www.ajbrui.org

Afr. J. Biomed. Res. Vol. 22 (September, 2019); 257- 262

Research Article

An Open Label Clinical Study Evaluating the Effectiveness of a *Cryptolepis sanguinolenta* based Herbal Antimalarial Agent

***Thomford K.P[1], Thomford A.K[2], Akoto B.O[3], Appiah A.A[4], Yeboah R[5], Mensah M.L[1]**

[1]Department of Herbal Medicine, Kwame Nkrumah University of Science and Technology, Kumasi,Ghana.
[2]Department of Biomedical and Forensic Sciences, University of Cape Coast, Ghana.
[3]Scientific Information, [4]Phytochemistry and [5]Clinical Research Departments, Centre for Plant Medicine Research, Mampong- Akuapem, Ghana

ABSTRACT

Medicinal plants are key in the treatment of malaria in many developing countries. This study reports on the effectiveness of *Mist Nibima*, a Ghanaian herbal product from the Centre for Plant Medicine Research, Mampong-Akuapem. The product is a proprietary remedy prepared from the roots of *Cryptolepis sanguinolenta*. A non-comparative open label study was undertaken involving 33 subjects diagnosed with uncomplicated malaria. Mean parasitaemia at baseline was 3454 (± 2507) declining to 64.11 (± 66.16) after 7 days. In terms of the achievement of the primary outcome, 24 (72.72%) subjects had total parasite clearance with the other 9 (27.27%) attaining partial clearance by Day 7. No treatment failure and parasite recrudescence was also observed among the study subjects. The product Mist Nibima was also well tolerated and shown to safe as biochemical and haematological indices were normal post treatment. *Cryptolepis sanguinolenta* and herbal products formulated from the plant may therefore hold some potential for use as a first-line antimalarial agents.

Keywords: *Antimalarial, Cryptolepis sanguinolenta, Clinical Study, Herbal Medicinal Products*

*Author for correspondence: *E-mail*: *kpthomford@hotmail.com* ; Tel. +233 (27) 3900-517

Received: August 2018; Accepted: March, 2019

Abstracted by:
Bioline International, African Journals online (AJOL), Index Copernicus, African Index Medicus (WHO), Excerpta medica (EMBASE), CAB Abstracts, SCOPUS, Global Health Abstracts, Asian Science Index, Index Veterinarius

INTRODUCTION

Medicinal plants play a key role in the delivery of healthcare for developing countries. It continues to be reported that about 80% of people living in developing societies rely on some form of traditional therapy for their primary healthcare needs. Although heavily criticised for being unscientific and characterised by a lot of intangibles, the traditional practice of herbalism continues to evolve, thrive and expand (WHO, 2001; Bandaranayake, 2006). Over the years, we have come to appreciate that the treatments employed, in this case the medicinal herbs, can be decoupled from the various traditional medical practices to make them more applicable and acceptable for different societies (Fabricant and Farnsworth, 2001; Chothani and Vaghasiya, 2011; Rivera, Loya and Ceballos, 2013). The frontiers being broken today by herbal medicines are mainly the result of this conscious separation.

The increased interest in medicinal plants has come with its own attendant issues. It is quite common to find huge ethnobotanical/pharmacological studies that seek to explore the therapeutic potential of specific local flora. Majority of these studies are aimed at obtaining lead compounds for further development into conventional pharmaceutical products (Barrett and Bannister, 2000; Olufunke, 2012). The communities from which this knowledge originate rarely benefit from these studies as the end products from such research can be predicted to be beyond the financial reach of the indigenes. The means of dissemination of such knowledge also precludes any improvement in the traditions of the people from whom such knowledge emanates. Natural product scientists therefore have an obligation to ensure that knowledge acquired is not only beneficial to the giant pharmaceutical industries but to the traditional practitioner and his society as well. The ability of such research to have this trickledown effect to its source can greatly improve the health of the populace in poor and developing countries.

