UNIVERSITI PUTRA MALAYSIA

In Vivo EVALUATION OF SWEET POTATO LEAF (Ipomoea batatas (L.)Lam.) EXTRACTS FOR TREATMENT OF PSORIASIS USING MOUSE MODEL

ANUAR BIN SANI

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By

ANUAR BIN SANI

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

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DEDICATION

It has been a roller coaster of almost seven years to finish this endeavour. Juggling study, families and work commitments was never easy. First and foremost, BIG thank you to USIM and JPA for the sponsorship and to my supervisors for never ending support and belief (Prof. Dr Wan Omar, Prof. Dr Adel and Dr. Ngah Zasmy). Abundant love to my wife and children of whom understanding and patience were tested to the limit during preparation of this thesis.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the Degree of Doctor of Philosophy

In Vivo EVALUATION OF SWEET POTATO LEAF (*Ipomoea batatas (L.)*Lam.) EXTRACTS FOR TREATMENT OF PSORIASIS USING MOUSE MODEL

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ANUAR SANI

April 2017

Chairman : Professor Wan Omar Bin Abdullah, PhD
Faculty : Medicine and Health Sciences

Psoriasis is a complex genetic disease involving both autoimmune and inflammatory components though its exact aetiology remains unknown. It is prevalent worldwide and affects both men and women over a wide age range. In Malaysia, about 4% of the population are affected.

Topical medications especially corticosteroids are used for localised disease. Phototherapy and climatotherapy are effective for more extensive disease. Systemic therapies are reserved for patients with refractory disease. The use of complementary and alternative medicines is also common among psoriasis patients. In Malaysia, sweet potato leaves have been used as an alternative therapy for psoriasis. In light of these subjective observations and under continuous pressure of finding new remedies to meet the unmet needs in psoriasis treatment, the researcher examined two different extracts derived from sweet potato leaves against experimentally induced psoriasis aiming to draw a distinction between the patients' subjective observations and the scientific evidence, risks and benefits of treatments.

This study offered a novel research based on examination of lipophilic and hydrophilic extracts from sweet potato leaves (SPL) of Gendut MSP94 cultivar in experimental animal model. The hydrophilic (ethanolic) extraction of SPL was done based on the protocol described by Park *et al. (2010)*. The Lipophilic (hexane) extraction was based on the protocol described by Teow *et al. (2007).* The concentrated extracts obtained were in the form of thick dark greenish pastes which were ideal for direct application onto the induced psoriasis. Hydrophilic extract showed high levels of chlorogenic and caffeic acids which were similar to earlier studies. However, it is strongly recommended that ultra-analysis of Gendut SPL extracts should be considered in the future studies to define the traces of bioactive chemicals not been identified in the

current research, as it was beyond its scope. The total phenolic content of Gendut SPL ethanolic extracts was assessed using *Amin et al. (2004)* protocol. It was found to be nearly 50% of the values obtained from other studies done on different cultivars of sweet potatoes.

The mouse model of psoriasis was induced chemically by topical Imiquimoid onto shaved skin of BALB/c mice, following the same protocol described by *van der Fits et al. (2009).* Histologically, the resulting lesions were typical to human's psoriasis vulgaris as confirmed by dermatologist and histopathologist. Flow cytometry showed increased levels of $CD3^+$, $CD4^+$ and $CD8^+$ cells and TNF-alpha in the peripheral blood which were signs of inflammatory reaction seen in acute psoriasis. Upon treatment, results showed significant clinical improvement in the lipophilic SPL extract-treated group, as scored by modified PASI, compared to hydrophilic SPL extract-treated and negative control groups. Histopathological changes showed significant decrease of epidermal thickness and rete ridges. Immunological and molecular parameters showed significant decrease in the inflammatory biomarkers namely TNF-alpha and the percentage of double negative T cells. In conclusion, this study shows a substantial evidence of anti-psoriatic properties of SPL lipophilic extract that should encourage us to look further into its active compound(s) responsible for the effects.

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

PENILAIAN IN-VIVO EKSTRAK DAUN UBI KELEDEK (*Ipomoea batatas*) (L) Lam.) TERHADAP RAWATAN PENYAKIT PSORIASIS MENGGUNAKAN MODEL TIKUS

Oleh

ANUAR SANI

April 2017

Pengerusi : Profesor Wan Omar bin Abdullah, PhD
Fakulti : Perubatan dan Sains Kesihatan

Psoriasis adalah penyakit genetik yang kompleks melibatkan kedua-dua komponen autoimun dan keradangan, namun punca bagi psoriasis masih tidak diketahui. Psoriasis mempunyai kesan penyebaran serata dunia dan melibatkan lelaki dan wanita pada julat umur yang luas. Di Malaysia, lebih kurang 4% penduduk adalah terkesan dengan psoriasis.

