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Review

A review of the traditional use of southern African medicinal plants for the treatment of malaria

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ABSTRACT

Ethnopharmalogical relevance: Malaria is one of the most prevalent and deadly parasitic diseases globally, with over 200 million new cases and nearly 500,000 deaths reported annually. It is estimated that approximately half of the world's population lives in malaria endemic areas. Malaria is substantially less prevalent in South Africa than in other African regions and the disease is limited to some regions of the Limpopo, Mpumalanga and KwaZulu-Natal provinces. However, it still has a significant impact on the health of the populations living in those regions. Traditional medicines have long been used in South Africa by multiple ethic groups and many people continue to rely on these natural therapies for their healthcare. The usage of South African medicinal plants in several traditional healing systems to treat malaria have been documented (particularly for Zulu and Venda traditional medicine), although ethnobotanical investigations of other ethnic groups living in endemic malaria areas remains relatively neglected.
Aim of the study: To document the use of South African medicinal plants known to be used traditionally to treat *Plasmodium* spp. infections. We also critically reviewed the literature on the therapeutic properties of these and other South African plants screened against *Plasmodium* spp. parasites with the aim of highlighting neglected studies and fostering future research in this area.
Materials and methods: Books and ethnobotanical reviews were examined for medicinal plants used specifically for fever. Exclusion criteria were studies not involving southern African medicinal plants. Furthermore, while fever is a common symptom of malaria, if not accompanied by the term "malaria" it was not considered. Databases including PubMed, ScienceDirect, Scopus and Google Scholar were used to source research relevant to southern African plants and malaria. Exclusion criteria were those publications where full articles could not be accessed.
Results: Eighty South African plant species were identified as traditional therapies for malaria. The majority of these species were documented in Zulu ethnobotanical records, despite malaria occurring in only a relatively small portion of the Zulu's traditional territory. Surprisingly, far fewer species were reported to be used by Venda, Ndebele, northern Sotho, Tsonga, Tswana, and Pedi people, despite them living in endemic malaria areas. Interestingly many of the identified species have not been investigated further. This review summarises the available ethnobotanical and laboratory research in this field, with the aim of promoting and focusing research on priority areas.
Conclusion: Although malaria remains a serious disease affecting millions of people, medicinal plants while used extensively, have not been given the attention warranted for further investigation.

1. Introduction

Malaria is a serious parasitic illness that is relatively common in tropical and sub-tropical regions globally. It is particularly prevalent in developing countries with inadequate healthcare and/or vector control, where pregnant women and young children are most frequently affected. Malaria is perhaps the most significant and concerning parasitic disease globally because of the numbers of people affected and the

Abbreviations: SI, Selectivity Index; THF, tetrahydrofolate; WHO, World Health Organisation

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related high mortality rate. Indeed, it has been estimated that 3.2 billion people (approximately half of the world's population) live in malaria-affected areas (Centre for Disease Control and Prevention, 2018). Recent statistics from the World Health Organisation (WHO) estimate that approximately 216 million cases of malaria were reported in the year 2016 alone (World Health Organisation, 2018a). Of further concern, malaria may result in high levels of mortality if not promptly treated. The same WHO study reported that malaria infections caused approximately 445,000 deaths worldwide in 2016. Africa is particularly affected by this disease, with approximately 91% of the malarial deaths in 2016 occurring on that continent. The majority of these deaths occur in the tropical central, western and eastern African countries.

The symptoms of malaria generally become apparent 8–25 days after an infective mosquito bite (Ashley et al., 2018). Once contracted, malaria initially manifests as flu-like symptoms and it may be difficult to diagnose the illness. The early stage symptoms of malaria often resemble sepsis, gastroenteritis, or a number of viral diseases. Infected people may experience fever, headache, joint pain, chills, vomiting and haemolytic anaemia. The parasite destroys erythrocytes, resulting in the release of haemoglobin, which can often be detected as free haemoglobin in the blood. If not rapidly treated, malaria can progress to a substantially more severe form of the disease, with several life threatening complications including respiratory distress, metabolic acidosis, pulmonary oedema, and severe anaemia. Multi-organ involvement is frequent and if left untreated, malaria is often fatal.

1.1. *Plasmodium spp. parasites*

Malaria is caused by single-celled parasites of the genus *Plasmodium*. In humans, the disease may be caused by *P. falciparum*, *P. malariae*, *P. ovale*, *P. vivax* and *P. knowlesi*, although *P. falciparum* infections are generally more serious and substantially more frequent than for the other *Plasmodium* spp. (Ashley et al., 2018). Indeed, *P. falciparum* accounts for approximately 75% of all human malarial infections and nearly all deaths globally. This is the predominant *Plasmodium* species throughout Africa and causes substantial loss of life. *P. falciparum* replicates very rapidly in the blood and can cause severe anaemia. *P. vivax* is the other *Plasmodium* species that contributes to malaria disease in southern Africa. This parasite causes a less severe form of malaria than *P. falciparum,* although it also is a substantial problem in this region (Guerra et al., 2010). *P. vivax* often has longer lasting effects than *P. falciparum* as the parasite may enter a dormant liver phase (Hulden and Hulden, 2011). When the parasite becomes dormant, there is a reservoir of parasites in the liver, which can invade the bloodstream for several months (or even several years) after the initial disease symptoms regress, causing a malaria relapse. Therefore, the *P. vivax* parasite can be difficult to eradicate as most antimalarial drugs target the blood phase of the life cycle. These are the only *Plasmodium* spp. that contribute substantially to the malarial burden in southern Africa.

Malaria can be controlled and elimination may even be possible. Indeed, the elimination of malaria is now a priority of the WHO's Global Malaria Program in some areas, including the southern Africa region (Delacollette and Rietveld, 2006; Tanner and de Savigny, 2018). In particular, South Africa, Botswana and Swaziland have been highlighted as good candidates for malaria elimination because of their relatively low malarial burden. However, malaria eradication programs are expensive and put considerable financial burden on regions where they are instigated. Furthermore, in many of the countries in which malaria is endemic, westernised models for controlling malaria may not be realistic due to geopolitical factors. There is a need to develop new cost effective antimalarial drugs to assist in controlling malaria and reducing its impact in these areas until eradication programs become realistic. One approach to the development of novel antimalarial drugs is to reinvestigate traditional medicines.

1.2. *Plasmodium spp. lifecycle*

Malarial parasites require two hosts during their life cycle (Ashley et al., 2018). Female Anopheles mosquitos serve as vectors for the infective (sporozoite) form of the parasite (Fig. 1). During a blood meal, malaria infected mosquitos introduce the sporozoites into the human host. The sporozoites initially infect the host's hepatocytes where they mature into schizonts, which subsequently rupture releasing merozoites into the bloodstream. Once they have infected erythrocytes, the *Plasmodium* spp. parasites undergo asexual replication/multiplication and ring stage trophozoites form. These subsequently mature into schizonts, which rupture, releasing further merozoites into the bloodstream. Some of these morozoites will infect further erythrocytes, whilst others differentiate to produce gametocytes. These blood stage parasites are responsible for the pathophysiology and clinical manifestations of malaria. When another Anopheles mosquito takes a blood meal from an infected person, the mosquito ingests the gametocytes. The parasites multiply in the mosquito's gut and the male parasites (microgametocytes) penetrate the female parasites (macrogametocytes),

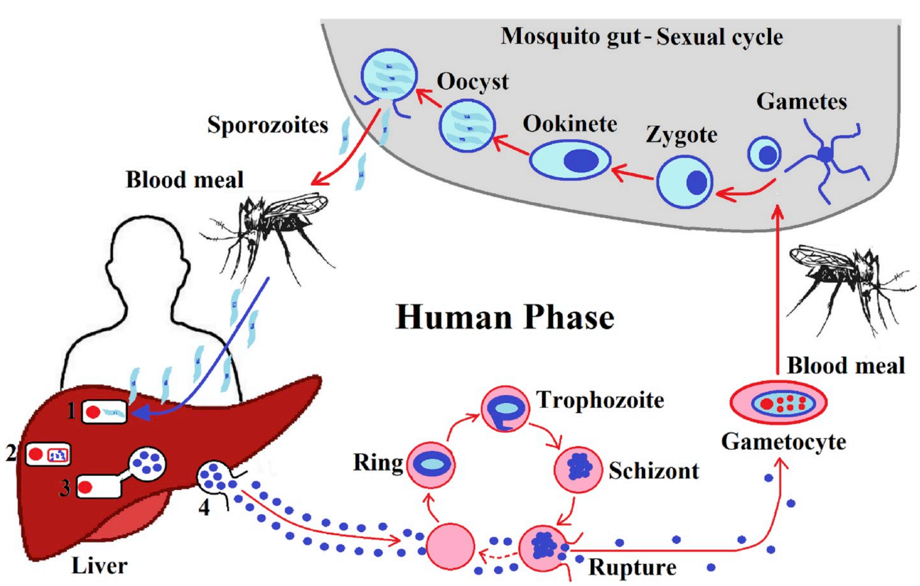

Fig. 1. The life cycle of *Plasmodium* spp. parasites in the human liver and erythrocytes, as well as in the mosquito vector. 1 = infected hepatocyte; 2 = hepatocyte with sporozoites differentiating into shizonts; 3 = mature hepatic schizont; 4 = ruptured schizont (merozoite).

resulting in zygotes. Morphological changes elongate the cell and convert it to the motile ookinete stage, which invades the mosquito's gut wall and develops into oocysts. When the oocysts rupture, sporozoites are released and are transferred to the mosquito's salivary gland. The sporozoites are then available to infect a new human host when the mosquito has its next blood meal.

The multiple phases of the *Plasmodium* spp. parasite life cycle provide several targets for the design of therapeutic and preventative drugs and several studies have targeted other phases of the parasite life cycle. The sexual gametocyte stage is a particularly relevant target, as it is essential for transmission by mosquitos. This stage has been targeted in several studies screening pure compounds (Peatey et al., 2009; Lelièvre et al., 2012). In contrast, relatively few studies examining crude plant preparations have examined the effects against gametocytes. One study reported that a traditional Burkino Faso plant remedy inhibited microgametocyte exflagellation in the blood and ookinete formation in the mosquito gut (Yerbanga et al., 2012). Similarly, some studies have reported activity of traditional medicines against other phases of the *Plasmodium* life cycle, including the hepatic stages. One study reported that some S. Tomé and Príncipe plants inhibited both the blood and hepatic phases of malaria and are thus particularly useful (De Madureira et al., 2002). However, the majority of studies still target the blood phases of the disease exclusively and these are particularly lacking against plants used in southern Africa. Eradication of Anopheles mosquitos is effective and can greatly reduce the incidence of malaria (Gachelin et al., 2018). However, the focus of this study is to review the traditional medicines used once an individual has caught the disease.

1.3. Current treatment options and drug resistance in Plasmodium spp.

A number of therapeutic options are currently available for the treatment of malaria and the choice is influenced clinically by many factors, including which *Plasmodium* species has caused the disease, the severity of the disease and the region in which the disease was contracted. Structurally, antimalarial drugs may be classified into several major groupings:

- Quinine based drugs. The bark of the South American tree *Cinchona officinalis* L. was perhaps the first effective malaria treatment. In 1820, quinine was isolated from the bark of the tree and made widely available clinically. It is still an effective treatment for some malarial strains, although many strains are now quinine resistant (Gachelin et al., 2018).
- Sulfadoxine/pyrimethamine drugs. The pyrimidine derivative drug pyrimethamine was introduced clinically in 1953. It was effective in treating both *P. falciparum* and *P. vivax* malaria and was particularly popular due to its high selectivity index (which compares efficacy to toxicity) (Okell et al., 2017). Unfortunately, *Plasmodium* spp. rapidly mutated their dihydrofolate reductase gene to block pyrimethamine binding, resulting in resistant strains (Okell et al., 2017). Indeed, a resistant *P. falciparum* strain was reported in Africa within less than a year after the introduction of the drug clinically. Nowadays, pyrimethamine is used in combination with sulfadiazine drugs such as sulfadoxine (which use different mechanisms to inhibit THF synthesis) to increase the treatment's efficacy. Unfortunately, some *Plasmodium* spp. strains that are resistant to the sulfadoxine/pyrimethamine combination were reported in the 1990's and resistance is now widespread throughout Africa (Okell et al., 2017).
- Mefloquine was developed by the US military and was released shortly after the Vietnam War. It proved effective in killing both *P. falciparum* and *P. vivax* parasites. Resistance to mefloquine is now common in parts of Asia, although resistance is still relatively rare in Africa (Menard and Dondorp, 2017).
- Artemisinin and its derivatives. Artemisinin is a sesquiterpenoid lactone originally isolated from *Artemisia annua* L. (Klayman et al., 1984). Nowadays, artemisinin is generally used in combination with other malaria medications to increase its efficacy and slow the emergence of resistance (Lin et al., 2010). Indeed, in many regions of the world (including South Africa) the use of artemisinin-based monotherapies is prohibited (World Health Organisation, 2018b).

Furthermore, due to both economic considerations and a lack of therapeutic availability in rural and developing regions, malaria may also be treated with traditional remedies. Some of these medicines have very good efficacy. Indeed, two of the classes of drugs described above (quinine and artemisinin derivatives) are derived from traditional medicines. Often these traditional medicines have more potent antimalarial activity than the pure compound(s) isolated from them. The extracts can be several-fold more potent than the pure drug (Cock, 2018). Similarly, alkaloids isolated from *Cinchona* spp. bark can potentiate the antimalarial activity of quinine (also isolated from *Cinchona* spp. bark), thereby making the drug effective again, even in quinine resistant *Plasmodium* spp. (Cock, 2018).

2. Materials and methods

This study aimed to identify southern African plants used *in situ* for the treatment of malaria in humans and to analyse and review the published literature for scientific evidence to support their use in southern African traditional healing systems. Information presented in this review was sourced from a variety of ethnobotanical books (Watt and Breyer-Brandwijk, 1962; Hutchings et al., 1996; Von Koenen, 1996; Van Wyk et al., 2009) and ethnobotanical reviews (Gerstner, 1941; Mabogo, 1990; Prozesky et al., 2001; Nundkumar and Ojewale, 2002; Pillay et al., 2008; Chinsembu and Hedimbi, 2010; Philander, 2011; De Beer and van Wyk, 2011; Kose et al., 2015; Ngarivhume et al., 2015; Asowata-Ayodele et al., 2016 etc.). The analysed papers were selected from three electronic databases (Pubmed, Science-Direct and Scopus) during the periods of 2017–March 2019. No limit was given to dated manuscripts. Traditional medicines are often used to target disease symptoms and therefore it is often difficult to discern between treatments for diseases with similar symptoms. For example, ethnobotanical records may record a traditional medicine as useful in the treatment of fever, which may be a symptom of numerous diseases, including malaria. It is often difficult to determine whether a particular traditional medicine used to alleviate fever is also used for the treatment of malaria. Therefore, plant selection for herbal medicine research is often based on the symptoms that are treated, rather than on the disease. Only plant species that were reported to be treatments for malaria are included here. Where the basis for the therapeutic usage was ambiguous, the plant species has been excluded from this review.

Original scientific research papers were identified and selected using the Google-Scholar, PubMed, Scopus and ScienceDirect electronic databases. The filters used included the following terms, searched either alone or in combinations: “South African”, “medicinal plant”, “traditional medicine”, “ethnobotany”, “parasite”, “malaria”, “*Plasmodium falciparum*”, “antimalarial”, “antiplasmodial”, “blackwater fever” (defined as a severe form of malaria where blood cells are observed in the urine), “malarial monotherapy” and “combinational malaria therapy”. The study was non-biased, without emphasis on endemic species, nor with any taxonomic preference. We initially aimed to document the usage of all plant species used to treat malaria in South Africa. Eighty South African plant species were identified as traditional therapies for malaria. The vast majority of these are native southern African plants, although a few introduced species that are widely cultivated and are now considered an integral part of the pharmacopeia of at least one ethnic group were also included. A thorough literature review was then undertaken on each of the identified plant species to identify any malaria research studies relevant to each identified species.

