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Traditional Kenyan herbal medicine: exploring natural products' therapeutics against schistosomiasis

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Abstract

Praziquantel (PZQ) remains the only drug of choice for the treatment of schistosomiasis, caused by parasitic flatworms. The widespread use of PZQ in schistosomiasis endemic areas for about four decades raises concerns about the emergence of resistance of *Schistosoma* spp. to PZQ under drug selection pressure. This reinforces the urgency in finding alternative therapeutic options that could replace or complement PZQ. We explored the potential of medicinal plants commonly used by indigenes in Kenya for the treatment of various ailments including malaria, pneumonia, and diarrhoea for their antischistosomal properties. Employing the Soxhlet extraction method with different solvents, seven medicinal plants *Artemisia annua*, *Ajuga remota*, *Bredilia micranta*, *Cordia africana*, *Physalis peruviana*, *Prunus africana* and *Senna didymobotrya* were extracted. Qualitative phytochemical screening was performed to determine the presence of various phytochemicals in the plant extracts. Extracts were tested against *Schistosoma mansoni* newly transformed schistosomula (NTS) and adult worms and the schistosomicidal activity was determined by using the adenosine triphosphate quantitation assay. Phytochemical analysis of the extracts showed different classes of compounds such as alkaloids, tannins, terpenes, etc., in plant extracts active against *S. mansoni* worms. Seven extracts out of 22 resulted in <20% viability against NTS in 24 h at 100 µg/ml. Five of the extracts with inhibitory activity against NTS showed >69.7% and ≥72.4% reduction in viability against adult worms after exposure for 24 and 48 h, respectively. This study provides encouraging preliminary evidence that extracts of Kenyan medicinal plants deserve further study as potential alternative therapeutics that may form the basis for the development of the new treatments for schistosomiasis.

Research Paper

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Introduction

Schistosomiasis or bilharzia is one of the most common parasitic neglected tropical diseases. It is caused by the flatworms in the genus *Schistosoma*. The World Health Organization (WHO) estimates that more than 230 million people from 78 countries including the Middle East, South America, East Asia and sub-Saharan Africa are at risk with about 200,000 deaths each year (World Health Organization, 2022). The main burden of the disease is in sub-Saharan Africa, which accounts for over 90% of all incident cases (Colley *et al.*, 2014). The primary schistosome species infecting humans are *Schistosoma mansoni*, *Schistosoma haematobium* and *Schistosoma japonicum* and transmission is mainly by contact with contaminated freshwater, whereby infective larvae released from freshwater snails, for instance, *Biomphalaria glabrata*, penetrate the host skin, develop within circulation and mature into *Schistosoma* adult worms in the mesenteric or bladder veins of human host (Colley *et al.*, 2014). The egg deposition within the liver and or bladder and in some cases the central nervous system and pulmonary systems of the human host evokes immunological responses with associated disease pathophysiology (Colley *et al.*, 2014).

There is no vaccine for schistosomiasis treatment and the only existing drug recommended by the WHO for chemotherapy praziquantel (PZQ) has been utilized for the past four decades. The widespread use of PZQ monotherapy in African endemic communities has raised concerns about the selection of drug resistant schistosomes. Even though evidence of clinically relevant emergence of PZQ resistance is lacking, low cure rates in response to PZQ in the

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Table 1. Botanical information of medicinal plants used for anti-schistosomal study.

Family name	Botanical name	Common name	Part used	Preparation	Traditional use
Asteraceae	*Artemisia annua*	sweet wormwood	leaf, flower	decoction	malaria, psoriasis, infections
Lamiaceae	*Ajuga remota*	bugleweed	leaf	decoction	malaria, chest pains
Solanaceae	*Physalis peruviana*	cape gooseberry	leaf	decoction	typhoid, pneumonia
Rosaceae	*Prunus africana*	red stinkwood	stem bark	decoction	pneumonia/chest pain, loss of appetite
Boraginaceae	*Cordia africana*	giku	bark, leaf	decoction	fatigue, anti-inflammatory
Fabaceae	*Senna didymobotrya*	candelabra tree	leaf	decoction, steam	pneumonia
Euphorbiacece	*Bridelia micrantha*	mitzeeeri	stem bark	chew	chest pains