An area where the contribution of herbal medicines has been enormous is in malaria research (Saxena et al., 2003;

Willcox and Bodeker, 2004; Batista, De Jesus Silva Júnior and De Oliveira, 2009; Oliveira et al., 2009; Chinsembu, 2015). Tons of medicinal plants have been screened for the identification of biologically active isolates and the contribution has been significant. Quinine from Cinchona bark and very recently artemisinin from Artemesia annua are prominent among such proven isolates (Kaur et al., 2009; Biamonte, Wanner and Le Roch, 2013).

Cryptolepis sanguinolenta (Lindl.) Schltr (Periplocaceae) The West African plant C. sanguinolenta, grows as a thin-stemmed twining and scrambling shrub with orange-coloured sap in the cut stem which becomes red on ripening. Traditionally, the herb is used in the treatment of various diseases such as malaria, bacterial respiratory diseases, hypertension, and diarrhoea (Appiah, 2009; Ameyaw, 2012). Although, *Cryptolepis sanguinolenta* may not have attained international popularity like Artermesia annua, probably because it is yet to produce a hit antimalarial compound, for West Africa this plant is still economically important for the treatment of malaria. The plant is one of the most widely used material in antimalarial formulations in Ghana. The estimation is that about 40% of all Ghanaian herbal antimalarials have *C. sanguinolenta* a component (Komlaga *et al*., 2015).

The plant is also well explored with verified claims about its antiplasmodial, antibacterial and anti-inflammatory effect (Paulo *et al*., 2000; Agboke, Attama and Momoh, 2011; Barku, Opoku-Boahen and Dzotsi, 2012; Kirimuhuzya Claude, 2012). *C. sanguinolenta* has also been studied for its anticancer effects (Ansah and Mensah, 2013). Clinical studies on the plant have mainly been in relation to its antimalarial properties. In both cases the authors reported of a significant effect in subjects treated (Addae-Kyereme, 2004; Bugyei, Boye and Addy, 2010). Our study also reports on the antimalarial efficacy of another product formulated from this plant to highlight the need to consider the adoption of such products formulated from the plant as first-line antimalarial agents. The product under assessment is registered by the Food and Drugs Authority of Ghana and manufactured by the Centre for Plant Medicine Research, (CPMR) Mampong-Akuapem. This product has been in use at the institution for more than 25 years and sold under the trade name *Mist Nibima.*

MATERIALS AND METHODS

Ethical Considerations: Ethical approval for the study was obtained from the Supervisory Committee for Human Research of the Centre for Plant Medicine Research, Mampong-Akuapem. Consent was also obtained from all the participants involved in the study after the purpose of the study, guarantees of anonymity and their rights were explained to them in either English or one of the local Ghanaian languages they could comprehend. The study and its protocols were conducted in accordance with the Helsinki declaration for Good Clinical Practice.

Study Design and Population: The study was prospective and noncomparative in design. It involved patients visiting the outpatient clinic of the Centre for Plant Medicine Research, Mampong-Akuapem in the Eastern region of Ghana and diagnosed with uncomplicated malaria which was confirmed using a thin and thick blood film. Malaria in this case was defined as a parasite density of >1000 per µl of blood, together with the cardinal signs and symptoms of the disease.

On Day 0 (Baseline), the trial protocol and related procedures were explained to eligible participants. After obtaining a written consent, phlebotomy was done to obtain samples for blood film and safety assessment. This procedure was repeated on Day 7 for all subjects. Blood film was also repeated for all participants on Day 14, 28 and 45 to establish possible recrudescence.

Inclusion and Exclusion Criteria: Participants recruited into the study comprised male and females between the ages of 18-65 yrs with parasitaemia of > 1000 per µl of blood an axillary temperature of >37.5°C but < 40.0°C at the baseline. Participants were also recruited if they had no history of ingestion of any known anti-malaria product within the past 28 days, able and willing to return for follow up, complete the informed consent process or a guardian who could do so on the behalf of the subject.

Participants were excluded from the study if they were diagnosed or deemed to be at risk of developing complicated malaria. Subjects with severe hypertension, dehydration, excessive vomiting, the severely malnourished, febrile illness from other causes other than malaria, pregnant or breastfeeding women, haemoglobin of less than 8g/dl, patients with liver and/or renal disease(s) and comorbidities which might compromise the renal, hepatic or any other body system were all excluded from the study.

