UNIVERSITI PUTRA MALAYSIA

ANTIPLASMODIUM AND CHLOROQUIN RESISTANCE REVERSING EFFECTS OF SELECTED PURE PHYTOCHEMICALS

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By

ZAID OSAMAH IBRAHEEM

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia in Fulfillment of the Requirement for the Degree of Doctor of Philosophy

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DEDICATION

In The name of the Almighty God, the most Beneficent and the most Merciful

This thesis is dedicated to my parents and siblings for their immense support encouragement and patience during the whole years of the study

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in Fulfilment of the requirement for the degree of Doctor of Philosophy

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ZAID OSAMAH IBRAHEEM

April 2017

Chairman : Associate Professor Rusliza Binti Basir, PhD
Faculty : Medicine and Health Sciences

Malaria is a devastating parasitic multi-organ disease afflicting millions and killing thousands of people annually. Emergence of drug resistant strains of the parasite has worsened the catastrophe of its dissemination. This urged the scientists to search for safe alternatives or drugs resistance reversing agents. This study was comprised of two sections which studied the antiplasmodium and chloroquine resistance reversing effects of eleven selected phytochemicals, namely; andrographolide, embelin, mangostin, mangoferin, harmalol, harmol, harmaline, 3-aminocoumarin, scopoletin, esculetin and umbelliferone, both *in vivo and in vitro*. In the *in vitro*study, *Plasmodium falciparum* K1 and 3D7; the chloroquine resistant and sensitive strains, were used. The compounds safety was screened through comparing their potency against the mentioned parasite with that against Vero cells (mammalian cells) or intact RBCs. SYBRE-Green -1 based drug sensitivity, MTT and RBCS stability assays were used for this purpose. Isobologram technique was used to find their effect against chloroquine resistance in *Plasmodium falciparum* K1. Their impact on hemozoin formation was assessed through running β-haematin formation and haem fractionation assay to elucidate their molecular mechanism. Meanwhile, RBCs osmotic fragility and merozoites invasion assays were performed to assess their impact on RBCs membrane. Finally, the *in vivo* anti-plasmodium and chloroquine resistance reversing effects of those; which succeeded to give a safe and productive effect, *in vitro*was screened using chloroquine resistant and sensitive *Plasmodium berghei* infected ICR mice model. The *in vitro*study showed that all the test compounds had weak to moderate anti-plasmodium effect which turned them illegible to be implemented as conventional anti-malaria drugs. Hemozoin formation was affected only by embelin, mangostin, mangoferin and 3-aminocoumarin. Unlike the others; embelin has affected the RBCs stability profoundly so it was considered to be unsuitable for this purpose while mangostin exerted milder effect. On the other hands, simple coumarins (umbeliferon,

scopoletine and esculetine) produced weak antiplasmodium effect and failed to reverse chloroquine resistance.

Only andrographolide, mangostin and harmaline were chosen for the *in vivo* study as they were the only drugs that showed optimistic outcomes in the *in vitro*study. Their effect was tested against a chloroquine resistant clone of *Plasmodium berghei* that was experimentally prepared through continuous exposure of the sensitive parasite to chloroquine. The study showed that mangostin and harmaline were lethal to the plasmodium infected mice in spite of their safety against the uninfected ones and in the *in vitro*mammalian cells culture. Meanwhile andrographolide was more potent *in vivo* and could have reduced the extent of the disease induced damage.