Criteria for inclusion in this study included ethnomedicine, human usage, medicinal plants of southern African and other key words related to malaria infections. Scientific evidence to support traditional use was not included in the initial ethnobotanical literature search, but was included in further searches to determine if the traditional usage has been validated. Studies describing the use of southern African plants in ethnobotanical veterinary medicine and in vector mitigation have been excluded. Several studies have thoroughly reviewed malaria and its traditional treatment with botanical drugs from other regions of the world (for example Willcox and Bodeker, 2004; Soh and Benoit-Vical, 2007; Batista et al., 2009; Lemma et al., 2017), including several other regions of Africa (Irungu et al., 2007; Odugbemi et al., 2007; Memvanga et al., 2015; Chinsembu, 2015). Plants traditionally used for vector control and eradication are not considered here. Similarly, this study focuses on therapies for the treatment of malaria once a mosquito has bitten an individual and contracted the disease and does not focus on preventative therapies. Instead, the study highlights southern African plants traditionally used to treat malarial disease in humans.

Surprisingly, there are relatively few similar reviews of the antimalarial uses of South African plants. Indeed, we are aware of only a single review of the antimalarial activity of South African plants and that study was published a decade ago (Pillay et al., 2008). Furthermore, that study did not focus on plants that have traditionally been used to treat malaria. The plant species screened in the other studies reviewed by Pillay et al. (2008) were selected based on other criteria, including random selection. Several other studies (Tetyana et al., 2002; Van Zyl and Viljoen, 2002; Kamatou et al., 2005, 2008) selected plants for screening based on their genus, rather than their ethnobotanical use. Our study aimed to update the earlier review and to take a greater ethnobotanical focus on species inclusion. We aimed to summarise the published traditional South African ethnopharmacological knowledge and discuss the plant species traditionally used to treat malaria, with the hopes of highlighting plant species for future testing against malaria and to foster future research in this area.

3. An overview of malaria in South Africa

Whilst less prevalent than in many regions of sub-Saharan Africa, malaria is still relatively common in some regions of southern Africa (Fig. 2). The WHO estimates that nearly 4500 cases of malaria occur annually in South Africa, resulting in approximately 35 deaths annually (based on 2015 statistics, World Health Organisation, 2018b). The same website reports considerably higher prevalence in neighbouring southern African countries, with approximately 8,500,000 confirmed cases (1685 confirmed deaths) in Mozambique; 25,000 confirmed cases (65 confirmed deaths) in Namibia; 5,000,000 cases (1827 confirmed deaths) in Zambia; and 300,000 reported cases (351 confirmed deaths) in Zimbabwe during the same period. Lower incidences were also reported in Botswana (716 confirmed cases, three confirmed deaths) and Swaziland (350 confirmed cases, three confirmed deaths) during 2015. Therefore, malaria is considered to be of serious concern to public health in southern Africa.

Plasmodium falciparum is responsible for nearly all reported cases of malaria in South Africa, as well in the neighbouring southern African countries (World Health Organisation, 2018b). *Plasmodium vivax* transmission also contributes to the reported cases of malaria in southern Africa, although the *P. vivax* form of malaria is substantially less severe than *P. falciparum* malaria and has a much lower mortality rate (Ashley et al., 2018). Both parasites are transmitted by infected female *Anopheles* mosquitos and prevention of mosquito reproduction with insect repellents and physical barriers (e.g. mosquito nets), or via mosquito control with insecticides, is effective in preventing the disease. However, once an individual has caught malaria, rapid diagnosis with prompt and effective treatment is crucial for the patient's survival, especially for the *P. falciparum* form of the disease. However, front line clinical therapies are not always available to patients in remote and

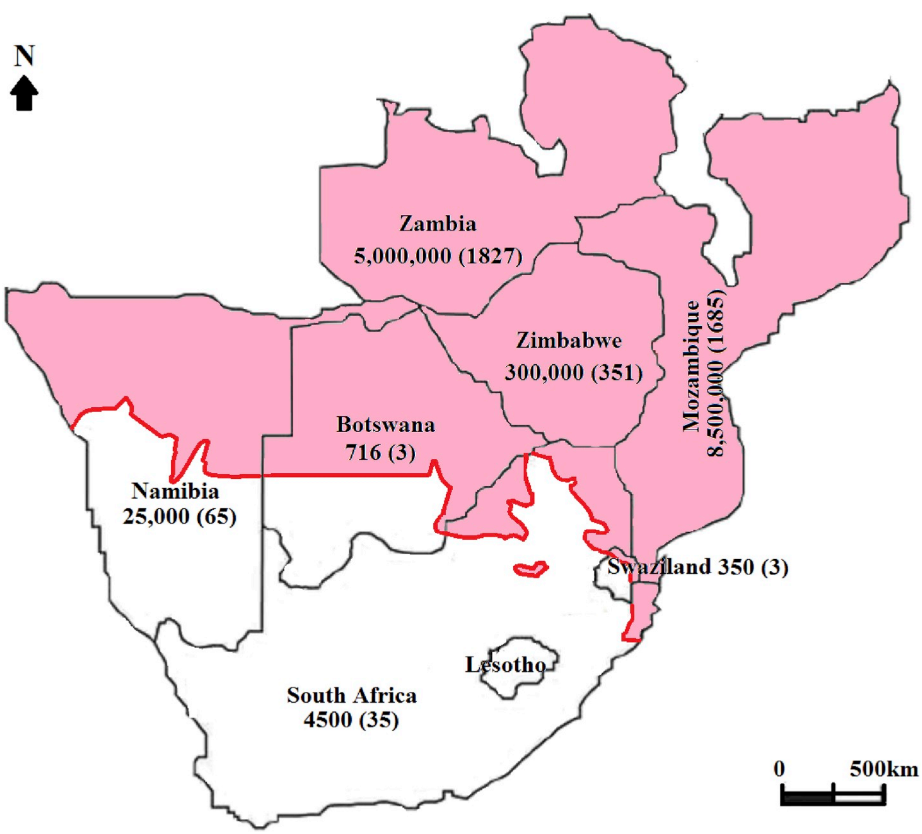

Fig. 2. A map of southern Africa showing areas where malaria is endemic (shaded). The number of confirmed cases and the number of confirmed deaths (in parentheses) for each of the southern African countries is provided for each affected country. All confirmed case/death figures were sourced from the WHO website (World Health Organisation, 2018b) and use data recorded for the year 2015.

rural areas as medical clinics may be distant to the patient and they frequently run out of appropriate medications. Many rural patients rely instead on traditional healers for the treatment of malaria. Furthermore, owing to high levels of travel between South Africa and neighbouring countries with high levels of malaria (particularly Mozambique, Zimbabwe and Zambia), trans-border control is required to manage malarial transmission in the region (Maharaj et al., 2013). Further exacerbating the problem, many *Plasmodium* spp. strains are developing resistance to currently used drugs and there is an urgent need to develop novel antimalarial chemotherapies.

In South Africa, malaria is limited to the warmer, low-altitude regions of Limpopo, Mpumalanga and KwaZulu-Natal provinces (World Health Organisation, 2018b). Unlike many regions further north, the transmission of malaria is highly seasonal in South Africa, with the majority of confirmed malarial cases reported during the warmer October to May period. The annual incidence of malaria varies widely in South Africa and closely correlates with climatic conditions. Since 2007, there has been a general trend in South Africa towards lower levels of malarial transmission (World Health Organisation, 2018b). However, across this period, there were some notable peaks in the number of reported cases of malaria in South Africa. The number of confirmed malaria cases were particularly high in 2011 and 2014, corresponding to climatic conditions favourable for transmission of the parasite. Both of these years experienced high levels of rainfall in the north-eastern regions of South Africa. Indeed, the provinces of Limpopo and Mpumalanga experienced extended periods of high precipitation, resulting in extensive flooding during the early months in 2014 (South African Weather Service, 2018).

Despite the promising trends in South Africa, it is likely that increased efforts will be required in the future to maintain the relatively low incidence of malaria, or ideally, further decrease (or even eradicate) the disease. A major emerging issue in the prevention and treatment of malaria is the increasing incidence of drug resistant *Plasmodium* spp. parasites. *P. falciparum* strains that are resistant to quinine-based therapeutics (e.g. chloroquine, hydroxychloroquine) and several artemisinin drugs are already common in southern Africa (Lu et al., 2017; Okell et al., 2017). Indeed, the WHO website reports that artemether-lumefantrine (AL) therapy failed in nearly 9% of malarial cases reported in Zimbabwe and approximately 5% of cases in Mozambique between 2010 and 2014 (World Health Organisation, 2018b). Whilst the WHO website has not reported any cases of AL failure in South Africa during that period, changing climatic conditions, population migration and the incorrect usage of anti-malarial drugs is likely to result in similar resistances in South Africa in the future. Already, chloroquine and artemisinin resistances have been reported against some *P. falciparum* strains in South Africa (Lu et al., 2017; Okell et al., 2017). Although primaquine is required in order to eradicate liver stages of *P. vivax,* malaria therapy now generally follows with blood schizontocide treatments such as artemisinin based combinational therapies (ACTs).

4. South African medicinal plants used traditionally to treat malaria

Here we report 80 South African plants as having traditional uses to treat malaria (Table 1). Given the serious nature of this illness and its relatively high mortality rate, this number may seem relatively low when compared to the number of plants reported as traditional therapies for other parasitic diseases. For example, in a recent study, we listed more than 80 plants used to treat intestinal worms, 26 species used for bilharzia and approximately 20 species used to treat other assorted parasitic infestations (Cock et al., 2018). The parasites included in our previous report, whilst highly prevalent in South Africa, cause far less suffering and loss of life than malaria. A number of aspects may contribute to the lower than expected number of species used to treat malaria. Firstly, many traditional healers prescribe medicines based on the symptoms treated rather than specifically to treat a disease. Thus, it is possible that traditional medicines that have been reported to treat fever or anaemia (symptoms of malaria) may have also been used to treat malaria. Future studies may find that other plant species targeting symptoms such as fever are useful in treating malaria.

A further reason that lower than expected numbers of plant species were identified despite the seriousness of the disease is that malaria is confined to relatively small areas of South Africa. Ethnobotanical studies are confined to specific ethnic groups and often to relatively small areas. Indeed, only a small portion of KwaZulu-Natal province (with substantial Zulu populations) is in an endemic malaria area. A single study has reported the screening of South African plants for antimalarial activity based on Zulu ethnobotany (Nundkumar and Ojewale, 2002). That study highlighted several species including, *Barringtonia racemose* (L.) Roxb., *Psidium guajava* L., *Rauvolfia caffra* Sond., *Sclerocarya birrea* A. Rich.) Hochst. *Vangueria infausta* Burch. and *Warburgia salutaris* (G. Bertol.) Chiov. as plant species traditionally used to treat malaria. Twenty-seven other plant species (*Acacia xanthophloea* Benth., *Adenia gummifera* (Harv.) Harms, *Annona muricata* L., *Antidesma venosum* E. Mey. Ex Tul., *Artemisia afra* Jacq. Ex Willd., *Artemisia annua* L., *Cannabis sativa* L., *Cassia siamea* Lam., *Cissampelos mucronata* A. Rich., *Cissus quadrangularis* L., *Clematis brachiata* Ker Gawl., *Cordia sinensis* Lam., *Cussonia spicata* Thunb., *Gardenia thunbergia* L.f., *Gnidia cuneate* Meisn., *Lippia javanica* Spreng., *Momordica charantia* L., *Pavetta crassipes* K. Schum., *Plantago major* L., *Senna occidentalis* (L.) Link, *Siphonochilus aethiopicus* (Schweinf.) B. L. Burtt, *Solanum nigrum* L., *Spilanthes olerace* L., *Tetradenia riparia* (Hochst.) Codd, *Uvaria scheffleri* Diels, *Vernonia natalensis* Sch. Bip. Ex Walp and *Vetiveria zizanioides* Nash.) used to treat malaria by the Zulu's were identified with reference to Hutchings extensive Zulu ethnobotanical study (Hutchings et al., 1996). Thus, more than 50% of plants identified as useful to treat malaria were identified by reference to Zulu ethnobotany studies, despite the relatively small area of the Zulu's traditional territory being in malarial areas.

In contrast, a single ethnobotanical study reviewed plants used by the Venda people to treat malaria (Prozesky et al., 2001). The Venda are from the northern regions of South Africa, adjacent to the border with Zimbabwe, in an area with some of the highest incidences of malaria in South Africa. That study identified five other species (*Combretum molle* R.Br. Ex G.Don, *Entandophragma caudatum* (Sprague) Sprague, *Erythrina lysistemon* Hutch, *Ozoroa engleri* R.A. Fernandez and *Rhamnus prinoides* L'Herit) as traditional Venda treatments for malaria. Due to the incidence of malaria in Venda areas, this relatively low number of traditional malaria therapies is surprising. It is likely that future studies into Venda ethnobotanical medicine may highlight other plants used to treat malaria. Similarly, the ethnobotanical studies of other ethnic groups that live in endemic malaria areas in South Africa such as the Ndebele, northern Sotho, Tsonga, Tswana, and Pedi are less extensive.

A number of plant species documented in southern Africa for the treatment of malaria, have also been noted in other African countries. *Cissampelos mucronata* for example is used as an antimalarial in Kenya (Mukungu et al., 2016). *Strophanthus hispidus* DC. is used as an antimalarial in south-eastern Nigeria (Odoh et al., 2018). Many similar examples exist amongst those documented in Table 1.

5. Scientific studies into the anti-Plasmodium activity of South African plants

Multiple studies have screened South African medicinal plants for antimalarial activity (Table 2). Investigations into the antimalarial and/or antiplasmodial properties of South African medicinal plants have generally been achieved via two protocols: challenging infected human erythrocytes with plant extracts and recording the differences in parasite infection, or treating infected rodents with the extracts and monitoring the symptoms and/or parasite load. When the infected human erythrocyte model is used, the erythrocytes are infected with *P. falciparum*, cultured and exposed to the plant extracts at varying

Table 1
Southern African plants used traditionally to treat malaria.