Classification of Treatment Efficacy: The primary outcome of interest in this study was total clearance of parasites by Day 7 of the study. Participants achieving this outcome were defined as having a complete cure. Partial efficacy was said to have occurred if participants were able to clear more than 75 % of initial parasite count by Day 7 and treatment failure when less than 75 % of the parasites were cleared. Subjects who recorded treatment failures by Day 7 were referred to receive the conventional antimalarial treatment.

Follow-up and Monitoring for Recrudescence: Participants in this study were followed up for a period of 45 days. Review days were set at Day 7, 14, 28 and Day 45. Monitoring for recrudescence was performed through the thin and thick blood film on Day 14, 28 and 45.

Safety Evaluation: Adverse effects associated with the use of the product was monitored using the WHO adverse reaction questionnaire and an evaluation of the kidney, liver and the haematological profile of the participants.

Interventional Drug: Participants were assigned to receive a decoction of the Ghanaian herbal product *Mist Nibima* packaged in 330ml amber coloured bottles. *Mist Nibima* is prepared as an aqueous decoction from the roots of *Cryptolepis sanguinolenta* (Lindl.) Schltr according to a proprietary formula of the institution.

Participants were counselled to administer the product at a dose of 30 mls three times a day. For subjects with severe clinical symptoms and/or a temperature > 39.0°C the dose of the product was adjusted to 100 mls three times a day for the first 3 days and then at the recommended dose of 30 mls three times a day for the next 4 days. Participants with the latter presentation were followed up through a phone call and asked to report back if symptoms were not improving after 48 hours. In cases where subjects experienced a deterioration in symptoms or failed to achieve clearance of more than 75 % of the initial parasite count on Day 0, they were referred to receive the standard orthodox treatment.

Statistical Analysis: Data for efficacy and safety assessments were analysed using a paired *t*-test, results were considered significant if $p < 0.05$. All other data was presented as Mean ± SD.

RESULTS

Study Population

In all 70 patients were screened for recruitment into the study. As per the inclusion and exclusion criteria 45 patients were considered eligible. Of the initial 45 participants, 33 (73.3%) were able to complete the study. Participants who defaulted cited reasons as the distance of their residence from the study site and the length of the follow up period since they knew they were already cured.

The 33 participants who completed the study were made up of 12 (36.36%) females and 21 (63.63%) males. The mean age of the population used was 34.0 (±11.07) yrs.

Effectiveness of the Herbal Treatment

Clinical Symptoms and Body Temperature: All participants presented with either all or some of the symptom's characteristic of uncomplicated malaria: Fever/Chills, Malaise/Myalgia, Headaches, Oral bitterness and Vomiting. The summary of the symptoms and the response after treatment is reported in Table 1. Generally, majority of the participants reported a decline in their symptoms after completing the 5-day dosage regimen. Body temperature also declined from the baseline of 38.57 (±0.84) to 37.55 (±0.33) by Day 7 and remained in the physiological range throughout the study.

Effect of Treatment on Parasitaemia: Parasitaemia of participants declined significantly compared to the baseline (Table 2). Mean parasitaemia on Day 0 (Baseline) was 3454 (± 2507) with this figure declining to 64.11 (± 66.16) during the first follow-up. In terms of the achievement of the primary outcome of complete cure, 24 (72.72%) had total parasite clearance and 9 (27.27%) attained partial clearance by Day 7. No treatment failures were recorded during the study.

Safety Assessment of the Treatment

Haematological Indices: Baseline haematological indices for the participants were normal but for two participants who had a haemoglobin level lower than 10.45 mg/dl. After follow-up on Day 7, the low haemoglobin had resolved. The treatment did not also appear to have any untoward effect on the haematological parameters as reported in Table 3.

Renal and Hepatic Indices: Safety monitoring of the product did not also indicate any adverse effect on the kidneys and liver. The parameters monitored were all within the physiological range as reported in Table 4 for the renal function and Table 5.0 for the hepatic function. The herbal product was also well tolerated by participants with no report of adverse effects.

