UNIVERSITI PUTRA MALAYSIA

EVALUATION OF WOUND HEALING PROPERTIES OF Clinicanthus nutans (Burm.F.) Lindau (BELALAI GAJAH) AND ITS RELATED BIOCHEMICAL ACTIVITIES ON MALE SPRAGUE-DAWLEY RATS.

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By

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EVALUATION OF WOUND HEALING PROPERTIES OF *Clinicanthus nutans* (Burm.F.) Lindau (*BELALAI GAJAH*) AND ITS RELATED BIOCHEMICAL ACTIVITIES ON MALE SPRAGUE-DAWLEY RATS.

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Clinacanthus nutans Lindau (*C. nutans*), also known as Sabah Snake Grass, of the Acanthaceae family has been widely used in traditional medicine and scientific investigations of this plant have shown multitude therapeutic benefits ranging from anticancer, antioxidant, antidiabetic, antimicrobial, immunomodulatory, anti-inflammatory and analgesic activities. *C. nutans* has also shown promising properties in preliminary wound healing rat models by the integrity of epidermal tissue at the lesion sites. The objective of this study is to determine the most potent solvent extracts of *C. nutans* to develop a topical herbal cream that will be efficacious on the wound lesions in Sprague Dawley rat models along the lines of biochemical and histological assessments. The plant leaves were subjected to hot solvent extraction and crude extracts were derived from ethanol, methanol, chloroform and water. The extracts were subjected to both phytochemicals assessments which comprised of phenols, flavonoids and tannins and antioxidant activity assessments by (2,2-diphenyl- 1-picrylhydrazyl) DPPH and (Azino-bis-3-ethylbanzthiazoline-6-sulphonic acid) ABTS assays prior to conducting the *in vivo* excision wound experiment in rat models. Methanol extract demonstrated the highest phenolic, flavonoid and tannin content of (12.96 ± 1.91 mg GAE/gm), (10.06 ± 1.68 mg QUE/gm) and (7.15 ± 0.64 mg TAE/gm). It was found that, methanol extract could scavenge DPPH with the maximum scavenging activity of 56.37 ± 0.70% and with an IC_{50} of 222.69 ± 0.29 µg/ml and for ABTS, aqueous extract showed highest scavenging activity of 57.50 ± 0.52% with an IC_{50} of 149.45 ± 0.24 µg/ml respectively. The rats were arranged into 6 groups, each group consist of 6 rats except the negative control group which consist of 3 rats. Group 1 (control), group 2 (standard / Dettol antiseptic cream), group 3 was aqueous extract of *C. nutans* with dose 1 (12.5 mg/ml of aqueous extract of *C. nutans)*, dose 2 (25.0 mg/ml of aqueous extract of *C. nutans)* and dose 3 (50.0 mg/ml of aqueous extract of *C.*

nutans). Group 4 was methanolic extract of *C. nutans* with dose 1 (12.5 mg/ml methanolic extract of *C. nutans)*, dose 2 (25.0 mg/ml methanolic extract of *C. nutans)* and dose 3 (50.0 mg/ml methanolic extract of *C. nutans)* group 5 (cream base), group 6 (herbal cream). The most effective dosages were 12.5 mg/ml of methanol extract and 50.0 mg/ml of aqueous extract, combined and produced a topical herbal cream which was tested *in vivo* using rat models again. Subsequently, the mechanism of action of the *C. nutans* topical herbal cream was assessed using biochemical parameters like hydroxyproline, collagen and hexosamine and histopathological changes. Topical herbal cream by incorporating methanol extract 12.5 mg/ml and aqueous extract 50.0 mg/ml showed a significant wound repair and skin regeneration about (99.5 ± 0.22%) wound contraction at Day 15 compared to control groups. Biochemical parameters like hydroxyproline (64.11 ± 0.01 mg/g), hexosamine (31.37 ± 1.79 mg/g) and collagen (478.24 ± 1.12 mg/g) turnover were found to be significantly increased ($p<0.05$) in test topical herbal cream treated animals as compared to controls. All statistical analysis was performed using SPSS statistical version 20.0 software package and *P*-value was set as <0.05 for all analysis. Histopathological findings revealed that the cream confirmed that the epidermis layers with complete re-epithelialization and dermis show dense bundles of collagen fibers. In conclusion, all these investigations indicate significant wound healing potential of *C. nutans* topical herbal cream in Sprague Dawley excision wound models.

Keywords: *C. nutans*; wound healing; rat; biochemical changes; antioxidant; excision wound model;

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

PENILAIAN AKTIVITI PENYEMBUHAN LUKA *Clinacanthus nutans* (Burm.F.) Lindau (*BELALAI GAJAH*) DAN AKTIVITI BIOKIMIA YANG BERKAITAN PADA TIKUS SPRAGUE-DAWLEY LELAKI.