Plant species	Common name	Family	Plant part specified and use where indicated	Reference
Acacia xanthophloea Benth.	Fever tree (English), koorsboom (Afrikaans), mooka-kwena (northern Sotho), umHlosinga (Zulu), nkelenga (Tsonga), munzhelenga (Venda)	Fabaceae	Powdered bark of the stem and root used prophylactically when entering a malarial area	Watt and Breyer-Brandwijk (1962); Hutchings et al. (1996)
Acrotome inflata Benth.	Unknown	Lamiaceae	A water extract of the whole plant	Von Koenen (1996)
Adansonia digitata L.	Baobab, monkey-bread tree, lemonade tree (English), kremetartboom (Afrikaans, isimuku, umShimulu, isiMuhu (Zulu), ximuwu (Tsonga), mowana (Tswana), muvhuyu (Venda)	Bombacaceae	Bark, leaf decoction taken prophylactically	Watt and Breyer-Brandwijk, 1962; Von Koenen, 1996; Chinsembu and Hedimbi, 2010
Adenia gummifera (Harv.) Harms	Monkey rope, wild granadilla (English), Slangklimop (Afrikaans), impinda, impindamshaye, umphindamshaya (Zulu)	Passifloraceae	Root decoctions	Hutchings et al., 1996; Philander, 2011
Aloe littoralis Baker	Mopane Aloe (English), Mopane-aalwyn, Windhoek-aalwyn, bergaalwee (Afrikaans), mokgophta (Tswana), tshikhopha (Venda)	Aloaceae	Leaf extract taken daily over a period of time	Von Koenen (1996)
Annona muricata L.	Soursop (English)	Annonaceae	Leaves	Hutchings et al. (1996)
Anthocleista zambesica Baker	Big-leaf, Forest big-leaf, Forest fever tree (English), Gururu (Shona)	Loganiaceae	A decoction of bark	Watt and Breyer-Brandwijk (1962)
Argemone mexicana L.	Devil's fig, Texas poppy, yellow-flowered Mexican poppy (English), geelblombloudissel (Afrikaans)	Papaveraceae	Aerial parts	Watt and Breyer-Brandwijk, 1962; Willcox et al., 2007
Artemisia afra Jacq. Ex Willd.	African wormwood (English), wildeals (Afrikaans), umhlonyane (Xhosa), mhlonyane (Zulu), lengana (Tswana), zengana (Sothern Sotho)	Asteraceae	Leaves	Watt and Breyer-Brandwijk, 1962; Hutchings et al., 1996; Elgorashi et al., 2003; De Beer and van Wyk, 2011; Kose et al., 2015
Artemisia annua L.	Chinese wormwood (English)	Asteraceae	Leaves	Hutchings et al. (1996)
Barringtonia racemosa (L.) Roxb.	Powderpuff tree (English), poeierkwasboom (Afrikaans), iBhoqo (Zulu)	Lecythidaceae	Fruit	Hutchings et al., 1996; http://pza.sanbi.org/barringtonia-racemosa
Cannabis sativa L.	Marijuana (English), dagga (Afrikaans), umya (Xhosa), metekwane, patse (northern Sotho), nsangu (Zulu)	Cannabaceae	Leaves	Hutchings et al. (1996)
Capparis tomentosa Lam.	Woolly caper bush (English), wollerige kapperbos, wag-'n-bietjie (Afrikaans), inkunzi-ebomvu, iqwaningi, umqoqolo, ukhokhwana, umabusane (Zulu), imfishlo, intshihlo, umpasimani (Xhosa)	Capparaceae	Root bark	Watt and Breyer-Brandwijk, 1962; Hutchings et al., 1996
Cassia abbreviata Oliv	Long-tailed cassia (English), sambokpeul (Afrikaans)	Leguminosae	Roots	Von Koenen, 1996; Mongalo and Mafoko 2013
Cassia fistula L.	Golden Shower, purging Cassia, golden chain tree, Indian laburnum (English)	Fabaceae	pod	Watt and Breyer-Brandwijk (1962)
Cassia siamea Lam.	Yellow cassia (English)	Caesalpiniaceae	Leaves	Hutchings et al. (1996) Ajaiyeoba et al. (2003)
Catunaregam spinosa (Thunb.) Tirveng	Emetic nut, mountain pomegranate (English)	Rubiaceae	Unknown	Gerstner (1941)
Cephalanthus natalensis Oliv.	Quinine berry, tree strawberry (English)	Rubiaceae	Fresh berry is eaten	Watt and Breyer-Brandwijk (1962)
Cissampelos mucronata A. Rich.	Hairy heartleaf, heart-leaved vine (English), Davidjies, Davidjieswortel (Afrikaans), umbombo (Zulu), nyakuta, ruzambu (Shona)	Menispermaceae	Rhizomes and roots	Hutchings et al. (1996)
Cissus quadrangularis L.	Cactus vine, succulent stemmed wild grape, veld grape, kangaroo vine (English)	Vitaceae	Steam and leaf decoctions	Hutchings et al. (1996)
Clausena anisata (Willd).Hook.F.ex Benth	Umtuto (Xhosa)	Rutaceae	Leaf infusion	Asowata-Ayodele et al. (2016)
Clematis brachiata Ker Gawl.	Travellers joy, old man's beard, wild clematis (English), klimop, lemoenbloeisels (Afrikaans), ityolo (Xhosa), mogau Tswana), morara (Sotho), umDlonzo (Zulu)	Ranunculaceae	Leaves, roots and stems where a hot decoction is used for steaming	Watt and Breyer-Brandwijk (1962); Hutchings et al. (1996)
Clerodendrum ternatum Schinz	Dwarf cat's whiskers (English), umalanjana, umqotshanja (Ndebele)	Lamiaceae	Root is crushed and made into a water extract. This is used twice daily as an enema	Von Koenen (1996)
Combretum molle R.Br. Ex G.Don	Velvet bush willow (English), fluweelboswilg, basterrooibos (Afrikaans), mokgwethe (northern Sotho), modubatshipi, moduba (Tswana), mugwiti (Venda), umBondwe-omhlope (Zulu)	Combretaceae	Roots and leaves	Prozesky et al. (2001)

(*continued on next page*)

Table 1 (*continued*)

Plant species	Common name	Family	Plant part specified and use where indicated	Reference
Combretum zeyheri Sonder	Large-fruited bushwillow, Zeyher's bushwillow (English), raasblaar, fluisterboom (Afrikaans), moduba-tshipi (Pedi), umbondwe wasembudwini (Zulu), mufhatelathundu (Venda)	Combretaceae	Combine with *Ochna pulchra* or a multiple combination including *Burkea africana* and *Diospyros chamaethamnus* where roots and leaves are used in steam bath nightly	Von Koenen (1996)
Cordia sinensis Lam.	Grey-leafed saucer berry (English)	Boraginaceae	Milk decoction	Hutchings et al. (1996)
Croton megalobotrys Mull. Arg.	Feverberry (English)	Euphorbiaceae	Bark, seeds, leaves, roots	Watt and Breyer-Brandwijk (1962); Von Koenen, 1996; Maroyi (2017)
Cussonia spicata Thunb.	Cabbage tree (English), kiepersol (Afrikaans), umsenge (Sotho, Xhosa, Zulu), motshetshe (northern Sotho)	Araliaceae	Bark and roots	Watt and Breyer-Brandwijk (1962); Hutchings et al. (1996)
Diplorhynchus condylocarpon (Mull. Arg.) Pichon	Rhodesian rubber tree, horn-pod tree, wild rubber (English), horingpeultjieboom, melkbos (Afrikaans), mutowa (Shona), tsowa (Tsonga), ntsowa, mulya (Tswana), muthowa (Venda)	Apocynaceae	Root decoction	Von Koenen (1996)
Entandrophragma caudatum Sprague	Wooden banana, mountain mahogany (English), bergmahonie (Afrikaans), muzhounzhou (Venda) umsikili (Ndebele)	Meliaceae	Stem bark	Prozesky et al. (2001)
Erythrina lysistemon Hutch	Coral tree, lucky bean tree (English), gewone koraalboom, kanniedood (Afrikaans), umsintsi (Xhosa), muvhale (Venda), mophete (Tswana), mokhungwane (Sotho), umsinsi (Zulu)	Fabaceae	Stem bark	Prozesky et al. (2001)
Eucalyptus globulus Labill	Blue gum or fever tree (English), blougom (Afrikaans)	Myrtaceae	Used as a prophylactic but no plant part specified	Watt and Breyer-Brandwijk (1962)
Gardenia thunbergia Thunb.	White gardenia, wild gardenia English), witkatjiepiering, buffelsbal, kannetjieboom (Afrikaans), umKhangazi (Xhosa), umValasangweni, umKhwakhwane (Zulu)	Rubiaceae	Roots	Hutchings et al. (1996); http://pza.sanbi.org/gardenia-thunbergia
Gnidia cuneate Meisn.	Unknown	Thymelaeaceae	Root infusion	Hutchings et al. (1996)
Gynandropsis pentaphylla (L.) DC.	Spider-wisp (English), Bangara, nyevhe, rudhe, runi, tsuna (Shona), ulude (Ndebele)	Capparaceae	Leaves and seeds	Watt and Breyer-Brandwijk (1962); Borgio et al. (2011)
Kedrostis nana Cogn.	Bitter patat (Afrikaans)	Cucurbitaceae	Not specified	Philander (2011)
Lablab purpureus (L.) Sweet.	Hyacinth bean	Fabaceae	Strong doses of boiled bark are used	Von Koenen (1996)
Lannea edulis Engl.	Wild grape (English), wildedruif (Afrikaans), umGabunkhomo (Sotho), mutsambatsi (Shona), intakubomvu (Ndebele)	Anacardiaceae	Strong doses of boiled bark are used	Von Koenen (1996)
Lantana brasiliensis Link	Lantana (English)	Verbanaceae	Not specified, but suggested as a quinine substitute	Watt and Breyer-Brandwijk (1962)
Leucadendron concinnum R. Br.	Ivory cone bush (English), Kinabossie, Langbeentjie (Afrikaans),	Proteaceae	Not specified	Watt and Breyer-Brandwijk (1962)
Lichtensteinia interrupta E.Mey.	Inthlashane (Zulu), tloro-ya-ngwale (Sotho), umbungashe (Xhosa)	Apiaceae	Not specified	Watt and Breyer-Brandwijk (1962)
Lippia javanica Spreng.	Fever tea (English), koorsbossie (Afrikaans), mumara (Shona), musukudu, bokhukhwane (Tswana), inzinziniba (Xhosa), umsuzwane (Zulu)	Verbenaceae	Leaf infusion	Watt and Breyer-Brandwijk (1962); Hutchings et al. (1996); Mabogo (1990)
Maytenus senegalensis (Lam.) Exell.	Unknown	Celastraceae	Stem bark	Watt and Breyer-Brandwijk (1962); Malebo et al. (2015)
Momordica charantia L.	Bitter gourd, balsam pear, bitter melon, karela, African cucumber (English)	Cucurbitaceae	Fruit/gourd	Hutchings et al. (1996)
Mundulea sericea (Willd.) A. Chev.	Cork bush, silver bush, Rhodesian silver-leaf (English), kurkbos, blou-ertjieboom, olifantshout, visboontjie, visgif, mangaanbos (Afrikaans), mosetla-thlou (northern Sotho), umSindandlovana (Swazi), ntsandzandlopfu, maibana, mohato, mosikatse, mosit-thlou, moswaatlou (Tswana), mukunda-ndou (Venda), umHlalantethe, umSindandlovu (Zulu)	Leguminosae	Root extract is used as an enema, Alternatively, the root is dried, crushed and spread over glowing embers where the patient is placed and covered with a blanket to aid access to smoke.	Von Koenen (1996)
Nerium oleander L.	Ceylon rose (English)	Apocynaceae	leaf and bark	Watt and Breyer-Brandwijk (1962)
Oxygonum dregeanum Meisn.	Starstalk (English)	Polygonaceae	Entire plant is mixed with *Pergularia daemia* and taken orally or administered as an enema	Von Koenen (1996)
Ozoroa engleri R.Fern. & A.Fern.	Resin tree, bushveld ozoroa (English), harpuisboom (Afrikaans), isifice (Zulu), monoko (northern Sotho/Pedi), mudumbula (Venda)	Anacardiaceae	Unknown	Prozesky et al. (2001)
Pavetta crassipes K. Schum.	Gland-leaf tree, large leaved brides bush (English), kliertjiesboom (Afrikaans), isiMuncwane, isaMunyane, uMafayindlala, umFayindlala (Zulu)	Rubiaceae	Aerial parts	Hutchings et al. (1996); Hermans et al. (2004)
Plantago major L.	Common plantain, greater plantain (English)	Plantaginaceae	Leaf sap	Hutchings et al. (1996)

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Table 1 (*continued*)

Plant species	Common name	Family	Plant part specified and use where indicated	Reference
Plumbago zeylanica L.	Wild plumbago, leadwort (English)	Plumbaginaceae	Roots	Von Koenen (1996); Ngarivhume et al. (2015)
Psidium guajava L.	Guava (English), koejawel (Afrikaans), ugwava (Zulu)	Myrtaceae	Leaves	Nundkumar and Ojewale (2002); Hutchings et al. (1996)
Pterocarpus angolensis DC.	Bloodwood, wild teak, Transvaal teak (English), kiaat, bloedhout, grienhout (Afrikaans), morôtô (Sotho), mokwa, morotômadi (Tswana), umvangazi, umbilo (Zulu)	Fabaceae	Bark	Von Koenen (1996); Lukwa et al. (2001)
Rauvolfia caffra Sond.	Quinine tree (English), kinaboom (Afrikaans), umhlambamase (Xhosa), umhlambamanzi (Zulu)	Apocynaceae	Bark, roots	Watt and Breyer-Brandwijk (1962); Nundkumar and Ojewale (2002); Hutchings et al. (1996)
Rhamnus prinoides L'Herit	African dogwood, camdeboo stinkwood, glossy leaf (English), blinkblaar, camdeboostinkhout (Afrikaans), umGlindi, umlindi (Xhosa), amGilindi, uNyenye, umHlinye (Zulu), liNyenye (Swazi), mofifi (southern Sotho)	Rhamnaceae	Bark, roots	Prozesky et al. (2001); Watt and Breyer-Brandwijk (1962)
Salix mucronata Thunb.	Wild willow (English), wilde wilger, rivierwilger (Afrikaans)	Salicaceae	Leaves, twigs	Von Koenen (1996)
Schkuhria pinnata (Lam.) Thell.	Dwarf marigold(English), Klein-gousblom (Afrikaans)	Asteraceae	Powdered leaf is swallowed with water	Watt and Breyer-Brandwijk (1962)
Sclerocarya birrea Hochst.	Marula (English), morula (Sotho), mufula (Venda), ukanyi (Tsonga)	Anacardiaceae	A tea is made from the bark	Hutchings et al. (1996); Von Koenen, 1996
Securidaca longipedunculata Fresen	Tree violet, Wild wisteria (English), Krinkhou (Afrikaans), Maaba (northern Sotho), Maba (Tswana)	Polygalaceae	Roots	Watt and Breyer-Brandwijk (1962)
Senna occidentalis (L.) Link	Septic weed, coffee senna, coffeeweed, stinkweed (English), isinyembane (Zulu), lilyanyoka (Swazi)	Caesalpiniaceae	Leaf extract	Watt and Breyer-Brandwijk (1962); Hutchings et al. (1996); Von Koenen, 1996
Sesamum capense Burm. f.	Wild foxglove (English), molokelela (Sotho)	Pedaliaceae	Decoction of the leaf is used	Watt and Breyer-Brandwijk (1962)
Sesamum indicum L.	Wild foxglove (English), molokelela (Sotho)	Pedaliaceae	Decoction but no plant part specified	Watt and Breyer-Brandwijk (1962)
Siphonochilus aethiopicus (Schweinf.) B. L. Burtt	African ginger (English), isiphephetho, indungulo (Zulu)	Zingiberaceae	Rhizomes and roots	Hutchings et al. (1996); Philander (2011)
Solanum nigrum L.	Black nightshade, potato bush, bush tomato, poison-berry, deadly nightsghade (English), galbessie, nastergal, inkbossie, nagtegaalbossie (Afrikaans), umsobo (Zulu)	Solanaceae	Tea made from leaves	Watt and Breyer-Brandwijk (1962); Hutchings et al. (1996)
Solanum panduriforme E. Mey.	Bitter apple, poison apple, snake apple, Sodom apple, thorn apple (English), bitterappel, bitterappeltjie, geelappel, gifappel (Afrikaans), intuma, intumemncane (Zulu), moralane (northern Sotho), seylwane, tholana (Sothern Sotho), intume, umdulukwa (Ndebele), munhomboro, munhundurwa (Shona)	Solanaceae	Leaves	Watt and Breyer-Brandwijk (1962); Mabogo (1990)
Spilanthes oleracea L.	Toothache plant, paracress (English)	Asteraceae	Flowers, roots	Hutchings et al. (1996)
Strophanthus hispidus DC.	Zwezwe (Tswana)	Apocynaceae	Bark and root decoction	Watt and Breyer-Brandwijk (1962)
Swartzia madagascariensis Desv.	Snake bean (English), mucherekese (Shona)	Leguminosae	Unspecified parts	Von Koenen (1996)
Synadenium volkensii Pax.	Northern dead-man's tree (English)	Euphorbiaceae	Root	Watt and Breyer-Brandwijk (1962)
Tetradenia riparia (Hochst.) Codd	Ginger bush (English), watersalie (Afrikaans), iboza, (Zulu)	Lamiaceae	Leaf infusion	Von Koenen (1996); Hutchings et al. (1996)
Thevetia peruviana K.Schum.	Bastard oleander (English)	Apocynaceae	Bark	Watt and Breyer-Brandwijk (1962)
Trichilia emetica Vahl	Natal mahogany (English), rooissenhout (Afrikaans), umathunzini (Zulu) mamba (northern Sotho), umkuhlu (Swazi), umkhuhlu (Xhosa), mutuhu (Venda)	Meliaceae	Leaves/twigs	Watt and Breyer-Brandwijk (1962); Komane et al. (2011)
Uvaria scheffleri Diels	Unknown	Annonaceae	Roots, fruit	Hutchings et al. (1996)
Vangueria infausta Burch.	Wild medlar (English), wilde mispel (Afrikaans), mmilo (northern Sotho), muzwilu, mavelo (Venda), unVilo (Xhosa), umViyo, umTulwa (Zulu), umbizo (Ndebele), mmilo, mothwanye (Tswana), amantulwane (Swazi)	Rubiaceae	Roots mixed with other unspecified plants	Watt and Breyer-Brandwijk (1962); Nundkumar and Ojewale (2002)
Vernonia natalensis Sch. Bip. Ex Walp. Also known as *Hilliardiellia aristata* (DC.) H.Rob.	Silver vernonia (English), ihlambihloshana, isibhaha, sasenkangala, umlahlankosi-omhlophe, ilileva (Zulu)	Asteraceae	Powdered bark	Hutchings et al. (1996); http://pza.sanbi.org/hilliardiella-aristata
Vetiveria zizanioides Nash. Also known as *Chrysopogon zizanioides* (L.) Roberty	Bunchgrass (English), vetiver (Tamil), muskus (Zulu)	Poaceae	Steam from root concoction is inhaled	Hutchings et al. (1996)

