Medicinal plants used for the treatment and management of malaria in Zimbabwe - review and perspectives.

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Research

Abstract

Background: Malaria is a global health problem that has been bedeviling many countries for millennia. Estimates suggest that over 90% of all malaria infections and deaths occur in Africa, with a 75% mortality in children. The world is struggling to effectively respond to this malaria crisis in part due to the growing Plasmodium falciparum drug resistance. Traditional medicinal plants have been used as alternative and complementary medicine, due to their ease of accessibility and low cost.

Methods: Extensive literature search focused on published abstracts and papers accessed from online databases, scientific reports, book chapters, textbooks and theses available in repositories at Zimbabwe Universities.

Results: In total, 70 species of plants belonging to 35 families have been used to treat and manage malaria in Zimbabwe. The family with the highest number of medicinal plants used in Zimbabwe was the Fabaceae family, represented by a total of 10 species. The dominant plant parts used in the preparation of remedies were roots (43%). About 75.7% of the antimalarial plants reported have been scientifically validated and documented to exhibit anti-plasmodial activity. In-vitro anti-plasmodial activity reports of 22 of the plants extracts exhibiting high anti-plasmodial activity towards P. falciparum.

Conclusions: While this review concentrates on the identification of antimalarial plants documented in previous studies in Zimbabwe including their pharmacological and toxicological profiles. More definitive research into the mechanisms of action, as well as pharmacodynamic and pharmacokinetic profiles, could significantly contribute to the standardisation of herbal preparations.

Keywords: Herbal medicine Ethnobotanical, ethnomedicine, pharmacological, toxicology, traditional plants, malaria, Zimbabwe, *Plasmodium falciparum*

Background

Malaria is a life-threatening disease caused by a parasite that is transmitted through the bites of infected mosquitoes. According to the World Health Organization (WHO), there were 249 million cases of malaria worldwide in 2022, with an estimated 619 000 deaths (WHO 2023). Despite efforts to control and eliminate malaria, the burden of the disease remains disproportionately high in Africa. As of 2021, Africa accounted for approximately 95% of all reported malaria cases and 96% of malaria-related deaths worldwide. Children under the age of five are the most vulnerable group affected by malaria, accounting for 80% of all malaria deaths worldwide (WHO 2023). Malaria is a major public health problem in Zimbabwe, with more than 5 million people at risk of contracting malaria annually in Zimbabwe (WHO 2023). Malaria is also reported to account for nearly 40% of outpatient attendances with recordings of 144 508 positive malaria patients from January to August 2023 (Mugarisi 2023). Malaria transmission is seasonal, the peak season spans from January to May and the disease is most prevalent in the country's rural areas (Mabaso *et al.* 2006, Mundagowa *et al.* 2020, Gavi *et al.* 2021).

It has been reported that the incidence of malaria is high in 33 of the 59 rural districts in Zimbabwe and that close to 50% of the country's population is at risk of contracting malaria (Midzi *et al.* 2004, Ministry of Health and Child Welfare 2008, WHO 2013). It is no secret that nature, particularly plants have historically provided a large portion of the human medicinal arsenal and their use can be traced back to ancient African, Chinese and Indian traditional knowledge systems. In China, the use of the herb *Artemisia annua* L. for the treatment of fevers was recorded in a medical text dating back to the fourth century (Tu 2011). Cinchona species (*Cinchona officinalis* L.) contain quinine, which is still used today in modern medicine for the treatment of malaria. In Africa, traditional healers have long used a variety of plant-based remedies to treat malaria. Given the challenges of accessing conventional malaria treatment in some areas of Zimbabwe, many people rely on traditional herbal remedies to manage the disease.

A number of studies have documented the use of medicinal plants in the treatment of malaria in Zimbabwe (Munodawafa *et al.* 2017, Mabona *et al.* 2013; Gweru *et al*. 2015, Chikwambi & Musvuugwa 2017). These studies have identified a range of plants that are used for this purpose, notably *Artemisia afra* Jacq. ex Willd. and *Cassia abbreviata* Oliv. *Plasmodium falciparum* in particular deserves increased focus amongst other malaria-causing *Plasmodium* species because of its excessively large malarial burden. The parasite is responsible for more than 95% of total malarial cases (WHO 2019). To effectively control *P. falciparum*, new anti-malarial drugs have to be discovered. There is concern that the world is struggling to effectively respond to this malaria crisis in part due to the growing drug resistance of the *P. falciparum*, which is the most lethal, of the four species of *Plasmodium* that cause malaria in humans (Bagavan *et al.* 2011, Ngarivhume *et al.* 2015, Mangoyi *et al.* 2014).

Maqbool *et al.* (2019) maintain that medicinal plants and herbs have increasingly gained momentum as a potential source for the development of the next generation of antimicrobial drugs, given their reported potency and efficacy, and the fact that close to 80% of the existing drugs used in Western countries are plant-derived. Moreover, identification of novel drug leads in modern drug development has come from traditional medicine. Despite the significant potential of plant-based remedies in advancing modern medical treatments, research in this area is still behind (Miller 2011). The reason for this may be partially attributed to the slow and expensive nature of conventional plant drug discovery methodologies. The integration of bioinformatics in drug design and discovery from medicinal plants can lead to more efficient and effective development of new drugs. Through the application of computational methods, bioinformatics can aid in the identification of potential drug targets, the prediction of drug efficacy and toxicity, and the optimization of drug structures.

Medicinal plants have been used for anti-malarial purposes in Zimbabwe and Africa at large for generations (Lukwa 1994, Ngarivhume *et al.* 2015), and this paper focuses on a review of plants that are used for such purposes in Zimbabwe. The idea is to identify common medicinal plants that are used to prevent and treat malaria in Zimbabwe, with the ultimate aim being to identify candidate species for further research. The paper offers a review of the literature regarding the various plants that are being used in Zimbabwe for anti-malaria purposes, and how these can be tested, and possibly developed into commercial herbal products that can be effective in the fight against malaria.

Materials and Methods

Protocol Development

Our protocol was drafted using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR) (Page *et al.* 2020) and reviewed by two members of the research team (see Figure 1). Ethics approval was not required for this scoping review.

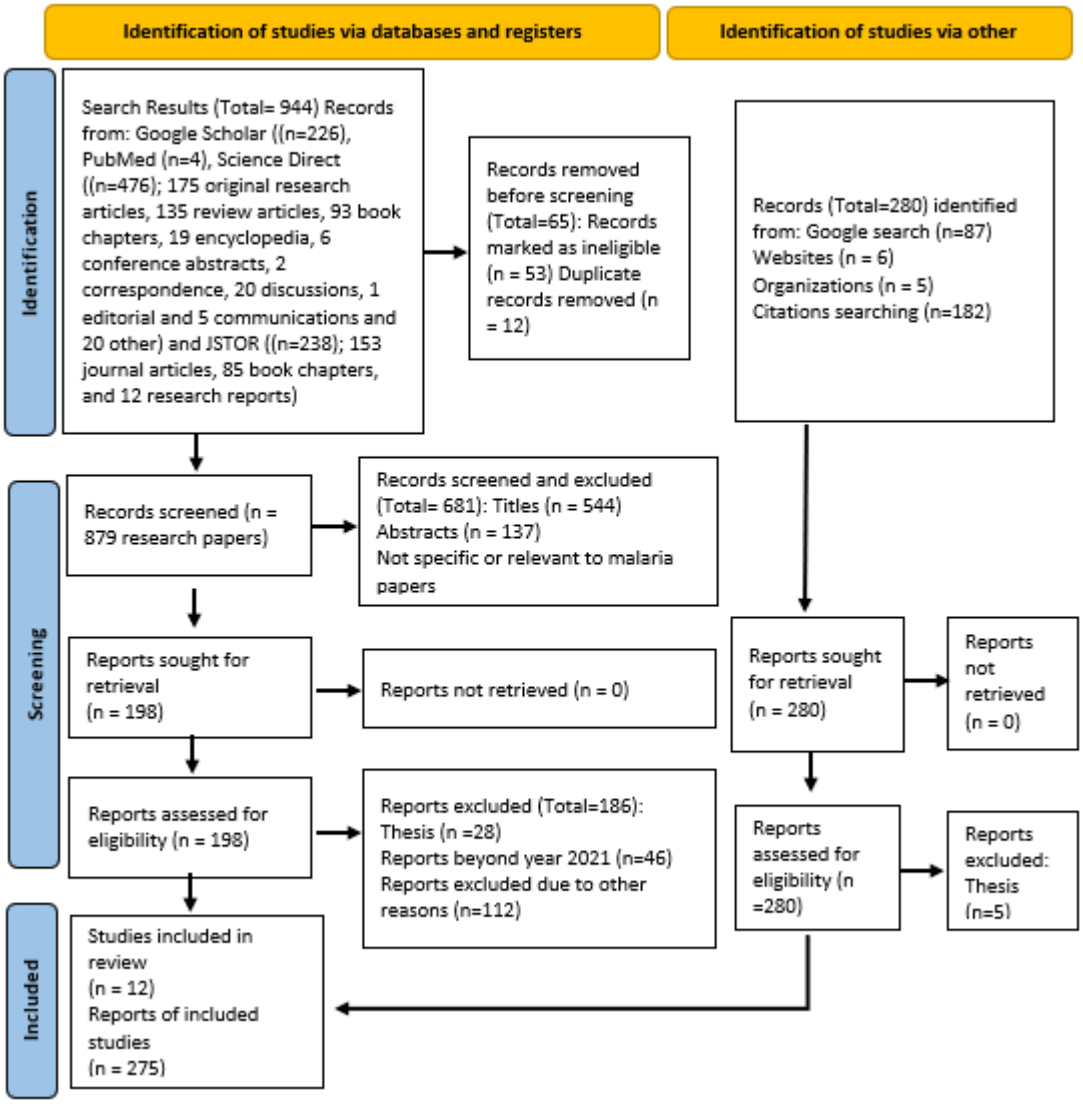

Figure 1. PRISMA Flow Diagram (adopted from Page *et al*. 2020)

Eligibility Criteria

To be included in this scoping review, papers needed to have been: published between 1900 and 2020, involve malarial research.

Information Sources

Searches were performed in databases relevant to the research question, that include Science Direct, PubMed, JSTOR and Google Scholar. The Literature Cited lists or bibliographies of included studies were searched, and for unpublished data or grey literature Google, websites and organisations such as university libraries were used. Two co-authors then screened titles and abstracts.

