

EXTRACT OF *Morinda lucida* LEAF RESCUES HYPOGLYCAEMIC AND DYSLIPIDAEMIC CONDITIONS IN *Plasmodium berghei*-INFECTED MICE

ADAM OLAITAN ABDULKAREEM^{1,4,*}, ABDULKAREEM OLAREWAJU BABAMALE^{2,5},
ABASS TOBA ANIFOWOSHE^{6,7}, OLUFUNKE ADENIKE OPEYEMI², NUSIRAT
OLORIEGBE¹, COMFORT ADAMOLEKUN², SAMSON ADETULA¹, ADEOLA
ADEFOLUKE ALA³

¹Animal Physiology Unit, Department of Zoology, University of Ilorin, Ilorin, Nigeria

²Parasitology Unit, Department of Zoology, University of Ilorin, Ilorin, Nigeria

³Animal Physiology Unit, Department of Zoology, University of Ibadan, Ibadan, Nigeria

⁴Pharmacology Division, CSIR-Central Drug Research Institute, Lucknow, India

⁵Taiwan International Graduate Program in Molecular Medicine, National Yang-Ming Chiao Tung University and Academia Sinica, Taipei Taiwan

⁶Department of Molecular Reproduction, Development and Genetics, Indian Institute of Science, Bangalore, India

⁷Department of Zoology, Faculty of Life Sciences, University of Ilorin, Ilorin, Nigeria

ABSTRACT

Increasing drug resistance is a great threat to malaria control. Therefore, a continuous investigation into alternative therapy to mitigate malaria-associated damages is important. In this study, we investigated the anti-hypoglycaemic and anti-hyperlipidaemic effects of aqueous extract of *Morinda lucida* leaf in *Plasmodium berghei*-infected mice. Twenty-five mice were randomly grouped into five: Uninfected, infected-untreated, chloroquine (20 mg/kg, per oral), and extract-treated (400 mg/kg and 800 mg/kg, respectively, per oral) groups. Fasting blood glucose was measured before parasite inoculation and after the last treatment. Blood was collected for lipid profile assay at the end of the 4-day treatment. Our results revealed that both chloroquine and the extract lowered parasite growth ($p < 0.05$), while chloroquine and 400 mg/kg of the extract improved blood glucose in *Plasmodium berghei*-infection. More so, all the treated groups showed attenuated *Plasmodium berghei*-induced dyslipidaemia, with 400 mg/kg of the extract exhibiting better efficacy. Therefore, this study suggests that *Morinda lucida* leaf extract can be harnessed as a therapeutic regimen for improved malaria treatments and associated complications. Further study is recommended to elucidate the mechanism of anti-hypoglycaemic and anti-hyperlipidaemic activities of the extract and the possible bioactive compound(s) involved.

Keywords: Malaria, Hypoglycaemia, Dyslipidaemia, *Morinda lucida*, *Plasmodium berghei*.

INTRODUCTION

Despite a remarkable reduction in global incidence and mortality rate in the previous decade, malaria remains one of the life-threatening diseases, especially in sub-Saharan Africa and Southeast Asia (WHO, 2020). As of 2018, these regions accounted for approximately 85% of global malaria deaths, most of which occur in children under five. Meanwhile, Nigeria with 23%, leads the six most affected countries, followed by the Democratic Republic of the Congo (11%). Others include the United Republic of Tanzania (5%), Burkina Faso, Mozambique, and Niger (4% each) (WHO, 2019). The majority of malaria-related death in sub-Saharan Africa, including Nigeria, is attributed to *Plasmodium falciparum* (Satish & Ranjana, 2013; Oladeji et al., 2020a) with complex pathological progression as

previously reported (Babamale et al., 2017; Geleta & Ketema, 2016; Plewes et al., 2018).