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Table 1 (*continued*)

Plant species	Common name	Family	Plant part specified and use where indicated	Reference
Warburgia salutaris (G. Bertol.) Chiov.	Pepper bark tree (English), peperbasboom (Afrikaans), shibaha (Tsonga), mulanga, manaka (Venda), isibhaha (Zulu)	Canellaceae	Bark	Watt and Breyer-Brandwijk (1962); Hutchings et al. (1996); Nundkumar and Ojewale (2002)
Warburgia ugandensis Sprague	Pepper bark tree (English),	Canellaceae	bark and root bark	Watt and Breyer-Brandwijk (1962); Elgorashi et al. (2003)
Xysmalobium undulatum R. Br.	Milk bush (English), bitterwortel (Afrikaans), ishongwe (Xhosa and Zulu), leshokxwa (Sotho)	Asclepiadaceae	An infusion of the root is given orally	Watt and Breyer-Brandwijk (1962)
Xysmalobium undulatum (L.) W.T.Aitonf. var.*undulatum*	Poho-ts'ehla (Sesotho)	Asclepiadaceae	Unspecified	Von Koenen (1996)
Ziziphus mucronata subsp. *mucronata* Willd.	Buffalo thorn (English), blinkblaar-wag-'n-bietjie (Afrikaans), mokgalo (Tswana), mutshetshete (Venda), umPhafa (Xhosa), unPhafa, umLahlankosi, isiLahla (Zulu)	Rhamnaceae	Cold water extract of leaves, where one teaspoonful is given to children with fever	Von Koenen (1996); Watt and Brandwijk (1962)

concentrations. This is generally considered the preferred model system for screening antimalarial properties of plant extracts as they allow the investigator to screen against the clinically most relevant human *P. falciparum* parasite. Whilst the rodent model allows the investigator to test the therapy in an *in vivo* system, the rodents must be screened using the rodent infective parasite *Plasmodium berghei* (Builders, 2015). As different *Plasmodium* spp. may have different drug susceptibilities, screening against *P. berghei* may not be relevant to the human parasite and this model is best considered an intermediate step in screening potential antimalarial therapies.

We have only included a few studies tested against *P. berghei*, but preference was given to activities of local medicinal plant extracts against the human parasite *P. falciparum* in this review. Furthermore, for the purposes of this review, a medicinal plant is classified as having clinically relevant antimalarial activity only if they have IC_{50} values ≤ 10 µg/mL, and a selectivity index (SI) of ≥10 (Bapela et al., 2014).

Multiple plant species have been reported to kill *Plasmodium* spp. For example, *B. racemosa*, *C. tomentosa*, *C. brachiata*, *C. zeyheri*, *C. spicata*, *G. thunbergia*, *G. cuneate*, *P. zeylanica*, *R. caffra*, *T. riparia* and *V. natalensis* were selected for antimalarial screening in their respective studies based on their traditional use to treat malaria. In contrast, there is no record of therapeutic use to treat malaria for many of the other species studied. Instead, the other plant species were selected for screening based on different criteria, including their taxonomic relationship to similar species that were used traditionally for this purpose. For example, extracts produced from *V. adoensis* (Nethengwe et al., 2012) and *V. amygdalina* (Melariri et al., 2012) were screened for antimalarial activity based on their taxonomic relationship to *V. natalensis*, which is documented as a Zulu remedy for malaria (Hutchings et al., 1996). Similarly, *A. littoralis* was used traditionally to treat malaria in Namibia (Von Koenen, 1996). Several related *Aloe* spp. species were screened for antimalarial activity across several studies, based on this taxonomic relationship (Clarkson et al., 2004; Van Zyl and Viljoen, 2002). Similarly, it is likely that *A. senegalensis* (Clarkson et al., 2004), *C. glabrum* and *S. petersiana* (Bapela et al., 2014) were selected for study based on their taxonomic relationship to other traditional medicines. Many of the other species previously screened for antimalarial activity have therapeutic properties consistent with treating the symptoms of malaria.

For the purposes of this review, several exotic species have also been included, including *C. papaya* L. and *S. petersiana* (Bolle) Lock. Whilst these species have been introduced to South Africa, they are now widely cultivated and have been included in the pharmacopeia's of several South African ethnic groups. The following South African native and introduced medicinal plants were found to be cytotoxic towards *P. falciparum*, with IC50 values ≤ 10 µg/mL and SI values ≥ 10: *A. versicolor, B. mollis, C. tomentosa, C. papaya, C. pulchella, C. spicata, D. cinerea, D. gerradii, G. thunbergia, O. genistifolia, P. guajava, T. elegans, V. infausta, V. adoensis* and *X. parviflora* (Bapela et al., 2014; Mokoka et al., 2011; Nethengwe et al., 2012; Melariri et al., 2012). Of the plants with good antimalarial activity, the least toxic species was *C. papaya* (SI = 249.25/185.37 against chloroquine sensitive and resistant *P. falciparum* strains respectively). *Psidium guajava* (SI = 249.25/185.37), *D. gerradii* (SI = 101.2 against chloroquine sensitive strains) and *V. adoensis* (SI > 100 against chloroquine sensitive strains) (Bapela et al., 2014; Mokoka et al., 2011; Melariri et al., 2012; Nethengwe et al., 2012) also had good selectivity values. Several South African medicinal plants with potent anti-*P. falciparum* activity were not screened for toxicity and therefore their selectivity indices are not available. Further investigations are needed to establish whether these extracts have potential as antiplasmodial therapies, or if they are simply cytotoxic and therefore not suitable as human antimalarial drugs.

Notably, several of the reviewed studies compared the activities of the plant extracts against chloroquine sensitive and chloroquine resistant *P. falciparum* strains. Interestingly, of the plant species with

Table 2
Scientific evaluation of the anti-Plasmodium spp. activity of southern African plants.

Plant species	Common name	Family	Plant part used	Type of sample tested (extract)	Some evidence of further investigation	Reference
Abrus precatorius L.	Bead vine, coral bean, crabs eye, licorice vine, red bean vine, weather vine (English), amabope (Ndebele), nsimani (Shangaan), umkhokha (Zulu)	Fabaceae	Roots and seeds	DCM/ethanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 14.10 ± 5.73 µg/mL)	Mokoka et al. (2011)
Acacia nilotica (L.) Willd. Ex Delile	Scented pod acacia (English), lekkerruikpeul (Afrikaans), mogohlo (northern Sotho), motsha (Tswana), umNqawe (Zulu)	Fabaceae	Twigs	DCM/methanol (1:1)	IC_{50} = 13 µg/mL	Clarkson et al. (2004)
Acacia tortilis (Forssk) Hayne	Umbrella thorn acacia (English), ingoka, isanqawe, umsasane (Ndebele)	Fabaceae	Whole plant		IC_{50} = 4.8 µg/mL	
Acacia xanthoploea Benth.	Fever tree (English), koorsboom (Afrikaans), mooka-kwena (northern Sotho), umHlosinga (Zulu), nkelenga (Tsonga), munzhelenga (Venda)	Fabaceae	Stem bark	Acetone	IC_{50} = 10.1 µg/mL	Prozesky et al. (2001)
Acanthospermum australe (Loefl.) Kuntze	Creeping starbur, Prostrate starbur (English)	Asteraceae	Not given	dichloromethane	5 µg/ml	Nethengwe et al. (2012)
Achyranthes aspera L.	Devil's horsewhip, prickly chaff flower (English)	Amaranthaceae	Whole plant	DCM/methanol (1:1). Also water	IC_{50} = 9.9 µg/mL and > 100 µg/mL for solvent and water extracts respectively	Clarkson et al. (2004)
Adansonia digitata L.	See Table 1		Stem bark peels	Methanol	400 mg/kg exhibited the highest chemosupressive activity in the mice model	Adeoye and Bewaj (2018)
Adenia gummifera (Harv.) Harms			Stems	Petroleum ether/ ethyl acetate (1:1)	IC_{50} ~50 µg/mL	Kraft et al. (2003)
Agathosma apiculata E.Mey.	Garlic buchu (English), knoffelboegoe (Afrikaans)	Rutaceae	Whole plant	DCM/methanol (1:1)	IC_{50} = 5.2 µg/mL	Clarkson et al. (2004)
Agathosma puberula (Steud.)	Unknown		Roots, stem		IC_{50} = 19 µg/mL and 15 µg/mL for root and stem extracts respectively	
Ageratum conyzoides L.	Billy goat weed, blue top, white weed (English)	Asteraceae	Whole plant		IC_{50} = 27 µg/mL	
Albertisia delagoensis N.E. Br. Forman	Umgandaganda (Zulu)	Menispermaceae	Leaves and rhizome	Methanol	IC_{50} 4.1 µg/ml (leaves) and IC_{50} 1.6 µg/ml (rhizome).	De Wet et al. (2007)
Albizia versicolor Welw. Ex Oliv.	Poison pod albizia, large-leaf false thorn (English)	Leguminosae	Roots, bark	DCM/methanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 2.1 and 23.8 ug/mL against chloroquine sensitive and resistant *P. falciparum* strains respectively	Bapela et al. (2014)
Alepidea amatymbica Eckl. & Zeyh.	Larger tinsel flower (English), kalmoes (Afrikaans), iqwili (Xhosa), ikhathazo (Zulu)	Apiaceae	Whole plant	DCM/methanol (1:1). Also water	IC_{50} = 12.5 µg/mL and > 100 µg/mL for solvent and water extracts respectively	Clarkson et al. (2004)
Aloe ferox Mill.	Bitter aloe (English), bitteraalwyn, kaapse aalwyn (Afrikaans), umhlaba (Sotho, Xhosa, Zulu)	Aloaceae	Whole plant, fruit, stem, roots	DCM/methanol (1:1)	IC_{50} = 8 µg/mL, 14 µg/mL, 15.5 µg/mL and 8.5 µg/mL for whole plant, fruit, stem and root solvent extracts respectively	Clarkson et al. (2004)
Aloe maculata Forssk.	Common soap aloe (English), bontaalwyn (Afrikaans), icena (Zulu)		Whole plant, leaves		IC_{50} = 12.4 µg/mL	
Aloe marlothii A. Berger	Mountain aloe, Natal aloes (English), bergaalwyn, boomaalwyn (Afrikaans), umHlaba, imiHlaba (Zulu), kgopha (Sotho)		Whole plant	DCM	IC_{50} = 3.5 µg/mL	Clarkson et al. (2004)
Aloe viridiflora Reynolds	Unknown		Leaves	Methanol	IC_{50} = 31.7 µg/mL	Van Zyl and Viljoen (2002)
Annona muricata Wercklé	See Table 1		Stem bark	Crude ethanolic H_2O fraction CH_2Cl_2 fraction	IC_{50} = 1.45 ± 0.20 µg/mL IC_{50} = > 10 µg/mL IC_{50} = 1.50 ± 0.07 µg/mL	Yamthe et al. (2015)
Annona senegalensis Pers.	African custard apple, wild custard apple, wild soursop (English), wildesuikerappel (Afrikaans), muroro (Shona)	Annonaceae	Leaves	DCM	IC_{50} = 35 µg/mL	Clarkson et al. (2004)
Anthocleista grandiflora Gilg	Forest fever tree, big-leaf fever tree, cabbage tree, tobacco (English), grootblaarboom, koorsboom, wildetabakboom (Afrikaans), umhobohobo,	Loganiaceae	Bark	DCM/methanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 8.7 and > 50 against chloroquine sensitive and resistant *P. falciparum* strains respectively)	Bapela et al. (2014)

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Table 2 (*continued*)