Search Strategy

The following search terms were used: “medicinal plants malaria Zimbabwe”. Appropriate controlled vocabulary and free text terms were used to refine searches in the online databases.

Results and Discussion

Several scientific papers were reviewed based on ethno-botanical surveys of different areas of Zimbabwe and are presented in the following sections.

Literature search of antimalarial medicinal plants traditionally used in Zimbabwe

Our searches returned over 944 manuscripts. We removed duplicates and ineligible studies using Zotero software. Two authors then screened 879 remaining reports for eligibility. Most of the screened titles (n= 544) and abstracts (n= 137) were excluded for not being specific or relevant to malaria. Of the 198 reports that were sought for retrieval, 186 were found to be ineligible for being either dissertations (n= 28) or being published beyond the year 2021 (n= 46). However, majority of excluded studies had no full text freely available, or were from elsewhere in the world, other than Zimbabwe or Southern Africa. Of the 12 studies included, three are reviews, four are botanical survey reports, two are experimental studies and three are scientific reports. The total number of relevant papers was low by international standards, which made the authors to consider grey literature from organisations, websites, Google search and retrieve Literature Cited citations (Total= 280 reports) for data on pharmacology and toxicity of medicinal plants used in Zimbabwe for management of malaria. Following exclusion of theses when the reports were assessed for eligibility, 275 studies were included in the review. The few publications that reported on medicinal plants used as antimalarials in Zimbabwe demonstrate a huge research gap that need to be filled for generation of indigenous knowledge and scientific validation.

Ethnobotanical surveys and distribution of antimalarial medicinal plants traditionally used in Zimbabwe

The current review indicates that there are at least 70 plant species, belonging to 58 genera in 35 families used to treat respiratory diseases in Zimbabwe (Table 1). While numbers documented in this review are large, are lower than those reported in Ethiopia with 71 families and 200 different plant species (Alebie *et al.* 2017). A review by Cock et al. (2019) of antimalarial plants used in South Africa, reported a total of 80 plant species. Of the plants reported in this review, a total of 17 (24.3%) were also cited by Cock *et al.* (2019). These plants include: *Adansonia digitata* L,, *Adenia gummifera* (Harv.) Harms, A. afra, *Cassia abbreviata* Oliv., *Cissampelos mucronata* A.Rich., *Cussonia spicata* Thunb., *Diplorhynchus condylocarpon* (Müll.Arg.) Pichon, *Gymnosporia senegalensis* (Lam.) Loes, Harungana madagascariensis Lam. ex Poir., Hilliardiella aristata (DC.) H.Rob., *Lippia javanica* (Burm.f.) Spreng., *Plumbago zeylanica* L., *Pterocarpus angolensis* DC., *Sclerocarya birrea* (A.Rich.) Hochst., *Senna occidentalis* (L.) Link, *Senna siamea* (Lam.) H.S.Irwin & Barney, *Vangueria infausta* Burch. and *Warburgia salutaris* (G.Bertol.) Ch.

Table 1. Plant species reportedly used for anti-malaria purposes in Zimbabwe as reported in the literature

Family	Botanical name of Plant	Indigenous name of plant and other names	Part of plant used	Preparation	Literature Cited
Anacardiaceae	*Lannea discolor* (Sond.) Engl.	**Chizhenje (S), live-long (E), mugan'acha (S), muhumbukumbu (S) Tree grape (E)**	Leaf, bark, and root	Leaf, bark, and root infusion taken orally	Maroyi 2018b
Anacardiaceae	*Sclerocarya birrea* (A.Rich.) Hochst. subsp. *caffra* (Sond.) Kokwaro	**Marula (E), mufuna (S), mupfura (S), mganu (N)**	Bark	no information	Lukwa *et al*. 2001, Viol, 2009
Apocynaceae	*Catharanthus roseus* (L.) G.Don	**Muruwa (S), madagascar periwinkle (E), rosy periwinkle (E)**	Roots	Decoction	Ngarivhume *et al*. 2015
Apocynaceae	*Diplorhynchus condylocarpon* (Müll.Arg.) Pichon	**Mutowa (S) horn-pod tree (E), inkamamasane, (N), wild rubber (E)**	Stem Bark	Infusion	Lukwa *et al.* 2001, Ngarivhumse *et al.* 2015
Apocynaceae	*Holarrhena pubescens* Wall.ex G.Don	**Masunugure (Shona) chigafusi (S), fever-pod (E), jasmine-tree (E), mugashu (S), muhatsu (S)**	Root	Decoction	Ngarivhume *et al.* 2015

Apocynaceae	*Tabernaemontana elegans* Stapf	**Muchenya (S) muchanga (S), toad-tree (E),**	Roots	Hot Infusion	Ngarivhume *et al.* 2015
Araliaceae	*Cussonia spicata* Thunb.	**Cabbage tree (E), Mufenje (S)**	Bark, flowers, fruits, roots, and stems	no information	Kraft *et al.* 2003, Maroyi 2019a
Aristolochiaceae	*Aristolochia albida* Duch.	**Ruzangariro (S), zagariro (S), scrambling dutchman's pipe (E)**	Tuber	Hot Infusion	Gelfand *et al.* 1985, Ngarivhume *et al*. 2015)
Aristolochiaceae	*Aristolochia heppii* Merxm.	**Chividze (S)**	Root	Hot Infusion	Ngarivhume *et al.* 2015
Asparagaceae	*Asparagus africanus* Lam.	**Bush asparagus (E)**	Root and leaves	no information	Matowa *et al.* 2020
Asphodelaceae	*Aloe chabaudii* Schönland var. *chabaudii*	**Dwala aloe (E)**	no information	no information	Lukwa *et al*. 2001
Asphodelaceae	*Aloe excelsa* A. Berger var. *excelsa*	**Chigiakia (H), chikohwa (S), chinungu (S), chinyangami (T) imangani (N), inhlaba (N), munhanganhuru (S), ruhwati (S),**	no information	no information	Lukwa *et al.* 2001
Asphodelaceae	*Aloe greatheadii* Schönland var. *greatheadii*	**Greathead's spotted leaf aloe (E)**	no information	no information	Lukwa *et al*. 2001
Asteraceae	*Artemisia afra* Jacq. ex Willd.	**African Wormwood (E)**	Leaves	no information	Kraft *et al*. 2003
Asteraceae	*Baccharoides adoensis* (Sch. Bip.ex Walp.) H.Rob.	**Chipenembe, musikavakadzi (S),**	Leaves	Hot Infusion	Ngarivhume *et al*., 2015
Asteraceae	*Brachylaena huillensis* O.Hoffm.	**Muphahla (N), silver Oak (E)**	Root	Hot Infusion	Ngarivhume *et al*. 2015, Maroyi 2020
Asteraceae	*Dicoma anomala* Sond.	**fever bush, stomach bush (E)**	Root	Root infusion taken orally	Marekerah, 2014, Maroyi 2018a, Chota *et al*. 2020
Asteraceae	*Erythrocephalum longifolium* Benth. ex Oliv.	**muhloni (N) red rays (E)**	Root	Cold Infusion	Ngarivhume *et al.* 2015
Asteraceae	*Hilliardiella aristata* (DC.) H.Rob.	**Chiwanika (S)**	Leaves and root	no information	Kraft *et al.* 2003
Asteraceae	*Tithonia diversifolia* (Hemsl.) A.Gray	**Mexican sunflower (E)**	no information	no information	Chinsembu 2015
Asteraceae	*Vernonia colorata* (Willd.) Drake	**Lowveld tree vernonia (E), musikavakadzi (S), Star-flowered bitter-tea (E)**	Leaves and root	no information	Kraft *et al.* 2003
Canellaceae	*Warburgia salutaris* (G.Bertol.) Chiov.	**Muranga (S), pepper-bark tree (E)**	Bark Root	Powdered bark used as infusion or decoction	Maroyi 2008, 2014, Ngarivhume *et al.* 2015
Caricaceae	*Carica papaya* L.	**Mupopo (S),**	Root	Decoction	Lukwa *et al*. 2001,

		melon-tree (E), papaya (E), pawpaw (E)			Ngarivhume *et al.* 2015
Celastraceae	*Gymnosporia senegalensis* (Lam.) Loes.	**Chivhunabadza musosawafa (S), isihlangu (N), ibalalatune (T)**	Twigs Root Leaves	no information	Viol 2009
Chrysobalanaceae	*Parinari curatellifolia* Planch ex. Benth.	**Hissing tree (E), mobola plum (E), mubuni (S), muchakata (S), muhacha (S) muisha, (S), umkhuna (N)**	Bark	no information	Kraft *et al.* 2003
Clusiaceae	*Garcinia buchananii* Baker	**Granite garcinia (E), granite mangosteen (E), mutunduru (S)**	no information	no information	Lukwa *et al.* 2001
Combretaceae	*Combretum elaeagnoides* Klotzsch	**Large-fruited jesse-bush combretum (E), oleaster bushwillow (E)**	no information	no information	Magwenzi *et al.* 2014
Combretaceae	*Terminalia sericea* Burch. ex DC.	**Mangwe (S), silver cluster-leaf (E), silver terminalia (E), umangwe (N)**	no information	no information	Lukwa *et al.* 2001
Cucurbitaceae	*M. foetida* Schumach.	**Muchukubaba (S)**	Leaf	Relish	Ngarivhume *et al.* 2015
Cucurbitaceae	*Momordica balsamina* L.	**Ngaka (S), balsam Apple (E), balsam pear (E)**	Leaf	Relish	Ngarivhume *et al.* 2015
Ebenaceae	*Euclea divinorum* Hiern	**Diamond-leaved euclea (E), magic guarri (E), mubhununu (S), mudziviriratsuro (S), mugarazvuru (S), mugurameno (S), munyenya (S), mushangura (S), umtshekesane (N)**	no information	no information	Lukwa *et al.* 2001
Ebenaceae	*Euclea natalensis* A.DC. subsp. *acutifolia* F.White	**Mushangura (S), chipambati (S), large-leaved guarri, (E), murunze (S), mushangura (S), natal guarri (E), nyakabvuri (S)**	Leaves, sap and root	Charred and powdered root taken in porridge, leaf sap applied topically or leaf, root decoction taken orally.	Ngarivhume et al. 2015, Maroyi, 2017d
Euphorbiaceae	*Croton gratissimus* Burch. var. sub*gratissimus* (Prain) Burtt Davy	**Gunukira (S), lavender fever berry (E), mufandemengwe (S), mufarata (S)**	no information	no information	Mangoyi *et al*. 2014
Euphorbiaceae	*Croton megalobotrys* Müll.Arg.	**Fever-berry (E), umtshape (N), mubvukuta (S), mushape (S), mutonga (T)**	Bark, root, seed	Decoction	Maroyi 2017a