Table 1
Progression of Disease Symptoms over the Study Period as Reported by the Participants.

SYMPTOMS	Baseline	Day 7	Day 14	Day 28	Day 45
Fever/Chills	33 (100)	14 (42.42)	3 (9.09)	-	-
Malaise/Myalgia	33 (100)	8 (24.24)	-	-	-
Headache	26 (78.78)	9 (27.27)	-	-	-
Loss of Appetite /Oral Bitterness	24 (72.72)	2 (6.06)	-	-	-
Vomiting	7 (21.21)	-	-	-	-

Data presented as n (%).

Table 2
Effect of the Herbal Product *Mist Nibima* on Parasitaemia and Temperature of Participants.

Parameter	Baseline	Day 7	Day 14	Day 28	Day 45
Parasitaemia	3454 (2507)	64.11 (66.16)***	15.0 (0.0)	-	-
Temperature	38.57 (0.85)	37.55 (0.33)***	37.41 (0.34) ***	37.52 (0.19) ***	37.83 (0.30) ***

Data presented as Mean (±SD); *** $p < 0.01$ compared to the baseline

Table 3
Comparison of the Haematological Indices of Treated Participants During the Study.

Parameter	Baseline	Day 7
WBC	5.19 (1.56)	4.87 (0.95)
RBC	4.37 (0.81)	5.18 (0.99)
HGB	12.39 (1.19)	12.82 (1.03)
HCT	39.89 (4.52)	42.22 (4.53)
PLT	336.9 (52.0)	340.0 (49.71)

Data presented as Mean (±SD), paired t-test did not indicate a significant difference

Table 4
Comparison of the Renal Indices for the Treated Participants During the Study.

Parameter	Baseline	Day 7
Urea	3.41 (0.91)	3.38 (0.89)
Creatinine	72.76 (10.03)	73.36 (9.79)

Data presented as Mean (±SD), paired t-test did not indicate a significant difference

Table 5
Comparison of the Liver Indices for the Treated Participants During the Study.

Parameter	Baseline	Day 7
Albumin	41.47 (3.94)	42.17 (3.16)
GGT	20.64 (6.13)	16.55 (3.33)
AST	14.06 (2.25)	13.28 (1.93)
ALT	16.57 (3.07)	15.91 (2.27)
ALP	135.9 (22.26)	149.1 (17.96)

Data presented as Mean (±SD), paired t-test did not indicate a significant difference

DISCUSSION

The results of this study indicate the efficacy of the plant *Cryptolepis sanguinolenta* and specifically the herbal medicinal product *Mist Nibima* for the management of uncomplicated malaria. Disease indicators that were of interest were the parasite clearing properties of the product, resolution of cardinal signs of the disease and a low recrudescence among subjects. Significantly, all participants were successfully treated albeit an extra 7 days for 9 (27.27%) participants who still carried some parasites after the first follow up day. In terms of the attainment of the primary outcome of complete cure by Day 7 of treatment, 24 (72.72%) of subjects reached this goal and the 9 (27.27%) reaching an outcome classified as partial efficacy. As defined by the study protocol none of the subjects had a treatment failure.

The clinical activity of *C. sanguinolenta* observed in this report confirms the numerous reports about its in vitro and *in vivo* antimalarial property (Cimanga *et al.*, 1996, 1997; Paulo et al., 2000). The plant is also one of the most studied in relation to this effect. In one instance Grellier and colleagues in their report on an aqueous root extract of the plant specified that it significantly inhibited parasites *in vitro* at an IC50 of 1-2µg/ml (Grellier et al., 1996). Again, Paulo and his co-workers indicated a remarkable activity when an aqueous and ethanolic extract of the leaves, roots and seven alkaloids isolated from these extracts were tested against Plasmodium falciparum K1 (multidrug-resistant strain) and T996 (chloroquine-sensitive clone). All the extracts inhibited 90 % of P. falciparum K1 growth at concentrations < 23 µg/ml (Paulo et al., 2000). On the contrary, other authors have also reported that the major alkaloidal component of the plant responsible for its activity, the indoloquinolone alkaloid cryptolepine, did not demonstrate significant biological effect when tested in vivo although the *in vitro* assessment of the isolate was notable (Kirby et al., 1995). The lack of interest in the plant as an antimalarial agent compared to other plants like *Artemesia annua* may potentially be the result of such conflicting reports and the cytotoxicity of the plant extract and its isolate cryptolepine (Ansah and Gooderham, 2002).

