Journal of Medicinal Plants Research Vol. 3(3), pp. 148-154, March, 2009
Available online at http://www.academicjournals.org/JMPR
ISSN 1996-0875© 2009 Academic Journals

Full Length Research Paper

In vivo antiplasmodial, analgesic and anti-inflammatory activities of the leaf extract of *Lippia multiflora* mold

Ali A. Jigam[1]*, Helmina O. Akanya[1], Emmanuel O. Ogbadoyi[1], Bukar E. N. Dauda[2] and Egwim, C. Evans[2]

[1]Malaria and Trypanosomiasis Research Unit, Department of Biochemistry, Federal University of Technology, Minna, Nigeria.
[2]Department of Chemistry, Federal University of Technology, Minna, Nigeria.

Accepted 15 February, 2009

Leaf extracts of *Lippia multiflora* Mold have reputation in Northern Nigeria as remedy for different ailments including fevers attributed to malaria. The plant was hence analysed for safety, antiplasmodial activity against *Plasmodium berghei* in mice, analgesia and anti-inflammatory effects in rats. Crude extracts were further subjected to bioactivity-guided fractionation. The results showed leaf extracts had no adverse side effects at 800 mg/kg body weight (bw) with LD_{50} value of 3000 mg/kg bw. Significant ($p < 0.05$) suppressive but only slight curative and prophylactic effects of the crude extracts were obtained with parasitized mice. Also significant ($p < 0.05$) dose dependent analgesic and anti-inflammatory activities were obtained in rats treated with the extracts. Fractions obtained from the partial purification of crude *L. multiflora* Mold, extracts were individually found to be devoid of antiplasmodial action. Phytochemical screening indicated the presence of alkaloids, tannins, flavonoids, saponins and volatile oils.

Key words: *Plasmodium berghei,* analgesia, anti-inflammatory, bioactivity, prophylaxis, phytochemicals.

INTRODUCTION

Malaria is a disease experiencing a renaissance. It is transmitted by female anopheles mosquitoes and caused by four protozoan parasites *Plasmodium malarie, Plasmodium ovale, Plasmodium vivax* and *Plasmodium falciparum* (Cox, 2002). Recently *P. vivax* and most importantly *P. falciparum* have become resistant to commonly used therapeutic agents including aminoquinolines and antifolate drugs (Bloland, 2001). Unfortunately, *P. falciparum* accounts for 80% of all malaria infections and 90% of the disease (Carter et al., 2005). This in conjunction with failures in other control measures have led to an alarming rate of morbidity and mortality due to malaria. About 400 – 900 million acute infections and 3 million deaths occur annually representing at least one death every 30 seconds (Hay et al., 2004; Fletcher, 2007). A vast majority of cases occur in children under 5 years of age (Greenwood et al., 2005). Pregnant women are also vulnerable. Statistics are unreliable since many cases occur in rural areas without hospitals and hence remain undocumented. Malaria is a disease of poverty and underdevelopment such that 85 - 90% of fatalities occur in sub-Saharan Africa alone (Hay et al., 2004).

Viable and relevant vaccines are unavailable for most parasitic infections and in the case of malaria, despite much research a break through remains elusive (Giles, 2005; Matuscheski, 2006). Chemotherapy thus remains the fulcrum of malaria control. New drugs have to be sourced to replace those compromised by parasite resistance. The scientific evaluation of relevant medicinal plants used in traditional health care offers some hope in the identification of novel anti-malaria phamacophores (Okunji et al., 2000).

Lippia multiflora mold

The genus *Lippia* belongs to the family *verbanaceae* which includes approximately 200 species of herbs, shrubs and small trees (Munir, 1993). *L. multiflora* is a stout woody, perennial and aromatic shrub mainly distri-

*Corresponding author. E-mail: alijigam@yahoo.com. Tel.:+234 803 613 6862. Fax: +234 66 222422.

tributed throughout tropical Africa, South and Central American countries (Pascual et al., 2001). It occurs in a wide ecological range throughout West Africa. In undisturbed sites, the plant can grow to a height of 2.7 to 4.0 m. It possesses white, sweet-scented flowers stalked on cone-like heads in a terminal panicle nearly 120 mm long (Munir, 1993).