Plant species	Common name	Family	Plant part used	Type of sample tested (extract)	Some evidence of further investigation	Reference
	luvungu (Swazi), mophala (northern Sotho)					
Argemone Mexicana L.	See Table 1		Aerial parts	Water decoction	Clinical trial where few patients had complete parasite clearance, but at day 14, 67% of patients with ACR had a parasitaemia < 2000/µl	Willcox et al. (2007)
Artabotrys brachypetalus Benth.	Short petalled artabotrys (English), uMazwenda omnyama (Zulu) mudzidzi (Venda)	Annonaceae	Leaves, twigs	DCM/methanol (1:1). Also water	Twigs IC_{50} > 100 µg/mL for all extracts respectively	Clarkson et al. (2004)
Artabotrys monteiroae Oliv.	Red hook-berry (English)	Annonaceae	Leaves, twigs		Twigs IC_{50} = 8.7 µg/mL and > 100 µg/mL for solvent and water extracts respectively. Leaves IC_{50} = 22 µg/mL and 23 µg/mL for solvent and water extracts respectively	
Artemisia afra Jacq. Ex Willd.	See Table 1		Leaves	DCM/methanol (1:1). Also DCM and water	IC_{50} = 5 µg/mL, and 7.3 µg/mL and 8 µg/mLfor DCM, DCM/methanol and water extracts respectively	Clarkson et al. (2004); Van Zyl and Viljoen (2002)
Asparagus virgatus Baker	Broom asparagus, slender asparagus, broom fern (English), makkatdoring, katstertjie (Afrikaans), ibutha, ihabiya, iphinganhloya, unwele (Zulu)	Asparagaceae	Whole plant	DCM/methanol (1:1). Also water	IC_{50} = 8 µg/mL and > 100 µg/mL for solvent and water extracts respectively.	Clarkson et al. (2004)
Asystasia gangetica T.Anderson	Chinese violet, coromandel, creeping foxglove (English), isihobo (Zulu)	Acanthaceae	Twigs and leaves		Twigs IC_{50} = 16 µg/mL and > 100 µg/mL for solvent and water extracts respectively. Leaves IC_{50} = 7 µg/mL and > 100 µg/mL for solvent and water extracts respectively	
Balanites maughamii Sprague	Manduro, torchwood (English), groendoring (Afrikaans), ugobandlovu (Zulu)	Balanitaceae	Stem bark	DCM extract	IC_{50} = 1.9 µg/mL	Prozesky et al. (2001)
Barringtonia racemosa Roxb.	See Table 1		Twigs	DCM/methanol (1:1)	IC_{50} = 5.7 µg/mL	Clarkson et al. (2004); Nundkumar and Ojewale (2002)
Berula erecta (Huds.) Coville	Lesser water-parsnip (English)	Apiaceae	Whole plant	DCM/methanol (1:1). Also water	IC_{50} = > 100 µg/mL and 6.6 µg/mL for solvent and water extracts respectively.	Clarkson et al. (2004)
Bidens pilosa L.	Black jack (English), chuchuza (Swazi)	Asteraceae	Leaves	DCM/methanol (1:1) extract. Also DCM a	IC_{50} = 8.55 µg/mL and 11 µg/mL for DCM, DCM/methanol extracts respectively	Clarkson et al. (2004)
Bridelia micrantha Baill.	Coastal golden leaf (English), mitseeri, bruin stinkhout (Afrikaans), motsere (Sotho), ndzerhe (Tswana)	Euphorbiaceae	Twigs	DCM/methanol (1:1)	IC_{50} = 59.3 µg/mL	Clarkson et al. (2004)
Bridelia mollis Hutch.	Velvet sweetberry, velvet-leafed bridelia (English), mudenhanyani, mufukusi, muhumbakumba, munyani (Shona), umgojomba, umkumbakumba, umwane (Ndebele)	Euphorbiaceae	Roots	DCM/methanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 3.1 and 28.6 ug/mLagainst chloroquine sensitive and resistant *P. falciparum* strains respectively)	Bapela et al. (2014)
Bruguiera gymnorhiza (L.) Lam.	Black mangrove (English), swart-wortelboom (Afrikaans), isikhangati (Xhosa), isihlobane (Zulu)	Rhizophoraceae	Twigs, leaves	DCM/methanol (1:1)	IC_{50} = 11.7 µg/mL and 15.3 µg/mL for twig and leaf extracts respectively	Clarkson et al. (2004)
Burchellia bubalina (L.f.) Sims	Wild pomegranate (English) wildegranaat (Afrikaans), iThobankomo (Xhosa), isiGolwane (Zulu)	Rubiaceae	Twigs, leaves		IC_{50} = 18 µg/mL and 50 µg/mL for twig and leaf extracts respectively	
Cannabis sativa L.	See Table 1		Dried leaves, twigs, and seeds	Dried plants as feed	Studies on mice demonstrated reduction in symptomatic manifestation of malaria disease, although no change to levels of parasitaemia	Akinola et al. (2018)
Capparis tomentosa Lam.			Roots	DCM/methanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 2.2 and 29.2 ug/mLagainst chloroquine sensitive and resistant *P. falciparum* strains respectively	Bapela et al., 2014; Clarkson et al., 2004
Cardiospermum halicacabum L.	Balloon vine, blister creeper, heart seed, love in a puff (English)	Sapindaceae	Whole plant	DCM/methanol (1:1)	IC_{50} = 20 µg/mL	Clarkson et al. (2004)
Carica papaya L.	Papaya, pawpaw (English)	Caricaceae	Leaves			

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Table 2 (*continued*)

Plant species	Common name	Family	Plant part used	Type of sample tested (extract)	Some evidence of further investigation	Reference
				Several organic solvents	Individual and combination extracts effects. Extracts synergistic with those of *P. guajava*, *C. citratus* and *C. limon* against both chloroquine sensitive and resistant strains of *P. falciparum*. Single extracts: IC_{50} = 3 and 4 ug/mL against chloroquine sensitive and resistant *P. falciparum* strains respectively	Melariri et al. (2012)
Cassia abbreviate Oliv.	See Table 1		Roots	Petroleum ether and thereafter methanol	Active against the chloroquine-sensitive (IC_{50} = 20.56 g/mL) and the chloroquine-resistant (IC_{50} = 13.31 g/mL) against strains of *P. falciparum*	Kiplagat et al. (2016)
Cassia siamea (Lam.) Irwin et Barneby			Stem bark	Aqueous EtOH	IC_{50} = > 1000 μg/mL against strains of *P. falciparum*	Ohashi et al. (2018)
Catha edulis Vahl.	Bushman's tea (English), boesmanstee (Afrikaans), khat (Arabic)	Celastraceae	Leaves, roots, seeds	DCM/methanol (1:1)	IC_{50} = 6.9 μg/mL, 4.8 μg/mL and 10 μg/mL for leaf, root and seed extracts respectively. Showed 40% *in vitro* inhibition of *P. falciparum* NF54 early stage gametocyte	Clarkson et al. (2004)
Centella asiatica Urb.	Pennywort (English), varkoortjies (Afrokaans)	Apiaceae	Leaves		IC_{50} = 8.3 μg/mL	
Cephalanthus natalensis Oliv.	See Table 1		Leaves, twigs		IC_{50} = 24.3 μg/mL and 16.5 μg/mL for the leaf and twig extracts respectively	
Cissus quadrangularis L.			Whole plant	DCM and methanol	IC_{50} = 23.9 μg/mL (DCM extract); IC_{50} = 23.9 μg/mL (methanol extract)	Bah et al. (2007)
Combretum molle R.Br. ex G.Don			Seed	Methanol	Results demonstrated a 63.5% parasite suppression in mice infected with *Plasmodium berghei* ANKA (PbA) murine parasite	Anato and Ketema (2018)
Cymbopogon citratus Stapf.	Lemon grass, citronella grass (English), isiqunga (Zulu)	Poaceae	Leaves	Several organic solvents	Extracts synergistic with those of *C. papaya* against both chloroquine sensitive and resistant strains of *P. falciparum*. Single extracts: IC_{50} = 5.01 ± 0.32/5.99 ± 0.39 μg/mL, SI: 49.30/41.23. Combined extracts with *C. papaya*: IC_{50} = 3.01 ± 0.55/2.95 ± 0.78. SI: not done. Methanol IC_{50} > 100 μg/mL	Melariri et al. (2012)
Clausena anisata (Willd.) Hook. f.	See Table 1		Roots	DCM/ethanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 3.61 ± 1.82 μg/mL). Cytotocity on rat L6-cells (SI = 7.15)	Mokoka et al., 2011; Clarkson et al., 2004
Clematis brachiata Ker Gawl.				DCM/methanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 5.4 and > 50ug/mL against chloroquine sensitive and resistant *P. falciparum* strains respectively)	Bapela et al., 2014; Clarkson et al., 2004
Clerodendrum glabrum E. Mey.	Tinderwood (English), tontelhout (Afrikaans), moswaapeba (Sotho), mohlokohloko (northern Sotho), umqwaqwanam (Xhosa), munukha-tshilongwe (Venda), xinhunwelambeva (Tswana), umQoqonga (Zulu)	Lamiaceae	Leaves	DCM/methanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 8.9 and > 50 ug/mL against chloroquine sensitive and resistant *P. falciparum* strains respectively	Bapela et al. (2014)
Clutia hirsuta Müll.Arg.	Unknown	Euphorbiaceae	Whole plant	DCM/methanol (1:1)	IC_{50} = 15 μg/mL	Clarkson et al. (2004)
Clutia pulchella L.	Lightning bush, warty-fruited lightning bush (English), gewone bliksembos, oumeisieknie, vratjievrug-bliksembos, weeligbos (Afrikaans), iqadi, ufiyo, umsipane (Xhosa), ikhambi lenkosi, umembesa, ungwaleni (Zulu)	Euphorbiaceae	Roots	DCM/ethanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 3.2 μg/mL)	Mokoka et al., 2011
Combretum zeyheri Sond.	See Table 1		Twigs	DCM/ethanol (1:1)	IC_{50} = 15 μg/mL	Clarkson et al. (2004)
Conyza albida Spreng.	Fleabane, hairy horseweed, flax-leaf fleabane (English)	Asteraceae	Whole plant	DCM/methanol (1:1). Also water	IC_{50} = 2 μg/mL	Clarkson et al. (2004)
Conyza podocephala DC.	Horseweed, butterweed (English)				IC_{50} = 6.8 μg/mL	
Conyzya scabrida DC.	Ondbos, bakbos, paddabos (Afrikaans)		Flowers, leaves, twigs	DCM/methanol (1:1). Also water	IC_{50} = 7.8 μg/mL, 11.5 μg/mL and 11 μg/mL for flower, leaf and twig extracts respectively	Clarkson et al. (2004)
Crinum macowanii Baker	River crinum, river lily, Cape coast lily (English), rivierlelie, boslelie, Sabielelie (Afrikaans),	Amarylidaceae	Bulbs		IC_{50} = 26 μg/mL and 25 μg/mL for solvent and water extracts respectively	

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Table 2 (*continued*)

Plant species	Common name	Family	Plant part used	Type of sample tested (extract)	Some evidence of further investigation	Reference
	intelezi (Xhosa), umduze (Zulu)					
Crotalaria burkeana Benth.	Rattle bush (English), dronkgras, klapperbos, klappersa, styfsiektebossie (Afrikaans)	Leguminosae	Leaves and roots	DCM/methanol (1:1)	IC_{50} = 50 µg/mL and 13 µg/mL for leaf and root extracts respectively	Clarkson et al. (2004)
Croton gratissimus Burch.	Lavendar croton (English) gunukira, mubangwa, mufarata (Shona)	Euphorbiaceae	Leaves	DCM	IC_{50} = 3.5 µg/mL	Clarkson et al. (2004)
Croton menyhartii Pax	Rough-leafed croton (English)		Leaves, twigs	DCM/methanol (1:1)	IC_{50} = 1.7 µg/mL and 15 µg/mL for leaf and twig extracts respectively.	Clarkson et al. (2004)
Croton pseudopulchellus Pax.	Lavendar leafed croton (English), uHubeshane (Zulu)		Stem bark	Chloroform	IC_{50} = 3.5 µg/mL	Prozesky et al. (2001)
Cussonia arborea Hochst. ex A. Rich.	Octopus cabbage tree (English), ufenje, Mushondya and Mutobvi (Shona)	Araliaceae	Leaves	MEOH and aqueous	IC_{50} = 13.68 and > 50 µg/mL for organic and aqueous extracts respectively	De Villiers et al. (2010)
Cussonia sphaerocephala Strey	Forest cabbage-tree, Natal forest cabbage tree (English), boskiepersol (Afrikaans), umsenge-wehlathi (isiXhosa & isiZulu), umsenge (siSwati)				IC_{50} = 32.31 and > 50 µg/mL for organic and aqueous extracts respectively	
Cussonia spicata Thunb.	See Table 1		Root bark Leaves	DCM/methanol (1:1) MEOH and aqueous	*In vitro* testing on infected human red blood cells (IC_{50} = 3.3 and > 50 µg/mL against chloroquine sensitive and resistant *P. falciparum* strains respectively). IC_{50} = 32.31 or 28.20 (depending on sample) and > 50 µg/mL for organic and aqueous extracts respectively	Bapela et al., 2014; Clarkson et al., 2004; Tetyana et al., 2002 De Villiers et al. (2010)
Cymbopogon validus Stapf ex Burtt Davy	African bluegrass, giant terpentine grass (English)	Poaceae	Whole plant	DCM/methanol (1:1)	IC_{50} = 5.8 µg/mL	Clarkson et al. (2004)
Dichrostachys cinerea (L.) Wight & Am.	Sickle bush (English), sekelbos (Afrikaans), ugegane, umthezane (Zulu)	Leguminosae	Roots	DCM/methanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 2.1 and > 50 µg/mL against chloroquine sensitive and resistant *P. falciparum* strains respectively)	Bapela et al. (2014)
Diospyros mespiliformis Hochst. Ex A. DC.	African ebony, jackal-berry (English), jakkalsbessie (Afrikaans), musuma (Venda), mgula (Tsonga)	Ebenaceae			*In vitro* testing on infected human red blood cells (IC_{50} = 4.4 and 28.4 µg/mL against chloroquine sensitive and resistant *P. falciparum* strains respectively)	
Diplorhynchus condylocarpon (Mull. Arg.) Pichon	Horn pod tree, wild rubber (English), inkamamasane (Ndebele), musikanyimo, mutohwa, tsowa (Shona)	Apocynaceae	Roots	DCM/methanol (1:1). Also water	IC_{50} = 24 µg/mL and > 100 µg/mL for solvent and water extracts respectively	Clarkson et al. (2004)
Dodonaea viscosa Jacq.	Sand olive (English), mukonachando (Shona)	Sapindaceae	Leaves	DCM/methanol (1:1)	IC_{50} = 15.5 µg/mL	
Drypetes gerrardii Hutch.	Forest ironwood, forest ironplum (English)	Euphorbiaceae	Stems	DCM/ethanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 0.5 µg/mL)	Mokoka et al., 2011
Ekebergia capensis Sparrm.	Cape ash (English), essenhout (Afrikaans), mmidibidibi (northern Sotho), umnyamathi (Zulu)	Meliaceae	Fruit	DCM/ethanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 6.8–10 µg/mL).	Mokoka et al., 2011; Clarkson et al., 2004
Elaeodendron transvaalense (Burtt Davy) R.H.Archer	Bushveld saffron (English), bosveldsaffraan, lepelhout (Afrikaans), iNgwavuma, uMgugudo (Zulu), shimapana (Tsonga), monamane (Northern Sotho)	Celastraceae	Not given	Dichloromethane	5 µg/ml	Nethengwe et al. (2012)
Elephantorrhiza elephantina (Burch.) Skeels	Elandsbean (English), elandsboontjie (Afrikaans), mupangara (Shona), mositsane (Sotho, Tswana), intolwane (Xhosa, Zulu)	Leguminosae	Roots, leaves	DCM/methanol (1:1)	IC_{50} = 28 µg/mL and 26 µg/mL for root and leaf extracts respectively	Clarkson et al. (2004)
Entandophragma caudatum Sprague	See Table 1		Stem bark	DCM	IC_{50} = 2.9 µg/mL	Prozesky et al. (2001)
Erythrina lysistemon Hutch				Acetone	IC_{50} = 4.8 µg/mL	
Euclea natalensis A. DC.	Natal gaurri, Natal ebony, large leaved gaurri (English), Natalghwarrie, berggwarrie, swartbasboom (Afrikaans), umTshekisani, umKhasa (Xhosa), iDungamuzi,	Ebenaceae	Roots	DCM/methanol (1:1)	IC_{50} = 5.1 µg/mL	Clarkson et al. (2004)

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Table 2 (*continued*)