During adaptation to the intracellular compartment of the host's erythrocyte, *Plasmodium* spp. require a large amount of glucose. Therefore, they increase their hexose permeability through hexose transporter of the erythrocyte for improved glucose uptake that then results in reduced host blood glucose level -a condition called hypoglycemia, accompanied by suppression of erythropoiesis (Zijlmans et al., 2014; Pathak & Gosh, 2016). This is the hallmark of several pathological conditions such as anaemia, thrombocytopenia, and nutrient deficiency that are associated with severe malaria, as reported (Slavic et al., 2010; Babamale et al., 2017; Plewes et al., 2018).

Lipid derangement is another diagnostic and prognostic indicator of parasitic infection, including malaria (Mohapatra et al. 2014, Kullu et al., 2018). Lipids play crucial roles in *Plasmodium* spp. metabolism, facilitating their proliferation and transmission (Gulati et al., 2015; Kilian et al., 2018). Their quest

*Corresponding author: abdulkareem.ao@unilorin.edu.ng

for host lipids during the pre-erythrocytic stage of development leads to a lipid homeostatic imbalance and hepatocellular damage (Warjri et al., 2016).

Multiple drug resistance has been a major setback in combating malaria and its complicated outcome until the discovery of Artemisinin-based Combination Therapy (ACT) in the 20th century. The efficacy of ACT was again short-lived by resistance (WHO, 2015), thus necessitating the continuous search for alternative antimalarial drugs that are not only safe but are also accessible and affordable. In many African countries, the use of medicinal plants and their products has gained tremendous recognition as an alternative treatment strategy for many infectious diseases, including malaria (Idowu et al., 2010; Oladeji et al., 2020b). One of such medically-important plants is *Morinda lucida*- a tropical rainforest plant (family Rubiaceae) which occurs throughout the year in the South-Western part of Nigeria (Adeneye, 2013; Adeleye et al., 2018; Oladeji et al., 2020a).

Despite the wide usage of crude extracts of the plant for local malaria treatment in Nigeria (Adebayo et al., 2010, Idih et al., 2017; Afolabi & Abejide, 2020), information regarding the efficiency of *M. lucida* on malaria-induced hypoglycaemia and dyslipidaemia is scarce. Therefore, this study investigated the effect of aqueous leaf extract of *M. lucida* on blood glucose and lipid profile in *P. berghei*-infected mice. We reported that the extract has the potential to ameliorate pathological alterations in the glucose and lipid profiles of the infected mice.

MATERIALS AND METHODS

Plant collection, identification and extraction

The fresh leaves of *M. lucida* were obtained from Rot-Tund farms Nigeria investment limited, Ila-Orangun, Osun State, Nigeria, and identified at Forest Research Institute of Nigeria, Ibadan, Nigeria. The modified method of Ojewunmi et al. (2013) was used for the extraction. Briefly, the plant was thoroughly washed, air-dried at room temperature, and macerated. Macerated leaf (100 g) was soaked in 1000 mL of distilled water and stirred intermittently for 24 hours. Thereafter, the mixture was filtered with muslin cloth and then with filter paper. The filtrate was evaporated to dryness using a rotary evaporator at 55°C. The extract was refrigerated at 4 °C before use.

Experimental animals

Twenty-five male Swiss albino mice with an average weight of 20g were obtained from the central animal house, Department of Anatomy, University of Ibadan, Ibadan Oyo state. They were subsequently transferred to the animal house, Zoology department, University of Ilorin, for acclimation and experimental set-up under standard conditions including free access to food and clean water. The rats were handled in accordance with the rules and regulations of the Animals Care

and Use Committee (ACUC) and the Institutional Ethical Review Board of the University of Ilorin throughout the study.

Parasite inoculation

Plasmodium berghei (ANKA strain)-bearing mice were obtained from the laboratory, Biochemistry Department, University of Ilorin, Ilorin, Nigeria. 1ml of blood was taken from donor mice and diluted with normal saline; such that 0.2 ml of the infected blood contained inoculums of 1×10^7 infected red blood cells. Twenty out of the total used parasite-free mice were inoculated intraperitoneally with 0.2 ml of infected blood and parasites were allowed to incubate before treatment commenced.