Lippia species have a long history of traditional medicinal application some of which have scientific validation. They are mostly used in the treatment of respiratory and gastro intestinal disorders. Additionally, they exhibit antimalarial, spasmolitic, sedative, hypotensive and anti-inflammatory activities (Pham et al., 1988a, 1988b; Abena et al., 1998).

In Nigeria, *L. multiflora* is commonly found along river beds in the central region around Abuja the federal capital territory. It is variously called bush tea, healer herb or *Bunsurun fadama* (Hausa, Northern Nigeria). The leaves are used by different tribes as a hot beverage. Tea-like infusions are used as remedy against malaria fever, stress, hypertension, conjunctivitis, veneral diseases and as a laxative (Oladimeji et al., 2000; Aquaye et al., 2001). Most of these effects have been attributed to the glycolside, essential oils and other phytochemical components of *Lippia* (Valentin et al., 1995; Terblanche and Korneliies, 1996; Taubi et al., 1997).

L. multiflora tea is commonly consumed in Northern Nigeria as remedy for malaria fever. Literature reports also indicate the plant as having antimalarial properties (Abena et al., 1998; Aquaye et al., 2001). Antiplasmodial, analgesic and anti-inflamatory tests were thus carried out with crude leaf extracts of the plant in an effort to validate such claims.

MATERIALS AND METHODS

Plant materials

Fresh leaves of *L. multiflora* mold were collected between March and April in Abuja, Northern Nigeria and authenticated at the Department of Biological Sciences, Federal University of Technology, Minna where a voucher specimen (FUT/BIOL/058) was also deposited.

Preparation of crude extracts

40 g of air dried leaves were micronised and extracted exhaustively (48 h) in the cold with 1.5 l each of hexane, (Sigma-Aldrich Europe), ethylacetate and methanol in that order. The marc was filtered with muslin cloth and solvents removed under reduced pressure in a rotary evaporator. Green coloured pastes were obtained and weighed prior to further analysis.

Animals

Healthy swiss albino mice of either sex of about 6 weeks old weighing between 20 – 30 g each and wister rats of about 180 – 200 g weights obtained from National Institute of Pharmaceutical Research and Development (NIPRD) Abuja, Nigerians were used for the experiments. The rodents were conveniently housed under standard environmental conditions, temperature 27 ± 2°C, 70% relative humidity, free access to commercial food pellets and water and natural 12 h day light/night cycles. Experiments were conducted in strict compliance with internationally accepted principles for laboratory animal use and care as contained in the Canadian Council on Animal Care Guildlines and Protocol Review (CCAC, 1997).

Parasites

P. berghei NK65 chloroquine sensitive strain was obtained from NIPRD Abuja, Nigeria and maintained in our laboratory by serial passage in mice.

Phytochemical analysis

Standard screening tests were used to detect secondary metabolites such as alkaloids, flavonoids, tannins, saponins, glycosides and volatile oils e.t.c. in the crude extract (Odebiyi and Sofowora, 1978, 1982 and 1986; Trease and Evans, 1989).

Safe dose and acute toxicity (LD_{50})

Five groups of four mice were used. The animals were given extracts intraperitoneally (i.p) at doses of 200, 400, 600, 800, 1200 mg/kg body weight (bw) respectively. Extracts were dissolved in dimethylsulphoxide (DMSO) (Sigma chemicals; St. Louis, M. O. USA).

A control group was given normal saline (0.9% w/v NaCl) at 20 ml/kg bw. Mice were observed over 72 h, clinical signs and mortality were recorded. LD_{50} was obtained as the intercept of % mortality (y-axis) and dosages (x-axis).

