivo* studies of selected traditionally employed plant species against *S. mansoni*

Plant species	Part used	Lethal doses	Model (*In vitro/in vivo*)	Main observations	References
Abrus precatorius L subsp. Africanus Verdc	Stem Root	LC $_{50}$ = 1.50.6 mg/mL (T = 1 h)	*In vitro*	Active concentration of the roots ranged from 0.6 mg/ml to 33.8 mg/ml and 1.5 mg/ml for the stem on *S. mansoni*	(Mølgaard et al. 2001)
Anonidium mannii	Root	IC_{50} = 10–20 µM *Sm*NAD^+ catabolizing enzyme (T = 6 h)	*In vitro*	Compounds from the plant *A.manni* namely Aristolactam A-II and piperolactam D had good activity on adult *S. mansoni* and its NAD^+ catabolizing enzyme respectively	(Toussi Matchi et al. 2020)
Artemisia annua *Artemisia afra*	Leaves	33,5-55.9 mg 1.26mg (T = 7d)	*In vivo* (clinical trial)	96.4% cure rate for *A. annua* and 88.8% cure rate for *A.afra* with average *S. mansoni* parasite clearance of 1/day	(Panic et al. 2014; Liu et al. 2014; Munyangi et al., 2018;Gruessner et al. 2019)
Berkheya speciosa (DC.) O.Hoffm	Aqueous plant extracts	LC_{50} > 6.25 mg/mL (T = 1 h)	*In vitro*	Crude plant extracts were lethal against the schistosomules of both *S. mansoni* and *S. haematobium*	(Sparg et al. 2000)
Cucurbita pepo	Seed oil	100% mortality at 10 µg/mL (T = 24 h)	*In vitro* *In vivo*	All stages of *S. mansoni* that were tested were susceptible to *C. pepo* seed oil. The seed oil was more effective than PZQ on juvenile worms and schistosomula	(Ammar et al. 2020; Beshay et al. 2019)
Euclea divinorum Hiem	Aqueous plant extracts	$LC_{50=}$ 50 mg/mL (T = 1 h)	*In vitro*	Significant anti-schistosomal activity on adult and juvenile *S. mansoni* at 50 mg/ml,	(Sparg et al. 2000)
Euclea natalensis A. (DC)	Aqueous plant extracts	LC_{50} > 3.13 mg/mL (T = 1 h)	*In vitro*	66.7% of the *S. haematobium* schistosomula worms were killed at a concentration of 3.13 mg/ml	(Sparg et al. 2000)
Maytenus senegalensis (lam) Excell.	Leaves & stem Root Root &bark	25 mg/mL 25 mg/mL 2.5 mg/mL (T = 1 h)	*In vitro*	A significant effect was observed on schistosomules of *S. mansoni*	(Mølgaard et al. 2001)
Ocimum americanum hexane, *Ocinmum americanum* water	Whole plant	Worm reduction in mice (68.7 and 63.4%) vs praziquantel (75.2%) (T = 1 h)	*In vivo*	68.7% *S. mansoni* worm reduction exhibited by *O.americunum* hexane; 63.4%, *O. americanum* water and 61.6%, *O. americanum* crude 52%	(Waiganjo et al.,2016)

(*continued*).

Table 1. Continued.

