UNIVERSITI PUTRA MALAYSIA

ANTIPRURITIC ACTIVITIES OF HARUAN EXTRACT ON CHEMICALLYINDUCED ITCH AND DRY SKIN ITCH MOUSE MODEL

MUHAMAD 'IRFAN BIN MUHAMAD FAUZI

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By

MUHAMAD 'IRFAN BIN MUHAMAD FAUZI

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May 2021

Chair : Ahmad Akira bin Omar Farouk, PhD
Faculty : Medicine and Health Sciences

The objective of this study was to determine the antipruritic activity of Haruan extract against dry skin and chemically induced itch mice models. The study was designed as alternative method, as HE antipruritic potential cream has never been reported for specific dry skin itch. In attempt to established the pharmacological properties of HE, the antipruritic potential of HE was investigated using dry skin itch, histamine-itch and C48/80 itch mouse model. Throughout the study, the animals were divided into 18 groups. Each group divided by different inducer containing 8 mice per group. For the first stage of behavioural study, all rostral back of mice were shaved and acclimatise for 3 days. For dry skin itch model, AEW were topically applied to induce itch twice daily for five consecutive days. Histamine itch model were SC injected with 0.3mg/kg and C48/80 itch model were SC injected with 3.6mg/kg. All models were continuously applied with 3%, 7% and 10% of HE creams and placed in custom chambers on an elevated metal mesh floor and recorded for 30 minutes. The possible effect of Haruan extract cream on TNF-α gene expression level was determined by RNA extraction of skin followed by RT-PCR and analysed by relative quantification using comparative method. The morphological change of the skin was determined by stained with H&A and evaluated of general epidermal thickness using image analyser. The behavioral observed of dry skin itch, histamine, and C48/80 induced mice models were showed reduced in scratch duration shown by 10%, 7% and 3% HE creams treatment. The TNF-α gene expression showed the Histamine and C48/80 induced model were exhibit the reading of gene expression in HE creams treatment comparison to the negative control groups. The morphological findings that all different models which were treated with HE creams had produced an anti-oedematous and reduced the epidermal thickness with similar potential to that of steroid-based hydrocortisone 1% cream. In conclusion, this study highlights the potential antipruritic activity of HE that can be partly attributed to other probable mechanism for skin protective, which warrants further investigation.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia
sebagai memenuhi keperluan untuk Ijazah Master Sains

AKTIVITI ANTIPRURITIK OLEH EKSTRAK HARUAN DALAM TIKUS SECARA RANGSANGAN KIMIA DAN KULIT KERING

Oleh

MUHAMAD 'IRFAN BIN MUHAMAD FAUZI

Mei 2021

Pengerusi : Ahmad Akira bin Omar Farouk, PhD
Fakulti : Perubatan dan Sains Kesihatan

Objektif kajian ini adalah untuk menentukan aktiviti anti pruritik daripada HA pada gatal kulit kering dan gatal secara kimia. Kajian ini dibuat sebagai rawatan alternatif dimana HA yang tidak pernah dilaporkan. Dalam usaha untuk mewujudkan sifat-sifat farmakologikal HA, potensi anti-pruritik pada tikus rangsangan gatal kulit kering dan gatal secara kimia (Histamin dan C48/80). Sepanjang kajian, haiwan telah dibahagikan kepada 18 kumpulan. Setiap kumpulan dibahagikan kepada perangsang atau model yang berbeza dan mengandungi 8 tikus setiap kumpulan. Untuk peringkat pertama kajian tingkah laku, tikus dicukur bulu rostral dan dibiar menyesuaikan diri selama 3 hari. Untuk gatal kulit kering, AEW digunakan untuk merangsang sebanyak 2 kali sehari untuk 5 hari berterusan. Model gatal Histamin disuntik dengan 0.3 mg/kg dan model gatal C48/80 disuntik dengan 3.6 mg/kg. Semua model disapukan dengan 3%, 7% dan 10% krim HA. Kemudian, diletakkan dalam kotak khas diatas jaring besi dan direkodkan selama 30 minit. Potensi krim HA pada ekspresi gen TNF-α telah ditentukan dengan menggunakan ekstrak RNA dari kulit diikuti dengan RT-PCR dan dianalisa dengan kuantifikasi relatif menggunakan kaedah perbandingan. Perubahan morfologi kulit ditentukan dengan diwarnai dengan H&A dan dinilai ketebalan epidermis umum menggunakan penganalisis gambar. Kajian tingkah laku yang diperhatikan pada model tikus kulit kering, histamin, dan C48 / 80 menunjukkan penurunan tempoh garuan apabila diletakkan 10%, 7% dan 3% krim HA. Ekspresi gen TNF-α menunjukkan model yang dirangsang oleh Histamine dan C48 / 80 menunjukkan pengurangan ekspresi gen pada kumpulan rawatan HA jika dibandingkan dengan kumpulan kawalan negative. Penemuan morfologi bahawa semua model yang berbeza yang dirawat dengan krim HE telah menghasilkan anti-oedematous dan mengurangkan ketebalan epidermis dengan potensi yang serupa dengan krim hidrokortison 1% yang berasaskan steroid. Kesimpulannya, kajian ini menunjukkan potensi aktiviti antipruritik HE yang sebahagiannya dapat dikaitkan dengan mekanisme lain yang mungkin untuk melindungi kulit, yang memerlukan penyelidikan lebih lanjut.