Fabaceae	*Aganope stuhlmannii* (Taub.) Adema	**Muchemavanhu (S) mudzugu (S), mumwambizi (S), umthundulu (N), wing pod (E)**	Bark	Stamped bark is soaked and the strained liquid taken by mouth as required.	Chinemana *et al.* 1985
Fabaceae	*Albizia amara* (Roxb.) *Boivin* subsp. *sericocephala* (Benth.) Brenan	**Bitter albizia (E), muchangiza (S), muora (S), umbola (N)**	Fruits	no information	Kazembe *et al*. 2012
Fabaceae	*Amblygonocarpus andongensis* (Welw. ex Oliv.) Exell & Torre	**no information**	no information	no information	Lukwa *et al*. 2001
Fabaceae	*Cassia abbreviata* Oliv.	**Isihaqa (N), long-tail cassia (E), muremberembe murumanyama (S), muvheneka (S)**	Root Bark	Cold or Hot Infusion	Shumba *et al.* 2009, Ngarivhume *et al*. 2015
Fabaceae	*Colophospermum mopane* (J.Kirk ex Benth.) J.Léonard	**Iphane (N), mopane (E), mupane (S), musharu (S), turpentine tree (E)**	no information	no information	Lukwa *et al.* 2001
Fabaceae	*Dalbergia nitidula* Welw. ex Baker	**Glossy flat-bean (E), mudima (S), murima (S), purple-wood dalbergia (E)**	Bark and roots.	no information	Kazembe *et al.* 2012
Fabaceae	*Entada goetzei* (Harms) S.A.O'Donnell & G.P.Lewis	**Chiurayi (S), intolwane (N), mugudzuru (S), narrow-pod elephant root (E),**	Root	Hot Infusion	*Ngarivhume et al. 2015*
Fabaceae	*Pterocarpus angolensis* DC.	**Bloodwood (E), mubvamakovo (S), mubvamaropa (S), mukonambiti (S), mukula (T), mukurambira (S), mukwa (E), mushambaropa (S), muzwamulowa (T), umvagazi (N)**	no information	no information	Lukwa *et al*. 2001
Fabaceae	*S. septemtrionalis* (Viv.) H.S.Irwin & Barnaby	**Mumwahuku (S), smooth senna (E)**	Root	Decoction	Ngarivhume *et al*. 2015
Fabaceae	*S. siamea* (Lam.) H.S. Irwin & Barneby	**Kassod tree (E), siamese cassia (E)**	no information	no information	Chinsembu, 2015
Fabaceae	*Senna occidentalis* (L.) Link	**Coffee senna (E)**	no information	no information	Chinsembu 2015
Hypericaceae	*Harungana madagascariensis* Lam. ex Poir.	**Mukaranga (S), mutseti (S) mutsotso, (S) orange-milk tree (E), praying-hands (E)**		no information	Lukwa *et al*. 2001

Lamiaceae	*Ocimum americanum* L.	**Hoary basil (E), American basil (E)**	Leaves	Cold Infusion	Lukwa 1994
Lamiaceae	*Ocimum angustifolium* Benth.	**Mufuranhema (S)**	Tuber	Cold Infusion	Ngarivhume *et al.* 2015
Loganiaceae	*Strychnos potatorum* L.f.	**Mudyambira (Shona) black bitterberry (E), grape strychnos (E), mudanhapfunye (S), umlombelombe (N)**	Root	Decoction	Ngarivhume *et al.* 2015
Malvaceae	*Adansonia digitata* L	**Baobab (E), mbuyu (S), muuyu (S), umkhomo (N)**	Bark	Ground into powder and taken in porridge.	Kazembe *et al.* 2012
Meliaceae	*Azadirachta indica* A.Juss.	**Neem tree (E), nim tree (E)**	no information	no information	Chinsembu 2015
Menispermaceae	*Cissampelos mucronata* A.Rich.	**Chipombafodya (S), hairy heartleaf (E), nyakuta (S), ruzambu (S)**	Tuber	Hot Infusion	Ngarivhume *et al.* 2015
Passifloraceae	*Adenia gummifera* (Harv.) Harms	**Muore deveramvumi (S), dovoza (S), monkey rope (E), muboori (S), muhore (S), snake climber (E)**	Leaves and root	Cold or Hot Infusion	Kraft *et al*. 2003, Ngarivhume *et al*. 2015
Peraceae	*Clutia hirsuta* (Sond.) Müll.Arg.	**no information**	Leaves	no information	Kraft *et al.* 2003
Phyllanthaceae	*Flueggea virosa* (Roxb. ex Baill.) Royle	**Changa-ome (H), muchagauwe (S), mudyambuzi (S), mugurumhanda (S), snowberry tree (E), umhagawuwe (N), umklankomo (N),**	Leaves, roots, stem bark	no information	Kraft *et al.* 2003
Plumbaginaceae	*Plumbago zeylanica* L.	**Mhisepise (S), wild white plumbago (E)**	Root	Cold Infusion	Ngarivhume *et al.* 2015
Poaceae	*Zea mays* L.	**Maize (E)**	no information	no information	Lukwa *et al.* 2001
Rosaceae	*Prunus persica* (L.) Batsch	**Mupirikisi (S), peach (E)**	Leaves Root	Hot Infusion	Ngarivhume *et al.* 2015
Rubiaceae	*Crossopteryx febrifuga* (Afzel. ex G.Don) Benth.	**Crystal-bark (E), mubakatirwa (S), mugoko (S), umphokophokwana (N)**	Stem Bark	Cold Infusion or taken in porridge	Ngarivhume *et al*. 2015
Rubiaceae	*Hymenodictyon floribundum* (Hochst. & Steud.) B.L. Rob.	**Chiwirowiro (S), fire bush (E), murovabani (S), muwirowiro (S)**	Root	no information	Kraft *et al.* 2003
Rubiaceae	*Pavetta schumanniana* F.Hoffm. ex K.Schum.	**Chifukawi (S), chinama (S), chipindura chiduku (S), chitunguru (S), chityorabadza (S), mufuramhembwe (S),**	Root	Cold Infusion	Ngarivhume *et al.* 2015

		murambagaka (S), murunganyama (S), musauti (S), muwana (S), mwenje (S), nyapuna (S), nyaputa (S), poison bride's-bush (E), poison pavetta (E), umbodzani (N)			
Rubiaceae	*Vangueria infausta* Burch. subsp. *infausta*	**Mudzvirungombe (S), mutsviru (S), velvet wild medlar (E) umthofu (N), umviyo (N)**	Leaves and root	Leaf, root decoction taken orally	Maroyi 2018c
Rutaceae	*Vepris bachmannii* (Engl.) Mziray	**Munyabangwa (S), twin-Berry tree (E)**	Root	no information	Mullin 2006, Ngarivhume *et al.* 2015
Rutaceae	*Zanthoxylum asiaticum* (L.) Appelhans, Groppo & J.Wen	**Chikafusi (S), gato (S), mubhatakhamba (N), Rukato (S).**	Root	Decoction	Ngarivhume *et al.* 2015
Salicaceae	*Flacourtia indica* (Burm.f.) Merr.	**Batoka plum (E), governor's plum (E), mududwe (S), munhunguru (S), mutombototo (S) mutudza (S), mutunguru (S)**	Root and leaves	no information	Marekerah 2015
Sapindaceae	*Zanha africana* (Radlk.) Exell	**Muchenya (S), velvet-fruit zanha (E)**	no information	no information	Lukwa *et al.* 2001
Solanaceae	*Capsicum annuum* L.	**Mhiripiri (S), green pepper (E)**	Fruit	Fruits swallowed	Ngarivhume *et al*. 2015
Solanaceae	*S. incanum* L.	**African eggplant, bush tomato, poison berry, indian nightshade (E)**	no information	no information	Lukwa *et al.* 2001
Solanaceae	*Solanum campylacanthum* Hochst. ex A.Rich.	**Munhomboro, munhundurwa (S), poison apple (E), umdulukwa, intume (N)**	no information	no information	Lukwa *et al.* 2001
Verbenaceae	*Lippia javanica* (Burm.f.) Spreng.	**Zumbani (S), fever tea (E), kachigwere (S), lemon bush (E), musumba (S), umsuzwane (N), zumbani (S)**	Leaves	Cold Infusion	Lukwa 1994, Bhebhe *et al.* 2015

Legend: E=English, H=Hlengwe, N=Ndebele, S=Shona, T=Tonga

Some of the species in this review are not unique to Zimbabwe or to our review and have been cited in other reviews from other countries. Alebie *et al.* (2017) reviewed antimalarial plants and frequently cited species; *C. papaya* (20), *A. indica* (5), *A. afra* (4) and *Aloe sp.* (5), (*A. chabaudii, A. excelsa, A. greatheadii* current review), which were also cited in this review. Findings found similar plant families and genus which are not only unique to Zimbabwe from Alebie *et al.* (2017) citing *C. macrostachyus* reported to be cited 16 times, this review also cited similar plant species (*Croton gratissmus, C. megalobotrys*) and *V. amygdalina* reported to be cited 18 times, this review cited similar plant species (*B. adoensis, V. colorata, V. natalensis*). This therefore validates the genus ethnomeicinal use as antimalarial medicinal plants as they have been reported and cited numerous times in their use to treat and manage malaria.

The most well-known plant family with ethnopharmacological relevance and significance in Zimbabwe is the Fabeceae family. At least 665 Fabaceae plant species have been reportedly found in Zimbabwe, with an estimated 101 of these species are utilized as ethnomedicines (Maroyi 2023). According to Figure 2 the family with the highest number of medicinal plants in Zimbabwe was the Fabaceae family represented by a total of 10 plants. Previous reviews by (Nyagumbo *et al*. 2022, 2023) have subsequently concurred with the high frequent use of the Fabaceae family in treating and managing several illnesses. The plant family justifies its prevalent ethnomedicinal use across the country. Other families included the Asteraceae (n=8), Apocynaceae (n=4), Asphodelaceae (n=3), Solanaceae (n=3), Rubiaceae (n=3), Rutaceae (n=3), Anacardiaceae (n=2), Aristolochiaceae (n=2), Clusiaceae (n=2), Combretaceae (n=2), Cucurbitaceae (n=2), Ebenaceae (n=2), Euphorbiaceae (n=2) and Lamiaceae (n=2). A further 20 more plant families which only had one plant represented were also recorded, giving a total of 36 families. These included Araliaceae, Asparagaceae, Canellaceae, Caricaceae, Celastraceae, Chrysobalanaceae, Leguminosae, Loganiaceae, Malvaceae, Meliaceae, Menispermaceae, Passifloraceae, Peraceae, Phyllanthaceae, Plumbaginaceae, Poaceae, Rosaceae, Salicaceae and Verbenaceae.