In conclusion, caution should be exercised while administration of herbal products in malaria patients without complete reliance on reports generated by the *in vvo* studies and suggests co-administration of andrographolide with chloroquine to get an additive effect

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

KESAN ANTIPLASMODIUM DAN KERINTANGAN CHLOROQUINE OLEH SEBATIAN FITOKIMIA TERPILIH

Oleh

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Pengerusi : Profesor Madya Rusliza Binti Basir, PhD
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Malaria merupakan penyakit parasit yang membinasakan yang menjangkiti berjuta dan membunuh beribu orang setiap tahun. Kemunculan jenis parasit yang rintang terhadap drug telah memburukkan lagi usaha menghapuskan penyakit ini. Ini telah mendesak saintis untuk mencari alternatif yang selamat atau agen yang boleh menterbalikkan kerintangan drug. Kajian ini terbahagi kepada dua bahagian di mana kesan antiplasmodia dan kesan berbalik kerintangan chloroquine dalam sebelas fitokimia terpilih, iaitu, andrographolide, embelin, mangostin, mangoferin, harmalol, harmol, harmalin, 3-aminocoumarin, scopoletin, esculetin dan umbeliferone telah diuji secara *in vitro* dan *in vivo*. Kajian *in vitro* menguji kesan terhadap *Plasmodium falciparum* K1 dan 3D7; masing-masing dari jenis rintang dan sensitif chloroquine (CQ). Keselamatan fitokimia tersebut disaring melalui perbandingan potensi mereka terhadap parasit dengan potensi terhadap sel mammalia atau sel darah merah yang utuh (RBCs).Asai-asai sensitiviti drug berasaskan SYBRE-Green-1, MTT dan kestabilan RBCs digunakan bagi tujuan ini. Teknik isobologram digunakan bagi menentukan kesannya terhadap kerintangan CQ dalam *Plasmodium falciparum* K1. Kesan terhadap pembentukan haemozoin dinilai melalui asai pembentukan β-haematin dan farksinasi heme bagi menjelaskan mekanisme molekul. Sementara itu, kesan terhadap membran RBCs yang dijangkiti dan tidak dijangkiti plasmodium disaring melalui penilaian kesan ke atas NPP (Lintasan Penyerapan Baru), asai kerapuhan osmotik RBCs dan pencerobohan merozoit. Akhir sekali, kesan *in vivo* antiplasmodium dan kesan berbalik kerintangan CQ fitokimia tersebut yang berjaya menghasilkan kesan selamat dan produktif, disaring menggunakan model tikus ICR yang dijangkiti *Plasmodium berghei.* Kajian *in vitro* menunjukkan kesemua sebatian yang diuji mempunyai kesan antiplasmodium antara lemah dan sederhana yang membolehkan mereka digunakan sebagai drug antimalaria konvensional. Hemozoin hanya terkesan oleh embelin, mangostin, mangoferin dan 3-aminocoumarin. Tidak

seperti yang lain, embelin sangat memberi kesan kepada kestabilan RBCs jadi ianya dianggap tidak sesuai untuk tujuan ini manakala embelin menghasilkan kesan yang sederhana. Hanya andrographolide, mangostin dan harmaline dipilih untuk kajian *in vivo* kerana ianya menunjukkan hasil yang optimistik berdasarkan kajian isobologram. Kajian ini menunjukkan mangostin dan harmaline adalah amat merbahaya kepada individu yang dijangkiti *Plasmodium falciparum* walaupun selamat dalam individu tidak dijangkiti dan juga kultur mamalia sel *in vitro*. Sementara itu andrographolide lebih poten *in vivo* dan boleh mengurang julat kerosakan yang dirangsang oleh jangkitan.

Secara kesimpulannya, kajian ini mencadangkan supaya lebih berhati-hati dalam pemberian produk herba kepada pesakit malaria tanpa merujuk laporan kajian secara *in vivo* dan ianya juga mencadangkan adminnistrasi bersama andrographolide dengan CQ bagi mendapatkan kesan tambahan.

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Finally, I request the Almighty Allah to make my efforts fruitful and open the road for me to benefit other people with whatever I learnt during my study.