field after extensive mass drug administration in Egypt and Senegal have been reported (Simoben *et al.*, 2018). Furthermore, *S. mansoni* isolates from Kenyan patients showed lower susceptibility to PZQ, including one isolate from a patient who was never fully cured after repeated PZQ treatment over several years and PZQ-resistance can be generated in the laboratory (Fallon & Doenhoff, 1994; Bergquist *et al.*, 2017). The continual administration of PZQ most likely will select for schistosomes with reduced susceptibility, which could accelerate the emergence of resistance as large reservoirs of untreated schistosomes become exposed to PZQ. There is, therefore, the need for alternative therapeutic options that could be used in place of or to complement PZQ.

Plants, bacteria and fungi are good sources of pharmacologically active natural products used in the treatment of various diseases (Simoben *et al.*, 2018) and traditional, plant-based medicines are a potential source for new drugs. Research efforts have intensified in search of new, potent, affordable and effective drugs to treat parasitic diseases due to the limited treatment options and the lack of vaccines targeting the parasitic diseases. Plant parts have been used as traditional medicine for schistosomiasis for centuries in many African countries. *Phytolacca dodecandra* berries are used as a molluscicide to control schistosomiasis in Ethiopia (Esser *et al.*, 2003). *Breonia decaryana*, *Citrus reticulata*, *Dalbergia monticola*, *Senna alata* and *Zingiber zerumbet* are used for schistosomiasis treatment in Madagascar (Rakotoarivelo *et al.*, 2015). In Mali, *Cissus quadrangularis* and *Stylosanthes erecta* (Bah *et al.*, 2006), *Rauvolfia vomitoria* (Tekwu *et al.*, 2017), *Elephantorrhiza goetzei* and *Pilistigma thonningii* are used as remedies for schistosomiasis (Maroyi, 2013). Due to the enormous therapeutic properties shown by many plants, in this study we explored the potential of seven plants used in Kenya for treating malaria, pneumonia, and diarrhoea for their schistosomicidal activity: *Artemisia annua* (Anibogwu *et al.*, 2021); *Ajuga remota* (Cocquyt *et al.*, 2011; Yikna & Yehualashet, 2021); *Bredilia micranta* (Maroyi, 2017); *Cordia africana* (Lelamo, 2021); *Physalis peruviana* (Kasali *et al.*, 2021); *Prunus africana* (Kathambi *et al.*, 2020); and *Senna didymobotrya* (Schmelzer *et al.*, 2008).

Material and methods

Collection and preparation of plant material

The botanical information on the traditional medicinal plants of Kenya used in this study are presented in table 1. Dry powdered material of seven plants (*A. remota*, *B. micrantha*, *S. didymobotrya, C. africana*, *P. peruviana*, *P. africana*, and *A. annua*) were obtained from the Department of Pharmacognosy, Pharmaceutical Chemistry and Pharmaceutical & Industrial Pharmacy, Kenyatta University, Nairobi, Kenya. The plant material was first extracted with boiling water by decoction and then sequentially extracted with methanol and hexane in a Soxhlet apparatus. Plant material was also extracted non-sequentially using acetone with Soxhlet extraction. The extraction solvents (methanol, acetone and hexane) were evaporated under nitrogen gas, and water extracts were dried by lyophilization. Depending on sample availability and extraction yield, the samples were tested for anti-schistosomal activity. The yields of crude extracts are shown in table 2.