Plant species	Part used	Lethal doses	Model (*In vitro/in vivo*)	Main observations,	References
Origanum majorana	Aqueous extract	90% mortality at 500, 250 µg/ml (T = 6 and 12 h)	*In vitro In vivo*	100% mortality of schistosomula and adult worms (Egyptian *Schistosoma* strains) of *S. haematobium* at 500, 250, and 125 µg/ml concentrations	(Fadladdin 2021)
Pterocarpus angolensis DC	Leaves Stem bark	LC_{50} = 102 mg/mL LC_{50} = 33.8 mg/mL LC_{50} = 51.3 mg/mL (T = 1 h)	*In vivo*	The efficacy of *P. angolensis* was comparable to that of praziquantel on *S. haematobium*	(Cock et al. 2018; Ndamba et al. 1994)
Pulsatilla chinensis (Hederacolchiside A1)	Whole plant	LD_{50} = 21.05 mg·kg−1 (T = 1 h)	*In vitro In vivo*	HSA had high activity against *S. japonicum* and *S. mansoni* less in 11 h days old parasites *in vivo*	(Kang et al. 2018)
Rauwolfia vomitoria	Root and stem bark	< 1000 µg/mL.(cecarie) < 1000 µg/mL.(inhibition value on adults) (T = 2 h)	*In vitro*	All *S. mansoni* cercariae were killed within 2 h of exposure at a concentration range of 62.5–1000 µg/mL and 250–1000 µg/mL of stem bark and roots, respectively	(Tekwu et al.,2017)
Scierocarya birrea (A. Rich.) Hochest. Subsp, Caffra		LC_{50} > 25 mg/mL (T = 1 h)	*In vivo In vitro*	Lethal at 50 mg/ml, killing either 66.7 or 100% of the *S.mansoni* schistosomula worms	(Sparg et al. 2000).
Zingiber officinale	Root / tuber	500, 250, and 125 µg/ml led to 100% mortality (T = 6 h)	*In vitro In vivo*	The crude aqueous extract at a dose of 500 mg/kg body weight exhibited anti-schistosomal activity on *S. mansoni*	(El-derbawy1 et al. 2019; El-Nour et al. 2021)
Ziziphus spina-christi	Aqueous extract	18.90ppm (T = 25 h)	*In vivo*	100% mortality of *S.mansoni* schistosomule and adult worms observed at 500, 250, and 125 µg/ml concentrations	(Fadladdin 2021;Yousif et al. 2007)

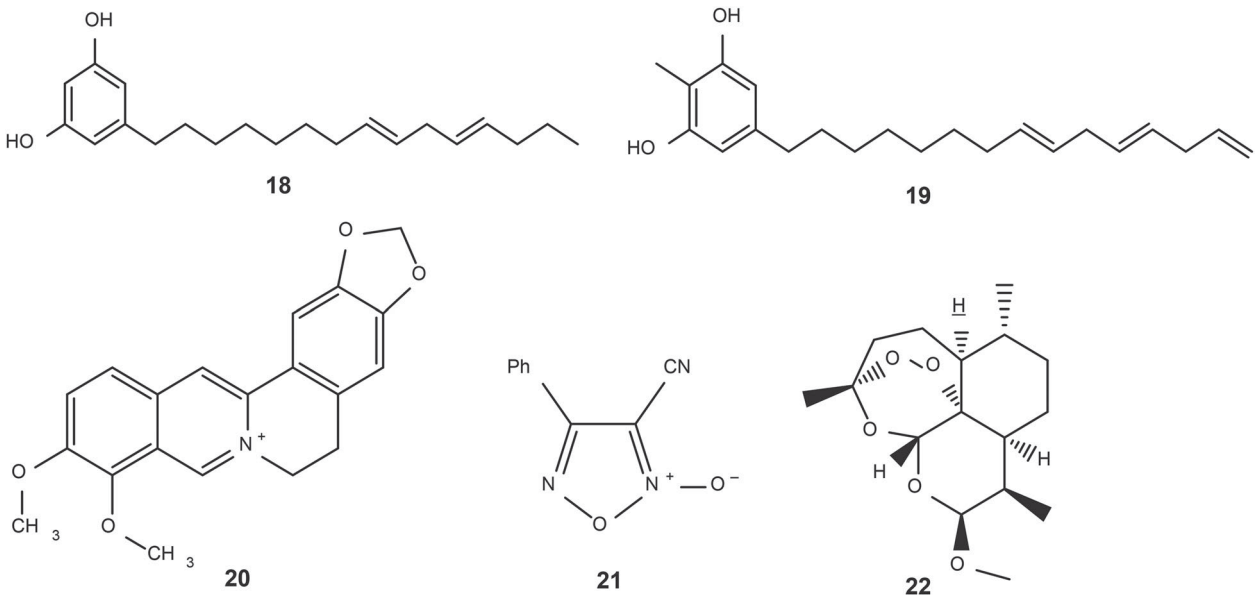

Figure 1. Structures of various bioactive molecules against schistosomiasis (Ghosh et al. 2019).

been screened in high-throughput screening projects (Hernandez et al. 2019; Guidi et al. 2017; Neves et al. 2016; Kuhn et al. 2010). One of the latest studies reported an *in vitro* and *in vivo* screening of the Medicines for Malaria Venture (MMV) Pathogen Box containing 400 compounds. The study revealed that MMV022029 and MMV022478 had the highest worm burden reduction and granted a series of new potent scaffolds and pharmacophores that could be used to design and develop appropriate alternative(s) to PZQ (Pasche et al. 2019). The pharmacophores' structures are shown in Figure 2.