I certify that a Thesis Examination Committee has met on (10th April 2017) to conduct the final examination of (Zaid Osamah Ibraheem) on his thesis entitled "Anti plasmodium and chloroquine resistance reversing effects of selected pure phytochemicals" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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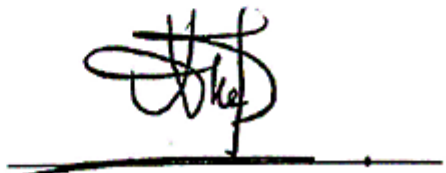

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I hereby confirm that:

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This is to confirm that:

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(I)	inoculum value
[Fe-S]	Iron sulphate complex
[K3Fe(CN)6]	Potassium Ferricyanide
•OH	Hydroxyl Radicals
ANOVA	Analysis Of Varriance
BHT	Butylated HydroxyToluen
BSA	Bovine Serum Albumin
BSC	Biosafety Cabinet
cMCM	Complete Malaria Culture Medium
CPD	Citrate Phosphate Dextrose
CQ	Chloroquine
CQ1	*Plasmodium berghei* ^{S} infected ICR mice and treated with chloroquine at 1 mg/kg.
CQ5	*Plasmodium berghei* ^{S} *i*nfected ICR mice and treated with chloroquine at 5 mg/kg.
CQ10	*Plasmodium berghei* ^{S} infected ICR mice and treated with chloroquine at 10 mg/kg.
CQ20	*Plasmodium berghei* ^{S} infected ICR mice and treated with chloroquine at 20 mg/kg
CQED50	CQ dose required to inhibit the parasite growth by 50%
CQR	Untreated Plasmodium berghei R infected ICR mice
CQR5	*Plasmodium berghei* ^{R} infected ICR mice and treated with chloroquine at 5mg/kg
CQR10	*Plasmodium berghei* ^{R} infected ICR mice and treated with chloroquine at 10 mg/kg
CQR20	*Plasmodium berghei* ^{R} infected ICR mice and treated with chloroquine at 20 mg/kg
CQR30	*Plasmodium berghei* ^{R} infected ICR mice and treated with chloroquine at 30 mg/kg
DMSO	Di-methylsulphoxide
e.t.c	et cetera (and the other things)
EDTA	Ethelene Diamine Tetr Acetic acid
ELISA	Enzyme linked Immune-Sorbant assays
FIC50	Fractional Inhibitory Concentration for IC50
FIC90	(Fractional inhibitory concentration for IC90
FP	Ferri-proto-porphyrins
g.m.wt	Gram Molecular Weight
g	Gram
H2O2	Hydrogen peroxide
Hb	Hemeoglobin
HCL	Hydrochloric acid
Hct	Hemeatocrit
HEPES	(4-(2-hydroxyethyl)-1-piperazine-ethan-sulphonic acid)
HRP-2	Histidine Rich Protein
i.e,	That is
I.M,	Intra Muscular
I.P	Intraperitoneal
I.V	Intravenous
IC50	Inhibitory concentration to reduce the growth by 50%
IC50vero,	Inhibitory concentration to reduce growth of Vero cells by 50%
ICAM	Intracellular Adhesion Molecules

iMCM	incomplete Malaria Culture Medium
IMR	Institute of Medical Research Malaysia
KCL	Potassium chloride
KH2PO4	Dihydrogen phosphate
LD50,	Lethal dose that kill 50 % of animals
min	Minute
ml	Milliliter
Mm	Milli Molar
mosmol	Milli osmole
MTT	(3[4, 5-dimethylthiozol-2-yl]-2, 5-diphenylterazolium bromide)
Na2HPO4	Disodium Hydrogen Phosphate
NaCl	Sodium Chloride
NADPH	Nicotinamide adenine dinucleotide
NaOH	Sodium hydroxide
NC	Negative uninfected control.
NF-Kb	Natural factor-κB
nM	Nano Molar
O.Dmax	Maximum optical density
O.Dtest	Optical density of the test sample
P%	Parasitemia percentage
PBS	Phosphate buffer saline
PC	Positive untreated control
PVM	Parasite Vacuolar Membrane
RBCs	Red Blood Cells
rpm	Revolution per minute
S.c	Subcutaneous
SIRBCs	Selectivity index to plasmodium as compared to RBCs
SIvero	Selectivity index to plasmodium as compared to RBCs
T0.5.	Half-life
TCA	Tri-Chloro-Acetic Acid
UPD	Up and Down
USA	Unite Sates of America
VCAM.	Vascular cells Adhesion Molecules
VD	volume of distribution
WHO	World health Organization
µl	Mico liter
Mm	Milli molar