Evaluation of schistosomicidal activity

Preparation of schistosomula

Biomphalaria glabrata (strain NMRI) infected with *S. mansoni* (strain NMRI) were obtained from the National Institute of Allergy and Infectious Diseases Schistosomiasis Resource Center of the Biomedical Research Institute. After infections were patent, snails were exposed to bright light for 1 h to obtain cercariae. Cercariae were mechanically transformed to schistosomula as described (Lombardo *et al.*, 2019). Briefly, cercariae were placed on ice for 30 min and then centrifuged at 350 × g for 10 min. The supernatant was decanted and 2 ml of serum-free M199 medium was added to cercarial pellets and vortexed for 1 min until cercarial tails were detached. Newly transformed schistosomula (NTS) were purified by layering on 4°C Percoll gradient suspension containing Eagle's minimum essential medium, penicillin–streptomycin (10,000 U per ml penicillin/10,000 U per ml streptomycin), and 1 M 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid in 0.85% sodium chloride with cercariae suspension and centrifuged at 500 × g for 15 min. Cercarial pellets were resuspended and washed thrice in serum-free M199 medium and collected at 100 × g for 5 min. NTS (240) were transferred to U-bottom 96 well assay plates containing 200 µl of M199 medium supplemented with 5.5 mM D-glucose, penicillin–streptomycin and 5% heat inactivated fetal bovine serum and incubated at 37°C in a 5% carbon dioxide (CO_2) incubator overnight.

Preparation of adult worms

Swiss Webster mice (Charles River) housed in the Comparative Research Center of Rush University Medical Center were infected by percutaneous tail exposure to about 200 *S. mansoni* cercariae through natural transdermal penetration of the cercariae for one hour (Tucker *et al.*, 2013). Mice were euthanized 7-weeks post infection using a lethal dose of 0.018 ml of Euthasol and 5.85 mg/ml heparin to prevent blood coagulation (injection volume of 400 µl). Perfusion was performed by flushing pre-warmed

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Table 2. Crude extraction yield from Kenyan medicinal plants.

	Percentage mass extracted per plant			
Plant Species	Water	Methanol	Hexane	Acetone
Ajuga remota	14.20%	8.15%	10.65%	8.90%
Artemisia annua	15.28%	2.91%	10.08%	11.85%
Bridelia micrantha	23.28%	3.77%	0.63%	21.15%
Cordia africana	8.56%	8.02%	2.36%	21.55%
Prunus africana	17.16%	2.57%	9.79%	6.24%
Physalis peruviana	8.85%	4.48%	4.23%	7.69%
Senna didymobotrya	10.29%	10.56%	8.03%	10.49%

Roswell Park Memorial Institute (RPMI) containing phenol red and L-glutamine through a 25- and 3/8-gauge needle placed into the aorta attached to Tygon® tubing aided by the Masterflex™ L/S perfusion pump as described (Tucker *et al.*, 2013). Adult worms were carefully washed in phenol red free RPMI medium and subsequently incubated in phenol red free RPMI medium supplemented with 5.5 mM D-glucose, penicillin–streptomycin and 5% heat inactivated fetal bovine serum and at 37°C in a 5% CO_2 incubator overnight.

Schistosomicidal activity of extracts against S. mansoni *schistosomula and adult worms*

The dimethyl sulphoxide (DMSO) formulated plant extracts were diluted with phenol red free M199 medium or RPMI medium for NTS and adult worms, respectively, at <1% DMSO final concentrations. NTS and adult worms from overnight cultures were tested against extracts in triplicate at 100 µg/ml. Controls were treated with DMSO alone or 5 µM auranofin as a positive control in appropriate medium (Kuntz *et al.*, 2007). NTS and adult worm viability was assessed at 24 h by measuring adenosine triphosphate (ATP) content of worms using the CellTiter-Glo® Assay (Promega) following manufacturer's instructions as described (Lalli *et al.*, 2015).

Statistical analysis for schistosomicidal activity

Schistosome viability in the presence of the crude extracts were assessed using this formula:

$$\%\text{viability} = \frac{\text{Averages of Test}}{\text{Averages of DMSO Control}} \times 100$$

Phytochemical analysis

Qualitative phytochemical characterization was performed by placing 5 µl of solution onto a silica plate and then subjecting to standard reagents used for phytochemical analysis. The following reagents were used for the phytochemical analysis: anisaldehyde/sulphuric acid reagent for steroids (Xu & Liu, 2021); Dragendorff reagent for alkaloids (Dube *et al.*, 2021); potassium hydroxide (Bornträger reaction) (Henzelyová *et al.*, 2020) for coumarins (365 nm) and anthraquinones (vis. and 365 nm); 5% ethanolic solution of sulphuric acid (H_2SO_4) for cardiac glycosides (Onyema, 2019); aluminium chloride ($AlCl_3$) solution (1% ethanolic $AlCl_3$) for flavonoids (Gwatidzo *et al.*, 2018); iron (III) chloride ($FeCl_3$) reagent (3% $FeCl_3$) for tannins and phenolic compounds (Fu & Chen, 2019); ninhydrin for amino acids, amines and amino sugars (0.2% ethanolic ninhydrin solution) (Tyagi *et al.*, 2019); phenol/ $H2SO_4$ solution for carbohydrates (Su *et al.*, 2020; Oh *et al.*, 2021); and vanillin/H_2SO_4 solution for terpenes/terpenoids (Jiang *et al.*, 2016).