Experimental design and animal grouping

After parasite incubation, the mice were randomly grouped as follows: Groups 1 (uninfected) and 2 (infected-untreated): received distilled water. Group 3 (chloroquine): infected and treated with 20 mg/kg body weight (b.w) chloroquine. Groups 4 and 5 (extract): infected and treated with 400 mg/kg and 800 mg/kg b.w aqueous extract of *M. lucida* leaf, respectively. Both the vehicle (distilled water) and the extract were orally administered for 4 days.

Estimation of parasitaemia and percentage parasite inhibition

Blood was obtained from the caudal tip of the animals on the first treatment day (Day 0), smeared on a clean glass slide, and stained with Giemsa for parasite count. The procedure was repeated on Days 2 and 4. The parasitaemia and percentage (%) parasite inhibition were then determined as previously described (Adetutu et al., 2016).

Blood glucose determination

The blood glucose was measured by obtaining a drop of blood from the tail after a 24hr fast using a Glucometer (Elased et al., 1996). Fasting blood glucose was measured before parasite inoculation and after the last treatment.

Lipid profile assay

Estimations of total cholesterol (TC) and triglyceride (TG) were carried out by colorimetric methods, using assay kit obtained from Fortress Diagnostics Ltd. (Antrim, United Kingdom). High-density lipoprotein (HDL)-cholesterol concentration was estimated using the precipitation method of Warmick et al. (1982), while low-density lipoprotein (LDL)-cholesterol was estimated using modified Friedewald's formula (Friedewald et al., 1972).

RESULTS

Aqueous extract of Morinda lucida inhibits plasmodia growth in P. berghei mice

The efficacy of malaria therapy is a measurement of its ability to reduce the burden of the infection associated with

parasite proliferation. Our data in Table 1 show that *P. berghei* infection significantly increased ($p < 0.05$) parasitaemia after a 4-day curative test. However, treatments with chloroquine (CQ) and aqueous leaf extract of *M. lucida* lowered ($p < 0.05$) the parasitaemia and significantly inhibited ($p < 0.05$) parasite proliferation (Fig. 1). Percentage parasite inhibition recorded in the CQ-treated group (75.88 %) was higher than the values observed in groups treated with 400 mg/kg extract (52.79 %) and 800 mg/kg extract (51.34 %).

Table 1. Effect of aqueous extract of *Morinda lucida* on parasitaemia (% infected RBC) in *Plasmodium berghei*-infected mice. Both chloroquine and aqueous extract of *M. lucida* leaf significantly lowered parasitaemia in *P. berghei*-infected mice.

Parasitaemia(%)			
GROUPS	DAY 0	DAY 2	DAY 4
Uninfected	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Infected untreated	27.32 ± 0.61	36.40 ± 3.58	41.22 ± 3.49*
CQ	89.95 ± 5.45	27.15 ± 1.73***	21.70 ± 2.30***
400mg/kg	64.60 ± 2.31	56.60 ± 6.57	30.50 ± 1.73**
800mg/kg	39.25 ± 6.00	34.00 ± 2.31	19.10 ± 1.15*

* $p < 0.05$ vs Day 0; ** $p < 0.01$ vs Day 0; *** $p < 0.001$ vs Day 0 (n=3).

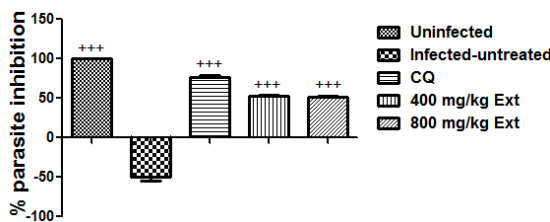


Figure 1. Inhibitory effect of chloroquine (CQ) and aqueous extract of *Morinda lucida* (Ext) on *P. berghei* growth in mice. There was progressive parasite growth in the infected-untreated group, whereas, CQ and Ext significantly inhibited parasite growth, on Day 4 post-treatment. Values were expressed as mean ± S.E.M of 3 mice per group (+++ $p < 0.001$ vs infected-untreated).