Rawatan topikal, terutamanya kortikosteroid, digunakan untuk psoriasis setempat. Rawatan fototerapi dan klimatoterapi berkesan kepada psoriasis yang lebih serius. Terapi sistemik dikhaskan untuk pesakit yang mempunyai psoriasis refraktori. Penggunaan rawatan pelengkap dan alternatif adalah biasa dikalangan pesakit psoriasis. Di Malaysia, ada pesakit psoriasis menggunakan daun ubi keledek sebagai rawatan alternatif bagi psoriasis. Berdasarkan pemerhatian subjektif dari pesakit psoriasis dan sememangnya ada keperluan berterusan untuk mencari rawatan yang baru untuk penyakit ini, penyelidikan ini telah memeriksa dua jenis ekstrak yang diperolehi daripada daun ubi keledek terhadap psoriasis terinduksi secara eksperimental dengan matlamat untuk membuat perbezaan antara pemerhatian subjektif pesakit dengan bukti saintifik, risiko dan faedah rawatan.

Penyelidikan ini menawarkan kajian novel berdasarkan pemerhatian ekstrak lipofilik dan hidrofilik daripada daun ubi keledek (SPL) kultivar Gendut MSP94 menggunakan model eksperimental haiwan. Pengekstrakan SPL hidrofilik (etanol) dilakukan berdasarkan protokol yang telah dinyatakan oleh Park dan rakan-rakan. (2010). Pengekstrakan SPL lipofilik (heksana) pula dilakukan berdasarkan protokol yang telah dinyatakan oleh Teow dan rakan-rakan (2007). Ekstrak pekat yang diperolehi dalam bentuk pes hijau gelap sesuai untuk aplikasi secara terus kepada psoriasis terinduksi. Ekstrak SPL hidrofilik menunjukkan tahap asid klorogenik dan caffeic yang tinggi

seperti dalam kajian-kajian yang dilakukan sebelum ini. Namun, dicadangkan supaya analisis ultra ekstrak SPL Gendut dilakukan untuk kajian yang akan datang bagi menjelaskan lagi unsur surih bahan kimia bioaktif yang tidak dikenalpasti di dalam kajian kini kerana ia berada di luar skop kajian. Jumlah kandungan fenol di dalam ekstrak Gendut SPL diuji menggunakan protokol Amin dan rakan-rakan (2004). Jumlah kandungan fenol yang adalah mendekati 50% daripada jumlah nilai yang didapati daripada kajian awal mengenai kultivar ubi keledek yang berbeza.

Tikus BALB/c telah diinduksikan dengan psoriasis secara kimia dengan mengaplikasikan topikal Imiquimoid kepada kulit tikus yang telah dicukur, mengikut kepada protokol yang dinyatakan oleh van der fits dan rakan-rakan (2009). Secara histologikal, lesi yand didapati adalah sama seperti psoriasis vulgaris manusia sebagaimana disahkan oleh pakar dermatologi dan histopatologi. Sitometri aliran menunjukkan peningkatan tahap sel CD^{3+}, CD^{4+}, CD^{8+} dan TNF-alfa dalam darah periferi. Ini merupakan petanda tindak balas keradangan yand dilihat dalam psoriasis akut. Selepas rawatan, hasil menunjukkan kemajuan klinikal yang signifikan untuk kumpulan yang dirawat menggunakan ekstrak SPL lipofilik, seperti yang diskorkan menggunakan PASI terubahsuai, berbanding dengan kumpulan yang dirawat dengan ekstrak SPL hidrofilik dan kumpulan kontrol negatif. Perubahan histopatologikal menunjukkan pengurangan yang signifikan bagi ketebalan epidermal dan aluran rete. Parameter immunologi dan molekular menunjukkan pengurangan yang signifikan bagi petunjuk biologi keradangan, terutamanya TNF-alfa dan peratusan negatif berganda sel T. Kesimpulannya, kajian ini menunjukkan bukti yang kukuh bagi ciri-ciri anti-psoriasis untuk ekstrak SPL lipofilik. Ini seharusnya meyakinkan kita untuk melihat lebih dalam kepada sebatian-sebatian aktif yang bertanggungjawab kepada kesan-kesan anti-psoriasis.

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I certify that a Thesis Examination Committee has met on 21 April 2017 to conduct the final examination of Anuar bin Sani on his thesis entitled "*In Vivo* Evaluation of Sweet Potato Leaf (*Ipomoea batatas* (L.) Lam.) Extracts for Treatment of Psoriasis Using Mouse Model" 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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This thesis submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirementfor the degree of Doctor of Philosophy. The members of the supervisory Committee are as follows:

