UNIVERSITI PUTRA MALAYSIA

IN VITRO AND IN VIVO ANTITRYPANOSOMAL ACTIVITIES OF SELECTED MEDICINAL PLANTS

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By

DYARY HIEWA OTHMAN

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

May 2013

DEDICATION

Dedicated with love to:

My dear parents, brothers and sisters

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirements for the degree of Doctor of Philosophy

IN VITRO AND *IN VIVO* ANTITRYPANOSOMAL ACTIVITIES OF SELECTED MEDICINAL PLANTS

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Chairman: Associate Professor Arifah Abdul Kadir, PhD

Faculty: Veterinary Medicine

Surra, a hemoprotozoan disease caused by *Trypanosoma evansi*, is considered endemic to livestock in Peninsular Malaysia and currently the very few drugs available for treatment of the disease are old, toxic or ineffective. This study was conducted to evaluate the potential antitrypanosomal activities of the aqueous and ethanolic extracts of seeds of *Nigella sativa* and bulbs of *Allium sativum*, as well as the aqueous and ethanolic extracts of leaves of 11 medicinal plants, namely *Acanthus ilicifolius*, *Aquilaria malaccensis*, *Cordyline terminalis*, *Derris elliptica*, *Garcinia hombroniana*, *Goniothalamus tapis*, *Goniothalamus umbrosus*, *Maesa ramentacea*, *Pereskia grandifolia*, *Plumeria rubra*, and *Strobilanthes crispus*. The potency of each plant extract against *T. evansi* strain Te7 was screened through the determination of the median inhibitory concentration (IC_{50}) on trypanosomes cultures in 24-well microtiter plates. The results of the study showed that the IC_{50}

for *G. umbrosus* ethanolic extract was 2.30 ± 0.90 µg/mL and for *S. crispus* aqueous extract it was 800.97 ± 278.33 µg/mL. *In vitro* cytotoxicity assay was performed to determine the median cytotoxic concentration (CC_{50}) of the extracts. The MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) cell proliferation assay was conducted and the results showed variable toxicity levels of the extracts towards the mammalian cell lines, Vero cells. Median cytotoxic concentration of *G. umbrosus* ethanolic extract on Vero cells was 29.10 ± 7.36 µg/mL and 14533.87 ± 296.86 µg/mL for *G. hombroniana* aqueous extract. The selectivity index (SI) was calculated from CC_{50} and IC_{50}. For the *G. hombroniana*, *A. malaccensis*, and *C. terminalis* aqueous extracts, the SI values were 616.36, 47.38, and 27.17, respectively. The mode of action of *G. hombroniana* aqueous extract *in vitro* was elucidated by culturing *T. evansi* with the extract for 24 hours followed by staining the trypanosomes with the DNA-binding fluorescent stain bisbenzimide H33258. The results of the study showed that the extract might act via inhibition of kinetoplast division during mitosis of *T. evansi*. Acute toxicological effects of *G. hombroniana* aqueous extract, at concentrations of 300, 2000 and 5000 mg/kg body weight, were investigated through the oral acute toxic class (ATC) method on 24 female Sprague-Dawley rats. No significant difference in body weight or food and water consumption ($p>0.05$) was observed among groups of experimental rats. The hematological parameters were determined in the *G. hombroniana* aqueous extract-treated rats, which included erythrocyte, leukocyte and thrombocyte counts, hemoglobin concentration, packed cells volume, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and plasma proteins, and did not show significant differences ($p>0.05$) among groups. The serum biochemical parameters including albumin,

alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, cholesterol, creatinine, γ-glutamyl transferase (GGT), glucose, urea, total protein, and lactate dehydrogenase (LDH) did not reveal significant differences ($p>0.05$) among the groups. The histopathological changes in the liver, spleen, kidneys, and heart were not significant ($p>0.05$) between control and treated groups, except for the rats given 5000 mg/kg body weight of the extract. In the later rats, there was slight congestion of the liver and kidneys, narrowing of the liver sinusoids and an increase in the number of Kupffer cells around the portal areas. The median lethal dose (LD_{50}) of the extract was higher than 5000 mg/kg body weight, which is beyond the limit permitted to be used for testing in rats. Phytochemical screening of *G. hombroniana* aqueous extract revealed the presence of flavonoids, phenols, tannins, and saponins. The aqueous extract of *G. hombroniana* was tested on experimentally *T. evansi*-infected rats. The results of the test showed that the post-infection survival time in the untreated control group was 6.60 ± 0.24 days, while in the groups treated with 600 and 1200 mg/kg body weight *G. hombroniana* it was 12.80 ± 0.20 and 12.80 ± 0.37 days, respectively, which was significantly ($p<0.05$) longer than that observed in the untreated control group of rats. These findings suggest that the *G. hombroniana* aqueous extract has potential and is effective in the treatment of trypanosomiasis.

In summary, the study suggests that the possible mode of action of *G. hombroniana* aqueous extract in its antitrypanosomal activity is through inhibition of kinetoplast division during mitosis of *T. evansi*, the LD_{50} of *G. hombroniana* aqueous extract is higher than 5000 mg/kg body weight and the extract significantly extended the post-infection survival of rats experimentally infected with *T. evansi*.

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

AKTIVITI ANTITRIPANOSOM *IN VITRO* DAN *IN VIVO* TUMBUHAN UBAT PILIHAN

Oleh

DYARY HEIWA OTHMAN

Mei 2013

Pengerusi: Profesor Madya Arifah Abdul Kadir, PhD

Fakulti: Perubatan Veterinar

Sura, suatu penyakit hemoprotozoa disebabkan oleh *Trypanosoma evansi*, dianggap endemik untuk ternakan di Semenanjung Malaysia dan kini beberapa drug yang wujud untuk rawatan penyakit ini adalah usang, toksik dan tidak berkesan. Kajian ini dijalankan untuk menilai potensi aktiviti antitripanosom ekstrat akueus dan etanol biji *Nigella sativa* dan mentol *Allium sativum*, serta ekstrak akueus dan etanol daun daripada 11 tumbuh-tumbuhan perubatan, iaitu *Acanthus ilicifolius*, *Aquilaria malaccensis*, *Cordyline terminalis*, *Derris elliptica*, *Garcinia hombroniana*, *Goniothalamus tapis*, *Goniothalamus umbrosus*, *Maesa ramentacea*, *Pereskia grandifolia*, *Plumeria rubra*, dan *Strobilanthes crispus*. Potensi setiap satu ekstrat ini terhadap strain *T. evansi* Te7 disaring melalui penentuan kepekatan rencatan median (IC_{50}) pada kultur tripanosom dalam plat mikrotiter 24-mangkuk.

Hasil kajian menunjukkan IC_{50} untuk ekstrat etanol *G. umbrosus* adalah 2.30 ± 0.90 µg/mL dan untuk ekstrat akueus *S. crispus* 800.97 ± 278.33 µg/mL. Asai kesitotoksikan *in vitro* dijalankan untuk menentukan kepekatan kesitotoksikan median (CC_{50}) ekstrat. Ujian pemproliferatan sel MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) dilakukan dan hasilnya menunjukkan aras kesitotoksikan ekstrat terhadap titisan sel mamalia, sel Vero, adalah berbeza. Kepekatan kesitoksikan median ekstrat etanol *G. umbrosus* terhadap sel Vero adalah 29.10 ± 7.36 µg/mL dan untuk ekstrat akueus *G. hombroniana* adalah 14533.87 ± 296.86 µg/mL. Indeks pemilihan (SI) dikira daripada CC_{50} dan IC_{50}. Untuk ekstrak akueus *G. hombroniana*, *A. malaccensis*, dan *C. terminalis* nilai SI masing-masing adalah 616.36, 47.38, dan 27.17. Mod tindakan *in vitro* ekstrat *G. hombroniana* telah dijelaskan dengan mengkultur *T. evansi* bersama ekstrat selama 24 jam dan diikuti pewarnaan tripanosom dengan pewarna pendarfluor pengikat DNA, bisbenzimide H33258. Hasil kajian menunjukkan yang ekstrat ini mungkin bertindak melalui perencatan pembahagian kinetoplas semasa *T. evansi* mitosis. Kesan toksikologi akut ekstrat akueus *G. hombroniana* pada kepekatan 300, 2000, dan 5000 mg/kg berat badan, diselidik melalui kaedah kelas toksik akut oral (ATC) pada 24 ekor tikus Sprague-Dawley. Tiada perbezaan tererti ($p>0.05$) dalam berat badan atau pengambilan makanan dan minuman dilihat dikalangan kumpulan tikus ujikaji. Parameter hematologi yang ditentukan dalam tikus diperlaku dengan esktrat akueus *G. hombroniana* termasuk bilangan eritrosit, leukosit dan trombosit, kepekatan hemoglobin, isipadu sel padat, min isipadu korpuskel, min hemoglobin korpuskel, min kepekatan hemoglobin korpuskel, dan protein plasma, tidak menunjukkan perbezaan tererti ($p>0.05$) dikalangan kumpulan. Parameter biokimia serum termasuk albumin, alanin transaminase (ALT), aspartat transaminase (AST),