Antiplasmodial screening

Mice were pre-screened by microscopy of thin and thick tail tip blood smears. This was necessary to exclude the possibility of test animals harboring rodent *Plasmodium species.*

Suppressive test

The method by Fidock et al. (2004) was used. It involved treatment with the extract immediately after mice had been inoculated (early infection). Twenty four male and female mice were divided into four groups of six each. A mouse infected with *P. berghei* (parasitaemia of about 20 - 30%) was anaesthetized with chloroform and its blood collected by cardiac puncture with a sterile syringe and needle earlier flushed with heparin. The blood was diluted with normal saline such that 0.2 ml contained about 1×10^7 infected cells. Each of the twenty four clean mice were inoculated (i.p.) with 0.2 ml diluted blood. The extract at dose levels of 200 and 400 mg/kg bw respectively were administered subcutaneously once daily for four days (D0, D1, D2 and D3). A parallel test with chloroquine (5 mg/kg bw) in the third group served as reference. The fourth group was given normal saline and served as control. Thick and thin films were made from tail blood from D1 - D4, fixed with methanol and stained with 4% Giemsa (pH7.2) for 45 min before being examined under a microscope. Five fields were examined on each slide and the number of infected and uninfected red blood cells (RBC) counted and means taken.

Percentage suppression of parasitaemia was calculated using values from controls related to those of treated animals. Standard drug equivalent was also determined from the ratio of chloroquine (standard) dose to dose of test drug giving identical average per-

percentage suppression.

Curative test

This was similar to the suppressive test above except that treatment with the extract (200 and 400 mg/kg bw) and chloroquine (5 mg/kg bw) commenced on D3 and continued to D7 with simultaneous examination of parasitaemia on stated days. Means were taken and standard drug equivalent also calculated.

Prophylaxis

Twelve mice were kept in three groups of four animals each and administered 400 mg/kg bw (i.p) plant extracts for three days. A group was inoculated with *P. berghei* on D4, another on D7 and the third on D14. Equal number of untreated mice were also infected to serve as controls. Tail blood smears were examined from each group on the second and third days post inoculation and for twenty one days subsequently. At the end of this period, blood from the animals were injected into clean mice which were examined for infection over fourteen days. Percentage suppression of parasites and pyrimethamine (standard) equivalent dose were determined.

Analgesic activity

Analgesia was assessed by the method of Koster et al. (1959). Twenty four mice were divided into four groups. The extracts (200 and 400 mg/kg bw i.p.) were administered mice in groups A and B respectively an hour before they were challenged with acetic acid (0.75% v/v). Animals in group C were however pretreated with (Acetyl salicylic acid) (50 mg/kg bw i.p.) as reference drug while group D which were given normal saline (20 ml/kg bw) served as controls. 5 min were allowed to elapse before the number of abdominal constrictions induced by acetic acid were counted. Observations were made over 10 min and mean values for each group calculated. Percentage inhibition of abdominal constriction by the plant extracts at the two doses and ASA were determined in relation to the control. ASA equivalent was also calculated.

Anti-inflammatory activity

The anti-inflammatory activity of the extract was tested using egg albumin induced paw oedema in rats (Winter et al., 1962). Adult wister rats of either sex were divided six each per treatment group. Inflammation was induced by the injection of 0.01 ml egg albumin into the sub-planter surface on the right hind paw 30 min after administering the extracts (200/400 mg/kg bw i.p).

The increase in volume (cm^3) of the hind paw was measured with a LETICA digital Plethysmometer (LE 7500) before and at 20 min interval after the injection of egg albumin for a period of 2 h. Control rats received an equivalent amount of normal saline while ASA (150 mg/kg bw) served as reference. The percentage inhibition of oedema was calculated for each dose.

Extract purification

Air-dried *L. multiflora* leaves (80 g) were micronised and exhaustively (48 h) extracted in the cold sequentially with 1.5 L (x2) each of hexane, ethyl acetate and methanol. The marc was dried after extraction with a single solvent. The extracts were filtered using muslin cloth and the solvent recovered under reduced pressure with a rotary evaporator. The crude extracts were each weighed and employed in the mice challenged with *P. berghei.* The most promising methanolic extract was partitioned in chloroform and water (1:1) before subjecting the active chloroform fraction to column chromatography (3.0 cm i.d. x 30 cm) over silica gel (G60, 70 - 230 mesh; Merck). A mixture of methanol/hexane/ethylacatate/butanol (2:3:3:2) was used to elute the column. 4 bands were visible and collected as separate fractions. Each fractions were evaluated for activity against *P. berghei* in mice.

Statistical analysis

Results are expressed as mean ± S.E.M. between control and experimental animals in the groups. Statistical significance was analyzed by one way ANOVA and Duncan's post HOC tests between homogeneous subsets, Values of $P < 0.05$ were regarded as significant.