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LIST OF ABBREVIATIONS

APC	Antigen-presenting cells
CD	cluster of differentiation
CAM	Complementary and Alternative medicine
CLCL	cumulative life course impairment
DCs	Dendritic cells
dw	dry weight
FC	Folin-Ciocalteu
GAE	Gallic acid equivalent
g	gram
H&E stain	Hematoxylin and Eosin stain
HPLC	High performance liquid chromatography
HETG	Hydrophilic Extract Test Group
IFN-alpha	Inteferon -alpha
IFN-γ	interferon-gamma
IL	interleukin
IB	ipomoea batatas
LETG	Lipophilic Extract Test Group
NCG	Negative Control Group
PCG	Positive Control Group
PASI	Psoriatic Assessment and Severity Index
Treg	Regulatory T cells
SPL	sweet potato leaves
Th1	T helper cell 1
Th2	T helper cell 2
TF	total flavonoids
TP	total phenolic

TPC	Total phenolic content
TNF-α	tumour necrosis factor- alpha

CHAPTER 1

INTRODUCTION

1.1 Overview of psoriasis

Psoriasis is a common chronic disfiguring inflammatory immunological disorder essentially of the skin. In between 1.3% and 34.7% of skin psoriasis, joints are involved as psoriatic arthritis which causes severe disability (Lebwohl, 2003).

Skin psoriasis is one of the prototypic papulosquamous diseases which involves skin and nails, and is associated with several comorbidities. The typical aetiology is unknown, however there are consistent pathological and immunological features of epidermal hyperproliferation, T cell expansion, cytokine over production and angiogenesis mostly related to dysregulation of the immune system. So, immunological, genetic and environmental factors interplay and influence the pathophysiology and the outcome of the disease (Lebwohl, 2003).

Psoriasis has a great negative impact on patients'quality of life. The emotional and social consequences should not be underestimated. Many patients have severe humiliation because of their visible lesions. They withdraw from the society, develop depression, anxiety, and have increased suicidality (Olivier, Robert, Daihung, Urbà, Catalin, Hywel & Gelfand, 2010). At the community level, psoriasis causes significant social and economic burden. Work absenteeism and other complications related to psoriasis are known as cumulative life course impairment (CLCI) (Warren, Kleyn, & Gulliver, 2011; Pearce, Singh, Balkrishnan, Kulkarni, Fleischer & Feldman, 2006).

A spectrum of anti-psoriatic treatment modalities are available. The severity of the disease usually determines the therapeutic approach and approximately 70 to 80% of all patients with psoriasis can be treated adequately with topical preparations (Mitra, Morrissey & Lim, 2013). Despite the recent advances in psoriasis therapeutics, the disease remains as lifelong incurable ailment of relapse and remission. The main goal of treatment remains to establish and prolong periods between flares (Global report on psoriasis-WHO, 2016). None of available therapies induce a permanent remission and all therapies are associated with side effects such as skin atrophy due to topical steroids or even immune suppression by anti metabolites that can place limits on their uses. As such, Complementary and Alternative Medicines (CAM) are widely used by psoriatic patients worldwide.

The common modalities of CAMs include traditional Chinese medicine (TCM), herbal therapies, dietary supplements, climatotherapy, and mind/body interventions. Herbal and dietary therapies seem to have the most evidence for efficacy (Talbott & Duffy, 2015).

1.2 The rationale of studying sweet potato leaves (SPL) effects on experimentally induced psoriasis in BALB/c mice

The idea of studying the topical effects of Sweet Potato (*Ipomoea batatas*) Leaves (SPL) on induced psoriasis lesions in animal model, came from the anecdotal observations of Malaysian patients who failed to achieve satisfactory response to conventional therapies, but observed significant remission after trying topical SPL paste. Furthermore, plenty of research were done especially in Japan, Taiwan and China on immune-modulatory potential of sweet potato leaves and considered as one of the healthiest food (Johnson & Pace, 2010). Coupled with the known side effects and high cost of conventional treatments of psoriasis, the need to look for an alternative in the form of locally available and cheap to get is even more pressing, thus sweet potato leaves fits the bill.

Scientific research based on investigating an observable event is a standard way of getting new knowledge, and correcting and integrating previous information. Successful studies based on examination of observations can help to construct a hypothesis and draw a conclusion. This study used mixed quantitative and semi-quantitative methodologies to process and analyse the obtained data.

1.3 Objectives

General: To determine the potential action of topical hydrophilic and lipophilic extracts of Sweet Potato Leaves (*Ipomoea batatas*) on experimentally induced psoriasis in animal (mouse) model.

Specific:

i) To assess response of induced psoriatic lesions when subjected to topical SPL extracts using modified PASI score.
ii) To compare the histological response of induced psoriasis lesions following topical application SPL extracts.
iii) To examine the liver, spleen and kidney histological sections before and following topical application of SPL extracts.
iv) To evaluate the effects of topical application of SPL extracts on immuno-parameters of cellular and molecular components of the psoriatic induced mice.

1.4 Hypothesis

The hypothesis was that topical application of SPL extracts on the induced psoriatic lesions would speed up the recovery by reversing the induced lesions to near normality as compared to leaving the induced lesions to heal by itselves. And, it would be interesting to find out, if there was such an effect, which of the extracts would work better.

It was also hypothesized that the positive healing effect would be accompanied by changes in cellular and molecular immune-parameters.

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