bilirubin sepenuh, kolesterol, kreatinin, γ-glutamiltransferase (GGT), glukosa, urea, protein sepenuh, dan laktat dehydrogenase (LDH) tidak menunjukkan perbezaan tererti ($p>0.05$) dikalangan kumpulan. Perubahan histopatologi pada hati, limpa, ginjal, dan jantung tidak berbeza tererti ($p>0.05$) diantara kumpulan kawalan dan terperlaku, kecuali pada tikus yang diberi 5000mg/kg berat badan ekstrat. Dalam tikus tersebut, terdapat kesebakan hati dan ginjal, penyempitan sinusoid hati dan peningkatan bilangan sel Kupffer di sekitar kawasan portal. Dos maut median (LD_{50}) ekstrat adalah lebih tinggi daripada 5000 mg/kg berat badan, yang melebihi had yang dibenarkan dalam pengujian pada tikus. Penyaringan fitokimia ekstrat akueus *G. hombroniana* menunjuk kewujudan flavonoid, fenol, tannin dan saponin. Ekstrat akueus *G. hombroniana* diuji pada tikus yang dijangkitkan secara ujikaji dengan *T. evansi*. Hasil daripada ujian ini menunjukkan tempoh kemandirian pasca-jangkitan dalam kumpulan kawalan tidak diperlaku adalah 6.60 ± 0.24 hari, sambil dalam kumpulan yang diperlaku dengan 600 dan 1200 mg/kg berat badan *G. hombroniana,* masing-masing adalah 12.80 ± 0.20 dan 12.80 ± 0.37 hari, yang merupa tempoh lebih lama tererti ($p<0.05$) daripada apa yang dilihat pada kumpulan tikus kawalan tidak diperlaku. Penemuan ini menyarankan yang ekstrat akueus *G. hombroniana* ada potensi dan berkesan dalam rawatan tripanosomiasis.

Ringkasannya, kajian ini menyarankan mod tindakan mungkin ekstrat akueus *G. hombroniana* dalam aktiviti antitripanosomnya ialah melalui perencatan pembahagian kinetoplas semasa *T. evansi* mitosis, LD_{50} ekstrat akueus *G. hombroniana* adalah lebih tinggi daripada 5000 mg/kg berat badan dan ekstrat ini secara tererti memanjangkan tempoh kemandirian pasca-jangkitan tikus dijangkitkan secara ujikaji dengan *T. evansi*.

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I certify that a Thesis Examination Committee has met on 21 May 2013 to conduct the final Examination of Dyary Hiewa Othman on his Doctor of Philosophy thesis entitled "*In vitro* and *in vivo* antitrypanosomal activities of selected medicinal plants" in accordance with 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 candidate be awarded the relevant degree.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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DECLARATION

I declare that the thesis is my original work except for quotations and citations which have been duly acknowledged. I also declare that this work has not been previously, and is not concurrently, submitted for any other degree at Universiti Putra Malaysia or at any other institution.