Some of the leads are currently used in structure–activity relationships in various ongoing experiments and quantitative structure–activity relationships (QSAR) (Melo-Filho et al. 2016). Despite the urgent need to find new schistosomiasis drugs, there is no single drug candidate that is close to reaching the market at present (Lombardo et al. 2019). Of the 402 new chemical entities that were registered between 2000 and 2013, none targeted schistosomiasis nor NTDs (Ferreira et al. 2015).

Application of advanced techniques in schistosomiasis drugs discovery

Currently, drug design and development are driven by the modernisation and knowledge of a combination of experimental and computational approaches (Neves et al. 2016b). The integration of molecular and computer-aided drug design (CADD) in drug development alongside organic synthesis has led to increased availability of biological, structural and chemical data (Ferreira et al. 2018; Herrera Acevedo et al. 2017; Neves et al. 2015). Many molecular targets from the *Schistosoma* species have been evaluated (Mafud et al. 2016). The disclosure of the genomes of the three species of schistosomes that are usually implicated in infection has been a breakthrough in the field as it led to increased comprehension of the molecular machinery involved in the parasite–host relationship and, therefore, in the disease pathophysiology (Ferreira et al. 2018). Various proteins are emerging as cutting edge potential drug targets. Examples of the proteins are; G-protein-coupled receptors, kinases, ion channels, reductases, acetylases and proteases. Presently, 238 schistosomes' protein structures are registered in the Protein Data Bank and the majority of the proteins were obtained through X-ray crystallography. The existence of large virtual libraries of small molecules has assisted medicinal chemists in virtually screening possible drug candidates for NTDs. Libraries such as the ZINC, GDB-17, Chemspider, ChemMine, Drug Bank and PubChem contain small molecules ranging between 5000 and 100 billion and are readily available online (Lin et al. 2020; Banegas-Luna et al. 2018). This information has brought schistosomiasis drug discovery into the molecular age and opened various new possibilities in the field. Currently, schistosomiasis drug discovery programs are

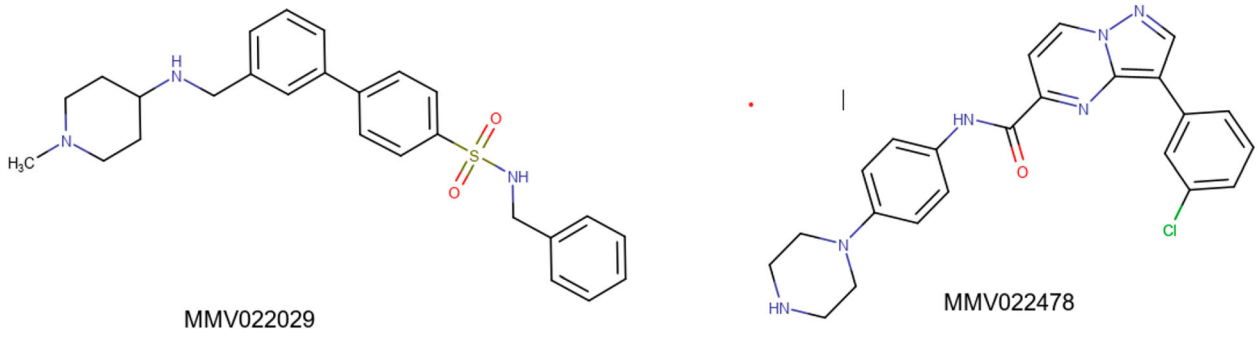

Figure 2. The structures of the MMV pharmacophores with schistosomicidal properties.

carried out through the implementation of unprecedented molecular modelling coupled with drug repositioning research, structure-based drug design and target-focused compound screening (Ferreira et al. 2018). Computational techniques used in schistosomiasis' drug discovery are generally categorised under structure-based drug design (SBDD) and ligand-based drug design (LBDD) (Wilson and Lill 2011).