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

Ahmad Akira bin Omar Farouk, PhD
Senior Lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Enoch Kumar A/L Perimal, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

_____

ZALILAH MOHD SHARIF, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 19 May 2022

Declaration by Members of Supervisory Committee

This is to confirm that:

- the research and the writing of this thesis were done under our supervision;
- supervisory responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2015-2016) are adhered to.

Signature: _____
Name of Chairman of Supervisory Committee: _____

Signature: _____
Name of Member of Supervisory Committee: _____

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ANOVA	Analysis of variance
C. striatus	*Channa striatus*
SC	Stratum corneum
TEWL	transepidermal water loss
PUFA	polyunsaturated fatty acids
COX	Cyclooxygenase
DHA	Docosahexanoic acid
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
RNA	Ribonucleic acid
GABA	Gamma Aminobutyric acid
GF	Growth factor
GSH	Gluthathione
HCl	Hydrochloric acid
IACUC	Institutional Animal Care and Use Committee
L-NAME	N-Nitro-L-Arginine Methyl Ester
ND	Not determined
NSAIA	Non steroidal anti-inflammatory agent
NSAIDs	Non Steroidal anti-inflammatory drug
OH	Hydroxide ion
PGs	Prostaglandins
PGD	Preimplantation genetic diagnosis
RNA	Ribonucleic acid
Rpm	Rotation per minute

AEW	Acetone, diethylether and water
C48/80	Compound 48/80

CHAPTER 1

INTRODUCTION

Itch was defined more than 361 years ago by the German physician Samuel Hafenreffer as an unsavory sensory and emotional experience that associated with an actual or perceived disruption to the skin that produces a strong desire to scratch (Rothman, 1941). This definition is still valid, but is also currently differentiated into acute and chronic pruritus, and it is understood that chronic itch is a complex sensory experience with many similarities to pain. Also, a mechanism-based definition of itch has been proposed that separates itch that is induced in a healthy nervous system by peripheral (pruriceptive) and central (neurogenic) mechanisms from itch that is caused by diseased neurons (neuropathic). However, the pathophysiology of most clinical itch conditions is unclear (Ikoma A et al., 2006). Unlike the sensation of pain, where an organism will try to withdraw from that unpleasant stimulus, itch compels the affected to seek out the source and respond with a scratch (Nutten., 2015). Researchers have clarified some differences between itch and pain, but have also blurred the distinction between them. Itch and pain appear to be independent sensations because nociceptive and pruriceptive stimuli each elicit unique behavioral responses (LaMotte., 2014), and revealing that the neural processing of itch is more diverse and complex than previously thought.

Acute itch is sensation that can usually stop or relief by shortly scratching near the area of itching, and usually not longer than 6 weeks (Ikoma A et al., 2006). There are central and peripheral components for acute itch. Peripheral components include histaminergic peripheral neurons where cardiologist Thomas Lewis termed the triple response, with redness, flare, and swelling around the site of histamine injection (Lewis, 1926). Another one is nonhistaminergic itch, which is not cause by histamine, yet another pruritogen is the tiny hairs or spike derived from the plant cowhage (*Mucuna* pruriens). Proteinase mucunain is active ingredient in Cowhage (Reddy et al., 2008) is capable to produce a strong dose itch in human without any vasodilation.

Chronic itch is difficult and complex to abolish, and usually longer than 6 weeks. Local scratching often provides little relief and can instead exacerbate the problem (Ikoma, A. et al, 2006). Chronic pruritus underlies multiple dermatologic conditions, such as atopic dermatitis (AD), contact dermatitis and psoriasis. It also associated with a variety of systemic medical conditions such chronic kidney disease (CKD), liver dysfunction, malignancy, various infections and even psychiatric disease (Ji R-R., 2012). Recent scientific advances have revealed previously unrecognized itch-specific pathways that are regulated by particular mediators, including neurotransmitters, pharmacologic agents and inflammatory cytokines (Bautista., 2014).