DYARY HIEWA OTHMAN

Date: 21 May 2013

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LIST OF ABBREVIATIONS

°C	Degree Celsius
µg	Microgram
µL	Microliter
µmol	Micromole
Ab	Antibody
ACUC	Animal Care and Use Committee
Ag	Antigen
ALT	Alanine transaminase
ANOVA	Analysis of variance
AST	Aspartate transaminase
ATC method	Acute toxic class method
BW	Body weight
CC_{50}	Median cytotoxic concentration
CO_2	Carbon dioxide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
ELISA	Enzyme-Linked Immunosorbent Assay
fL	Femtoliter
g	Gram
GGT	Gamma-glutamyl transferase
h	Hour
HCT	Hematocrit centrifugation technique
HMI-9 medium	Hirumi's modified Iscove's medium 9
IC_{50}	Median inhibitory concentration
Kg	Kilogram
L	Liter
LD_{50}	Median lethal dose
LDH	Lactate dehydrogenase
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MEC	Minimal effective concentration

mg	Milligram
mL	Milliliter
mmol	Millimole
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
N1K0	One nucleus with no kinetoplasts
N1K1	One nucleus and one kinetoplast
N1K2	One nucleus and two kinetoplasts
N2K0	Two nuclei with no kinetoplasts
N2K1	Two nuclei and one kinetoplast
N2K2	Two nuclei and two kinetoplasts
ng	Nanogram
OECD	Organization for Economic Co-operation and Development
OIE	World Organization for Animal Health
p	Probability value
PBS	Phosphate buffered saline
PCR	Polymerase chain reaction
PCV	Packed cells volume
pH	Potential of hydrogen (logarithm of the reciprocal of hydrogen ion concentration)
ppm	Part per million
RBCs	Red blood cells
RoTat 1.2	Rode Trypanozoon antigen type 1.2
rpm	Round per minute
SD	Standard deviation
SEM	Standard error of the mean
SI	Selectivity index
U/L	Units per liter
UV	Ultraviolet
w/w	Weight per weight
WBCs	White blood cells

CHAPTER 1

INTRODUCTION

1.1 Introduction

Surra is a parasitic disease of domesticated livestock and wildlife animals, caused by the hemoflagellate protozoan parasite *Trypanosoma evansi* (Stevens and Brisse, 2004). The disease was first discovered by Griffith Evans in camels and equines in India in 1880 as the first isolated pathogenic protozoa (Luckins, 1988).

Surra is distributed worldwide and it is endemic in Africa, Asia, Central and South America (OIE, 2010). The disease was first reported in Southeast Asia more than a century ago. Now the disease is prevalent in many Asian countries including China (Liao and Shen, 2010), Indonesia (Davison *et al*., 2000), the Philippines (Reid, 2002), Vietnam (Holland *et al*., 2004), Thailand (Desquesnes *et al*., 2009) and Malaysia (Adrian *et al*., 2010; Nur Mahiza, 2010).

Many species of animals can be infected by *T. evansi*, to include camels, horses, cattle, buffalos, dogs, cats, sheep, goats, as well as a variety of wildlife animals (Luckins, 1988). The disease is mechanically transmitted via the bite of flies, especially those belonging to the genera *Tabanus* and *Stomoxys* (Stevens and Brisse, 2004). In South America, vampire bats are also involved in the transmission of this disease (Hoare, 1972).

Since surra is infective to many species of domesticated and wild animals, cross-infection can occur easily among different species. Wildlife animals are often inflicted with the chronic form of the disease, but they usually act as a reservoir of

the parasite (Taylor and Authie, 2004). Wildlife animals also often act as a source of spread of the disease to domesticated livestock, making control of the disease difficult, especially when vaccine against trypanosomes infection is yet to be developed. Currently, treatment of the disease is the only way of controlling trypanosomiasis.

Current therapeutic approaches to surra are limited to only a few drugs namely diminazene aceturate, quinapyramine, suramin, isometamidium and melarsomine. Melarsomine has been in use for more than two decades, while the other four drugs were discovered more than half a century ago (Delespaux and de Koning, 2007). All of the mentioned therapies produce toxic side-effects. On top of that, there is continuous emergence of resistant strains of *T. evansi* in different parts of the world (El Rayah *et al*., 1999; Zhou *et al*., 2004), making treatment of the disease problematic.