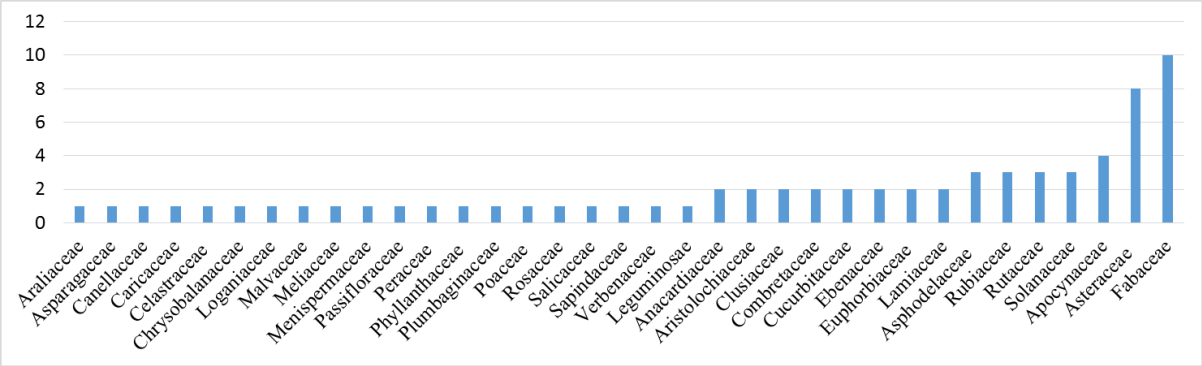

Figure 2. Families of antimalarial plants used in Zimbabwe.

According to Figure 3, (Cock *et al.* 2019) reported similar frequencies of plant families with this review, these include: Araliaceae, Caesalpiniaceae, Celastraceae, Combretaceae, Cucurbitaceae, Euphorbiaceae, Loganiaceae, Menispermaceae, Passifloraceae, Plumbaginaceae, Poaceae, Salicaceae. A total of 24 of the plant families were similar to a review by Cock *et al.* 2019 (Figure 3).

Parts used of antimalarial medicinal plants traditionally used in Zimbabwe

The use of the various plant parts was as follows: roots (43%), leaves (24%), bark (16%), stem (4%), tuber (4%), fruits (4%), flowers (2%), twigs (1%), seed (1%) and sap (1%) (Figure 4). The predominantly used plant parts are mainly the roots with frequent use of the leaves and bark as primary sources on medicine. Combined reviews by (Nyagumbo *et al.* 2022, 2023, Maroyi 2023) have highlighted the significant use of roots as a primary source of ethnomedicine in Zimbabwe. The high use of roots endangers the life of antimalarial plants, as opposed to use of leaves, which often regrow under ideal conditions to maintain the existence of the medicinal plant. Conservation policies, availability, accessibility, indigenous knowledge systems and local people's ethnic beliefs are some factors that may influence the selection of plant plants as antimalarials. Other preferred sources include flowers, fruits and seeds however these are seasonal and some are also consumed as food.

Pharmacological evaluation of antimalarial medicinal plants used by local people in Zimbabwe

According to our search, pharmacological evaluation studies were conducted on 65 (92.9%) medicinal plants among all the listed medicinal plants most of the plants were reported to exhibit anti-plasmodial activity (Table 2). According to Table 2, 53 (81.5%) of the medicinal plants were validated by research to exhibit anti-plasmodial activity similar to chloroquine and hydroxychloroquine. They were also reported to possess anti- inflammatory (Müller-Calleja *et al.* 2017, Kanvinde *et al.* 2018), antitumor (Bedoya 1970, Pascolo 2016, Levy *et al.* 2017) and antiviral (Al-Bari, 2017, Plantone *et al.* 2018, D'Alessandro *et al.* 2020) properties. Artemisinin is an antimalarial drug derived from *Artemisia annua* L. (Woodrow *et al.* 2005, Ho *et al.* 2014) that has been reported to possess antiviral (Efferth *et al*. 2008, Milbradt *et al.* 2009), anti-parasitic (De Clercq *et al.* 2002, Mishina *et al.* 2007), antifungal (Galal *et al.* 2005, Gautam *et al*. 2011), anti-inflammatory Wang *et al.* 2006, 2008), anti-allergic (Cheng *et al.* 2011, 2013), anti-angiogenic (He *et al.* 2011) and anticancer (Gong *et al.* 2013, Sertel *et al.* 2013) activities.

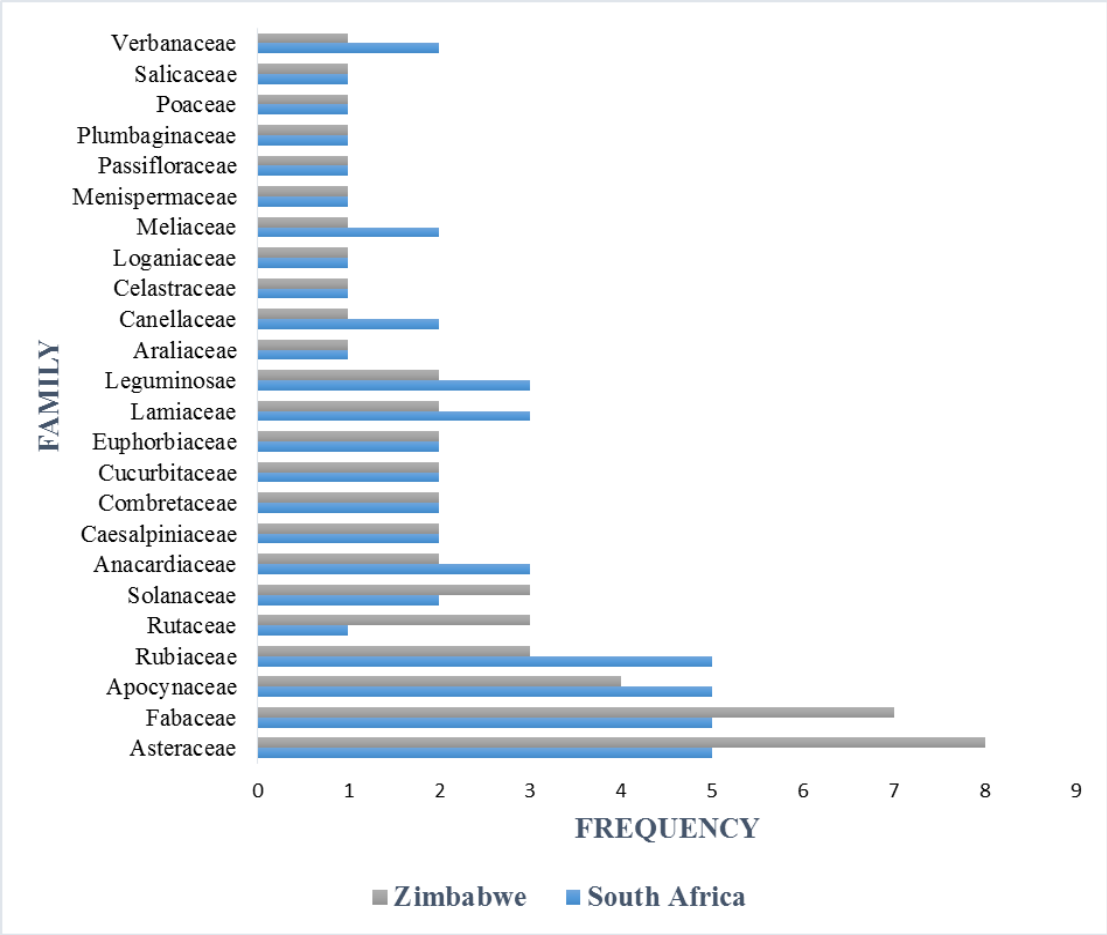

Figure 3. Relationship between Zimbabwe and South Africa antimalarial plant families.

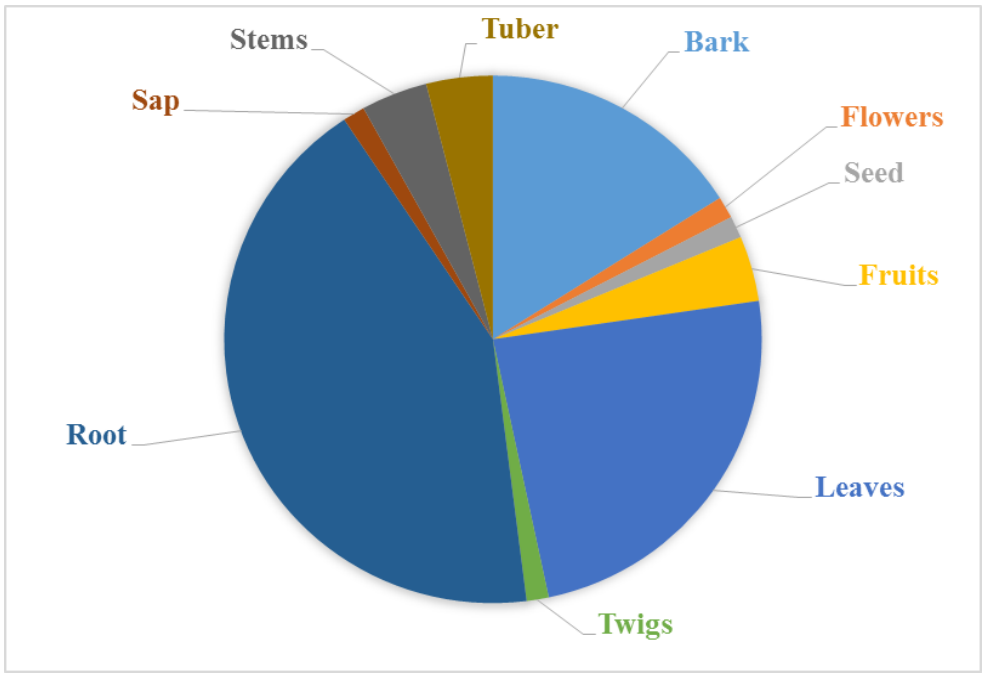

Figure 4. Plant parts used as medicine in Zimbabwe.