RESULTS

Crude extract yields were 1.8 g (hexane), 2.2 g (ethylacetate) and 3.6 g (methanol) corresponding with 23.68, 28.21 and 46.15%w/w respectively of the original dry leaves. Alkaloids, tannins, flavonoids, saponins and volatile oils were detected from phytochemical screening.

Safe dose and LD_{50} of crude extract

Doses below 800 mg/kg bw were safe and devoid of any adverse clinical symptoms, LD_{50} was 3000 mg/kg bw.

Antiplasmodial activity

Results of parasitological parameters

Parasite suppression

Table 1 indicates parasites were significantly suppressed using 400 mg/kg bw plant extract. Chloroquine standard gave an 86% suppressive effect. Chloroquine equivalent of the plant extract was calculated as 167.88.

Curative activity

Table 2 indicate the curative potential of *L. multiflora* extracts at 400 mg/kg bw to be minimal. Survival period (days) was high and the standard CQ treatment exhibited the highest number of days.

Prophylactic activity

Results of the prophylactic effects of crude extracts of *L. multiflora* in *P. berghei* infected mice are given in Table 3. Values ranged from only 1.32 - 8.94% compared to 80.96% for the standard pyrimethamine treatment.

Analgesia

Table 4 indicates significant analgesic activity by leaf extracts of *L. multiflora* at the two doses used.

Table 1. *P. berghei* suppression by *L. multiflora* leaf extracts in mice.

Treatment	Dose (mg/kg bw)	Mean parasitaemia[b]	% Suppression
L. multiflora	200	122.17±6.70	13.35
L. multiflora	400	69.17±6.72	50.94
CQ	5	24.83±4.90	82.39
N. S.[a]	20ml	141.00 ± 5.77	-

a. N. S. = normal saline
b. mean ± SEM and n = 24

Table 2. Curative effect of leaf extracts of *L. multiflora* against *P. berghei* in mice.

.

Treatment	dose (mg/kg bw)	mean-parasitaemia[b]	% decrease of parasitaemia	Survival Period (days)
L. multiflora	200	128.38±10.46	3.86	12.83±0.83
L. multiflora	400	83.83±8.34	37.44	18.00±1.29
CQ	5	15.17±1.68	86.79	36.33±6.54
N. S.[a]	20 ml	134.00± 8.60	-	11.83±0.98

a. N. S. = normal saline
b. mean ±SEM n = 24

Table 3. Prophylactic effect of L. multiflora extracts against *P. berghei* in mice.

Treatment	Dose (mg/kg bw)	Activity (%)	Pyreth. equivalent	Parasitaemia on sub inoculation
L. multiflora (D4)	400	5.30	3819	+ + +
L. multiflora (D7)	400	8.94	2264	+ + +
L. multiflora (D14)	400	1.32	15333	+ + +
Pyrimethamine	150	80.96	-	+
N. S.[a]	20 ml	0.00	-	+ + +

N. S.[a] = normal saline
+ = parasites slightly present
+++ = parasites highly present

Table 4. Inhibition of acetic acid induced abdominal constriction by *L. multiflora* extract in mice (analgesia).

Treatment	Dose (mg/kg bw)	Abdominal constriction (/10min.)[b]	Inhibition (%)
L. multiflora	200	19.4	59.58
L. multiflora	400	11.2	76.67
ASA	150	6.2	87.08
N. S.[a]	20 ml	48.0	-

a. N. S. = normal saline
b. mean(n) = 24

Anti - inflammatory activity

Results of the effect of *L. multiflora* in egg-albumin induced oedema in test mice are shown in Figure 1. Oedema was greatly suppressed irrespective of the dose level of extract used and was comparable to the standard ASA treatment.

Anti-plasmodial effect of partially purified *L. multiflora* extract

Results of the antiplasmodial effects of different fractions of *L. multiflora* in mice are shown in Table 5, none exhibited antiplasmodial action.