Oleh

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Clinacanthus nutans Lindau (*C. nutans*), yang juga dikenali sebagai belalai gajah, dari keluarga Acanthaceae yang banyak digunakan dalam perubatan tradisional dan kajian saintifik tumbuhan ini telah menunjukkan banyak faedah terapeutik yang terdiri daripada antikanser, antioksidan, antidiabetik, antimikrobial, imunomodulator dan analgesik. *C. nutans* juga menunjukkan ciri-ciri yang menjanjikan dalam model tikus penyembuhan luka oleh integriti tisu epidermis pada luka. Objektif kajian ini adalah untuk menentukan ekstrak pelarut yang paling efektif dari *C. nutans* untuk merumuskan salap herba yang akan berefektif pada luka pada model tikus Sprague Dawley dengan mekanisme biokimia. Daun tumbuhan tertakluk kepada pengekstrakan pelarut panas dan ekstrak mentah diperoleh daripada etanol, metanol, kloroform dan air. Ekstrak tersebut tertakluk kepada penilaian fitokimia iaitu fenol, flavonoid dan tanin dan penilaian aktiviti antioksidan oleh (2,2-diphenyl-1-picrylhydrazyl) DPPH dan (Asid Azino-bis-3-ethylbanzthiazoline-6-sulfonat) sebelum melakukan eksperimen luka *in vivo* pada tikus. Ekstrak metanol menunjukkan kandungan fenolik, flavonoid dan tanin (12.96 ± 1.91 mg GAE/gm), (10.06 ± 1.68 mg QUE/gm) dan (7.15 ± 0.64 mg TAE/gm). Kajian ini menunjukkan bahawa ekstrak metanol dengan DPPH menunjukkan aktiviti maksimum 56.37 ± 0.70% dan dengan IC50 222.69 ± 0.29 µg / ml dan ABTS, ekstrak air menunjukkan aktiviti penimbunan tertinggi 57.50 ± 0.52% dengan IC50 149.45 ± 0.24 µg / ml. Dos yang paling berkesan adalah 12.5 mg/kg ekstrak metanol dan 50.0 mg/kg ekstrak air, digabungkan dan menghasilkan salap herba yang diuji di *in vivo* menggunakan model tikus sekali lagi. Seterusnya, mekanisme tindakan salap *herba C. nutans* dinilai dengan menggunakan parameter biokimia seperti hidroksiprolin, kolagen dan heksosamine dan perubahan histopatologi. Perumusan herba dengan menggabungkan ekstrak metanol 12.5 mg/ml dan ekstrak air 50.0 mg/ml menunjukkan pembedahan luka yang signifikan dan penyembuhan kulit (99.5 ± 0.22%) pengecutan luka pada 15 hari berbanding kontrol. Parameter biokimia

seperti hidroksiprolin (64.11 ± 0.01 mg/g), heksosamine (31.37 ± 1.79 mg/g) dan kolagen (478.24 ± 1.12 mg/g) didapati meningkat dengan ketara ($p < 0.05$) berbanding dengan kawalan. Semua analisis statistik dilaksanakan menggunakan pakej perisian versi statistik SPSS 20.0 dan nilai P ditetapkan sebagai <0.05 untuk semua analisis. Kesimpulan, kajian ini mendapati menunjukkan potensi penyembuhan luka dari salap herba *C. nutans* dalam model luka Sprague Dawley.

Kata kunci: *C.nutans*; penyembuhan luka; tikus; perubahan boikimia; antioksidan; model luka eksisi;

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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.

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LIST OF ABBREVIATIONS

ABTS	2,2'-azino-bis-3-ethylbenzothiazoline-6-sulphonic acid
AlCl3	Aluminum chloride
ANOVA	Analysis of Variance
DNA	Deoxyribonucleic acid
DMSO	Dimethyl sulfoxide
DPPH	1,1- diphenyl-2- picrylhydrazyl
ECM	Extracellular matrix
GAE	Gallic acid equivalent
HGF	Human gingival fibroblast
IC50	Inhibitory concentration at 50%
MPO	Myeloperoxidase
NaNO3	Sodium nitrate
NaOH	Sodium hydroxide
PBMC	Peripheral blood mononuclear cells
QE	Quercetin equivalent
ROS	Reactive oxygen species
SD	Standard deviation
Sdn Bhd	Sendrian Berhad
SPSS	Statistical Package of Social Sciences
TAE	Tannic acid equivalent
VZV	Varicella-zoster
WHO	World Health Organization
<	Less than
%	Percentage