Mas-related G protein-coupled receptor (Mrgpr) was identified by Liu et al in 2009 as a novel family of histamine-independent itch receptors expressed in the dorsal root ganglia (DRG), and their subtypes have been identified in both mice and humans (McNeil B et al., 2014).

Dry skin is chronic itch caused by disruption to the stratum corneum (SC) and cutaneous barrier. That reduced the water-holding capacity by reduction of hydration and by increase in transepidermal water loss (TEWL) (Long CC et al., 1992). Treatment with organic solvent and water or exposure in the dry environment can disrupt the barrier with the loss of aqueous components, including amino acid α-hydroxylates, pyrrolidone carboxylate and urea (Jokura Y et al., 1995). However, there is no animal model to use for the screening test of the medications for this AEW dry skin model (T. Miyamoto et al., 2001).

There are two well-known theories of itch signal transmission have been proposed. First, the intensity theory, it was suggested that low level nociceptor activation could initiate the sensation of itch whereas higher frequency should give rise to pain sensation. Second, the specificity and selectivity theory, it was suggested that itch and pain pathways were same but not identical (McMahon et al., 1992). Some itch-producing agents have been found to activate nociceptive primary afferent fiber and thus generate nociceptive sensation (LaMotte., 2014).

The natural product-based remedies have gained attention of many researchers as this type of remedies has many medicinal purposes and be considered as safe and cheap. Animal-based natural product is one of the families within natural product that have been studied well. *Channa striatus,* striped snakehead locally known as Haruan, is a freshwater fish species indigenous to Malaysia (Mat Jais.,2007). It is indigenous to many tropical and sub-tropical countries. Despite of being a predator fish, Haruan is not a good swimmer but with fast slippery action is quite able to catch prey, and as an air breather the fish needs to surface for air. Therefore, Haruan prefers water with slow running or still, shallow not more than 2 meters, with aquatic plants and some dead logs to hide under. However, Haruan has been also found in waters up to 12 meters deep and 4 to 80 meters width. Most of its natural habitats such ponds, lakes, small rivers, rice fields seem the most ideal habitats, but Haruan has been also found in various unexpected places such as rivers and drains with salinity about 10 ppt and higher ground with water temperature around 20°C (Mohsin et al., 1983**).** Haruan widely consumed in Malaysia and other Southeast Asian countries not only for its nutritional value but also for its effective effects on wound healing and lessen post-operative pain and discomfort (Mat Jais et al., 1994). Haruan's FDWE and SDWE protein fractions contain bioactive proteins that are highly similar to human proteins and thus could be involved in the wound healing process via specific biological pathways (Soon K et al., 2019).

Other than that, Haruan exhibited the anti-inflammatory and antinociceptive activities (Zakaria et al., 2008). High content of arachidonic acid from Haruan, is a precursor for prostaglandin production to stimulate the synthesis of mucus that required as a barrier against those truculent factors (Zakaria et al., 2004). Other applications of Haruan include its use in the treatment of skin conditions such as eczema and psoriasis as itch one of the symptoms.

Problem Statement

When comes to itch related diseases either acute or chronic itch, Antihistamine and corticosteroid are the current medication among the physicians. Antihistamine is ineffective against chronic itch especially on dry skin itch and eczema, and corticosteroid is given common side effect such as increase skin fragility, petechial and skin atrophy (Grundmann et al., 2011). In this study, we will investigate the potential of Haruan extract cream against dry skin itch and chemical-induce itch for minimizing the use of commercial chemical drugs.

Justification for studying the antipruritic potential of Haruan

Currently there are many problems faced by people suffering from chronic itch especially by side effect that prevent certain patients with certain health condition from consuming it. Other problems are due to the drug availability and high cost of available drugs. Therefore, it is warranted to search for alternatives to treat dry skin and chemically itch with less side effects, effective and readily available. Scientifically there is no specific study of Haruan extract cream on dry skin itch and chemically itch mice model. Previous studies on Haruan found the presence of wound-healing, anti-nociceptive, anti-inflammatory and antioxidant activities that is relevant on antipruritic activity. Since pain and itch may have the same pathway, this study is expected to uncover the antipruritic activity of Haruan.

Hypothesis

Haruan extract may have antipruritic activity on dry skin and chemically induced itch mice models.

General objectives:

- To determine the antipruritic activity of Haruan extract against dry skin and chemically induced itch mice models.

Specific objectives:

- To examine the effect of Haruan extract cream in suppressing scratching response on dry skin itch and chemically induce itch in male ICR mice.
- To examine the effect of Haruan extract cream on Tumor necrosis factor alpha (TNF-α) gene expression.
- To examine morphological changes on skin thickness after application of Haruan extract topical treatment.

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