Table 2. with scientifically validated antimalarial medicinal plants' pharmacological properties and toxicological evaluation from several studies. Plants with in-vitro anti-plasmodial activity on Chloroquine sensitive and Chloroquine resistant *Plasmodium falciparum* 3D7 and W2.

Botanic name of Plant	**Pharmacology and Toxicological assessment**	**Tested plant extract**	***In vitro* anti-plasmodial activity IC_{50} (µg/ml) CS**	***In vitro* anti-plasmodial activity IC_{50} (µg/ml) RS**	**Literature Cited**
A. digitata	Hypoglycemic, anti-dysenteric, anti-plasmodial antipyretic or febrifuge, immunostimulant, antiviral, antimicrobial, antitumor, antibacterial, anti-oxidant, hepatoprotective, cardio-protective, diaphoretic, anti-trypanosome and anti-inflammatory activities. Safe LC50 >1000 mg/ml LD50 >2000 mg/kg; LD50 >5000 mg/kg	Fruit pulp- no information	> 50	> 50	Kraft *et al.* 2003, De Caluwé, Halamová & Van Damme 2010, Kazembe *et al*. 2012, Musila *et al.* 2013, Rahul *et al.* 2015, Sundarambal, Muthusamy & Radha 2015, Muhammad *et al*. 2016, Abdoulaye *et al.* 2018, Braca *et al.* 2018
A. gummifera	Analgesic, antidepressant, antioxidant, antimicrobial, anxiolytic and anti-plasmodial activities. Safe LD50 - 4000 mg/kg	Stems - Petrol ether/ethyl acetate (1:1)	50	no information	Kraft *et al.* 2003, Adedapo *et al*. 2008, Annan *et al*. 2012, Adebiyi *et al.* 2013, Ishola *et al.* 2015, Uzoeto *et al*. 2018
A. stuhlmannii	Antitumor, antioxidant, antiviral, antimicrobial and anti-inflammatory activities. no information	no information	no information	no information	Chinemana *et al.* 1985, Selemani *et al.* 2020
A. amara	Anti-hyperlipidemic, anticancer, anti-plasmodial anti-arthritic wound healing, antimicrobial, anti-inflammatory, analgesic, antioxidant, anti-ovulatory, anti-spermatogenic and anti-androgenic activities. Safe LD50 - 2000 mg/kg body weight.	no information	no information	no information	Praveen *et al.* 2011, Kazembe *et al.* 2012, Gundamaraju *et al.* 2014, Thippeswamy *et al.* 2015, Indravathi G *et al.* 2016, *Kassem et al.* 2016, Nivetha *et al.* 2017, Abdurrahman *et al*. 2017, Devi *et al.* 2018
A. chabaudii	Antimicrobial activity. no information	no information	no information	no information	Mbanga *et al.* 2010
A. excelsa	Anti-mycological, trypanosomiasis, anti-plasmodial, cathartic, antibacterial, antifungal and antiseptic activities. no information however reported to be safe.	Leaves or roots- Methanol	no information	8.32 13.46	Van Zyl *et al.* 2002, Coopoosamy & Magwa 2007, Coopoosamy 2010, Cock 2015

A. greatheardii	Antioxidant, antibacterial, anti-diabetic, antiviral, anti-plasmodial, and antifungal activities. no information	Leaves- Petroleum ether Dichloromethane Ethyl acetate Ethanol	no information	4.90 ± 2.98 32.45 ± 6.58 43.18 ± 21.84 27.04 ± 12.	Van Dyk 2009, Loots *et al.* 2011
A. andongenis	Antipsychotic and antinociceptive activities. No anti-inflammatory or antimicrobial activities. Moderately toxic LD50 - 900 mg/kg body weight LD50) -547.7 mg/kg	no information	no information	no information	Nwinyi *et al*. 2006, Ighodaro & Bello 2011, Ebbo *et al.* 2020
A. albida	Antiplasmodial, antifeedant and prophylactic activities. Safe LD 50 - 5000mg/kg body weight	no information	no information	no information	Kazembe & Munyarari 2006, Kazembe *et al*. 2012, Khan *et al*. 2012, Latha *et al.* 2015
A. heppii	no information no information	no information	no information	no information	
A. affra	Antimicrobial, anti-plasmodial, anthelmintic, anti-histaminic, cardiovascular effects, analgesic, anti-inflammatory, anti-schistosomal, hypotensive, anti-tuberculosis and immune-modulating activities. Safe LD50s intraperitoneal and oral doses were 2450 and 8960 mg/kg, respectively. The LD50 >2500 mg/kg of body weight.	Leaves- DCM DCM/MeOH (1:1) MeOH Water Leaves, stem-Petrol ether/ethyl acetate (1:1)	5 7.3 8 > 100 8.9	15.3	Abrahams 1997, Kraft *et al.* 2003, Clarkson *et al.* 2004, Mukinda & Syce 2007, Liu *et al.* 2009, Ntutela *et al.* 2009, Suliman 2011, More *et al*. 2012, Molefe *et al.* 2012, Mesa *et al.* 2015, Munyangi *et al*. 2018, Kane *et al.* 2019, Omara, 2020
A. africanus	Antiprotozoal, analgesic, antihistaminic, antifertility, anti-plasmodial, anti-inflammatory and antimicrobial activities. Safe LD50 > 5000mg/kg in rats	no information	no information	no information	Oketch-Rabah & Dossaji 1997, Dikasso *et al.* 2006, Hassan *et al.* 2008, Kebede *et al.* 2016, Okolie *et al.* 2019, Okello *et al.* 2019, Mfengwana & Mashele 2019,
A. indica	Antiseptic, antimicrobial, antipyretic, anti-plasmodial, antifertility, spermicidal, hypoglycaemic antifungal, antiviral, antiperiodic, anti-	Leaves- Acetone/water Methanol Aqueous	20 11.76 3.42	no information	Bakr 2013, Raj 2014, Nishan & Subramanian, 2014, Momoh *et al*. 2015, Bijauliya *et al.* 2018, Zeenat *et al.*

	inflammatory and antipyretic activities. Safe LD50 was estimated to be >5000mg/Kg body weight.				2018, Oduor *et al.* 2019
B. adoensis	Anti-plasmodial, cancer prevention, antipyretic, antibacterial, anti-oxidative, hormone action, antifungal and enzyme stimulation activities. Safe LD50 >3000 mg/kg body weight.	Leaves- Methanol Acetone DCM MeOH Chlorine water and methanol Water	2.90 2.54 2.83 2.57 2.67 2.14	no information	Stangeland *et al*. 2010, Nethengwe *et al.* 2012, Anthoney et al. 2013, Zemicheal & Mekonnen 2018
B. huillensis	Antioxidant antibacterial, antiprotozoal and antifungal activities. no information	no information	no information	no information	Maroyi 2020
C. annuum	Anti-inflammatory, immuno-modulatory, anti-edema, antioxidant, antimicrobial, antiviral, anti-obesity, anticancer, analgesic, anti-angiogenic, anti-parasitic, antiplatelet, anti-arthritic, antifungal, muscle relaxant, antineoplastic, hypoglycemic, gastro-protective, larvicidal effects, potent anxiolytic and sedative activities. Safe LD50 - 12043 mg/kg (aqueous extracts) with 5,492mg/kg (70% ethanolic extracts) non-toxic (5-15g/kg body weight)	no information	no information	no information	Lagu & Kayanja 2013, Khan *et al.* 2014, Al-Snaf 2015, Fathim 2015, Jawad *et al.* 2017, Boiko *et al*. 2019
C. papaya	Antimicrobial, anthelmintic, anti-plasmodial, antifungal, anti-amoebic, anticonvulsant, effecting muscle smoothing, male & female antifertility, hepatoprotective, diuretic, topical use, immunomodulatory and histaminergic activities. Safe LD50 - 2000 mg/kg BW	Seed- Ethanol	519.38	no information	Krishna *et al.* 2008, Halim *et al.* 2011, Roshan *et al*. 2014, Patil *et al.* 2014, Ohashi *et al.* 2018, Alara *et al.* 2020, Omara 2020
C. abbreviata	Anti-plasmodial, anthelmintic, antioxidant,	Root- MeOH	13.31	no information	Ramalhete *et al.* 2008, Viol 2009, Mongalo & Mafoko

	anti-diabetic and antimicrobial activities. Safe LC50 values of 1319.37 ± 356.63µg/ml. LC50 values of 1800 µg/ml				2013, Maroyi, 2013, Kiplagat *et al*. 2016, Kaur *et al*. 2018
C. roseus	Antibacterial, anti-plasmodial, anti-hyperglycemic, anti-diabetic, anti-tumour antihypertensive and wound healing activities. Safe LD50 >5000mg/kg/body weight	Leaves - MeOH Whole plant - EtOH	>100 16.0	no information	Retna & Ethalsha 2013, Kabubii *et al.* 2015, Kaur *et al.* 2018
C. mucronata	Hypoglycemic, anti-plasmodial, antivenin, anti-diabetic, anti-ulcer, antispasmodic, anti-diarrhoeal and possess significant effects on male fertility activities. Safe LD50 > 5000 mg/kg body weight	no information	no information	no information	Tanko *et al.* 2007, Garba *et al.* 2014, Omara 2020
C. hirsuta	Anti-plasmodial activity. no information	Whole plant - DCM/MeOH (1:1) Water Leaves- Petrol ether/ethyl acetate (1:1) Roots- Petrol ether/ethyl acetate (1:1)	15 50 50 40.6	 29.4	Kraft *et al*. 2003, Clarkson *et al.* 2004
C. mopane	Antibacterial, anti-cancer, antioxidant anti-protease and antimicrobial activities. no information	no information	no information	no information	Ferreira *et al* 2003, Du *et al*. 2015, Kaarina *et al.* 2017
C. elaeagnoides	no information no information	no information	no information	no information	
C. febrifuga	Anti-inflammatory, anticonvulsant, analgesic, anti-plasmodial, antipyretic, antihyperglycemic, anti-proliferative and hypolipidemic property. Safe LD50 - 5000mg/kg	no information	no information	no information	Ramalhete *et al.* 2008, Salawu *et al*. 2009, Nnatuanya & Ohadoma 2014, Bassoueka *et al.*2014, Idris & Nenge 2019, Uchogu *et al*. 2020)
C. gratissmus	Antioxidant, anti-inflammatory, anti-plasmodial, antibacterial and antiviral activities.	Leaves - DCM DCM/MeOH (1:1) MeOH	3.5 11.5 29 95	no information	Clarkson *et al*. 2004, *Njoya et al*. 2018, Grace et al. 2003