Results

Schistosomicidal activity of crude extracts of Kenyan medicinal plants

Seven Kenyan medicinal plants were extracted with various solvents resulting in 22 different crude extracts (table 2). These were evaluated for schistosomicidal activity against *S. mansoni* NTS. Following 24-hour exposure of NTS to 100 µg/ml of each extract worm viability was determined by ATP quantitation. We observed variable viabilities among the crude extracts analysed. Greater than 80% reduction in NTS viability was detected after treatment with *A. annua* (acetone) – 97.9%, *P. africana* (acetone) – 96.4% *B. micrantha* (water) – 89.9%, *P. peruviana* (acetone) – 89.5%, *B. micrantha* (methanol) – 88.6%, *A. remota* (hexane) – 82.5%, and *S. didymobotrya* (acetone) – 82.4% compared to the DMSO treated NTS negative control as shown in fig. 1. While treatment with most of the extracts resulted in moderate viability reductions, treatment with *A. remota* (water) (4.2% reduction) and *B. micrantha* (hexane) (9.2% reduction) had minimal activity against NTS.

We further tested all nine extracts that showed >80% decrease in viability against NTS for activity against *S. mansoni* adult worms. Viability was determined for each extract after 24-hour and 48-hour exposure to adult worms. After 24-hour exposure, all extracts showed ≤36% viability against adult worms except *A. annua* (acetone) (48%) and *B. micrantha* (methanol) (51.5%) (fig. 2). Upon 48-hour exposure, about 10% increased reduction in viability was observed among the seven tested extracts with all compounds resulting in >55% mortality. The most active extract against *S. mansoni* adult worms was *B. micrantha* (water) with 81.6% reduction in viability (fig. 2).

Qualitative phytochemical screening results

Qualitative analysis of crude plant extracts showed the presence of various phytochemicals (table 3). The level of phytochemicals was categorized as high, moderate, low, or absent. *Artemisia annua* plant extracts showed high levels of steroids, tannins, anthraquinones and terpenes/terpenoids. Moderate levels of glycosides and flavonoids were present in *A. annua* extracts. Steroids and tannins were present at high levels in *B. micrantha* extracts. Alkaloids, anthraquinones and glycosides were moderately present in *B. micrantha* plant extracts. *Cordia africana* plant extracts showed steroids, tannins and proteins at high levels whereas glycosides and anthraquinones were scarcely present. *Ajuga remota* plant extracts showed steroids, flavonoids, terpenes/terpenoids, glycosides, proteins and anthraquinones eminently whereas tannins were scarcely present. *Prunus africana* plant extracts showed steroids, glycosides and anthraquinones at high levels whereas tannins, terpenes/terpenoids and flavonoids were present at low levels. *Senna didymobotrya* plant extracts showed steroids,