CHAPTER 1

INTRODUCTION

1.1 Problem statements

In spite of its good reputation in the field of malaria chemotherapy, chloroquine (CQ) implementation is replete with critical problems that compromised its importance as a potential chemotherapeutic drug, such as; loss of its potency due to emergence of CQ resistant strains of different plasmodium species, its pharmacokinetic behaviour and the difficulties to keep it at the desired level and the incidence of side effects that enhances patients' compliance. This problem urged the scientists to search for other alternatives or chemo sensitizers as a part of the dedicated efforts that aim to secure patient's recuperation.

Emergence of chloroquine resistance predestines taking one of the following actions; increasing its dose or protracting the treatment period. Both are not desired as they increase the incidence of its toxicity and induce a selection pressure that augments the dilemma of resistance and tolerance.

Previous studies revealed that CQ side effects, such as; prostration, hypotension, vomiting, tinnitus as well as dizziness, appear at plasma concentrations more than 500 nM. Meanwhile; higher doses put the patients at risk of the acute toxicity that is characterized by incidence of severe hypotension, cardiovascular collapse and neurological disorders (convulsion, prostration and collapse). Meanwhile, its long-term use is fraught with risks of the chronic toxicity that is characterized by hepatic, retinal and dermal damages. The previous clinical studies classified blood level of CQ into negative (< 31 nM, sub-therapeutic (31 nM- 1 μM), therapeutic (1-5 μM) and supra-therapeutic (> 5 μM).

Furthermore, its pharmacokinetic behaviour constitutes another constraint that limits its eligibility to treat the disease. There has been a great deal of evidence that most of the CQ dependent therapeutic protocols failed to keep its level within the therapeutic threshold level due the inter-individual discrepancy in its pharmacokinetic parameters especially among different age groups. The variation is seen widely in its volume of distribution that it is quiet low soon after CQ uptake and rises up by 100 folds after achieving the equilibrium concentration. This may be due to its model of distribution that makes the decline in its plasma level multi-exponential as it distributes first to the central compartment before distributing to the other organs. The volume of the central compartment is several orders of magnitude smaller than the apparent volume of distribution. This model of distribution creates a transient increase in its level after its uptake and increases the incidence of its toxicity

It is crucial to note that CQ potency is highly correlated with the parasite synchronicity. During their intra-erythrocytic cycle, plasmodia undergo cyclical morphological changes pouncing from rings to trophozoites and schizonts. The upmost activity was seen during the trophozoite stage which takes part during the

middle third period of the cycle. Meanwhile, the very young rings and the mature schizonts are less affected. This predestines playing with CQ dosing schedule to attain a congruity between the time when CQ reaches its peak and that when most of the parasites are in their middle third stage of the cycle. Nevertheless, this aim is difficult to achieve with the fluctuations and high inter-individual variations in CQ plasma level.

Co-administration of chemo-sensitizers with CQ may help to overcome these issues. Most of them act in a mode different from that of CQ, thus their maximum effect may be achieved at time points within the intra-erythrocytic cycle different from that achieved by CQ. This may help in potentiating CQ action if its peaking failed to match the period wherein most of the parasites are predominated with the target trophozoites.

Natural compounds are multifaceted molecules with plenty of pharmacological actions. They do not merely affect the parasite responsiveness to CQ but they may change its action through changing its pharmacokinetic behaviour, the responsiveness of the immune system to the infection or development of the disease pathogenesis.