The impact of the plant on reproductive function of users is also noteworthy as *C. sanguinolenta* has been reported to affect the reproductive function of rodents during long-term administration. Authors indicated changes in the morphometry of the testes and a related decline in the testosterone levels of animals treated. The possible anti-spermatogenic effect of the plant was also noted (Ansah et al., 2010; Akhigbe and Ajayi, 2012). As significant as these findings may be, the context of usage of the plant cannot be ignored. Considering that ailments for which the plant is traditionally and widely used may not require long periods of administration hence the risk of such untoward effects from *C. sanguinolenta* may be minimal. However, when new clinical applications of the plant require extended administration or the use among individuals who desire to conceive some careful consideration must be given to these concerns. In this study, none of the subjects reported of or had any adverse effect arising out of the use of the product. All the haematological and renal and hepatic indices remained normal throughout the study.

In relation to the effectiveness of the product, the number of participants achieving the primary outcome of complete cure confirmed earlier clinical evaluations that reported likewise for *C. sanguinolenta* in the management of malaria. These studies were carried on various proprietary products prepared from the same medicinal herb. Boye and colleagues indicated that total parasite clearance for all participants was reached by 3.3 days after treatment compared to 2.2 days for chloroquine the standard conventional antimalarial treatment at that time. The product tested by the author was an older formulation of the current one under assessment in this report (Addae-Kyereme, 2004). This previous formulation was administered at a dose of 90mls three times a day compared to the current one which is at a dose of 30mls three times a day. The communited dried roots of the plant administered as an infusion, was also evaluated for its antimalarial effect by Bugyei and colleagues. The authors reported that 50 % of study subjects were cleared of P. falciparum parasites by 72 hours, and all parasites by Day 7. Presenting symptoms such as fever, chills, nausea and vomiting were all rapidly cleared by Day 3 (Bugyei, Boye and Addy, 2010).

Parasite recrudescence was also absent among the study population. Participants were followed up for a minimum 30

days to measure the risk of recrudescence that may be associated with the product as high incidence would make the plant unsuitable for use as an antimalarial. Blood film performed during the follow up period for all the participants was negative for malaria parasites. A similar low rate of recrudescence has been reported among treated subjects with 2 (6.5%) participants out of a total of 44 having a positive blood films on Day 21 and 28 post treatment (Bugyei, Boye and Addy, 2010). The absence of blood parasitaemia post treatment for the period of the follow up in our report may point to a possible protection from reinfection and some prophylactic property of the plant that may need further investigation.

The study adds to the evidence backing the role herbal medicines can play as first-line antimalarial agents. The adoption of proven agents like *C. sanguinolenta* can reduce the time to first treatment which may in turn decrease the risk of complications and mortality associated with malaria. Again, the risk of drug resistance commonly associated with allopathic medicines can be greatly reduced when such herbal medicines are considered for first-line treatment. In the broader context, the ability of such prospective plants to serve as complementary or alternatives to current treatment regimen is very important if the goals of primary healthcare are to be achieved in Africa. Indeed, prospective medicinal herbs should not be ignored just because targeted chemical isolates do not exhibit expected biological activity.

In concluding, *Cryptolepis sanguinolenta* may therefore be a safe and efficacious herbal medicine that has the potential of serving as a recognised first-line antimalarial treatment. Similarly, there is the need to evaluate commonly used Phyto remedies to ensure the public is protected.

Conflict of Interest Statement

All authors associated with this manuscript have no conflicts of interest to declare.