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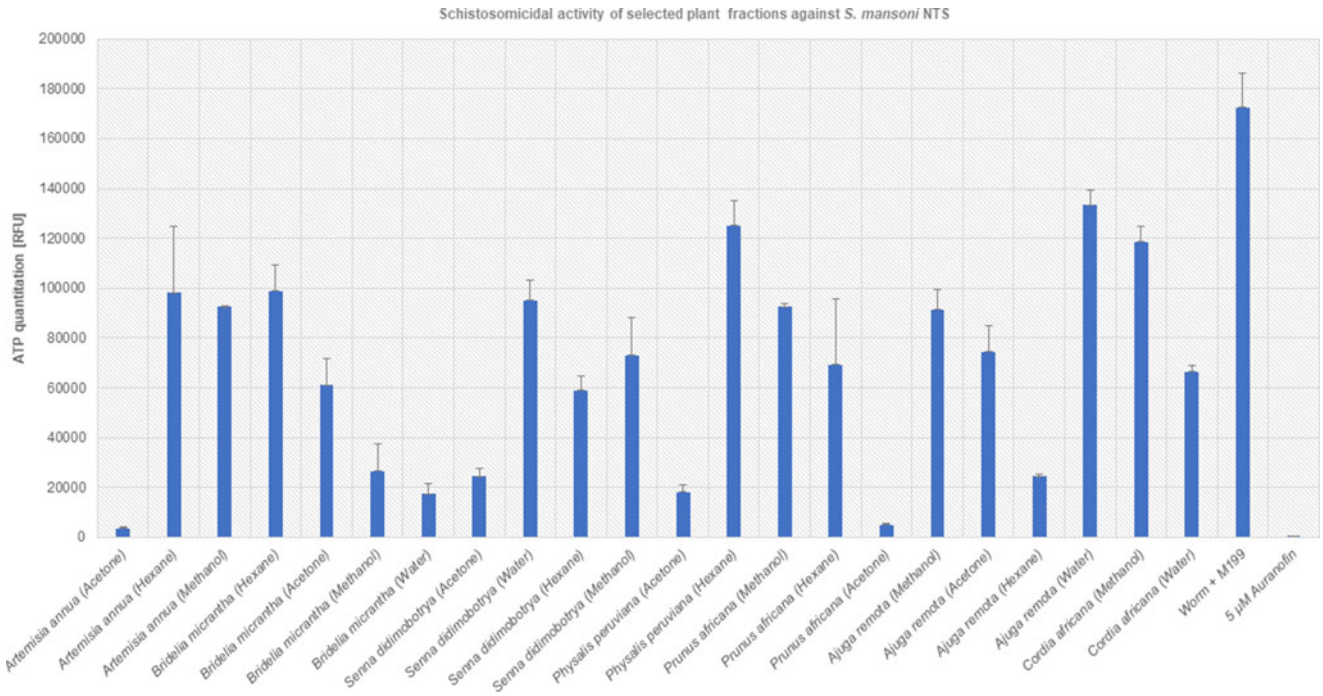

Fig. 1. *Schistosoma mansoni* newly transformed schistosomula viability against crude extracts from Kenyan medicinal plants. The error bars represent the standard deviation of three independent experiments.