Plant species	Common name	Family	Plant part used	Type of sample tested (extract)	Some evidence of further investigation	Reference
	iChitamuzi, umZimane, umTshikisane, inKunzane, (Zulu), umHlangula (Tsonga)					
Euclea undulata Thunb.	Small-leaved guarri (English), kleinblaarghwarrie (Afrikaans), gwanxe, inkunzane, umshekizane (Zulu)	Ebenaceae	Leaves and twigs	DCM/methanol (1:1)	IC_{50} = 11 µg/mL and 4.6 µg/mL for leaf and twig extracts respectively	Clarkson et al. (2004)
Eucomis autumnalis (Mill.) Chitt.	Pineapple flower, pineapple lily (English), wildepynappel, krulkoppie (Afrikaans), ubuhlungu becanti (Xhosa), umathunga, ukhikho (Zulu)	Hyacinthaceae	Bulbs	DCM/methanol (1:1)	IC_{50} = 9.5 µg/mL	Clarkson et al. (2004)
Euphorbia heterophylla L.	Fireplant, painted euphorbia, milkweed, desert poinsettia (English)	Euphorbiaceae	Whole plant	DCM/methanol (1:1)	IC_{50} = 40 µg/mL	Clarkson et al. (2004)
Euphorbia tirucalli L.	Pencil plant, rubber-hedge euphorbia (English), kraalmelboos (Afrikaans)	Euphorbiaceae	Leaves	DCM/methanol (1:1)	IC_{50} = 23.5 µg/mL	Clarkson et al. (2004)
Flueggea virosa (Willd.) Voigt	White-berry bush (English), witbessiebos (Afrikaans), mutangahuma (Venda), muhlakaume (Sotho)	Euphorbiaceae	Leaves, stem, roots	DCM/methanol (1:1)	IC_{50} = 27.5 µg/mL and 8 µg/mL for leaf and stem extracts respectively	Clarkson et al. (2004)
Gardenia thunbergia L.f.	See Table 1		Not given	Dichloromethane Methanol	10–20 µg/ml < 10 µg/ml	Nethengwe et al. (2012)
Gloriosa superba L.	Flame lily, climbing lily, Turk's cap, glory lily (English), vlamlelie, boslelie, geelboslelie, rooiboslelie (Afrikaans), ihlamvu, ihlamvu-labafana, ihlamvu-lomfana nentombazana, isikwali sasolwandle, isimieselo (Zulu)	Colchicaceae	Whole plant	DCM/ethanol (1:1)	IC_{50} = 17 µg/mL	Clarkson et al. (2004)
Gnidia cuneata Meisn.	Koorsbossie (Afrikaans)	Thymelaeaceae	Stems	DCM/methanol (1:1)	IC_{50} = 16 µg/mL	Clarkson et al. (2004)
Gnidia kraussiana Meisn.	Yellow heads (English), harige gifbossie (Afrikaans), isidikili, umsilawengwe (Zulu), umarhedeni (Xhosa)	Thymelaeaceae	Tuber, leaves/twigs	DCM/methanol (1:1)	IC_{50} = 16 µg/mL and 10.8 µg/mL for the tuber and leaf/twig extracts respectively	Clarkson et al. (2004)
Gomphocarpus fruticosus (L.) Spreng.	Milkweed, wild cotton (English), gansie, melkbos (Afrikaans), lebegane (Sotho), umsinga-lwesalukazi (Zulu)	Apocynaceae	Fruit	DCM/methanol (1:1)	IC_{50} = 26 µg/mL	Clarkson et al. (2004)
Helichrysum cymosum (L.) D. Don subsp. *cymosum*	Gold carpet (English), goue tapyt (Afrikaans), impepho (isiXhosa)	Asteraceae	Leaf	Acetone and essential oil	IC_{50} = 60.76 µg/mL (acetone extract), IC_{50} = 1.25 µg/mL (essential oil)	Van Vuuren et al., 2006
Helichrysum nudifolium (L.)	Hottentot's tea (English), hottentotstee (Afrikaans), letapiso (southern Sotho), ludvutfane (Swazi), icholocholo (Xhosa, Zulu)	Asteraceae	Whole plant	DCM/methanol (1:1)	IC_{50} = 6.8 µg/mL	Clarkson et al. (2004)
Helichrysum pedunculatum Hilliard & B. L. Burtt.	Isicwe (Zulu)	Asteraceae	Whole plant	DCM/ethanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 6.5 µg/mL). SI = 7.15	Mokoka et al., 2011
Hermannia depressa N.E.Br.	Doll's rose (English), Rooi-opslag (Afrikaans)	Sterculiaceae	Whole plant		IC_{50} = 6.9 µg/mL	Clarkson et al. (2004)
Hippobromus pauciflorus Radlk.	False horsewood, false horse urine (English), baster-perdepis (Afrikaans)	Sapindaceae	Leaves, twigs		IC_{50} = 34 µg/mL and 5.9 µg/mL for leaf and twig extracts respectively	
Hypericum superba L.	Unknown	Clusiaceae	Leaves/flowers		IC_{50} = 17 µg/mL	
Hyptis pectinata (L.) Poit.	Comb hyptis (English)	Lamiaceae	Leaves/stem/fruit		IC_{50} = 17.5 µg/mL	
Justicia flava Vahl	Yellow justicea (English), geelgarnaalbos (Afrikaans), impela (Zulu)	Acanthaceae	Whole plant	DCM/methanol (1:1). Also water	IC_{50} = 31 µg/mL and > 100 µg/mL for solvent and water extracts respectively	
Kigelia africana (Lam.) Benth.	Sausage tree (English), worsboom (Afrikaans), unVunguta, umFongothi (Zulu), modukguhlu (northern Sotho), muvevha (Venda)	Bignoniaceae	Leaves	DCM	IC_{50} = 51 µg/mL	Clarkson et al. (2004)

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Table 2 (*continued*)

Plant species	Common name	Family	Plant part used	Type of sample tested (extract)	Some evidence of further investigation	Reference
Kirkia wilmsii Engl.	Mountain kirkia, wild pepper tree (English), bersering, wildepeperboom (Afrikaans), modumela (northern Sotho)	Kirkiaceae	Leaves	DCM/methanol (1:1)	IC_{50} = 3.7 µg/mL	Clarkson et al. (2004)
Lannea discolor Engl.	Live-long grape tree (English), dikbas (Afrikaans), morulamopsane (Pedi), muvhumbu (Venda)	Anacardiaceae	Fruit	DCM/methanol (1:1). Also water	IC_{50} = 25 µg/mL and > 100 µg/mL for solvent and water extracts respectively	Clarkson et al. (2004)
Leonotis leonurus (L.) R. Br.	Wild dagga (English), wilde dagga (Afrikaans), umhlahlampetu (Shona), lebake (Sotho), umfincafincane (Xhosa), umunyane (Zulu)	Lamiaceae	Leaves, twigs, roots	DCM/methanol (1:1)	IC_{50} = 15 µg/mL	Clarkson et al. (2004)
Leonotis nepetifolia (L.) R.Br.	Christmas candlestick, lion's ear (English), klip dagga (Afrikaans)	Lamiaceae	Whole plant		IC_{50} = 5.4 µg/mL, 5.4 µg/mL and 15 µg/mL for leaf, twig and root extracts respectively	
Leonotis ocymifolia (Brum. F.) Iwarsson	Minaret flower (English)	Lamiaceae	Fruit, roots	DCM/methanol (1:1)	IC_{50} = 20 µg/mL and 28 µg/mL for fruit and root extracts respectively	Clarkson et al. (2004)
Lippia javanica Spreng.	See Table 1		Whole plant	Essential oil and isolated compound	Isolation of lippialactone, a new antimalarial compound. Essential oil has IC_{50} = 8 µg/mL against chloroquine sensitive D10 strain	Ludere vet al., 2013; Clarkson et al., 2004; Prozesky et al., 2001
Macrostylis squarrosa Bartl. & H.L. Wendl.	Unknown	Rutaceae	Stems	DCM/ethanol (1:1)	IC_{50} = 10 µg/mL	Clarkson et al. (2004)
Maesa lanceolata G. Don	False assegai (English), valsassegaai (Afrikaans), intendekwane (Xhosa), muunguri (Venda), ligucu, umbohlobohlo (Swazi), umalunguzalazikhakhona, inhlavubele, umaguqu, isidenda, ubhoqobhoqo (Zulu)	Myrsinaceae	Twigs		IC_{50} = 5.9 µg/mL	
Maytenus senegalensis (Lam.) Exell.	See Table 1		Roots		IC_{50} = 15.5 µg/mL	
Maytenus undata (Thunb.) Blakelock	Koko tree, South African holly, Transvaal holly (English), saffraan, kokoboom (Afrikaans), idohame, igqwabali, inqayi-elibomvu (Zulu), inqayi-elibomvu, umgora, umkokuza (Xhosa), mokokono (northern Sotho)	Celastraceae	Leaves, roots, stem	DCM/ethanol (1:1)	IC_{50} = 21 µg/mL, 36 µg/mL and 24 µg/mL for leaf, root and stem extracts respectively	Clarkson et al. (2004)
Momordica balsamina L.	Balsam pear (English), laloentjie (Afrikaans), mohodu (Sotho), intshungu (Zulu)	Cucurbitaceae	Whole plant, leaves, stem	DCM/ethanol (1:1)	IC_{50} = 18 µg/mL, 6 µg/mL and 5.3 µg/mL for whole plant, leaf and stem extracts respectively	Clarkson et al. (2004)
Momordica charantia L.	See Table 1		Leaves	Ethanol	12.5 (IC_{50} nM)	Olasehinde et al. (2014)
Ocimum americanum L.	American basil, hoary basil (English)	Lamiaceae	Whole plant	DCM/ethanol (1:1)	IC_{50} = 4.2 µg/mL	Clarkson et al. (2004)
Oedera genistifolia (L.) Anderb. & K. Bremer	Kleinperdekaroo (Afrikaans)	Asteraceae	Whole plant	DCM/ethanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 2.9 µg/mL). SI = 17	Mokoka et al., 2011
Olea europa L. subsp. africana (Mill.) P.S. Green	Wild olive (English), olienhout (Afrikaans), mohlware (northern Sotho), umnquma (Aulu, Xhosa), mutlhwari (Venda), motlhware (Tswana)	Olacaceae	Leaves, twigs	DCM/methanol (1:1)	IC_{50} = 12 µg/mL and 13 µg/mL for leaf and twig extracts respectively	Clarkson et al. (2004)
Oncosiphon piluliferum (L.F.) Kallersjo	Gansogie, karoostinkkruid, stinkruid (Afrikaans)	Asteraceae	Whole plant	DCM	IC_{50} = 2.6 µg/mL	Prozesky et al. (2001)
Osteospermum imbricatum L.	African daisy (English)	Asteraceae	Stem	DCM/methanol (1:1)	IC_{50} = 7.3 µg/mL	Clarkson et al. (2004)
Ozoroa engleri R.A. Fernandez	See Table 1		Stem bark	DCM	IC_{50} = 1.7 µg/mL	Prozesky et al. (2001)
Ozoroa sphaerocarpa R. Fern. & A. Fern.	Currant resin tree (English), monoko (Pedi), korenteharpuisboom (Afrikaans)	Anacardiaceae	Whole plant	DCM/ethanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 5.5–10 µg/mL). SI = 4	Mokoka et al., 2011
Pappea capensis Sond. & Harv.	Jacket plum, indaba tree, bushveld cherry (English),	Apiaceae	Roots	DCM/ethanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 5.5–10 and 24.8 µg/mL and	

(*continued on next page*)

Table 2 (*continued*)

Plant species	Common name	Family	Plant part used	Type of sample tested (extract)	Some evidence of further investigation	Reference
	doppruim (Afrikaans), ilitye, umgqalutye (Xhosa), umqhokwane, umvuna, indaba (Zulu), mongatane, mopsinyugane (northern Sotho), liletsa (Swazi), xikwakwaxu, gulaswimbi (Tsonga)				> 50 ug/mL against chloroquine sensitive and resistant *P. falciparum* strains respectively). SI = 3.7–9.9 and 2.2 against chloroquine sensitive and resistant *P. falciparum* strains respectively	Bapela et al., 2014; Mokoka et al., 2011
Parinari capensis Harv.	Mobola-plum, cork tree, hissing tree (English), grysappel, bosappel (Afrikaans), mmola (N. Sotho), mbulwa (Tsonga), mobola (Tswana), muvhula (Venda)	Chrysobalancea	Stems and leaves	Various	Stems Petroleum ether (IC_{50} = 1.11 mg/mL) Dichloromethane IC_{50} = 2.14 mg/mL) Ethyl acetate (IC_{50} = 53.17 mg/mL) Ethanol (IC_{50} = 187.79 mg/mL) Leaves Petroleum ether (IC_{50} = 151.52 mg/mL) Dichloromethane (IC_{50} = 65.16 mg/mL) Ethyl acetate (IC_{50} = 143.33 mg/mL) Ethanol (IC_{50} = 302.34 mg/mL)	Uys et al. (2002)
Parinari curatellifolia Planch. Ex Benth.	Mobola-plum, cork tree, hissing tree (English), grysappel, bosappel (Afrikaans), mmola (northern Sotho), mobola (Tswana), muvhula (Venda)	Chrysobalanaceae	Roots and leaves	DCM/methanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 7 and 16.9 ug/mL against chloroquine sensitive and resistant *P. falciparum* strains respectively)	Bapela et al., 2014; Clarkson et al., 2004
Parkinsonia aculeata L.	Palo verde, Jerusalem thorn, jelly bean tree (English)	Caesalpiniaceae	Twigs	DCM/methanol (1:1)	IC_{50} = 9 µg/mL	Clarkson et al. (2004)
Pavetta crassipes K.Schum.	See Table 1		Leaves	Alkaloid	The IC_{50} against six different isolates were 47, 25, 30, 31, 47 and 280 respectively	Sanon et al. (2003)
Pelargonium alchemilloides (L.) L'Her.	Lady's mantle-leaved pelargonium (English), wildemalva, rankmalva (Afrikaans), inkubele (Xhosa), amanzemnyama, ishwaga (Zulu)	Geraniaceae	Whole plant	DCM/methanol (1:1)	IC_{50} = 15 µg/mL	Clarkson et al. (2004)
Pentzia globosa Less.	Bitter karoo bush (English), bitterbultkaroo, bitterkaroobossie, goedkaro, rooikarobos (Afrikaans)	Asteraceae	Leaves, stem, roots		IC_{50} = 19.5 µg/mL, 15.5 µg/mL and 14 µg/mL for leaf, stem and root extracts respectively	
Piliostigma thonningii (Schumach.) Milne-Redh.	Camel's foot tree, monkey bread, Rhodesian bauhinia (English)	Leguminosae	Leaves, fruit, twigs		IC_{50} = 32 µg/mL, 32.4 µg/mL and 25.9 µg/mL for leaf, stem and root extracts respectively	
Pittosporum viridiflorum Sims	Cheesewood, wild cape beech (English), kasuur, witboekenhout (Afrikaans), umVusamvu, umkhwenkwe (Zulu), kgalagandwe (northern Sotho), mosetlela (southern Sotho), mpustinyapoqo, nkasur (Tswana), mulondwane (Venda), umgqwengqwe (Xhosa)	Pittosporaceae	Whole plant	DCM	IC_{50} = 3 µg/mL	
Plantago major L.	See Table 1		Whole plant	DCM	IC_{50} = 21.5 µg/mL	
Plumbago zeylanica L.	Wild plumbago, leadwort (English)	Plumbaginaceae	Leaves	DCM/methanol (1:1)	IC_{50} = 3 µg/mL	Clarkson et al. (2004)
Pollichia campestris [Soland.]	Wax berry plant, barley sugar bush (English), kafferdruiwe, suikerbossie (Afrikaans), utywala, behlungulu (Xhosa), ukudla kwamabhayi, umhlungulu (Zulu)	Illecebraceae	Whole plant, twigs, leaves, fruit	DCM/methanol (1:1)	IC_{50} = 25 µg/mL, 6.8 µg/mL, 17 µg/mL and 27 µg/mL for whole plant, twig, leaf and fruit extracts respectively	Clarkson et al., 200.
Psidium guajava L.	See Table 1		Leaves	Several organic solvents	IC_{50}: 3/4 µg/mL, SI: 249.30/185 against chloroquine sensitive and resistant *P. falciparum* strains respectively	Melariri et al., 2012; Nundkumar and Ojewale, 2002
Psiadia punctulata Vatke	Sticky Psiadia (English)	Asteraceae	Twigs, leaves	DCM	IC_{50} = 9 µg/mL and 14 µg/mL for twig and leaf extracts respectively	Clarkson et al. (2004)
Psoralea pinnata L.	Fountain bush (English), fonteinbos, bloukeur, penwortel (Afrikaans), umHlonishwa (Zulu)	Fabaceae	Leaves	DCM/ethanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 9.2 µg/mL). SI = 1.7	Mokoka et al., 2011
Ptaeroxylon obliquum (Thunb.) Radlk.		Ptaeroxylaceae		DCM/methanol (1:1)	IC_{50} = 19 µg/mL, 22.8 µg/mL and 5.5 µg/mL for root leaf and stem extracts respectively	Clarkson et al. (2004)