	Moderately toxic LC50 varying between 152.30 and 462.88 µg/mL	Water			Njoya *et al* 2018
C. megalobotrys	Antibacterial, anti-HIV, anti-plasmodial and radical scavenging activities. no information	Stem bark-Crude n-hexane Chloroform Aqueous n-butanol	3.12 ± 0.68 1.74 ± 0.47 8.34 ± 1.66 >50 >50	5.34 ± 0.78 3.78 ± 0.10 10.78 ± 0.68 40.28 ± 6.83 >50	Abosi & Majinda 2015, Maroyi 2017a
C. spicata	Acetylcholinesterase, antibacterial, antiviral, anti-inflammatory, antileishmanial, anti-plasmodial, antiprotozoan, antioxidant, larvicidal, molluscicidal, spermicidal, and cytotoxicity activities. Highly toxic LC50 value of 2.6 µg/mL	Leaves - DCM DCM/MeOH (1:1) MeOH Fruit- Water DCM/MeOH (1:1) Leaves Bark- Water Petrol ether/ethyl acetate (1:1)	45 13 27.5 90 14 > 100 45.1 >50	 47.5 67.9	Kraft *et al.* 2003, Clarkson *et al.* 2004, Maroyi 2019a
D. nitidula	Anti-spermicidal, ulcerogenic, anthelmintic, anti-plasmodial, antimicrobial, antipyretic, aphrodisiac, analgesic, larvicidal, astringent, expectorant and anti-inflammatory activities. Highly toxicLC50 - 0.87 µg/ml	no information	no information	no information	Moshi *et al.* 2004, Kazembe *et al*. 2012, Saha *et al.* 2013, Dzoyem *et al* 2014
D. anomala	Anthelmintic, anticancer, antihyperglycemic, anti-inflammatory, antimicrobial, antiviral, antioxidant, anti-plasmodial, and hepatoprotective activities. Safe LC50 value of 3 040±1060 µg/ml	no information	no information	no information	Munodawafa et al. 2016, Tripathy *et al.* 2017, Maroyi 2018
D. condylocarpon	Sympatholytic and anti-plasmodial activities. no information	Roots- DCM DCM/MeOH (1:1) Water	> 100 24 > 100	no information	Clarkson *et al.* 2004, Moura *et al*. 2018
E. goetzei	Antioxidant, anti-inflammatory, anthelmintic, antifungal, antibacterial, antiviral, antinociceptive, antibabesial, and antirickettsial activities. Moderately toxic LC 50 - 356.55µg/ml				Maroyi 2017c

*E. **longifolium***	no information no information	no information	no information	no information	
E. divinorum	Antimicrobial, diuretic and anti-plasmodial activities. Safe LD 50 - 2000mg/kg	Leaves	6.12 ± 0.45 17.29 ± 1.44	no information	Ng'ang'a 2011, Ngari *et al.* 2013, Woldemedhin *et al.* 2017
E. natalensis	Antibacterial, antidiabetic, antifungal, antiviral, antimycobacterial, antioxidant, anti-plasmodial, larvicidal, anti-schistosomal, molluscicidal, dentin permeability and hepatoprotective activities. Highly toxic	Stems-DCM/MeOH (1:1) Water Roots-DCM/MeOH (1:1) Water	5.3 > 100 5.1 > 100	no information	Clarkson *et al*. 2004, Maroyi 2017d
F. indica	Antimicrobial, hepatoprotective, anti-diabetic, antimalarial, anti-plasmodial, antioxidant, anti-inflammatory, anti-asthmatic and antiviral activities. Moderately toxic LC 50 - 467.31 ± 39.01 µg/ml	Roots - DCM DCM/MeOH (1:1) Water Leaves- EtOH EtOAc	86.5 78 > 100 0.5 10	no information	Kaur *et al*. 2003, Clarkson *et al.* 2004, Viol 2009, Kota *et al* 2012, Sashidhara *et al.* 2013, Hussain *et al*. 2016, Viol *et al.* 2016, Eramma 2016
F. virosa	Analgesic, anti-inflammatory, aphrodisiac, sedative, anti-arrhythmic, anti-diabetic, anti-HIV, anti-hepatitis C, anti-plasmodial, anti-diarrheal, cytotoxic, antimicrobial, antifungal, antioxidant, and laxative activities. Safe LD50 >10000mg/kg	Leaves/twigs; Leaves, stem - DCM/MeOH (1:1) Water Petrol ether/ethyl acetate (1:1)	 19 11.4 >50	no information	Kraft *et al*. 2003, Clarkson *et al.* 2004, Misonge *et al.* 2019, Ajaib & Wahla 2018, Omara 2020
G. buchananii	Chemotherapeutical, antibacterial, antiviral, anti-mycobacteria, antifungal and anti-trypanosomal activities. no information	no information	no information	no information	Bakana *et al*. 1987, Magadula & Mbwambo 2014
G. senegalensis	Antioxidant, antiviral, anti-plasmodial, antifungal, antibacterial and antileishmanial activities. Safe LC50 value of 2185.61 ± 872. 25µg/ml non-toxic LD50 > 1600mg/kg	Roots- DCM Water Stems- DCM DCM/MeOH (1:1) Water	15.5 > 100 42 48.3 > 100	no information	Kraft *et al.* 2003, Clarkson *et al.* 2004, Khalid *et al.* 2007, Viol, 2009; Malebo *et al.* 2015, Viol *et al*. 2016, Makgatho *et al.* 2018,
H. madagascariensis	Antioxidant, anti-plasmodial, anti-anemic, analgesic, anti-protozoan, anti-sickling, enzyme	Stem, bark-Ethanol	0.052 ± 0.517	no information	Iwalewa *et al.* 2008, 2009. Kengni *et al*. 2013, Lemma *et al.* 2017, Mba *et al.*

	inhibition, anti-modulatory effects, anti-trichomonal, antidiarrhoeal, hypotensive and cardioprotective activities. Safe LD50 > 5000 mg/kg. LD50 - 11600 g/kg and 13200 mg/kg				2017, Biduaya *et al*. 2020, Happi *et al*. 2020, Omara 2020, Shorinwa & Monsi 2020
H. pubescens	Analgesic, antibacterial, anti-amoebic, anti-inflammatory, anti-plasmodial, and antioxidant activities. Safe LD50 > 2000 mg/kg	Bark- EtOH Leaves- EtOH	4.5 7.0	no information	Kraft *et al.* 2003, Sinha *et. al*. 2013, Nondo *et al*. 2016, Singh 2018
H. aristata	Antibacterial, anti-inflammatory and anti-plasmodial activities. no information	Whole plant- DCM DCM/MeOH (1:1) Leaves- Water Roots- Petrol ether/ethyl acetate (1:1) Petrol ether/ethyl acetate (1:1)	19.5 24 > 100 43.9 50	no information 34.6	Kraft *et al*. 2003, Clarkson *et al.* 2004
H. floribundum	Anti-plasmodial activity. no information	Roots- Petrol ether/ethyl acetate 1:1	>50	no information	Kraft *et al*. 2003
L. discolor	Anthelmintic, antibacterial, antimycobacterial, antifungal, antioxidant, anti-plasmodial, and nematicidal activities. no information	Fruit- DCM MeOH/DCM Water	25 > 100 > 100	no information	Clarkson *et al*. 2004, Kazembe *et al.* 2012, Maroyi 2018b
L. javanica	Anti-inflammatory, oxidative, anti-microbial, antiamoebic, antibacterial, antifungal, antimycobacterial and anti-plasmodial activities. Safe LC50 1138 ± 1.33 µg/ml	Roots - DCM DCM/MeOH (1:1) MeOH Water Stems- DCM DCM/MeOH (1:1) MeOH Water	3.8 27 24 > 100 4.5 21.8 29.8 > 100	no information	Clarkson *et al*. 2004, Osunsanmi et al. 2019, Maroyi 2017b
M. balsamina	Analgesic anti-HIV, antiseptic anti-plasmodial, anti-viral, shigellocidal, anti-diarrheal, anti-bacterial, hepatoprotective, anti-microbial, hypoglycemic,	Whole plant- DCM/MeOH (1:1) Water Stem- DCM/MeOH (1:1) Water	18 > 100 5.3 > 100 6		Clarkson *et al.* 2004, Jigam *et al.* 2004, Benoit-Vical *et al.* 2006, Thakur *et al.* 2009, Ramalhete *et al*. 2008, Singh & Devi 2018, Omokhua-Uyi

	antioxidant and anti-inflammatory activities. Safe LD50 - 5000 mg/kg body	Leaves- DCM/MeOH (1:1) Water Aerial parts- Crude extracts Water Methanol Heptane Dichloromethane	> 100 > 100 > 100 30 28 ± 3 57 ± 13	> 100 > 100 17 ± 10 26 ± 1.5 73 ± 15	& Van Staden 2020, Sabiu *et al.* 2020 Jonathan *et al* 2020
M. foetida	Antioxidant, antimicrobial, antinicotinic, antidiabetic, antimuscarinic and anti-plasmodial activities. no information	Leaves- EtOAc MeOH Aq	23.32 52.65 6.16	no information	Kraft *et al*. 2003, Waako *et al*. 2005, Froelich *et al*. 2007, Odeleye & Oyedeji, 2008, Acquaviva *et al.* 2013, Omokhua-Uyi & Van Staden, 2020,
O. americanum	Antimicrobial, antioxidant, antidiabetic, anti-hyperlipidaemic insecticidal, anti-plasmodial, antimicrobial, antiemetic, antifertility, anti-asthmatic, anti-stress and anticancer activities. no information	Whole plant - DCM/MeOH (1:1)	4.2	no information	Clarkson *et al*. 2004, Joseph *et al.*2012, Behera *et al*. 2012, Dash *et al.* 2014, Ntonga *et al.* 2014, Rai *et al.* 2016, Gberikon *et al.* 2018
O. angustifolium	no information no information	no information	no information	no information	
P. curatellifolia	Antioxidant, anti-plasmodial, antibacterial and anti-diabetic activities. Safe LC50 >1000 µg/ml.	Leaves/flowers-DCM DCM/MeOH (1:1) MeOH Water Roots- DCM DCM/MeOH (1:1) MeOH Water Leaves, stem- Petrol ether/ethyl acetate (1:1)	17 40 46.5 81 5.3 22.5 30.5 63.5 50		Kraft *et al*. 2003, Clarkson *et al*. 2004, Mbunde *et al.* 2017
P. schumanniana	no information no information	no information	no information	no information	
P. zeylanica	Anti-inflammatory, anti-plasmodial, antiviral, anti-fertility, anti-microbial, anti-oxidant, blood coagulation, wound healing, memory enhancer and anti-cancer activities.	Roots- DCM DCM/MeOH (1:1) MeOH Water Leaves- DCM	43 34 77.3 > 100 3 4.8 5.5	no information	Clarkson e*t al*., 2004, Mandavkar & Jalalpure 2011, Jain *et al*. 2014, Ganesan & Gani 2013, Sharma & Kaushik 2014