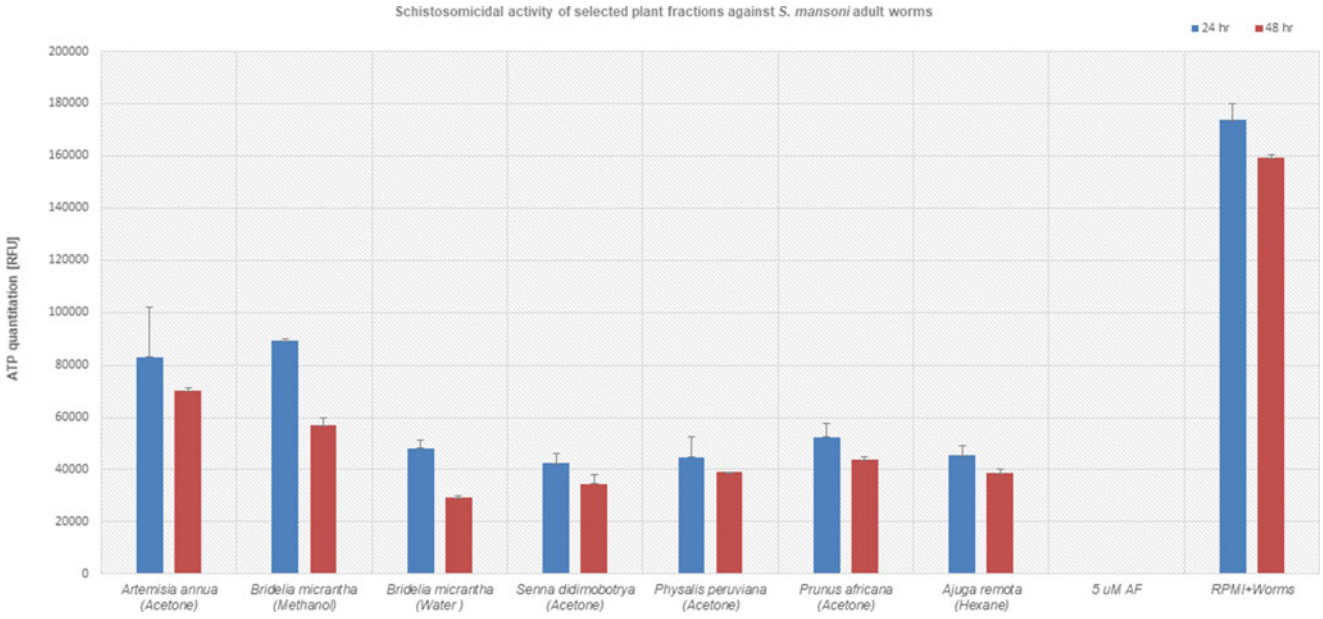

Fig. 2. *Schistosoma mansoni* adult worm viability after treatment with crude plant extracts with potent newly transformed schistosomula-killing activity. Viability (%) after 24 h (■) or 48 h (■) treatment with extract. The error bars represent the standard deviation of three independent experiments.

glycosides and anthraquinones at high levels whereas tannins, alkaloids and flavonoids were present at low levels or absent. *Physalis peruviana* plant extracts showed high levels of steroids and terpenes/terpenoids whereas tannins, flavonoids, and anthraquinones were present at low levels or absent.

Discussion

The lack of a vaccine or alternative drugs to PZQ for the management of schistosomiasis has necessitated the need to search for novel anti-infective agents. Even though the efficacy of PZQ for the past four decades has not been in doubt, concerns about the possible emergence of resistance due to selective drug pressure are inevitable, reinforcing the urgency towards the discovery of new schistosomicidal agents. Furthermore, PZQ has poor activity against migrating juvenile worms and treatment often results in incomplete cures (Pica-Mattoccia & Cioli, 2004). Plants have served as active components of many pharmacological products due to their broad spectrum of biological activity including cytotoxic, antiparasitic and antimicrobial properties (Heinrich & Lee

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Table 3. Phytochemical analysis from seven Kenyan plant extracts.

Plant extract	Steroids	Alkaloids	Tannins/phenolic compounds	Carbohydrates	Proteins/amino acids	Glycosides	Flavonoids	Anthraquinones	Terpenes/terpenoid
Artemisia annua									
acetone	+++	–	++	+	–	+	+	+++	++
hexane	+	–	–	–	–	–	–	–	++
methanol	++	–	++	+	+	+	++	+++	++
Bridelia micrantha									
hexane	–	–	–	–	–	–	–	–	+
acetone	+++	–	++	–	–	–	–	+	–
methanol	+++	++	+++	++	+	++	–	+++	–
water	++	+	+++	+	+	–	–	+	–
Senna didymobotrya									
acetone	+++	–	–	–	–	+	+	+	–
water	+++	–	+	+++	+	+++	+	+	–
hexane	–	–	–	–	–	–	–	–	+
methanol	++	+	++	++	–	++	++	+++	–
Physalis peruviana									
acetone	+++	–	+	++	+	+	++	+	+++
hexane	+	–	–	–	–	–	–	–	+++
Prunus africana									
methanol	+	–	+	+	–	+	+	+	+
hexane	–	–	–	–	–	–	–	–	+
acetone	+++	–	++	+	–	+++	+	+++	+
Ajuga remota									
methanol	++	–	+	++	+	++	++	++	++
acetone	++	–	–	–	–	+	–	+	++
hexane	+	–	–	–	–	–	–	–	++
water	+++	–	+	+++	+++	+++	+++	+++	+++
Cordia africana									
methanol	+++	–	–	+	–	+	–	–	–
water	++	–	++	++	++	+	–	+	–

+++ = high, ++ = moderate, + = low, – = absent.

