STUDIES OF THE THERAPEUTIC EFFICACY OF SELECTED MICRONUTRIENTS IN MALARIA

A THESIS SUBMITTED TO THE UNIVERSITY OF LAGOS, LAGOS, NIGERIA IN FUFILMENT OF THE REQUIREMENTS FOR THE AWARD OF DOCTOR OF PHILOSOPHY (Ph.D) DEGREE IN PHARMACOLOGY

BY

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DECLARATION

I hereby declare that this thesis titled "Studies of the Therapeutic Efficacy of Selected Micronutrients in Malaria" submitted to the School of Postgraduate Studies, University of Lagos, Lagos, Nigeria for the award of Doctor of Philosophy in Pharmacology was original research carried out by Iribhogbe, Osede Ignis in the Department of Pharmacology, Therapeutics and Toxicology, College of Medicine University of Lagos, under the supervision of Dr (Mrs) E.O. Agbaje and Dr A.I. Oreagba.

The work has not been submitted previously, in whole or in part, to qualify for any other academic award.

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DEDICATION

I dedicate this work to God Almighty, whose benevolence provided the grace, and strength with which this work was executed, to my wife and daughters from whose support I draw my strength as well as those who have been supportive to my educational pursuit.

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ABSTRACT

The role of selected antioxidant micronutrients in the course and therapy of malaria was elucidated *in vivo* and in a randomized controlled clinical trial. In this study, the rodent malaria model using *Plasmodium berghei* (NK-65 chloroquine sensitive and chloroquine resistant ANKA strain) was used. In the first stage of the experiment, a 4 day suppressive test was conducted using 40 mice of either sex weighing 20.05±0.02 g which were inoculated intraperitoneally with 1 x 10^7 million *Plasmodium berghei* infected erythrocyte and were administered with 0.2 ml of distilled water, 0.2 ml of vehicle; Tween 80 (control and vehicle group), chloroquine 25 mg/kg (standard drug group), vitamin A 60 mg/kg, vitamin E 100 mg/kg, selenium 1 mg/kg, zinc 100 mg/kg and vitamin C 200 mg/kg (represent test group D, E, F, G, H respectively which were administered orally) 3 hours post inoculation. Similarly, curative, curative synergistic and prophylactic tests were done. In the randomized controlled clinical trial, 150 participants (6 months-5 years) were recruited for the study from Faith-dome Medical Centre and Central Primary Health Centre Ekpoma, Edo State Nigeria, after obtaining ethical clearance from the ethical review Board of the Edo State Ministry of Health. The participants were randomized into 15 cohorts of 10 patients each. The patients in the active comparator group or control group were administered with oral doses of standard artemisinin based combination therapy, while the interventional cohorts were administered varying combinations of antimalarials (Artesunate or Amodiaquine) and micronutrients (vitamin A, vitamin E, zinc and selenium). Results showed that selenium demonstrated significant ($P < 0.05$) chemosuppressive (82.01%) and schizonticidal activity (76.16%) when compared with control during the 4 day suppressive and 4 day curative test respectively.

Curative synergistic study (using chloroquine resistant ANKA strain) showed that the artesunate + selenium combination group (2.40±0.40 days), had a more rapid parasite clearance time when compared with the artesunate + chloroquine group (2.60±0.24 days). This was significant ($F = 13.83$; $P < 0.05$) when compared to control and between groups. Findings from the clinical trial revealed that a more rapid parasite clearance time (PCT) was observed in the Artesunate + vitamin A + zinc treated group (26.00±4.82 hours) when compared with the active comparator groups (Amodiaquine + Artesunate; 27.00±3.00 hours and Artemether + Lumefantrine; 29.33±3.53 hours). Conclusively, the use of varying bi-combinations of antioxidant micronutrients as well as with standard antimalarials have been shown by this study to be of immense benefit in malaria therapeutics, hence this option should be explored as a low cost effective strategy in the management of acute uncomplicated *falciparum* malaria.