(*continued on next page*)

Table 2 (*continued*)

Plant species	Common name	Family	Plant part used	Type of sample tested (extract)	Some evidence of further investigation	Reference
	Sneezewood (English), nieshout (Afrikaans), umThathi (Xhosa)		Roots, leaves, stem			
Pterocarpus angolensis DC.	Transvaal teak (English), kiaat, bloedhout, dolfhout, grienhout (Afrikaans), moroto (northern Sotho), mokwa (Tswana), umvangazi, umbilo (Zulu)	Fabaceae	Stem, roots	DCM/methanol (1:1)	IC_{50} = 60 μg/mL and 25.5 μg/mL for stem and root extracts respectively	Clarkson et al. (2004)
Pyrenacantha grandiflora Baill.	Firethorn (English), sehlulamanya, velabahleke (Swazi)	Icacinaceae	Roots	DCM/methanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 5.8 and > 50 ug/mL against chloroquine sensitive and resistant *P. falciparum* strains respectively)	Bapela et al. (2014)
Ranunculus multifidus Pursh.	Common buttercup (English), botterblom (Afrikaans), hlapi (Sotho), isijojokazane, uxhaphozi (Zulu)	Ranunculaceae	Whole plant	DCM/methanol (1:1)	IC_{50} = 2.3 μg/mL	Clarkson et al. (2004)
Rauvolfia caffra Sond.	See Table 1		Bark, roots	DCM/methanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 2.1 and 10.8 ug/mL against chloroquine sensitive and resistant *P. falciparum* strains respectively)	Bapela et al., 2014; Clarkson et al., 2004; Nundkumar and Ojewale, 2002
Rhizophora mucronata Lam.	Red mangrove (English), rooiwirtelboom (Afrikaans), umhlume (Zulu), unhluma (Xhosa)	Rhizophoraceae	Leaves, twigs	DCM/methanol (1:1)	IC_{50} = 24 μg/mL and 5.6 μg/mL for the leaf and twig extracts respectively	Clarkson et al. (2004)
Ricinus communis L.	Castor oil plant (English), kasterolieboom (Afrikaans), mokhura (northern Sotho), umhlakuva (Xhosa, Zulu)	Euphorbiaceae	Stems		IC_{50} = 8 μg/mL	
Rumex crispus Cham. & Schltdl.	Curly dock, yellow dock, yellow sorrel (English), krultongblaar, weeblaar (Afrikaans)	Polygonaceae	Roots		IC_{50} = 14 μg/mL	
Rumex sagittatus Thunb.	Climbing dock, climbing sorrel, red sorrel (English), klimsuring, ranksuring, rooisuring (Afrikaans), bolila-bo-boholo (Sothern Sotho), Tshitamba-tshedzi (Venda), umdende (Zulu)	Polygonaceae	Whole plant		IC_{50} = 18 μg/mL	
Salvia africana L.	Golden sage, beach sage, dune sage, sand sage (English), bruinsalie, sandsalie, geelblomsalie (Afrikaans)	Lamiaceae	Aerial parts	Chloroform/ methanol	IC_{50} = 15–25 μg/mL	Kamatou et al. (2008)
Salvia albicaulis Benth.	White-stemmed sage (English), witstingelsalie (Afrikaans)	Lamiaceae	Aerial parts	Chloroform/ methanol Essential oils	IC_{50} = 15.8 μg/mL IC_{50} = 6.4 μg/mL	Kamatou et al. (2008) Kamatou et al. (2007)
Salvia aurita Thunb.	Oogseerbossie (Afrikaans)	Lamiaceae	Aerial parts	Chloroform/ methanol	IC_{50} = 8.9 μg/mL	Kmatou et al. (2008)
Salvia chamelaeagnea P.J. Bergius	Rough blue sage (English), bloublomsalie (Afrikaans)				IC_{50} = 8.7 μg/mL	
Salvia disermas L.	Wild giant sage, Transvaal sage (English), grootsalie, teesalie (Afrikaans), mogasane (Tswana)				IC_{50} = 24.2 μg/mL	
Salvia dolomitica Codd.	Dolomite sage, pilgrim's rest pink sage (English)			Chloroform/ methanol Essential oils	IC_{50} = 7.6 μg/mL IC_{50} = 6.4 μg/mL	Kamatou et al. (2008) Kamatou et al. (2007)
Salvia garipensis Benth.	Gariep sage (English), gariep salie (Afrikaans)			Chloroform/ methanol	IC_{50} = 14 μg/mL	Kamatou et al. (2008)
Salvia namaensis Schinz	Nama sage (English)				IC_{50} = 25.4 μg/mL	
Salvia radula Benth.	Scrappy African sage (English)				IC_{50} = 3.9 μg/mL	
Salvia repens Burch. Ex Benth.	Creeping sage (English), kruipsalie (Afrikaans), usikiki (Xhosa)	Lamiaceae	Whole plant	DCM/methanol (1:1)	IC_{50} = 10.8 μg/mL	Clarkson et al. (2004)
Salvia runcinata L.f.	Harde salie (Afrikaans)				IC_{50} = 16.6 μg/mL	
Salvia schlechteri Briq.	Xobo Valley sage (English)				IC_{50} = 17.5 μg/mL	
Salvia stenophylla Burch. Ex Benth.	Blue mountain sage (English)				IC_{50} = 6.5 μg/mL	
Salvia verbenaca L.					IC_{50} = 24 μg/mL	

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Table 2 (*continued*)

Plant species	Common name	Family	Plant part used	Type of sample tested (extract)	Some evidence of further investigation	Reference
	Wild clary, wilde sage (English), Wildesalie (Afrikaans)					
Scaevola plumieri Vahl	Unknown	Goodeniaceae	Twigs	DCM	IC_{50} = 11 μg/mL	
Schefflera umbellifera Baill.	False cabbage tree (English), valskeipersol (Afrikaans), umsenge, umkisiso (Xhosa), umgezisia, umbumbu, umbegele (Zulu), mosetshe (northern Sotho)	Araliaceae	Leaves, roots, stem	DCM/methanol (1:1). Also water	Leaf IC_{50} = 19.5 μg/mL and 49.5 μg/mL for solvent and water extracts respectively. Root IC_{50} = 5.8 μg/mL and > 100 μg/mL for solvent and water extracts respectively. Stem IC_{50} = 15 μg/mL and > 100 μg/mL for solvent and water extracts respectively	Clarkson et al., 2004; Tetyana et al., 2002
Schkuhria pinnata (Lam.) Thell.	Dwarf Mexican marigold (English), klein-gousblom, kleinkakiebos (Afrikaans), ruhwahwa (Shona)	Asteraceae	Whole plant	DCM/ethanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 2.2 μg/mL)	Mokoka et al., 2011
Sclerocarya birrea (A. Rich.) Hochst. subp. caffra (Sond.) Kokwaro	See Table 1		Leaf, stem	Aqueous	IC_{50} = 30–40 μg/mL	Nundkumar and Ojewale (2002)
Schotia brachypetala Sond.	Weeping boer-bean (English), huilboerboon (Afrikaans)	Fabaceae	Aril	MeOH	IC_{50} = 18.95 μg/mL	Du et al. (2014)
Securidaca longipedunculata Fresen.	See Table 1		Leaf	DCM	IC_{50} = 6.9 μg/mL	Bah et al. (2007)
Senna occidentalis (L.) Link				Ethanol	IC_{50} = 48.8 μg/mL	Murugan et al. (2015)
Senecio oxyriifolius DC.	False nasturtium (English), kappertjeiblaar (Afrikaans), idumbe, ihlula (Zulu)	Asteraceae	Whole plant	DCM/methanol (1:1)	IC_{50} = 13 μg/mL	Clarkson et al. (2004)
Senna didymobotrya (Fresen.) Irwin & Barneby	African senna, popcorn senna, candelabra tree, peanut butter cassia (English)	Caesalpiniaceae	Leaves, twigs, pods	DCM/methanol (1:1)	IC_{50} = 40 μg/mL, 9.5 μg/mL and 18 μg/mL for leaf, twig and pod extracts respectively	Clarkson et al. (2004)
Senna petersiana (Bolle) Lock	Dwarf cassia, eared cassia, monkey pod (English), mbaraka, mpingawaume (Swazi)	Leguminosae	Leaves	Dichloromethane/ methanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 22.5 and 22.1 ug/mL against chloroquine sensitive and resistant *P. falciparum* strains respectively)	Clarkson et al., 2004; Bapela et al., 2014
Setaria megaphylla T. Durand & Schinz	Ribbon grass, broad-leafed brittle grass (English)	Poaceae	Whole plant	Dichloromethane/ methanol (1:1)	IC_{50} = 4.5 μg/mL	Clarkson et al. (2004)
Siphonochilus aethiopicus (Schweinf.)	See Table 1		Not given	Dichloromethane	10–20 μg/ml	Nethengwe et al. (2012)
Solanum nigrum L.			Fruits	Methanol	IC_{50} = 10.29 against *P. falciparum* 3D7 strain; IC_{50} = 18.67 against *P. falciparum* K1 strain	Haddad et al. (2017)
Solanum panduriforme E. Mey.			Leaves	Acetone	IC_{50} = 3.6 μg/mL	Prozesky et al. (2001)
Withania somnifera (L) Dunal	Winter cherry (English), bitterappelliefie, geneesblaarbossie, koorshout (Afrikaans), bofepha (Sotho), ubuvuma (Xhosa), ubuvimbha (Zulu)	Solanaceae	Not given	Dichloromethane	5 μg/ml	Nethengwe et al. (2012)
Spilanthes oleracea L.	See Table 1		Flower heads	Hexane	IC_{50} (ppm) of 5.09 against *Anopheles stephensi*; IC_{50} (ppm) of 3.23 against *Anopheles culicifacies*	Pandey et al. (2007)
Strychnos pungens Soler.	Spine-leafed monkey-orange (English), stekelblaarklapper (Afrikaans)	Strychnaceae	Leaves	DCM	IC_{50} = 12.6 μg/mL	Clarkson et al. (2004)
Syzygium cordatum Hochst.	Water berry (English), waterbessie (Afrikaans), montlho (northern Sotho), umdoni (Xhosa, Zulu)	Myrtaceae	Leaves	DCM/methanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 6.2 and 10.4 μg/mL against chloroquine sensitive and resistant *P. falciparum* strains respectively). SI = 65.7 and 53.8 against chloroquine sensitive and resistant *P. falciparum* strains respectively)	Clarkson et al. (2004); Bapela et al. (2014)
Tabernaemontana elegans Stapf.	Toad tree (English), laeveldse paddaboom (Afrikaans), muchanga (Shona), umKhahlwana, umKhadlu (Zulu)	Apocynaceae	Bark		*In vitro* testing on infected human red blood cells (IC_{50} = 0.3 and 0.8 ug/mL against chloroquine sensitive and resistant *P. falciparum* strains respectively)	Bapela et al. (2014)
Tarchonanthus camphoratus L.	Camphor bush, wild camphor bush (English), wildekanferbos (Afrikaans), moologa (Venda), mofahlana (southern Sotho), igqeba emlimhlophe (Zulu)	Asteraceae	Whole plant, leaves, roots		IC_{50} = 6 μg/mL, 13 μg/mL and 24 μg/mL for whole plant, leaf and root extracts respectively	Clarkson et al. (2004)
Tecomaria capensis (Thunb.) Spach	Cape honeysuckle (English), kaapse kanferfoelie, trompetters (Afrikaans), umsilingi, icakatha	Bignoniaceae	Leaves		IC_{50} = 11.6 μg/mL	

(*continued on next page*)

Table 2 (*continued*)

Plant species	Common name	Family	Plant part used	Type of sample tested (extract)	Some evidence of further investigation	Reference
	(Xhosa), lungana, incwincwi, uchacha, udodo (Zulu), molaka (Sotho)					
Tetradenia riparia (Hochst.) Codd.	See Table 1		Leaves	DCM/methanol (1:1)	IC_{50} = > 100 µg/mL	Clarkson et al. (2004)
Trichilia emetica Vahl			Leaves/twigs		IC_{50} = 3.5 µg/mL	
Tridax procumbens L.	Coatbuttons, tridax daisy (English)	Asteraceae	Whole plant, leaves, roots		IC_{50} = 17 µg/mL	
Triumfetta welwitschii Mast. *var hirsuta* (Sprague & Hutch.) Wild.	Unknown	Tiliaceae	Leaves		IC_{50} = 3.6 µg/mL	
Turraea floribunda Hochst.	Honeysuckle tree (English), kanferoelieboom (Afrikaans), umdlozana (Swazi), umadlozane (Zulu)	Meliaceae	Leaves	DCM/ethanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 6.8 µg/mL). SI = 12.3	Mokoka et al., 2011; Clarkson et al. (2004)
Vangueria infausta Burch.	See Table 1		Roots	DCM/methanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 1.8 and > 50 ug/mL against chloroquine sensitive and resistant *P. falciparum* strains respectively)	Nundkumar and Ojewale (2002); Clarkson et al. (2004); Bapela et al. (2014)
Vernonia adoensis Sch. Bip. Ex Walp.	Musikavakadzi (Shona)	Asteraceae	Leaves and roots	Dichloromethane and methanol	10–20 µg/ml (dichloromethane extract of root); 5 µg/ml (methanol extract of leaf)	Nethengwe et al. (2012)
Vernonia amygdalina Delile	Bitterleaf (English)		Leaves	Several organic solvents	IC_{50} = 4/4.1 µg/mL, SI: 9.7/9.4 against chloroquine sensitive and resistant *P. falciparum* strains respectively	Melariri et al. (2012).
Vernonia colorata (Willd.)	English bitter leaf, bitters tree (English)		Twigs and leaves	DCM/methanol (1:1)	IC_{50} = 14.1 µg/mL and 4.7 µg/mL for twig and leaf extracts respectively	Clarkson et al. (2004)
Vernonia fastigiata Oliv. & Hiern.	Narrow-leaved Vernonia (English), bloutee, blouteebossie, langbeenbossie (Afrikaans), lehlanye (northern Sotho)		Leaves		IC_{50} = 15 µg/mL	
Vernonia hirsuta (DC.) Sch. Bip. Ex Walp.	Quilted-leaved Vernonia (English), wildesonsoekertjie (Afrikaans) ikhambi lenyongo (Zulu)		Whole plant		IC_{50} = 14 µg/mL	
Vernonia myriantha Hook. f.	Blue bitter-tea, blue Vernonia, poison tree-Vernonia (English), bloubittertee, bosbloutee (Afrikaans), uhluhlunga, umhlungahlunga (Zulu)		Roots, leaves		IC_{50} = 37.5 µg/mL and 13.5 µg/mL for root and leaf extracts respectively	
Vernonia natalensis Sch. Bip. Ex Walp.	Silver vernonia (English), ihlambihloshana, isibhaha sasenkangala, umlahlankosi-omhlophe, ileleva (Zulu)		Whole plant	DCM/ethanol (1:1)	IC_{50} = > 24 µg/mL	Clarkson et al. (2004)
Vernonia oligocephala (DC.) Sch. Bip. Ex Walp.	Bicoloured-leaved Vernonia (English), groenamarabossie (Afrikaans), ihlambihloshane (Zulu)		Roots, leaves	DCM/methanol (1:1)	IC_{50} = 20 µg/mL and 5.5 µg/mL for root and leaf extracts respectively	Clarkson et al. (2004)
Vetiveria zizanioides (L.) Nash	See Table 1		Roots	Ethanol	A reduced hatchability rate of *A. stephensi* eggs, and zero hatchability was exerted at 375 ppm. In the oviposition deterrent test, the extract alleviated the egg laying at a concentration of 375 ppm.	Aarthi and Murugan, 2012
Vite obovata ssp. *obovata* E.Mey.	Hairy fingerleaf (English)	Verbenaceae	Aerial parts	Acetone	IC_{50} = 14.35 µg/mL	Nyiligira et al. (2008)
Vitex pooara sensu K. Coates Palgrave	Smelly-berry fingerleaf (English)				IC_{50} = 13.15 µg/mL	
Vitex rehmannii Gürke	Pipe-stem fingerleaf (English),				IC_{50} = 9.16 µg/mL	
Vitex zeyheri Sond.	Pypsteelboom (Afrikaans)				IC_{50} = 12.42 µg/mL	
Warburgia salutaris (G. Bertol.) Chiov.	See Table 1		Bark	Aqueous	IC_{50} = 20–30 µg/mL	Nundkumar and Ojewale (2002)
Ximenia americana L.	Hog plum, wild plum, false sandalwood, seaside plum, small sour plum (English), kleinsuurpruim (Afrikaans)	Olacaceae	Roots and leaves	DCM/methanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 28.2 ug/mL). Cytotocity on rat L6-cells. SI = 2.5	Bapela et al. (2014)
Ximenia caffra Sond.	Large sourplum (English), grootsuurpruim (Afrikaans),		Roots and leaves	DCM/methanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 3 and > 50 ug/mL against	Clarkkson et al. (2004);