	Toxic LD50 - 65mg/kg body weight	DCM/MeOH (1:1) MeOH Water	> 100		
P. persica	Anticancer, antimicrobial, anti-allergic, anti-plasmodial, antibacterial, antitumor, anti-inflammatory, anti-obesity, analgesic, antipyretic, phytotoxic and insecticidal activities. Safe LD50 - 2000 mg/kg	no information	no information	no information	Misra *et al*. 1991, Aziz & Habib-ur-Rahman 2013, Kumar & Chaudhary 2017, Elshamy *et al*. 2019, Song *et al* 2019, Haleema *et al*. 2020,
P. angolensis	Antibacterial, anti-plasmodial and antifungal activities. Safe LC50 - roots 1 320 ± 266µg/ml.	Stems - DCM DCM/MeOH (1:1) MeOH Water	15 60 71 > 100	no information	Munodawafa *et al.* 2016, Zininga *et al.* 2017, Chipinga 2018
S. birrea	Anti-diarrhoeal, antidiabetic, antimicrobial, anti- inflammatory, anticonvulsant, anti-plasmodial, antihypertensive, antioxidant and antinociceptive activities. Safe LD50 > 1000 mg/kg LC50 value of 1112.37±210.04µg/ml.	Stem, bark-Aq Methanol	18.96 ± 5.32 5.91 ± 0.36	71.74 ± 4.36 24.96 ± 3.62	Gathirwa *et al.* 2008, Viol, 2009, Ojewole *et al.* 2010, Viol *et al.* 2016
S. occidentalis	Antibacterial, anti-plasmodial, antifungal, immunosuppression anti-inflammatory, anti-cancerous, antimutagenic, antioxidant and hepatoprotective activities. Safe LC50 >1000 µg/ml	Leaves- no information	48.80	54.28	Yadav *et al*. 2010, Vijayalakshmi *et al.* 2013, Murugan *et al.* 2015, Ali *et al*. 2019
S. septemtrionalis	Neuroprotection, anticancer, diuretic, anxiolytic-like, antidepressant-like, anticonvulsant, antiviral, anti-inflammatory, antibacterial, antioxidation, blood lipid regulation and antinociceptive activities. Safe The LD50 > 2000 mg/kg	no information	no information	no information	Alonso-Castro *et al.* 2019, Xie *et al.* 2019, Arana-Argáez *et al.* 2020
S. siamea	Anti-plasmodial, anti-inflammatory, anti-	Stem bark-Ethyl acetate	31.3		Ajaiyeoba *et al*. 2008, Kamagaté *et*

	diabetic, antimicrobial, antidepressant, analgesic, anticancer, hypotensive, diuretic, antioxidant, laxative, antipyretic, anxiolytic and sedative activities. Safe LD50 > 2000 mg/kg.	CHCl3 CHCl3:(CH3CO)^{2}O (1:1) CHCl3: EtOAc (85:15) Chloroform Ethanol Leaves-Aqueous Chloroform Ethanol Methanol Hydro-alcoholic - Aqueous Methanol Aqueous	15.6 15.6 5 21±3 31±5 > 100 2.41 7.06 3.08 5.19	< 10 < 10 < 10 23.15 11.35 12.85	*al.* 2014, Koffi *et al*. 2016, Gawade & Farooqui, 2020
S. campylacanthum	Antimicrobial, anti-schistosomal, orexic, anorexic, hypoglycemic, anti-fungal, anti-plasmodial, anti-cancer, antinociceptive, antipyretic and anti-spasmolytic activities. Safe LD50 > 15000 mg/kg	Fruit- Ethanol	no information	41.3±7.0	Zirihi *et al*., 2005; Assefa et al. 2007, Mwonjoria et al. 2014, Omara, 2020
S. incanum	CNS depressant, antibacterial, anthelmintic, anti-plasmodial, hepatoprotective, laxative, cardiotonic, antioxidant, anticancer and antihypertensive activities. Safe LD50 -2000 mg/kg	no information	no information		Zirihi *et al.* 2005, Abdel-Aziz *et al.* 2011, Sharma *et al.* 2017
S. potatorum	Contraceptive, nephroprotective, anti-inflammatory, antidiabetic, antipyretic, anti-diarrhoeal, antiarthritic, anti-plasmodial, antinociceptive and anti-microbial activities. Safe LD50 - 2000mg/kg body weight.	Leaves - DCM DCM/MeOH (1:1)	60 > 100	no information	Clarkson *et al.* 2004, Yadav *et al*. 2014, Behera *et al.* 2018
T. elegans	Antibacterial and anti-plasmodial activities. no information however studies revealed that it is relatively safe	DCM MeOH: H2O	0.33 0.83	no information	Ramalhete *et al*. 2008, Pallant *et al*. 2012, Bapela *et al*. 2014, Dzoyem *et. al*. 2016, Pallant, Cromarty and Steenkamp, 2012,

T. sericea	Antibacterial, anti-inflammatory, anti-neurodegenerative, anticancer, antioxidant, antifungal, antidiabetic and antiparasitic activities. Highly toxic LC50 <300µg/ml. The leaf extract had a result, LC50 - 66.66 ± 49.31 µg/ml	no information	no information	no information	Viol 2009, Viol *et al.* 2016, Nair *et al.* 2018
T. diversifolia	Anti-platelet activity, anti-inflammatory, antimicrobial, anti-fleas, antioxidant, analgesic, anti-obesity, anti-diarrhoeal, anti-plasmodial, antiemetic, antileishmanial effect, anti-hyperglycaemic, gastro-protective effect, hypolipidemic effect, antidiabetic, antiviral and anticancer activities. Safe LD50 >2000 mg/kg	Aerial parts-Ether Ethanol Petroleum ether Dichloromethane Leaves - Aqueous Flowers-Aqueous Leaves-Methanol Methanol and Leaves and flowers-dichloromethane Dichloromethane	0.75 31.25-62.5 < 2.0 < 1.5	0.83 15 10 10 15.6 24.5 < 2.0 < 1.5	Owoyele *et al*. 2004, Soares *et al*. 2012, Tagne *et al* 2018; Syarif *et al*. 2018, Maina *et al.* 2018, Agboola *et al*. 2020, Merciline & Dominic 2020
V. infausta	Antibacterial, antimycobacterial, antifungal, anti-inflammatory, antileishmanial, antioxidant, anti-plasmodial, antifeedant and prostaglandin synthesis inhibitory activities. Moderately toxic LC50 values of 338±23.4 µg/mL and 416 ± 28.3 µg/mL	Fruit-DCM/MeOH (1:1) Water	23 > 100	no information	Clarkson *et al.* 2004, Kazembe *et al.* 2012, Maroyi 2018c
V. bachmannii	no information no information	no information	no information	no information	
V. colorata	Anti-plasmodial, antimicrobial, anti-ascorbic, anti-norexic, antihelmintic, hypoglycaemic and anti-diabetic activities. Safe LD50 > 5000 mg/kg	Twigs - DCM/MeOH (1:1) Water Leaves - Petrol ether/ethyl acetate (1:1)	14.1 > 100 12.1	 17.8	Kraft *et al.* 2003, Clarkson *et al.* 2004, Sy *et al*. 2005, Golly *et al*. 2012, Idris *et al*. 2016

W. salutaris	Antimicrobial, anti-plasmodial, antioxidant, anti-inflammatory, cytotoxic, phytotoxic, piscicidial and molluscicidal activities. Moderately toxic Leaf and bark extracts, LC50 - 351.41 ± 29.58µg/ml and 359.66 ± 14.33µg/ml.	no information	no information	no information	Viol 2009, Maroyi 2013, Lawal *et al*. 2014, Viol *et al*, 2016, Nyaba *et al*. 2018, Soyingbe *et al*. 2018
Z. africana	Antibacterial, antifungal, antiviral, antidiabetic, anti-inflammatory, insecticidal, anti-trypanosomal and activities. Highly toxic LC50 values ranging from 41.1 µg/mL and 240.0 µg/mL	no information	no information	no information	Maroyi 2019b
Z. asiaticum	Anti-inflammatory, anti-bacterial, anti-tumour, antifeedant analgesic, anti-HIV, anti-plasmodial, antiviral, antiplatelet aggregation, wound healing, anticancer, spasmolytic activity and skin whitening activities. Weak or low toxicity or mildly toxic LD50 >1000 mg/kg	Fruit- EtOAc Hexane MeOH Aq Leaves- EtOAc Hexane MeOH Aq Root, bark- EtOAc MeOH Aq Hexane	6.45 ± 0.18 4.01 ± 0.39 20.04 ± 6.89 15.13 ± 2.36 1.98 ± 0.01 2.72 ± 0.45 31.57 ± 4.87 21.68 ± 1.70 10.02 ± 2.0 5.44 ± 0.78 16.54 ± 3.10	1.87 ± 0.61 6.27 ± 1.41 8.24 ± 0.14 6.89 ± 2.04 12.31 ± 2.35 13.35 ± 0.33 8.58 ± 0.65 5.11 ± 0.30 2.49 ± 0.06 2.43 ± 0.01 7.20 ± 0.36	Kraft *et al*. 2003, Rajkumar *et al.* 2008, Madhavan *et al*. 2012, Orwa *et al.* 2013, Nattudurai *et al*. 2014, Zhu *et al.* 2019, Omara 2020
Z. mays	Antioxidant, nephroprotective, anticancer, hepatoprotective, analgesic, anti-inflammatory and anti-plasmodial activities. Weak or low toxicity or mildly toxic The LD50 - 1732.05 mg/kg LD50 of 1874.83 mg/kg	Husk- Crude extract Pet. ether Chloroform Ethyl acetate Butanol Aqueous	45.52 ± 0.86 47.88 ± 0.36 8.46 ± 0.37 9.31 ± 0.46 35.35 ± 0.16 >100	38.51 ± 0.18 49.11 ± 0.15 3.84 ± 0.32 3.69 ± 0.66 44.81 ± 0.12 >100	Okokon *et al.* 2017 Udobang *et al.* 2019; Magaña *et al*. 2020

Legend: Dichloromethane DCM, Methanol MeOH, EtOAc - ethyl acetate, EtOH - ethanol, Aq - aqueous

Other reported pharmacological activities such as antipyretic, analgesic, immunostimulant or immunomodulatory, anti-parasitic, antiviral, antimicrobial, antibacterial, anti-oxidant, cardio-protective and anti-inflammatory properties may be involved in the management of malaria related symptoms which include: fever, sweating, chills that shake the whole body, headache, muscle aches, fatigue, chest pain, breathing problems, cough, diarrhoea, neurologic complaints (dizziness, confusion, myalgia, disorientation, coma), nausea and vomiting (CDC 2020).