Acknowledgements

Authors are very grateful for the technical assistance offered by the Scientific Information Department, Clinical Laboratory Unit of the CMPR and the participants who volunteered for the study

REFERENCES

Addae-Kyereme, J. (2004) '*Cryptolepis sanguinolenta*', in Willcox, M., Bodeker, G., and Rasoanaivo, P. (eds) *Traditional Herbal Medicines for Modern Times*. New York, USA: CRC Press, pp. 145–154.

Agboke, A. A., Attama, A. A. and Momoh, M. A. (2011) 'Evaluation of the antimicrobial activities of crude extract of *Cryptolepis sanguinolenta* and Crateva adansonii leaves and their interactions', *Journal of Applied Pharmaceutical Science*, 1(10), pp. 85–89.

Akhigbe, R. and Ajayi, A. (2012) 'Antifertility activity of *Cryptolepis sanguinolenta* leaf ethanolic extract in male rats', *Journal of Human Reproductive Sciences*, 5(1), p. 43. doi: 10.4103/0974-1208.97799.

Ameyaw, Y. (2012) 'Morpho-Histological Characters for the Identification of *Cryptolepis sanguinolenta* (Lindl .) Schtr .', *International journal of science and nature*, 3(2), pp. 331–339.

Ansah, C. *et al.* (2010) 'Reproductive and developmental toxicity of *Cryptolepis sanguinolenta* in mice', *Research Journal of Pharmacology*, 4(1), pp. 9–14. doi: 10.3923/rjpharm.2010.9.14.

Ansah, C. and Gooderham, N. J. (2002) 'The popular herbal antimalarial, extract of *Cryptolepis sanguinolenta*, is potently cytotoxic', *Toxicological Sciences*, 70(2), pp. 245–251. doi: 10.1093/toxsci/70.2.245.

Ansah, C. and Mensah, K. B. (2013) 'A review of the anticancer potential of the antimalarial herbal *Cryptolepis sanguinolenta* and its major alkaloid cryptolepine.', *Ghana medical journal*, 47(3), pp. 137–47. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3875281&tool=pmcentrez&rendertype=abstract.

Appiah, A. A. (2009) 'The golden roots of *Cryptolepis sanguinolenta*', in *ACS Symposium Series*, pp. 231–239. doi: 10.1021/bk-2009-1021.ch013.

Bandaranayake, W. (2006) *Quality control, screening, toxicity, and regulation of herbal drugs. Modern Phytomedicine Turning Medicinal Plants into Drugs.* Edited by I. Ahmad, F. Aqil, and M. Owai. Weinheim: Wiley-VCH GmbH & Co. KGaA.

Barku, V. Y. A., Opoku-Boahen, Y. and Dzotsi, E. Y. (2012) 'Isolation and pharmacological activities of alkaloids from *Cryptolepis sanguinolenta* (Lindl) schlt', *International Research Journal of Biochemistry and Bioinformatics*, 2(3), pp. 58–61.

Barrett, K. and Bannister, K. (2000) *Intellectual Property Right: Culture as a Commodity*, *Culture Survival*. Available at: http://www.culturalsurvival.org/publications/cultural-survival-quarterly/none/challengingstatus-quo-e (Accessed: 11 November 2017).

Batista, R., De Jesus Silva Júnior, A. and De Oliveira, A. B. (2009) 'Plant-derived antimalarial agents: New leads and efficient phytomedicines. part II. non-alkaloidal natural products', *Molecules*, pp. 3037–3072. doi: 10.3390/molecules14083037.

Biamonte, M. A., Wanner, J. and Le Roch, K. G. (2013) 'Recent advances in malaria drug discovery', *Bioorganic and Medicinal Chemistry Letters*, pp. 2829–2843. doi: 10.1016/j.bmcl.2013.03.067.

Bugyei, K. a, Boye, G. L. and Addy, M. E. (2010) 'Clinical efficacy of a tea-bag formulation of *Cryptolepis sanguinolenta* root in the treatment of acute uncomplicated falciparum malaria.', *Ghana medical journal*, 44(1), pp. 3–9.

Chinsembu, K. C. (2015) 'Plants as antimalarial agents in Sub-Saharan Africa', *Acta Tropica*, pp. 32–48. doi: 10.1016/j.actatropica.2015.08.009.