Aqueous extract of Morinda lucida improves fasting blood glucose and lipid profile

Table 2. Effect of aqueous extract of *Morinda lucida* on lipid profile (mg/dL) in *Plasmodium berghei*-infected mice. Both chloroquine and aqueous extract of *M. lucida* significantly reduced total cholesterol and low-density lipoprotein cholesterol in *P. berghei*-infected mice.

Parameters (mg/dL)	Uninfected	Infected-untreated	CQ	400 mg/kg Ext	800 mg/kg Ext
Total Cholesterol	104.4 ± 8.08	143.4 ± 5.19*	100.2 ± 6.35**	90.75 ± 5.19**	113.7 ± 5.75
Triglyceride	62.90 ± 2.88	62.73 ± 1.73	72.93 ± 4.04	63.57 ± 2.88	50.72 ± 4.61
HDL-c	54.13 ± 2.88	46.69 ± 2.88	47.11 ± 4.04	50.41 ± 2.30	49.59 ± 2.88
LDL-c	64.92 ± 4.04	109.2 ± 8.08**	67.72 ± 5.19**	53.25 ± 5.77***	74.25 ± 6.92 ⁺

* $p < 0.05$ vs uninfected; ** $p < 0.01$ vs uninfected; + $p < 0.05$ vs infected-untreated; ++ $p < 0.01$ vs infected-untreated; *** $p < 0.001$ vs infected-untreated (n=3). HDL-c, high-density lipoprotein-cholesterol; LDL-c, low density lipoprotein-cholesterol.

Hypoglycaemia and lipid derangements are important prognostic indicators of malaria complications; hence, amelioration of hypoglycaemia and dyslipidaemia offers a better treatment option in malarial infection. Our results reveal that, *Plasmodium berghei* infection significantly lowered fasting blood glucose level by Day 4 post-treatment ($p < 0.05$) compared with the uninfected group (Fig 2). In contrast, both chloroquine and 400 mg/kg *M. lucida* aqueous leaf extract improved the fasting blood glucose. On the other hand, total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-c) levels were higher ($p < 0.05$) in the infected-untreated group compared with the uninfected group (Table 2). Treatments with chloroquine and aqueous leaf extract of *M. lucida* significantly reduced ($p < 0.05$) both TC and LDL-c, with the best effect in 400 mg/kg extract. No significant differences were observed in triglycerides and high-density lipoprotein-cholesterol (HDL-c) levels, though; there was a slight decrease in HDL-c level in the infected-untreated level when compared with the uninfected group which was relatively improved in all the treated groups.

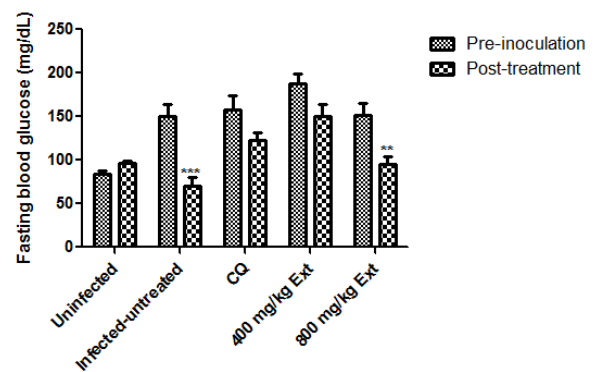


Figure 2. Effect of chloroquine (CQ) and aqueous extract of *Morinda lucida* (Ext) on fasting blood glucose in *Plasmodium berghei*-infected mice. *P. berghei* infection significantly decreased ($p < 0.001$) fasting blood glucose in mice while both CQ and 400 mg/kg Ext improved the fasting blood glucose after 4-day treatment. Values were expressed as mean ± S.E.M of 3 mice per group (** $p < 0.01$ vs pre-inoculation of the same group; *** $p < 0.001$ vs pre-inoculation of the same group).