On the other hand, the immune system plays a role in limiting malaria. In spite of its failure to eradicate the parasite, it plays an important role in limiting progression the disease pathogenesis. Malaria is associated with pathogenic changes characterized by hepatomegaly, splenomegaly, renal failure and cerebral and pulmonary hemeorrhage. They are either attributed to overstimulation of the immune response or intravascular sequestration of the parasites. Parasite sequestration results in diminution of the blood supply and infliction of tissue damage. It requires endothelial expression of cyto-adhesion molecules, such as; ICAM (Intracellular Adhesion Molecules) or VCAM. (Vascular cells Adhesion Molecules). Implementation of the herbal therapy may modulate the immune reaction or induce expression of the cyto-adhesion molecules. This may give them another privilege along with their intrinsic effect on the parasite.

Implementation of phyto-medicine in malaria therapy has several outcomes as they might have the aptitude to suppress the parasite growth, chemo-sensitize or altering the pharmacokinetic behaviour of the conventional anti-malarial drugs or modulating the host immune response or the cyto-adhesion mechanism of the infected RBCs (Red Blood Cells).

1.2 Research hypotheses

Phytochemicals are multifaceted molecules with a tendency to affect ceelular functions through different mechanisms. This character entitles them to be candidate drugs for different purposes. In the field of malaria, they may compromise the parasite growth, change the susceptibility of the parasite to the conventional anti malarials or changing the way that the host reacts toward the parasite through changing the immune response or progression of the pathogenic events.

The chemotherapeutic action of differebnt drugs relies on their ability to selectively compromise the parasite growth without affecting the host. Plasmodia are endowed

with unique organelles that are absent in mammals, such as; the digestive vacuoles wherein Hb is broken down or the apicolplasts that is involved in different biochenmical pathways.

Nawadays, drug resistance started to evolve in lots of plasmodia species. Resistance to chloroquine constitutes the most perilous event in the realm of malaria chemotherapy as it is still the most potent and cost effective drug amongst other antimalarials. It develops when the parasite get the ability to shuffle chloroquine outsid its target site of action. The resistant strains develop mutations in the gene of the transporters that pump chloroquine away from its site of action, such as; crt (chloroquine resistance transporter) or MDR (Multi drugs resistance protein).

Malaria is associated with plenty of pathogenic events that inflict most of the host body organs. Most of them occur due to overstimulation of the immune system or due to sequestration of the parasites in the microvasculature of the affected organs. The immune system stimulation is mediated by the interleukines that the immune system releases after recognition of the infected cells while the sequestration of the parasites is mediated by the interaction of the infected cells with ligand molecules expressed on the endothelium. Interference with these events may help in limiting progression of the malaria induced pathogenesis.

1.3 General objectives

The study aims at testing the eligibility of a set of eleven phytochemicals, namely; andrographolide, embelin, two xanthon derivatives (mangoferin and mangostin), three β-carbolines (harmaline, harmalol, harmal) and four simple coumarines (scopoletin, esculetin, umbeliferone and 3-aminocoumarin) as anti-plasmodial or chloroquine resistance reversing agents. This was attained through fulfilling the following objectives which have been attained both *in vitro*and *in vivo*

1.4 Specific objectives

1. Screening of the physiochemical properties and the antioxidant activity of the selected phytochemicals as a preliminary screening step.

2. *In vitro* assessment of the anti-plasmodial, chloroquine resistance reversing effects and selectivity of the abovementioned test compounds against *Plasmodium falciparum* 3D7 and K1.

3. Assessment of the impact of each of the mentioned phytochemicals against some molecular targtes, such as; hemozoin formation (*in vitro*β-haematin formation and haem fractionation assay as well as their effect on merozoites invasion).

After finishing the *in vitro*study, the *in vivo* study was run only for the phytochemicals that give optimistic outcomes in the preliminary *in vitro*study. Compounds; with poor anti-plasmodium and CQ resistance reversing effects or were revealed to be abnoxious, were excluded from this study. The objectives ar lister here after below.

1. Assessment of the anti-plasmodium effect of chloroquine and each phytochemical in a model of Plasmodium berghei (ANKA) infected ICR mice.

2. Assessment of the effect of each phytochemical on progression of the disease induced pathogenesis.

3. Assessment of the plausible in vivo synergistic or antagonistic effect of each phytochemical with CQ.

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