Chothani, D. L. and Vaghasiya, H. (2011) 'A review on Balanites aegyptiaca Del (desert date): phytochemical constituents, traditional uses, and pharmacological activity', *Pharmacogn Rev*, 5. doi: 10.4103/0973-7847.79100.

Cimanga K, De-Bruyne T, Lasure A, Van-Poel B, Pieters L, Claeys M, Vlietinck AJ. In vitro biological activities of alkaloids from *Cryptolepis sanguinolenta*. Planta Med 1996; 62: 22-27.

Cimanga, K. *et al.* (1997) 'In vitro and *in vivo* antiplasmodial activity of cryptolepine and related alkaloids from *Cryptolepis*

sanguinolenta', *Journal of Natural Products*, 60(7), pp. 688–691. doi: 10.1021/np9605246.

Fabricant, D. and Farnsworth, N. (2001) 'The value of plants used in traditional medicine for drug discovery.', *Environmental Health Perspectives*, 1.

Grellier P, Ramiaramanana L, Millerioux V, Deharo E, Schrevel J, Frappler F, Francois T, Bernard B and Jean-Louis P (1996) 'Antimalarial activity of cryptolepine and isocryptolepine, alkaloids isolated from *Cryptolepis sanguinolenta*', *Phytotherapy Research*, 10(4), pp. 317–321.

Kaur K1, Jain M, Kaur T, Jain R. (2009) 'Antimalarials from nature', *Bioorganic and Medicinal Chemistry*, pp. 3229–3256. doi: 10.1016/j.bmc.2009.02.050.

Kirby, G. C. A. Paine, D. C. Warhurst, B. K. Noamese, J. D. Phillipson (1995) 'In vitro and in vivo antimalarial activity of cryptolepine, a plant-derived indoloquinoline', *Phytotherapy Research*, pp. 359–363.

Kirimuhuzya Claude (2012) 'Efficacy of *Cryptolepis sanguinolenta* root extract on slow-growing rifampicin resistant Mycobacterium tuberculosis', *Journal of Medicinal Plants Research*, 6(7). doi: 10.5897/JMPR10.856.

Komlaga G, Agyare C, Dickson RA, Mensah ML, Annan K, Loiseau PM, Champy P (2015) 'Medicinal plants and finished marketed herbal products used in the treatment of malaria in the Ashanti region, Ghana', *Journal of Ethnopharmacology*, 22;172:333-46

Oliveira, A. B., Maria Fâni Dolabela M.F,. Braga F.C, Rose L.R.P. Jácome, Fernando P. Varotti and Marinete M. Póvoa (2009): 'Plant-derived antimalarial agents: New leads and efficient phythomedicines. Part I. alkaloids', *Anais da Academia Brasileira de Ciencias*, 81(4), pp. 715–740.

Olufunke, M. D. (2012) 'Developments in Phytochemistry', in Vallisuta, O. and Suleiman, M. O. (eds) *Drug Discovery Research in Pharmacognosy*. Rijeka, Croatia: Intech, p. 244.

Paulo, A. *et al.* (2000): Antiplasmodial activity of *Cryptolepis sanguinolenta* alkaloids from leaves and roots.', *Planta medica*, 66, pp. 30–34. doi: 10.1055/s-2000-11106.

Rivera, J. O., Loya, R. and Ceballos, A. M. (2013) 'Use of Herbal Medicines and Implications for Conventional Drug Therapy Medical Sciences', *Altern Integ Med*, 2, p. 130.

Saxena S, N. Pant, D. C. Jain, and R. S. Bhakuni (2003): Antimalarial agents from plant sources," Current Science, vol. 85, no. 9, pp. 1314–1329

WHO (2001) *Legal Status of Traditional Medicine and Complementary/Alternative Medicine: A Worldwide Review*. Geneva.

Willcox, M. L. and Bodeker, G. (2004) 'Traditional herbal medicines for malaria.', *BMJ (Clinical research ed.)*, 329(7475), pp. 1156–9. doi: 10.1136/bmj.329.7475.1156