DISCUSSION

The pathological impact of aqueous leaf extract of *M. lucida* was investigated in this study. The results showed that 400 mg/kg and 800 mg/kg aqueous extract of *M. lucida* leaf significantly reduced *P. berghei* proliferation in mice. We also showed that the extract (400 mg/kg) improved fasting blood glucose and dyslipidaemia in *P. berghei* infection. Comparatively, our findings emphasized that 400 mg/kg of aqueous leaf extract of *M. lucida* efficiently ameliorated *P. berghei*-associated dyslipidaemia better than 800 mg/kg of the extract and chloroquine.

Our findings of a higher curative effect in rats treated with 400 mg/kg extract, compared to those treated with 800 mg/kg, agree with the previous study of Afolabi and Abejide (2020) where the lowest of the used doses of *M. lucida* plant extract showed a highest curative effect in *P. berghei*-infected mice. However, 52.79 % parasite inhibition observed in the 400 mg/kg extract-treated group of this study is lower than the 83 % curative effect reported in their study. Similarly, the anti-plasmodial activity of *M. lucida* leaf extract reported in our study is lower than that earlier reported by Idowu et al. (2014). The difference in these findings may be due to the different extracting solvents used, period of extraction, and/or varied sites of leaf collection. Extracting solvent and the geographical location of a plant are key important factors that affect the quantitative yield of a plant's bioactive components, thereby affecting its presumed medicinal activity (Sultana et al., 2009; Gupta et al., 2011).

Hypoglycaemia is a common complication of malaria in pregnant women and children, which increases the risk of mortality in them (Ounjaijean et al., 2019). In this study, *P. berghei* infection resulted in decreased fasting blood glucose. This concurs with previous findings (Sihabud et al., 2015; Ounjaijeana et al., 2018). Although the underlying mechanism of hypoglycaemia in malaria is not well understood, increasing evidence suggests that suppression of gluconeogenesis by the parasites, and the host's inability to compensate for the parasite glucose uptake play major roles (Mehta et al., 2005; Zijlmans et al., 2014). Thus, the hypoglycaemia observed in this study following *P. berghei* infection may be attributed to increased glucose uptake by the parasite without compensatory production in the hosts. Administration of 400 mg/kg aqueous extract of *M. lucida* leaf improved blood glucose level, which compares favourably with chloroquine's effect. The observed improvement in blood glucose in the 400 mg/kg administered group may imply that the lower dose of *M. lucida* leaf extract enhanced gluconeogenesis in the hosts or it inhibited hexose transporter of the infected erythrocytes, thereby decreasing glucose uptake by the parasite (Ruan et al., 2012; Ahmad et al., 2016). Lipid metabolism is compromised during the exoerythrocytic stage of *Plasmodium* in parenchyma and Kupffer cells, leading to alterations in lipid profile and

subsequently dyslipidaemia (Oluba et al., 2012). The present study shows evidence of dyslipidaemia in *P. berghei* infection. This is in conformity with the previous studies that demonstrated increased TC and LDL-c in human and rodent malaria (Ngou-Milama et al., 1995; Krishna et al., 2009; Jacob, 2014) and rodents (Joshua et al., 2020). Treatments with both chloroquine and the extract lowered TC and LDL-c in *P. berghei*-infected mice, suggesting the efficiency of the extract in mitigating malaria-induced dyslipidaemia. However, a better ameliorative effect was observed in the 400 mg/kg extract-treated group. This may imply that aqueous extract of *M. lucida* leaf at 400 mg/kg possesses a better therapeutic potential to suppress dyslipidaemia in malaria than chloroquine.

Aqueous leaf extract of *M. lucida* has been previously shown to possess flavonoids, among other bioactive components (Unekwujo et al., 2011). Flavonoids are known for their antioxidant and anti-inflammatory properties. They can also inhibit low-density lipoprotein (LDL) oxidation and regulate serum lipid metabolism (Kerry & Abbey, 1997; Chen et al., 2011). Therefore, the anti-hyperlipidaemic effect of *M. lucida* leaf extract observed in the present study may be due to the bioactive components of the extract, especially flavonoids, which then aid in bringing lipid metabolism back to normal.