DISCUSSION AND CONCLUSION

The presence of a variety of phytochemicals in *L. multiflora* conforms with earlier reports about the secondary metabolites of this plant (Valentin et al., 1997; Oladimeji et al., 2000; Acquaye et al., 2001). The phytochemical diversity of a plant specie is indicative of its high medici-

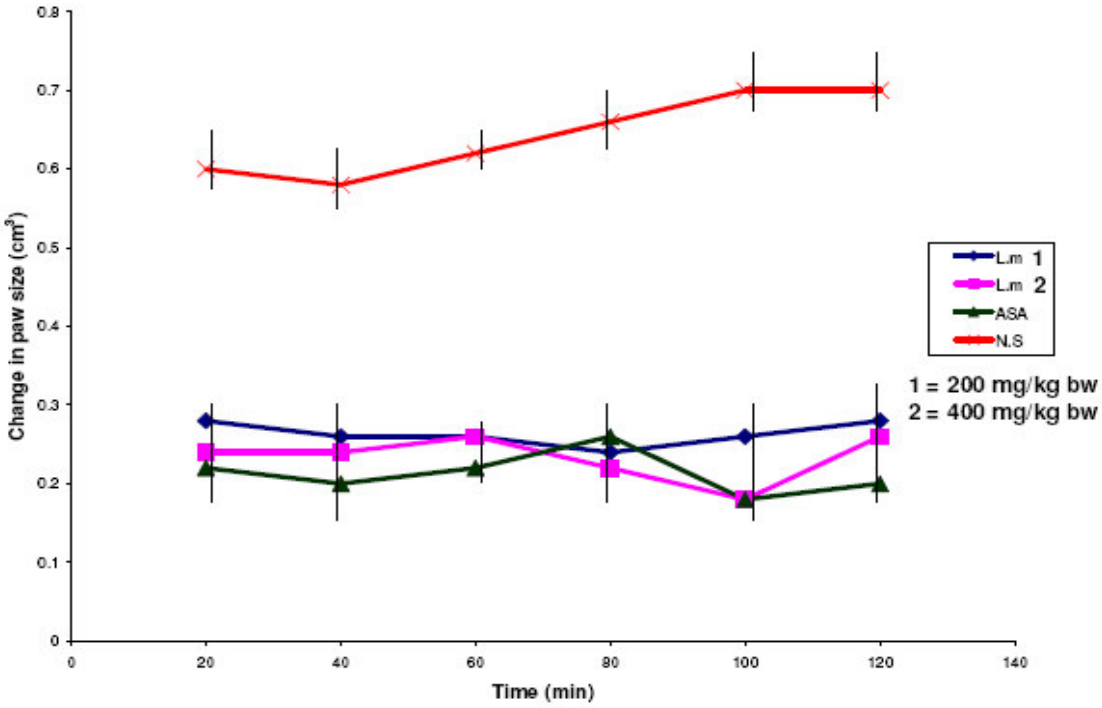

Figure 1. Anti-inflammatory effect of *L. multiflora* in egg-albumin induced oedema in mice.

Table 5. Parasitaemia in mice treated with individual fractions of *L. multiflora.*

Treatment	Dose(mg/kg bw)	Parasitaemia		
		a	b	C
L. multiflora 1	150	+ + +	+ +	*
L. multiflora 2	150	+ + +	*	*
L. multiflora 3	150	+ + +	+ + +	+ + +
L. multiflora 4	150	*	*	*
CQ	5	+	-	-
N.S	20 ml	+ + +	*	*

a, b, c = different mice, - = *Plasmodium* absent and + = *Plasmodium* slightly present
++ = *Plasmodium* moderately present and +++ = *Plasmodium* highly present
* = mortality, L1, L2, L3, L4 = different fractions.

nal and therapeutic potentials. This is because these compounds form the basis of the pharmacologic effects of such plants (Haidet, 2003;Jigam et al., 2004). Alkaloids rank among the most efficient and therapeutically significant plant compounds. Pure alkaloids and their synthetic derivatives are used as basic medicinal agents e.g. morphine is an analgesic, quinine is antiplasmodial, colchicine is used for gout, reserpine is a tranquilizer, vincristine and vinblastine have antitumor effects (Haidet, 2003).