SBDD is the design and optimisation of a chemical structure to identify a compound suitable for clinical testing as a drug lead (Batool et al. 2019). SBDD is based on knowledge of the drug's three-dimensional structure and how the shape of the drug and charge cause it to interact with its biological target. In SBDD, large databases or libraries of 3D structures of small molecules can virtually be screened on a 3D structure of schistosomiasis protein (Batool et al. 2019). Molecular docking is a process commonly used in screening good drug-like compounds. Through the application of specialised docking programs, the process searches the possible conformation or poses of molecules inside the binding pocket of drug targets and scores them according to their stability energy-wise (Xu et al. 2018). LBDD is an approach commonly used in default of the receptor 3D structure. LBDD is rooted in data of established molecules that bind to the biological target of interest. 3D QSAR and pharmacophore modelling are the most essential and extensively used tools in LBDD. They can offer predictive models well-suited for lead identification and optimisation.

One refined application that can speed up the discovery of drugs with schistosomicidal activity is virtual screening (VS). VS is the use of computational filters in a database of chemical structures to predict the bioactivity of a compound concerning a specific target. The major benefit obtained from VS is the reduced time and resources required for an *in vitro* screen of a chemical library of known compounds (Nunes et al. 2016).

Efforts have been made in using computational methods to develop new schistosomicidal agents or drugs. In this section (Table 2), we summarise the general categories of CADD methods used in the discovery of novel schistosomicidal drugs.

Most CADD efforts in schistosomiasis drug discovery have focused on the design and synthesis of schistosomicidal agents, followed by VS. Although the chemical space of current NPs databases is huge enough to attract VS projects, there are very few studies that have been done to advance the discovery of schistosomicidal agents. In a 2017 study (Akachukwu et al. 2017), African originated plant metabolites were evaluated for 'drug-likeness' and docked toward four selected validated *Schistosoma* drug targets; Glutathione S-transferase, Thioredoxinglutathione reductase, Histone deacetylase and *S. mansoni*. Out of a total of 27 bioactive compounds with anti-*Schistosoma* history, one of the compounds emerged as the most interesting candidate by both being drug-like and inhibiting the activities of the studied enzyme targets at the micromole arrangement.

For the past decade, African NP medicinal chemists and database developers have progressed much in the development of small compound NPs databases and libraries. Currently, there are more than ten NP libraries across the African continent, with 20000 chemical entries in total (Sorokina and Steinbeck 2020). Most of the libraries are not yet available online except for the Northern African NPs Database (NANPDB) (Ntie-Kang et al. 2017), Integrated Ethiopian traditional herbal medicine and phytochemicals database (ETM-DB) (Bultum et al. 2019) and South African natural compound database (SANCDB)

Table 2. The general categories of CADD methods used in the discovery of novel schistosomicidal drugs.

Techniques of CADD used	*S. mansoni* proteins targeted	Proposed drugs/molecules	References
Structure-based virtual screening (SBVS), Homology modelling	Dihydroorotate dehydrogenase (DHODH)	manitimus, capecitabine, brequinar analogue and leflunomide.	(Otarigho 2019)
Molecular docking, homology modelling	*Sm* ATPase	Licofavone B	(Aleixo de Carvalho et al. 2015)
Molecular docking	*Sm* TGR	8-hydroxyquinoline-5-sufonyl 1,4-diazepine derivative (Compound 7b)	(Allam et al., 2013)
QSAR-based virtual screening	*Sm* TGR	sorangicin A, A-349079-S1 and amphidinolide H1	(Mendonça et al., 2019)
Combi-QSAR-based virtual screening	*Sm* TGR	4-nitro-3,5-bis(1-nitro-1H-pyrazol-4-yl)−1H-pyrazole (LabMol-17) and 3-nitro-4-[(4-nitro-1,2,5-oxadiazol-3-yl)oxy]methyl−1,2,5-oxadiazole (LabMol-19)	(Melo-Filho et al. 2016)
Molecular docking, homology modelling	*S. mansoni* phosphofructokinase	C_2H_5 analogue of 6-gingerol	(Durojaye et al. 2019)
Molecular docking, VS, molecular dynamics and homology modelling	*Sm* HDAC1	(N,8-dihydroxy-8-(naphthalen-2-yl) octanamide zinc (ZINC13474421)	(Singh and Pandey 2015)
Molecular docking	*Sm* TGR	8-hydroxyquinoline-5-sulfonamido derivatives compound 3 and 4	(Eweas et al. 2013)