CONCLUSION

This study justifies the common practice of using *M. lucida* crude extracts for malaria treatment in the South-Western part of Nigeria. It also demonstrates that the aqueous extract of *M. lucida* leaf improved blood glucose and ameliorated lipid profile derangement in *P. berghei*-infected mice. We, therefore, suggest that *M. lucida* leaf extract can be harnessed as a therapeutic regimen for better treatment of malaria and associated complications. Further study is recommended to investigate the mechanism of anti-hypoglycaemic and anti-hyperlipidaemic activities of the extract and the possible bioactive compound(s) involved.

REFERENCES

- Adebayo, N. S., Abubakar, A. A., Emmanuel, A. S., Oluwabunmi, S. B., Ifeoluwa, J. D. & Blessing, O. 2020. Phyto Chemical Screening and Antiplasmodial Potential of *Morinda lucida* (Brimstone Leave) In Infected Mice. *J. Middle East North Afr. sci.*
- Adeleye, O. O., Ayeni, O. J. & Ajamu, M. A. 2018. Traditional and medicinal uses of *Morinda lucida*. *J. Med. Plants.*
- Adeneye, A. A. 2013. Profile of *Morinda lucida* leaf fractions on blood glucose and lipids in normal and Alloxan-induced hyperglycaemic rats. *Pharmacologia.*
- Adetutu, A., Olorunnisola, O. S., Owoade, A. O., Owoade, A. O. & Adegbola P. 2016. Inhibition of in vivo growth of *Plasmodium berghei* by *Launaeataraxacifolia* and