Natural products have been playing a significant role in the discovery of new drug entities. It seems that between 1981 and 2001, approximately 28% of new drug candidates were products or derivatives of natural products. Another 20% of new chemical entities discovered during that period were mimics of natural products. All together, natural products make 48% of new chemical/drug entities discovered in that period (Newman *et al*., 2003). From 1994 to 2007, 50% of the drugs approved for use were based on natural products, and in 2008 alone, 46 compounds from plant origin had undergone preclinical trial and over 60 drug candidates were subjected to clinical trial (Harvey, 2008) (Table 1).

Table 1: Development of natural product-based drugs

Stage of development	Number of drug candidates
Preclinical	46
Phase 1	14
Phase 2	41
Phase 3	5
Pre-registration	2
Total	108

(Source: Harvey, 2008)

The process of new drug discovery has led to the discovery of only one drug against *Trypanosoma brucei gambiense*, which is eflornihine. It seems that the traditional methods may be more effective in the discovery of new chemotherapies for the treatment of trypanosomiasis (Steverding, 2010).

1.2 Problem Statement

Trypanosoma evansi infects a wide variety of animal species including domesticated and wildlife animals. Unlike other trypanosomes, which need an intermediate host, *T. evansi* has developed a strategy for mechanical transmission through any means that will inject the parasite into the blood stream. This characteristic allows the parasite to be able to spread from tsetse fly areas in Africa to become distributed worldwide. Since there is no vaccine available for immunization of susceptible animals, chemotherapy seems to be the only available option in the control of the disease. The few currently available drugs against the parasite have been long in use and there are concerns over the development of

resistant strains. Hence, there is an urgent need for new safer compounds for the treatment of the disease to be discovered.

Discovery of innocuous compounds from medicinal plants that exhibit trypanocidal activity will involve testing and acquisition of information on the mode of action before the drug can be further developed as a therapeutic compound. Any new drug could be used in combination with the currently available ones for better efficacy, to improve their potency and/or pharmacological activities, as well to reduce the burden of use of old drugs.

1.3 Hypothesis

The aqueous and ethanol extracts of *Acanthus ilicifolius*, *Allium sativum*, *Aquilaria malaccensis*, *Cordyline terminalis*, *Derris elliptica*, *Garcinia hombroniana*, *Goniothalamus tapis*, *Goniothalamus umbrosus*, *Maesa ramentacea*, *Nigella sativa*, *Pereskia grandifolia*, *Plumeria rubra*, and *Strobilanthes crispus* are expected to possess antitrypanosomal activity with comparably high selective *in vitro* toxicity on *T. evansi*. These plant extracts with either anticancer or antifungal properties make a good candidate to be tested as antitrypanosomal compounds.

The antitrypanosomal activity of the extracts may be via inhibition of trypanosomal proliferation through inhibition of trypanosomal DNA replication.

1.4 Objective

The main objectives of this study were to determine the antitrypanosomal and cytotoxic activities, and mode of action of selected medicinal plants.

1.5 Specific Objectives

The specific objectives of the study were to (1) determine the *in vitro* antitrypanosomal activities of the aqueous and ethanolic extracts prepared from selected plant parts of 13 medicinal plants, namely *Acanthus ilicifolius*, *Allium sativum*, *Aquilaria malaccensis*, *Cordyline terminalis*, *Derris elliptica*, *Garcinia hombroniana*, *Goniothalamus tapis*, *Goniothalamus umbrosus*, *Maesa ramentacea*, *Nigella sativa*, *Pereskia grandifolia*, *Plumeria rubra*, and *Strobilanthes crispus*, (2) determine the cytotoxic effect of the aqueous and ethanolic extracts of the medicinal plants on Vero cells *in vitro*, (3) determine the effect of plant extracts with the highest (SI) on trypanosomal DNA, (4) determine the acute oral toxicity of *G. hombroniana* leaves aqueous extract using the oral acute toxic class (ATC) method, (5) determine the antitrypanosomal activity of *G. hombroniana* aqueous extract on experimental *T. evansi* infection in laboratory rats, and (6) screen the phytochemical constituents of *G. hombroniana* aqueous extract.

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