(Hatherley et al. 2015). The development of libraries allows medicinal chemists and drug developers to conduct in-depth *in silico* studies that can advance the discovery of schistosomicidal drugs.

Structure-based virtual screening

Structure-based virtual screening (SBVS) explores information about a 3D structure of targets that are either determined experimentally by, for example, X-ray crystallography and nuclear magnetic resonance or are computationally predicted through homology modelling to select suitable ligands (Neves et al. 2015).

In one of the most recent studies, an ecto-enzyme called *Sm*NACE in *S. mansoni* was discovered. *Sm*NACE has an encouraging topology because it is one of the uncommon recognised and characterised targets on the tegument of adult schistosomes that causes serious clinical problems and could be considered a prospective target for drug nominees (TousiMatchi et al. 2020). The enzyme purine nucleoside phosphorylase (PNP), one of the explored targets, is a crucial element in the purine recovery biochemical route (Pereira et al. 2020). Given that *Schistosoma* worms do not have a *de novo* purine biosynthesis pathway, they solely rely on the salvage pathway to fulfil their requirement for purines, as they are essential for the biosynthesis of nucleic acids (Torini et al. 2018). Based on these findings, PNP could be considered a pharmacological target for developing new schistosomicidal agents (Ferreira et al. 2018). Drug discovery studies that use diverse methods for drug screening are more likely to find new lead compounds (Tavares et al. 2016).

Drug repurposing

Drug repurposing/repositioning of approved drugs has been one of the starting points in identifying new schistosomiasis drug leads. Various drugs that have been FDA approved were assessed for the schistosomicidal potency (Gouveia et al. 2018). The initial and most extensively investigated drug class are the semisynthetic artemisinins, together with dihydroartemisinin, artemether, and artesunate, which are efficient against the juvenile schistosomes but less so against mature worms (Caffery et al. 2019; Gouveia et al. 2018).

Other drugs that have been investigated and exhibited potency include mefenamic acid which was shown to be effective against *S. mansoni* (Lago et al. 2019); promethazine on *S.mansoni* (Roquini et al. 2019); spironolactone on *S. mansoni* (Guerra et al. 2019); single oral fixed-dose of praziquantel-miltefosine-nano combination on *S. mansoni* (Eissa et al. 2020); miltefosine on *S. mansoni* (El-Faham et al. 2017); perhexiline maleate (Guidi et al. 2016); clofazimine and doramectin have also displayed schistosomicidal activity (Gemma et al. 2019). In these studies, it

is evident that repurposing approaches are useful as starting points in the discovery of novel drugs against *Schistosoma*.

Major hindrances in drug development and prospects

As the term implies, NTDs are neglected by the pharmaceutical production sector since the diseases affect mainly the poorest societies (Kefalidou et al. 2016; Moon et al. 2012). In these countries, the majority of people can barely afford a balanced diet, accommodation, clothes and formal health care. Thus, many resort to alternative traditional medicines (Length 2017). Firstly, major pharmaceutical companies' investment in the therapeutic areas is not financially appealing because of poor financial returns. It is also known that the drug discovery process is costly and with a high failure rate (Weng et al. 2018) thus, drug discovery against parasitic diseases, in general, has not been inspired by profit-making motives (Cheuka et al. 2017). As a result, pharmaceutical companies rather develop drugs that target chronic diseases, ensuring long-term sales (Kefalidou et al. 2016). Further, challenges also include ensuring the right to use of sufficient plant resources, licensed property rights concerns and the complications of NP chemistry with related incompetence of working with NPs (Cheuka et al. 2017). The number of well-validated molecular drug targets for tropical diseases is very negligible, partly because the detailed biology of many of the pathogens is yet to be understood (De Rycker et al. 2018). In the light of these hindrances, the application of *in silico* methods in the discovery of novel schistosomiasis drugs is also slackened.