Leaf extracts of *L. multiflora* had high safety levels (LD_{50} = 3000 mg/kg bw). The WHO – collaborating centre for scientific research into plant medicines (CSRPM) has demonstrated the long term safety of *lippia tea.* In a study involving 50 people over a time span of 25 years, no side effects or any toxicity were noticed with the consumption of the tea (Acquaye et al., 2001). Crude extracts of *L. multiflora* can hence be standardized and packaged to be used as phytomedicine. There was a significant suppression of *P. berghei* in mice dosed with *Lippia* but the extract was not effective as a curative or prophylactic agent. Most reports about the anti malarial effects of *lippia* do not specify whether the plant acted on the parasites or some other mechanisms. Such reports were also

based mostly on *in vitro* studies (Valentin et al., 1995; Taubi et al., 1997; Acquaye et al., 2001). It has been suggested that crude plant extracts tended to have better plasmodistatic than plasmodicidal effects because some unpurified bioactive principles may require initial conversions which time lag allows for parasite proliferation (Noedl et al., 2003). More over the active components might not be present in enough concentrations to effect rapid clearance of target organisms (Fidock et al., 2004).

The significant analgesic and anti-inflammatory effects of *Lippia* extracts in vivo is note worthy. Plants with these added pharmacological phenomena in conjunction with anti plasmodial effects are better antimalarials than species with the later potential only (Pascual et al., 2001). This also partly explains the high survival periods noted with *lippia* treated mice despite the high parasitaemia in the curative test procedure.

Individual fractions of partially purified crude *L. multiflora* extracts exhibited very low anti-plasmodial action. This is hardly surprising as earlier reports have indicated some crude plant extracts to be more potent than purified compounds. A far greater antiplasmodial activity was demonstrated by the total alkaloidal extracts of *Ancistrocladus peltatum* compared to any of the six pure alkaloids isolated subsequently (Francoise et al., 1994). Crude extract of *Cinchona ledgeriana* bark is more effective than quinine alone in the treatment of resistant *P. falciparum* infection. This has been attributed to the synergism between about 36 alkaloids in the crude extracts (Lewington, 1990).

Due to its high safety level, suppressive anti-plasmodial, analgesic and anti-inflammatory potentials, leaf extracts of *L. multiflora* can hence be used in the management of malaria expecially in endemic zones. In order to fully exploit its anti malarial potentials, the crude extracts can be used in combination therapy with plasmodicidal agents. It is suggested also that stem bark and roots of the plant be similarly analyzed for possible isolation of single pure compounds that can be used as templates in the synthesis of novel therapeutically more effective antimalarials.

ACKNOWLEDGEMENTS

The work was financed by a Ph.D grant to Dr. A. A. Jigam and Research grant (No. R/CA/37) to Professor H.O. Akanya both by the Federal University of Technology, Minna, Nigeria. Chloroquine sensitive *P. berghei* (NK65) strain was obtained by kind permission from Mr. Zakarraya of the National Institute for Pharmaceutical Research and Development, Abuja, Nigeria.

REFERENCES

Abena AA, Ngondzo – Kombeti GR, Bioka D (1998). Psychopharmacologic properties of *Lippia multiflora. Encephale* 24: 449-454.

Acquaye D, Smith M, Letchamo W, Simon J (2001). *Lippia* tea Centre for New Use Agriculture and Natural Products. Rutgers University, New Brunswick, New Jersey, USA.

Bloland PB (2001). Drug resistance in Malaria. Background Document for WHO Global Strategy for Containment of Antimicrobial Resistance. WHO, Switzerland pp. 3-27

Carter JA, Ross AJ, Neville BG, Obiero E, Katana K, Mung'ala—Odera V, Lees JANewton CR (2005). Developmental impairments following severe *falciparum* malaria in children. Tro.l Med. Int. Health 10:3-10.

CCAC (1997). Canadian Council on Animal Care Guidelines and Protocol Review

Cox F (2002). History of human parasitology. Clin. Microb. Rev. 15(4): 595 – 612.

Fidock DA, Rosenthal PJ, Croft SL, Brun R, Nwaka S (2004). Antimalarial drug discovery: efficacy models for compound screening. Supplementary documents. Trends Parasitol pp.18-19.

Fletcher E (2007). Traditional remedies-Searching their natural sources for the next malaria drug. TDR news 79: 8-13.