***In vitro* anti-plasmodial activity of antimalarial medicinal plants used by local people in Zimbabwe**

The study narrowed down to 43 antimalarial plants that were validated by research in-vitro anti-plasmodial activity on Chloroquine sensitive and Chloroquine resistant *Plasmodium falciparum* (Table 2). A total of 10 medicinal plants with anti-

plasmodial activity were excluded. Excluded studies tested activity on *Plasmodium berghei; W. salutaris* (Nyaba 2017), *S. campylacanthum* (Assefa *et al.* 2007), *P. persica (*Misra *et al.* 1991*), C. febrifuga* (Salawu *et al.* 2008), *C. mucronata* (Katsayal & Obamiro 2007), *A. africanus* (Dikasso et al. 2006), *A. albida* (Khan *et al.* 2012) and *A. digitata* (Adeoye *et al*. 2017). Furthermore, studies that did not clarify or specify the malarial parasite were on; *A. amara, A. albida* and *D. nitidula* (Kazembe *et al*. 2012). A study on *D. anomala* was excluded as it recorded anti-plasmodial activity on a pure compound dehydrobrachylaenolide, a eudesmanolide-typesesquiterpene lactone of the plant (Becker *et al.* 2011).

Plants with in-vitro anti-plasmodial activity on Chloroquine sensitive and Chloroquine resistant Plasmodium falciparum 3D7 and W2. Anti-plasmodial activity were classified as follows: high at $IC_{50} \leq 10$ µg/ml, moderate at 10-50 µg/ml, low at 50-100 µg/ml and inactive at >100 µg/ml (Gathirwa et al., 2008). The antimalarial medicinal plants exhibiting anti-plasmodial activity were 53 (75.7%) of the medicinal plants validated by research. Of the antimalarial plants of exhibiting in-vitro anti-plasmodial activity, 22 (51.2%) are regarded as highly active; 14 plants (32.6%) moderately active; 3 plants (7.0%) with low activity, 1 plant (2.3%) inactive and 3 (7.0%) unclassified. In-vitro anti-plasmodial activity of the plants were based on the chloroquine sensitive *P. falciparium* as all the reported antimalarial plants had information on the strain. The following plants had an IC_{50} value ≤ 10 µg/ml which denotes high activity - *A. affra, A. indica, C. siamea, C. gratissmus, C. megalobotrys, E. natalensis, E. divinorum, F. indica, H. madagascariensis, H. pubescens, L. javanica, M. balsamina, M. foetida, O. americanum, P. curatellifolia, P. zeylanica, S. birrea, T. elegans, T. diversifolia, T. asiatica, B. adoensis and Z. mays.*

Toxicological evaluation of antimalarial medicinal plants used by local people in Zimbabwe

The high prevalent use of medicinal plants as alternative and complementary medicine rides on the assumption of their safety, however they may potentially be toxic. Medicinal plants have been reported to consistently treat and manage illnesses and disorders however the major flaw is the lack of in-vivo and in-vitro studies on their safety, efficacy and mode of action. It is essential to conduct meticulously planned toxicity studies on medicinal plants using stipulated guidelines before claiming their safety (Subramanian *et al.* 2018). Constituents of medicinal plants may contain toxic substances and pharmacologically active substances. As a result of their phytochemical makeup, some medicinal plants can be intrinsically toxic if used improperly or inadequately. It is imperative that toxicity be evaluated prior to pharmacological screening and clinical application of a new drug (Pour *et al.* 2011, Sharwan *et al.* 2015).

In vitro and in vivo methods have been employed to assess the toxicity of medicinal plants however, in the past years, new technologies have been developed. Toxicity prediction tools such as the use of omics in toxicity evaluation has provided valuable insights in predicting plant toxicity. Next generation sequencing DNA platforms have successfully been developed to detect adulteration and contaminants (Jităreanu *et al.* 2022). The Brine Shrimp Lethality Test (BSLT) and the rodent acute toxicity test were evaluated in this review. Munodawafa *et al.* (2016), indicated that these two tests were reasonably simple to conduct, accurate, and cost-effective methods for evaluating the safety of herbal extracts. Out of the 48 species listed in Table 2, approximately 68.6% had documented toxicological evaluation studies, while the remaining 31.4% lack any reported studies.

Animal studies should comply with EMA, ICH (Aydın *et al.* 2016) and (OECD) guidelines (Rehman *et al*. 2022). To determine the dose that causes major life-threatening toxicity, the test sample is given to experimental animals in increasing doses (Aydın *et al.* 2016). It is crucial to determine the safety margin of the test compound at this preclinical stage (Rehman et al. 2022). The in vivo LD50 test is conducted by administering a single dose of the extract to laboratory albino rats in order to determine the maximum lethal dose (Mlozi *et al*. 2020). There are several routes of exposure: oral gavage, inhalation/mucosal, dermal; and injection into the bloodstream, abdomen, or muscles (Ifeoma *et al.* 2013). According to Munodawafa *et al*. (2016) and Erhabor *et al.* (2020) rodent acute toxicity tests, also known as Lethality Dosage (LD50) tests, determine the dosage of a substance that causes a 50% mortality rate in mice or rats. Classification of the acute toxicity was based on LD50 values according to Malebo *et al.* (2015) as demonstrated in Table 3.

The Brine Shrimp Lethality Test (BSLT) measures the Lethality Concentration (LC50) that causes a 50% mortality rate in brine shrimp (Subramanian *et al*. 2018). Classification of toxicity was based on LC50 values according to studies by Munodawafa *et al*. (2016) and Erhabor et al. (2020) as shown in Table 3. Erhabor *et al*. (2020), Bussmann *et al.* (2011), Konan *et al*. (2022) have revealed that LC50 values >1000 µg/mL are considered safe. Therefore, the lower the LC50 value, the greater the toxicity of the assayed plant extract. In addition to lower sensitivity, and difficulties standardizing and characterization of *Artemia* strains, the organism is resistant to several phytochemicals, including phenolic compounds and minerals (Svensson *et al.* 2005, Aydın *et al*. 2016).

Table 3. Toxicological evaluation antimalarial medicinal plants used by local people in Zimbabwe.

Toxicological profile	No of plants	Names of the plant species
Safe or nontoxic **LC_{50} ≥ 1000 µg/ml** **2,000 ≤ LD_{50} ≤ 5,000 mg/kg body weight**	34	*A. digitata, A. gummifera, A. amara, A. albida, A. affra, A. africanus, A. indica, C. anuum, C. papaya, C. abbreviata, C. siamea, C. roseus, C. mucronata, C. febrifuga, D. anomala, E. divinorum, F. virosa, G. senegalensis, H. madagascariensis, H. pubescens, L. javanica, M. balsamina, P. curatellifolia, P. persica, P. angolensis, S. birrea, S. occidentalis, S. septemtrionalis, S. campylacanthum, S. indicum, S. potatorum, T. diversifolia, B. adoensis, V. colorata*
Weak or low toxicity or mildly toxic **500 ≤ LC_{50} ≤ 999 µg/ml** **1,000 ≤ LD_{50} ≤ 2,000 mg/kg body weight**	2	*T. asiatica, Z. mays*
Moderately toxic **250 ≤ LC_{50} ≤ 499µg/ml** **300 ≤ LD_{50} ≤ 1,000 mg/kg body weight**	6	*A. andongenis, C. gratissmus, E. goetzei, F. indica, V. infausta, W. salutaris*
Toxic **50 ≤ LD_{50} ≤ 300 mg/kg body weight**	1	*P. zeylanica*
Highly toxic **LC_{50} ≤ 249 µg/ml** **0 ≤ LD_{50} ≤ 50 mg/kg body weight**	5	*C. spicata, D.nitidula, E. natalensis, T. sericea, Z. africana*
No information	22	*A. chabaudii, A. excelsa, A. greatheardii, A. heppii, B. huillensis, C. hirsuta, C. mopane, C. elaeagnoides, C. megalobotrys, D. condylocarpon, E. zambesianum, G. buchananii, H. floribundum, L. discolor, M. foetida, O. americanum, O. angustifolium, P. schumanniana, T. elegans, V. bachmannii, V. natalensis, A. stuhlmannii*

Plant-related and environmental factors must be placed under consideration when evaluating the potential toxicity of medicinal herbal extracts or products. Out of the 48 scientifically validated antimalarial plants with toxicological profiles, results indicated that 70.8% plants are classified as safe or non-toxic, 4.2% plants exhibited weak or low toxicity or mild toxicity, 12.5% plants as moderately toxic, 2.1% plants classified as toxic, and 10.4% of the plants as highly toxic (Table 3). Toxicological evaluation studies determine the toxic dose, evaluates potentially harmful effects, and provides the understanding of the mechanisms of action and the potential effects of herbal interventions on human health (Mensah *et al*. 2019, Prajapati 2024). Toxicity studies help drug formulations as they distinguish between therapeutic doses from toxic doses (Anwar *et al.* 2022).

Conclusion

A total of 70 species of plants belonging to 58 genera in 35 families have traditionally been used to treat and manage malaria in Zimbabwe. The family with the highest number of medicinal plants used in Zimbabwe was the *Fabaceae* family, represented by a total of 10 plants. The dominant plant parts used in the preparation of remedies were roots (43%). About 75.7% of the antimalarial plants reported have been scientifically validated and documented to exhibit anti-plasmodial activity. A substantial number (22) of the plants were found to have high anti-plasmodial activity towards chloroquine sensitive *P. falciparum.* Whilst this review focuses on the identification of plants reported in other studies, more conclusive studies on the mechanisms of action, pharmacodynamic and pharmacokinetic profiles may help in the development of standardisation of the herbal preparations.

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: The data supporting this systematic review are from previously reported studies and datasets, which have been cited. The processed data are available from the corresponding author upon request.

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