VS has arisen in drug discovery as a robust computational method of screening huge libraries of small molecules for new hits with preferred properties that would then be experimentally tried (Neves et al. 2018). Computational simulations used in VS strategies are very proficient in the identification of pharmacologically dynamic compounds or novel indications for drugs already used to treat other diseases. The use of this technology may speed up the pace at which schistosomiasis drug discovery is moving. Testing the candidate compounds *in silico* and selecting those with a high chance of binding to the target in the parasite is vital, as it lowers the costs of drug discovery (Pereira et al. 2020). Political leaders and governments need to identify schistosomiasis as a public health problem that needs to be given greater consideration in terms of funding and setting up effective monitoring and surveillance systems (Abe et al. 2020). More investigation of the therapeutic impact of a wide range of natural antioxidants and herbal extracts against these diseases may prove to be of great assistance for the poorest among the human population living in the tropical nations of Asia, Africa and North and South America where schistosomiasis is endemic (Ghosh et al. 2019). It is vital to employ CADD methods to minimise the costs involved in the discovery of new schistosomiasis drugs, considering that the most affected regions are low-income countries (Zorn et al. 2021).

Future directions in CADD based on novel anti-schistosomal compounds

While CADD has made significant contributions to the development of drugs that are in clinical use or undergoing clinical trials, additional and new strategies are needed to ensure the hit compounds that target schistosome proteins are further developed into lead compounds. Molecular dynamics can be used in upscaling drug discovery, for example, through energy calculations of a binding ligand (hit compound) considering free energy perturbations (Mortier et al. 2015). The availability of supercomputing facilities can help facilitate enhanced CADD through parallel processing, and advanced programs, algorithms, and tools which enable lead identification (Macalino et al. 2015).

Artificial intelligence (AI) is another approach that has varied applications in drug discovery. These include prediction of protein folding, protein–protein interaction, evaluation of ADMET properties, virtual screening, QSAR, and de novo drug design (Wang et al. 2019). Generating and labeling applicable chemical, biological, and physiological data for queries related to efficacy and safety is complicated when applying AI in drug discovery (Selvaraj et al.,2021). However, with proper understanding of which data to generate, and for which purpose, the discovery of anti-schistosomal drugs can be advanced using AI. This would be through measuring and capturing of appropriate biological endpoints *in vivo* and application of computational algorithms regarding the hit compounds 'efficacy and safety (Bender and Cortes-Ciriano 2019). Hence, AI and machine learning tools promise to enable dynamic applications in the future pharma and biomedical industries. With developments in diverse fields, a drift towards an automated and more accurate approach in anti-schistosomal drug discovery, with the aid of AI can be expected

(Selvaraj et al. 2021). Furthermore, identification of anti-schistosomal properties of approved drugs that are already used to treat other diseases can be done using CAAD (Prieto-Martínez et al. 2019). New applications of existing drugs may be found through repositioning them from their approved indications using information obtained through genomics, thus laying a crucial foundation for drug repurposing (Kiriiri et al. 2020).

Conclusions

The recent advances in CADD represent a new era in the discovery of anti-schistosomal drugs. While many plants have been tested against schistosomiasis and proved to be potent, none of them are close to reaching the market as new drugs. We propose using *in silico* methods to accelerate this process, as they are more accurate and more efficient than the conventional approaches. Considering that the schistosomiasis drug discovery process is already underfunded, the use of CADD methods will lead to the identification of hit and lead compounds at a lesser cost.

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Author contribution statement

Mtemeli F. L. – Conceived and designed the article and interpreted the relevant literature; drafted the article.
Ndlovu J. – Interpreted the relevant literature; revised the paper critically for important intellectual content.

Mugumbate G.¯ Interpreted the relevant literature; revised the paper critically for important intellectual content.

Makwikwi T. - Interpreted the relevant literature; revised the paper critically for important intellectual content.

Shoko R. - Conceived and designed the article and interpreted the relevant literature, revised the paper critically for important intellectual content; supervised the work.

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