Francois G, Bringmann G, Philpson JD, Ake-Assi Dochex C Rubenacker M (1994). Activity of extracts and naphythyl isoquinoline alkaloids from A.peltatum, A. *abbreviatus* and *A. barteri* against *P. falciparum* in vitro. Phytochem 35: 1461-1464.

Giles C (2005). Why don't we have a malaria vaccine? *Welcome Science* 1:12-13 Greenwood BM, Bojang K, Whitty CJ, Targett GA (2005). Malaria. Lancet 365: 1487-1498.

Haidet A (2003). The medicinal value of the rainforest. Final paper on tropical field courses submitted to the department of Interdisciplinary studies. Miami University, U. S. A.

Hay S, Guerra C, Tatetew A, Noor A, Slow R (2004). The global distribution and population at risk of malaria: past, present and future. Lancet of Infect. Dis. 4(6): 327-336,

Jigam AA, Akanya HO, Adeyemi JJ (2004). Antimicrobial and anti-plasmodial effects of *Momordica balsamina*. Nig. J. Nat. Prdt. Med. 8:11-12

Koster R, Anderson M, Debeer EJ (1959). Acetic acid method of analgesic screening. Curr. Opin. Immunol. 18:412

Lewington J (1990). Plants for man. 1st edition Natural History Museum, London. pp. 136-145

Matuscheski K (2006). Vaccine development against malaria. *Curr. Opin. Immunol* 18(4): 449 – 457.

Munir AA (1993). A Taxonomic revision of the genus *Lippia (Verbanacea)* in Australia.J. Adelaide Bot. Garden *15*: 129 – 145

Noedl H, Wongsrichanalai C, Wernsdorfer WH (2003). Malaria drug-sensitivity testing: new assays, new perspectives. Trends Parasitol. 19, 175-81

Odebiyi OO, Sofowora EA (1978). Phytochemical Screening of Nigerian Medicinal Plants II. Lloydia; 41: 234-235

Okunji CO, Acton N, Ellis WY, Iwu MM (2000). Identification of new anti malarial pharmacophores from West and Central African plants. Proceedings of the International Conference on Traditional Medicine for HIV/AIDS and Malaria. 5th -7th December, 2000. NICON HILTON HOTEL, Abuja Nigeria.

Oladimeji FA, Orafidiya OO, Oguniyi TA, Adewumi TA (2000). Pediculocidal and scabicidal properties of *Lippia multiflora* essential oil. J. Ethnopharmacol *7*2: 305-311

Pascual ME, Slowing K, Caretero E, Mara KD, Villar A (2001). *Lippia:* Traditional uses, chemistry and pharmacology: A Review J. Ethnopharmacol 76: 201-214

Pham HC, Koffi Y, Pham HA (1988a). Comparative hypotensive effects of compounds extracted from *Lippia multiflora* leaves. Planta Medica 54: 294-296

Pham HC, Koffi Y, Pham HA (1988b). Comparative hypotensive effects on TXA2 biosynthesis of products extracted from *Lippia multi flora Mold* leaves. Prostagladins, Leukotrienes and Essential Fatty Acids 34: 83-88

Sofowora A (1982). Medicinal plants and traditional medicine in Africa. John Wiley and sons Ltd USA. pp 142-145

Sofowora A (1986). The state of medicinal plants research in Nigeria. Nig. Soc. Pharmacog 25: 13-65

Taoubi K, Fauvel MT, Gleye J, Moulis C, Fouraste L (1997). Phenylpropanoid glycosides from *Lantana camara* and *Lippia multiflora.* Planta Medica 63: 192-193.

Terblanché FC, Kornelious G (1996). Essential oil constituents of the genus *Lippia* (Verbanaceae) – A Literature review. J. Essential Oil

Res. 8: 471-485
Trease GE, Evans WC (1989). Pharmacology. Bailliare Tindal London. pp 378-480
Valentin A, Pelissier Y, Benoit F, Marion C, Kone D, Mallie M, Bastide JM, Bessieres JM (1995). Composition and anti malaria activity *in vitro* of volatile components *of Lippia multiflora.* Phytochem. 40: 1439-1442
Winter CA, Risley EA, Nuss GV (1962). Carrageenin induced oedema in hindpaw of rats as an assay for anti-inflammatory drugs. Proc Soc Exptl Biol Med 3:544-547