(*continued on next page*)

Table 2 (*continued*)

Plant species	Common name	Family	Plant part used	Type of sample tested (extract)	Some evidence of further investigation	Reference
	unThunduluka-obmvu (Zulu), morokologa (Sotho)				chloroquine sensitive and resistant *P. falciparum* strains respectively)	Bapela et al. (2014)
Xylopia parviflora Vallot	Bushveld bitterwood, few red fingers (English),	Annonaceae	Roots	DCM/methanol (1:1)	*In vitro* testing on infected human red blood cells (IC_{50} = 2.2 and 14.2 ug/mL against chloroquine sensitive and resistant *P. falciparum* strains respectively)	Bapela et al. (2014)
Xysmalobium undulatum R. Br.	See Table 1		Whole plant	DCM/methanol (1:1). Also water	IC_{50} = 6 µg/mL and > 100 µg/mL for the solvent and water extracts respectively	Clarkson et al. (2004)
Zehneria scabra Sond. Subsp. *scabra*	Dawedjie (Afrikaans)	Cucurbitaceae	Whole plant	DCM/methanol (1:1)	IC_{50} = 5.6 µg/mL	Clarkson et al. (2004)
Ziziphus mucronata subsp. *mucronata*	See Table 1		Leaves	DCM	IC_{50} = 12 µg/mL	Prozesky et al. (2001); Clarkson et al. (2004)

antiplasmodial activity against chloroquine sensitive *P. falciparum* strains, only *T. elegans* passed the IC_{50} and SI requirements against the chloroquine resistant *P. falciparum* strains. Indeed, *T. elegans* was more selective against the chloroquine-resistant strain of *P. falciparum* (SI = 45.8) than the chloroquine-sensitive strain (SI = 14.1). Higher IC_{50} values were noted for *T. elegans* against the chloroquine resistant *P. falciparum* strains than against the chloroquine sensitive strains, although the IC_{50} value against the resistant strain (0.8 µg/mL) indicated potent antimalarial activity, highlighting this plant species as being a particularly useful treatment for malaria (Bapela et al., 2014).

The extraction solvent and protocol used in these studies had substantial influence on the antimalarial activity noted. Generally, the more lipophilic a solvent, the greater the antimalarial activity of the plant extract. Indeed, the greatest activities were generally seen when dichloromethane (DCM) was used as the extraction solvent (Bapela et al., 2014; Mokoka et al., 2011; Melariri et al., 2012; Nethengwe et al., 2012; Clarkson et al., 2004). *Carica papaya* was an exception to this trend, with greater antiplasmodial activity seen for an ethyl acetate extract than for the dichloromethane extract (Melariri et al., 2012).

6. Synergistic anti-*Plasmodium* spp. activity of plant combinations

Plants often contain compounds that, whilst lacking inherent therapeutic properties alone, may potentiate the effects of other medicines (Cheesman et al., 2017). Indeed, substantially lower doses of *A. annua* extracts (from which artemisinin is derived) are required to achieve the same effects as pure artemisinin alone (as reviewed by Cock, 2018). *Artemisia annua* infusions used to treat malaria in Traditional Chinese Medicine (TCM) contain approximately 20% of the artemisisin required to produce the same effects. *Artemisia annua* infusions also contain several flavonoids that are inherently inactive, yet potentiate the activity of artemisinin when used in combination (Ginsburg and Deharo, 2011). Similarly, the activity of quinine is potentiated in *Cinchona* spp. bark extracts by several alkaloid components in those extracts, even against quinine resistant *Plasmodium* spp. strains (Cock, 2018).

It is perhaps surprising that studies examining the combinational effects of plant extracts with either other plant extracts, or with conventional antimalarial drugs, are under-represented in antimalarial drug discovery research and much more work is required in this field. Combinational antimalarial drugs may not only lessen the development of malarial drug resistance, but may also provide new therapies for otherwise resistant strains.

Few studies have examined the combinational effects of South African medicinal plants against *Plasmodium* spp. parasites. Indeed, we were only able to find a single study reporting potentiation of antimalarial activity for extract combinations (Melariri et al., 2012). That study reported that several extract combinations displayed synergistic antimalarial activities compared to the effects of either extract alone. That study reported that the following combinations were synergistic: *C. limon* (L.) Osbeck with *P. guajava*; *C. papaya* Linn.with *Citrus citratus* Stapf; *C. limon* with *C. papaya*; and *C. papaya* with *P. guajava* (Melariri et al., 2012). All of these combinations were screened using equal volumes of each extract and the ideal ratios were not determined. The *C. limon* and *P. guajava* mixture was the most promising combination (IC_{50}: 3.4 and 3.8 µg/mL against chloroquine sensitive and chloroquine *P. falciparum* strains respectively; SI: 24.3 against the chloroquine sensitive strain). Furthermore, this was also the only combination tested that had strong antimalarial activity against both the chloroquine sensitive and chloroquine resistant *P. falciparum* strains. Unfortunately, the selectivity indices (SI) of other combinations were not investigated and further work is required to evaluate the potential of these combinations therapeutically. Whilst the field of synergistic combinational antimalarial therapy is still in its infancy, this malaria study does demonstrate the potential of these therapies. Substantially more research is required to not only test extract/extract combinations, but also to test extract/conventional drug combinations. Perhaps through such strategies, medical science may be able to not only discover new antimalarial medicines, but to also counteract *Plasmodium* spp. resistance mechanisms, thereby extending the effective life of the current antimalarial drug repertoire.

7. Discussion and conclusions

Malaria remains one of the most widespread and serious infectious diseases globally, with more than half of the world's population living in malaria affected areas. In many of those areas, the disease causes considerable suffering and high mortality rates. *P. falciparum* causes a particularly serious form of the disease and is responsible for the highest mortality rates of all *Plasmodium* parasites. Indeed, it is responsible for approximately 75% of the infections globally and nearly all of the malarial related deaths. *P. falciparum* is the most prevalent parasite on the African continent, accounting for the disproportionate mortality rate in Africa compared with other regions of the world. Indeed, more than 90% of all malaria associated deaths globally occur in Africa. However, malaria is not only treatable, but it can potentially be eradicated in several regions of the world. The southern Africa region and South Africa, Botswana and Swaziland in particular, have been highlighted by the WHO as countries where the eradication of malaria is not only possible, but also likely if effective eradication protocols are employed (Tanner and de Savigny, 2018; Delacollette and Rietveld, 2006). This would involve a multifaceted approach aimed at all aspects of the disease, from vector control and disease prevention, to educating the local population about the disease and providing timely treatment that is easy for the local populations to access, yet affordable enough for the entire population to use. Research is another important aspect of malaria eradication because new effective medications are constantly required as *Plasmodium* spp. parasites continually evolve to develop resistance to current treatment regimes. The current drugs generally focus on the blood phases of malaria and medicines targeting the hepatic events tend to be neglected. Further study is required in that area. Furthermore, as *P. vivax* contributes substantially to the malarial burden in southern Africa, it is recommended that further research focus on this species and not just solely on *P. falciparum*.

An effective and targeted way to develop new drugs is through a re-examination of traditionally used medicinal plants for potent, non-toxic and cost effective therapies. South Africa has one of the most diverse floras in the world. Over 30,000 South African plant species have been documented to date and therapeutic uses have been confirmed for approximately 3000 of those species (van Wyk, 2011). Furthermore, the ethnobotanical use of South African plants has been better documented for some diseases than for many other regions globally, thereby providing better targets for scientific study.

Evidence of ethnobotanical studies on southern African plants to treat malaria is surprisingly limited. The use of Zulu plants has been relatively well-documented (Nundkumar and Ojewale, 2002; Hutchings et al., 1996) and a number of promising leads were highlighted. For several of these plant species, the anti-*Plasmodium* activity has also been reported, although validation is still required for multiple other species. Perhaps surprisingly, the traditional plant use of other South African groups to treat malaria is lacking. In particular, future studies documenting the traditional use of plants to treat malaria by ethnic groups in endemic malaria areas are required. We were only able to find limited studies reviewing the use of traditional medicines by the Venda people for the treatment of malaria (Prozesky et al., 2001; Bapela et al., 2019). Similarly, ethnobotanical studies recording the traditional methods of treating malaria for the Ndebele, northern Sotho, Tsonga, Tswana, and Pedi are lacking. This is perhaps surprising as these ethnic groups inhabit the areas of South Africa in which malaria is endemic. It is therefore likely that they would have a good traditional understanding of the disease and the most effective plant species to treat it. Reference to traditional Zulu medicine has already identified several promising remedies, and it is likely that more extensive ethnobotanical studies involving other north-eastern ethnic groups may highlight other promising leads.

Furthermore, species selection for rigorous scientific study is often difficult as traditional remedies are often recorded for the treatment of a symptom, rather than for the treatment of a specific pathogen. Several ethnobotanical records list several South African plant species to treat fever and anaemia. As both fever and anaemia are symptoms of malaria, it is likely that these traditional medicines would be useful in people with malaria as they would decrease the life threatening symptoms and allow the body's immune system to combat the pathogen. However, not only are fever and anaemia symptoms of malaria, but they may also be caused by multiple other pathogens. Thus, it is often not be possible to discern whether a traditional therapeutic was used specifically to treat malaria, or if they are effective against other pathogens instead. For the purposes of our study, only remedies that were confirmed to be used specifically against malaria were included. However, it may be beneficial for future screening studies to also test plant species used to treat fever and/or anaemia.

Other challenges in studying traditional medicines for anti-malarial activity include evaluating the extraction techniques. Generally, decoctions and infusions are the most commonly preparation methods for traditional therapies. However, the use of aqueous extracts often limits the preparation to the higher polarity compounds. This is desirable for the treatment of malaria as mid-highly polarity compounds will be readily absorbed through the gut lumen and will be readily available in the bloodstream. However, other extraction systems may produce higher efficacy and should not be neglected. Relevant test models are also required for high throughput assays. Rodent test models are often used, although these test a different *Plasmodium* spp. and may not accurately reflect the susceptibility of the human Plasmodium parasite. When a drug candidate is highlighted by these assays, substantial further research is needed to test the plant preparation against the appropriate parasites. Furthermore, with some notable exceptions, most plant preparations are generally only tested against the blood phases of that Plasmodium life cycle. Some malarial drug discovery studies have tested against the hepatic and oocyte phases of the disease, but these studies are limited and further investigations are required to examine the activity of plant extracts towards these phases.

Interestingly, the antimalarial activity of most of the plant species screened generally corresponded to the lower polarity plant extracts in most studies. This is notable as decoctions and infusions are most commonly used in traditional healing systems. Water extraction is limited to the extraction of higher polar compounds and decoctions and infusions will lack lower polarity compounds. This is desirable under Lipinski's rules of 5 (Lipinski, 2004) as it would allow the therapeutic components to absorb through the gut lumen into the blood system where they are required. However, it may hinder the absorption of the bioactive components into the cell. Therefore, unless the active compounds function via cell surface receptors, polar components may not provide clinically relevant potency *in vivo*. Although chemical characterization of antimalarial compounds was not the main focus of this review, cognisance of the chemistry is important. In fact, more recently, NMR-based metabolomics have been used for in-depth studies into the phytochemistry of the compounds within in medicinal plants responsible for antimalarial activity (Bapela et al., 2019). Such studies hold promise for future structure elucidation studies.

Most studies screened the plant extracts in *in vitro* cell model assays. This also may not provide an accurate representation of the antimalarial properties of the extracts as the absorption of nonpolar bioactive components through the gut lumen would limit the bioavailability of the active compounds. In the cultured cell assays, the extract components are able to interact directly with the cells, without initially having to be absorbed from the gut. Therefore, the potency seen for these extracts may not accurately represent the efficacy *in vivo*. Further testing is required to confirm the antimalarial potential of the extracts by testing in animal models. However, this is also not ideal as different (non-human infective) *Plasmodium* spp. would be required for those assays, and different *Plasmodium* spp. may have different susceptibilities.

Another interesting feature highlighted in the previous screening studies is the correlation between the plant part tested and the antimalarial potency of the extract. Bark and root extracts generally had substantially greater potency than extracts produced using other plant parts. This may have implications on drug production should a plant species be chosen for the large scale production of malaria medicines as large scale wild-harvesting of bark is not sustainable. Therefore, if the activity is similar in leaf extracts, then these would be preferred as they are more rapidly renewed and the harvesting of leaves often does not unduly stress the plant. However, if there is a requirement for the bark, cultivation should be encouraged and wild harvest should be avoided.

Some of the plant species that are typically used for Malaria are well-known to be toxic. For example *S. volkensii* and *T. peruviana* are highly poisonous. For this reason it is imperative that toxicity studies be run in parallel with anti-*Plasmodium* spp. screening studies to provide an indication of the selectivity index. Even if a plant extract displays potent antimalarial activity, its therapeutic potential may be limited if it is also toxic to the host. Whilst toxicological evaluations have been reported for many of the antimalarial South African plants in other studies reporting different therapeutic properties, variability in extract compositions and efficacies between studies makes it difficult to link toxicology and activity results between studies. Uniformity is also required in defining toxicity between studies, and in the method of evaluation used.

In conclusion, despite the lack of ethnobotanical records for many southern African ethnic groups for the treatment of malaria, many species have already been tested. Over 180 of those species have been documented in antiplasmodial studies (Table 2). However, for many plant species (*A. xanthophloea, A. inflate, A. littoralis A. zambesiaca, A. venosum, C. spinose, C. ternatum, C. sinensis, C. megalobotrys G. cuneate, G. pentaphylla, K. nana, L. purpureus, L. edulis, L. brasiliensis, L. concinnum, L. interrupta, M. sericea, O. dregeanum, S. mucronata S. capense, S. indicum, S. hispidus, S. volkensii* and *U. scheffleri*) which have been documented as an antimalarial, no further evaluation of their efficacy could be found. Further research is needed to highlight and develop effective new medications which may find roles in larger malaria eradication programs.

Contribution of authors

I.E. Cock- Co-wrote the manuscript; M.I. Selesho-Initial drafting of manuscript; S.F. van Vuuren-designed the study and co-wrote the manuscript.

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Appendix A. Supplementary data

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