Teoh, 2004; Wright, 2010). In most healthcare resource-limited settings, indigenes rely extensively on plant medicines for primary healthcare services. We, therefore, explored the therapeutic potential of seven Kenyan herbal plants commonly used in the treatment of malaria, pneumonia and chest pains. We report herein the schistosomicidal properties of *A. annua, B. micrantha, P. peruviana, A. remota, S. didymobotrya* and *P. africana*, with a demonstrated potential to be repurposed as treatment for schistosomiasis.

The antimalarial, anti-inflammatory, antibacterial and analgesic properties of these extracts are known; however, their schistosomicidal properties are unclear. Our findings show that 100 µg/ml of acetone extracts of *A. annua, P. africana, P. peruviana* and *S. didymobotrya*, 100 µg/ml of water and methanol extracts of *B. micrantha* and 100 µg/ml of hexane extracts of *A. remota* had significant worm killing activity (>90%) against *S. mansoni* NTS after 24-hour exposure. These extracts further showed ≥69.7% and ≥72.5% killing activity in *S. mansoni* adult worms after 24 and 48-hours of exposure, respectively. The extracts show promise as possible leads by their killing potential on both the larval stage and adult worms of *S. mansoni*. Since PZQ is primarily active against only adult worms, combination therapy with the extracts may inhibit all the developmental stages of the parasite and may overcome the problem of drug resistance. Ethanolic extracts of *A. annua* has been shown to have schistosomicidal activity at 2 mg/ml (Ferreira *et al.*, 2011). In China, artemisinin extracted from *A. annua* and its derivatives artemether, artesunate and dihydroartemisinin, have efficacy against *S. japonicum*. Multiple doses of artemisinin at 6 mg/kg body weight showed preventive efficacies as high as 65–97% (Liu *et al.*, 2014). The extract dose of 100 µg/ml used in this study was comparatively lower in relation to similar studies where doses within the ranges of 1.25–2.5 mg/mL of different plant extracts resulted in 90% of the killing of *Paramphistomum cervi*, the causative agent of enteritis and anaemia in livestock mammals (Elango & Rahuman, 2011).

Phytochemical analyses of the extracts detected different classes of compounds comprising steroids, tannins, anthraquinones, glycosides and terpenoids mediating the observed *S. mansoni* worm killing. Bioactive components of plants display variable activities against different stages of pathogens (Ferreira *et al.*, 2011). The acetone extracts of *A. annua* which contained steroids, anthraquinones and terpenoids and *P. africana* with steroids, anthraquinones and glycosides as major compounds showed complete killing of NTS. However, worm killing activity was reduced after 48-hours of exposure against *S. mansoni* adult worms in some of the extracts. The reduced activity influenced by variable susceptibilities of the bioactive components could be as a result of poor uptake or efflux of the compounds by the adult worm. We observed a strong correlation in the worm killing activity of a water decoction extract *of B. micrantha*. After 24-hour exposure to extracts, 90.1% of NTS were killed while 72.2% and 81.6% adult worms were killed after 24 and 48-hour exposure, respectively. This suggests that tannins, the major phytochemical component in *B. micrantha*, possess schistosomicidal properties. Tannins obtained from *Lotus corniculatus, Hedysarum coronarium* and *Onobrychis viciifolia*, caused a remarkable reduction in *Trichostrongylus colubriformis* hatched eggs and inhibited the development of eggs in gastrointestinal nematodes (Molan *et al.*, 2000, 2002). Tannins have been shown to inhibit parasites by minimizing the formation of infective stage larvae, reduction of eggs excretion by the adult worms and reduction of eggs' development (Athanasiadou *et al.*, 2001). Simple tannins such as (-)-epicatechin are orally bioavailable (Zhu *et al.*, 2000; Serrano *et al.*, 2009) suggesting that they may be active against blood dwelling schistosome worms; similar tannins were identified in this study.

In summary, this study has found that extracts of seven plants used for the treatment of a variety of conditions in Kenya have schistosomicidal activity against cultured *S. mansoni* worms. Further studies of these extracts to identify the active components will provide promising lead compounds that can be developed to meet the urgent need for new drugs for the treatment of schistosomiasis.

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Conflicts of interest. No conflict of interest was reported by the authors.

Ethical standards. This study was approved by the Institutional Animal Care and Use Committee of Rush University Medical Center (20-069; Department of Health and Human Services animal welfare assurance number A-3120–01).

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