- Amaranthus viridis* in mice. *Malar Res Treat*. <https://doi.org/10.1155/2016/9248024>
- Afolabi, O. J. & Abejide, A. E. 2020. Antiplasmodial activities of *Morinda lucida* (Benth) and *Alstonia boonei* (De wild) in mice infected with *Plasmodium berghei*. *Bulletin of the National Research Centre*. <https://doi.org/10.1186/s42269-020-00342-8>
- Ahmad, W., Jantan, I. & Bukhari, S. N. 2016. *Tinosporacrispa* (L.) Hook. f. & Thomson: A Review of Its Ethnobotanical, Phytochemical, and Pharmacological Aspects. *Front. Pharmacol.* <https://doi.org/10.3389/fphar.2016.00059>
- Babamale, O. A., Abdulkareem, A. O., Akande, A. O., Afolayan, M. A. & Ugbomoiko, U. S. 2017. Malaria-induced anaemia and serum micronutrients in asymptomatic *Plasmodium falciparum* infected patients. *J Parasit Dis*.
- Babamale, O. A., Abdulkareem, A. O., Opeyemi, O. A. & Ugbomoiko, U. S. 2017. Alterations in T-helper cell type 1 and blood cell parameters in malaria-infected patients. *Egypt. j. basic appl. sci.* <http://doi10.1007/s12639-017-0940-4>
- Chen, L., Ma, X. B., Liang, Y. H., Pei, S. C., Feng, Y. P. & Wei, M. 2011. Effects of persimmon leaf total flavonoid on enzyme of lipoprotein metabolism and antioxidation in hyperlipidemia rats. *Chin. J. Nat. Med.*
- Elased, K. M., Taverne, J. & Playfair, J. H. L. 1996. Malaria, blood glucose, and the role of tumour necrosis factor (TNF) in mice. *Clin Exp Immunol.* 105, pp. 443-449.
- Friedewald, W. T., Levy, R. I. & Fredrickson, D. S. 1972. Estimation of the concentration of low density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem.*
- Geleta, G. & Ketema, T. 2016. Severe Malaria Associated with *Plasmodium falciparum* and *P. vivax* among Children in Pawe Hospital, Northwest Ethiopia. *Malar Res Treat*. <http://dx.doi.org/10.1155/2016/1240962>
- Gulati, S., Ekland, E. H., Ruggles, K. V., Chan, R. B., Jayabalasingham, B., Zhou, B., Mantel P. Y., Lee M.C., Spottiswoode, N., Coburn-Flynn O., Hjelmqvist D., Worgall T. S., Marti M., Di Paolo G. & Fidock D. A. 2015. Profiling the essential nature of lipid metabolism in asexual blood and gametocyte stages of *Plasmodium falciparum*. *Cell Host Microbe*.
- Gupta, S., Bhaskar, G. & Andola C. H. 2011. Altitudinal variation in essential oil content in leaves of *Zanthoxylum alatum* a high value aromatic tree from Uttarakhand. *Res. J. Med. Plants*.
- Idih, F. M., Ighorodje-Monago, C. C. & Ezim O. E. 2017. Antiplasmodial Effect of Ethanol Extract of *Morinda lucida* and *Mucuna pruriens* Leaves on NK65 Chloroquine Resistant Strain of *Plasmodium berghei* in Mice. *Clin Exp Pharmacol.* <https://doi.org/10.4172/2161-1459.1000234>
- Idowu, O. A., Babalola, A. S., Adenubi, O. T. & Olukunle, J. O. 2014. Anti-plasmodial activities of combined extracts of *Morinda morindoides*, *Morinda lucida* and *Vernonia amygdalina* in *Plasmodium berghei* infected-mice. *Zoologist (The)*.
- Idowu, O. A., Soniran, O. T., Ajana, O. & Aworinde, D. O. 2010. Ethnobotanical survey of antimalarial plants used in Ogun State, Southwest Nigeria. *Afr. J. Pharm. Pharmacol.* Jacob, E. A. 2014. Assessment of Altered Plasma Lipid Pattern in *Plasmodium Falciparum* Malaria Infected and Non Infected Individuals. *Int J Blood Res Disord*.
- Jacob E. A. 2014. Assessment of Altered Plasma Lipid Pattern in *Plasmodium Falciparum* Malaria Infected and Non Infected Individuals. *Int J Blood Res Disord*. <https://doi.org/10.12691/ijhd-1-1-5>
- Joshua, P. E., Okoro, I. J., Ekpo, D. E., Okagu, I. U. & Ogugua V. N. 2020. Methanol extract of *Erythrina senegalensis* leaves (MEES) ameliorates *Plasmodium berghei*-ANKA 65-parasitised aberrations in mice. *All Life*. <https://doi.org/10.1080/26895293.2020.1718777>
- Kerry, N. & Abbey M. 1997. Red wine and fractionated phenolic compounds prepared from red wine inhibit low density lipoprotein oxidation in vitro. *Atherosclerosis*.
- Kilian, N., Choi, J., Voelker, D. R. & Mamoun, C. B. 2018. Role of phospholipid synthesis in the development and differentiation of malaria parasites in the blood. *J. Biol. Chem.*
- Krishna, A. P., Chandrika, Kumar S., Acharya, M. & Patil S. L. 2009. Variation in common lipid parameters in malaria infected patients. *Indian J Physiol Pharmacol*.
- Kullu, B. K., Majhi, C., Pradhan, B. & Swain, D. K. 2018. Lipid profiles among *Plasmodium falciparum* infected, non malarial febrile patients and volunteers. *Int J Adv Med*.
- Mehta, M., Sonawat, H. M. & Sharma, S. 2005. Malaria parasite-infected erythrocytes inhibit glucose utilization in uninfected red cells. *FEBS Lett*.
- Mohapatra, S., Samantaray, J. C. & Ramakrishan, L. 2014. Lipid derangement as diagnostic and prognostic indicator for visceral leishmaniasis. *Trop Parasitol*.
- Ngou-Milama, E., Duong, T. H., Minko, F., Dufillot, D., Kombila, M., Richard-Lenoble, D. & Mouray, H. 1995. Lipid profile during specific malaria therapy in Gabonese children (in French). *Sante*.
- Ojewunmi, O., Oshodi T., Ogundele, O., Micah, C. & Adenekan S. 2013. Evaluation of the Anti-Diabetic and Antioxidant Activities of Aqueous Extracts of *Morinda lucida* and *Saccharum officinarum* Leaves in Alloxan-Induced Diabetic Rats. *Int J Biochem Res Rev*.
- Oladeji, O. S., Odelade, K. A. & Oloke J. K. 2019. Phytochemical screening and antimicrobial investigation of *Moringa oleifera* leaf extracts. *J. Sci. Technol. Innov. Dev*.
- Oladeji, O. S., Oluyori, A. P., Bankole, D. T. & Afolabi, T. Y. 2020. Natural Products as Sources of Antimalarial Drugs: Ethnobotanical and Ethnopharmacological Studies. *Scientifica*. <https://doi.org/10.1155/2020/7076139>
- Oluba, O. M., Olusola, A. O., Eidangbe, G. O., Babatola, L. J. & Onyeneke E. C. 2012. Modulation of lipoprotein cholesterol levels in *Plasmodium berghei* malarial infection by crude aqueous extract of *Ganoderma lucidum*. *Cholesterol*.
- Ounjaijeana, S., Chachiyob, S. & Somsak V. 2019. Hypoglycemia induced by *Plasmodium berghei* infection is prevented by treatment with *Tinosporacrispa* stem extract. *Parasitol. Int*.
- Pathak V. A. & Ghosh K. 2016. Erythropoiesis in Malaria Infections and Factors Modifying the Erythropoietic Response. *Anemia*. <https://doi.org/10.1155/2016/9310905>

- Plewes, K., Turner, G. D. H. & Dondorp, A. M. 2018. Pathophysiology, clinical presentation, and treatment of coma and acute kidney injury complicating falciparum malaria. *Curr Opin Infect Dis*.
- Ruan, C. T., Lam, S. H., Chi, T. C., Lee, S. S. & Su, M. J. 2012. Borapetoside C from *Tinosporacrispa* improves insulin sensitivity in diabetic mice. *Phytomedicine*.
- Satish, B. & Ranjana, K. 2013. Herbal plants used for the treatment of malaria- a literature review. *J PharmacogPhytochem*.
- Sihabud, M., Yongthawee, P., Chutoam, P., Klongthalay, S. & Somsak V. 2015. Effect of Black Tea Extract on Hypoglycemia Induced by *Plasmodium berghei* ANKA Infection in Mice. *Malar Cont Elimination*.
- Slavic, K., Straschil, U., Reininger, L., Doerig, C., Morin, C., Tewari, R. & Krishna, S. 2010. Life cycle studies of the hexose transporter of Plasmodium species and genetic validation of their essentiality. *Mol. Microbiol*.
- Sultana, B., Anwar, F. & Ashraf M. 2009. Effect of Extraction Solvent/Technique on the Antioxidant Activity of Selected Medicinal Plant Extracts. *Molecules*. <https://doi.org/10.3390/molecules14062167>
- Unekwujo, E. G., James, O. & Olubunmi A. R. 2011. Suppressive, Curative and Prophylactic Potentials of *Morinda lucida* (Benth) against Erythrocytic Stage of Mice Infective Chloroquine Sensitive *Plasmodium berghei* NK-65. *Br J Appl Sci Technol*.
- Warjri, S. B., Ete, T., Mishra, A., Barman, B., Mishra, J., Pala, S., Beyong, T. & Issar, N. K. 2016. Association between Clinical Malaria and Blood Lipids in North Eastern India.
- Warmick, G. R., Benderson, J. & Albers, J. J. 1982. Dextran sulphate-Mg²⁺ precipitation procedure for quantitation of high-density lipoprotein cholesterol. *Clin Chem*.
- WHO, World Malaria Report 2015. World Health Organization, Geneva, Switzerland.
- WHO, World Malaria Report 2019. World Health Organization, Geneva, Switzerland.
- WHO, World Malaria Report 2020. World Health Organization, Geneva, Switzerland.
- Zijlmans, W. C., van Kempen, A. A., Serlie, M. J., Kager, P. A. & Sauerwein, H. P. 2014. Adaptation of glucose metabolism to fasting in young children with infectious diseases: a perspective. *J Pediatr Endocrinol Metab*.