&	And
±	Plus and/or minus
µg/ml	Microgram per millilitre
µl	Microliter
g	Gram
mg	Milligram
GAE/gm	Milligram gallic acid equivalent per gram
QE/gm	Milligram quercetin equivalent per gram
TAE/gm	Milligram tannic acid equivalent per gram
mg/ml	Milligram per milliliter
mg/kg	Milligram per kilogram
ml	milliliter
mM	Millimolar
nm	nanometer
°C	Degree Celsius
®	Registered trademark

CHAPTER 1

INTRODUCTION

1.1 Background

Clinacanthus nutans (Burm. f) Lindau, otherwise called Sabah Snake Grass, from the family of Acanthaceae is a notable therapeutic plant in Thai folklore medicinal practices (Yong et al., 2013). It is known that the fresh leaves of *C. nutans* can be taken as unrefined vegetable or mixed in with other fresh squeezes, for instance, crushed apple and sugarcane press, or green tea, and filled in as restoring drinks. The dried leaves soak up high temperature water and prepared as tea concoctions (Shim et al., 2013). *C. nutans* is medicinal plant traditionally used in treating skin abnormalities like skin rashes, snakebite and burns (Aslam et al., 2015). Additionally, this plant has been utilized traditionally to treat malignancy in Malaysia. Nevertheless, it lacks verifiable studies backing the statements (Roosita et al., 2008; Shim et al., 2013).

Scientific studies on *C. nutans* have its potential along the lines of chemotherapeutics and chemoprevention, antidiabetic, antimicrobial, immunomodulatory, wound healing, analgesics and most as of late for the treatment and anticipation of malignant growth infections (P'ng et al., 2012); (Mustapa et al., 2015). Scientific studies evinced *C. nutans* to have an extensive antimicrobial and mitigating action towards genital herpes and varicella-zoster contamination (VZV) bruises analyzed in immunocompromised patients and effectively retards of unfavorable reactions due to insect bites (Sakdarat et al., 2009). *C. nutans* has likewise been for the treatment of hepatitis, skin-rashes and dermatitis (Mustapa et al., 2015).

Observation of all illnesses is the primary distinction between contemporary medicine and ancient medicine. Modern medicine heals illnesses with ease, yet it does not address the underlying causes. It also has the negative effect of causing the body of the living person to develop additional illnesses. Diseases may take a long time to heal with traditional medicine, but the core cause of the illness is destroyed (Fauzi et al., 2013). Thus, evidence-based medicine may be adopted by the whole medical sector, allowing for the reduction of adverse effects and the maximization of benefits from scientific study for patient care (More, 2016).

1.2 Problem Statement

Bioactive chemicals found in medicinal plants have been utilized to maintain human health, including prevention, diagnosis, and improvement or treatment of a wide range of human physical diseases for thousands of years (Zainol et al., 2019). Moderately, about eighty percent of resident's dependent on Asia, Africa and the Middle East upon customary prescriptions. There are 350000 higher plant species in nature, and around 80000 contain therapeutic qualities, according to recent reports. Bioactive chemicals and biological activities of just 5000 of the plants have been thoroughly investigated (Dar et al., 2017; Yuan et al., 2016). Globally, medical plants-derived medicines are popular since they are less expensive and have fewer negative effects (Marušk et al., 2010). Complex and lengthy treatments are causing an increased burden on healthcare expenses (Nuutila et al., 2014). *C. nutans* has been generally utilized in Asia for quite a long time for its restorative profile (Fong, 2015). Besides that, *C. nutans* improves the physiological appearance of wound. It will be cost effective since the number of healing days are lesser compared to modern methods (Ramasamy, 2016). Preliminary studies indicate detailed research should be done to show the properties of wound healing with *C. nutans* solvent extracts (Ramasamy, 2016).

Various customary restorative utilizes for *C. nutans* have appeared, yet clinical and scientific information bolster just a portion of these discoveries. Basically, the leaves of *C. nutans* exclusively utilized in customary prescriptions (Zulkipli et al., 2017). The use of this medicinal plant to treat Herpes virus contaminations is upheld by the aftereffects of various scientific studies and clinical preliminaries (Lipipun et al., 2011, Kunsorn et al., 2013). According to Yong et al. (2013), *C. nutans* extricates are cancer prevention agents with antiproliferative efficacies on a range of human malignant growth cell lines explicitly HepG2, IMR32, NCL-H23, SNU-1, Hela, LS-174T, K562, Raji, and IMR32. It was uncovered that the chloroform concentrate of this plant leaves have the majority basic constituents that equipped for rummaging free radicals and hinders the development of refined malignant growth cells. Notable inhibition on the generation of superoxide anion and elastase discharge by initiated neutrophils by the 80% ethanol concentrate of aerial part of *C. nutans.* The restraint was delivered by 10 mg/mL ethanolic concentrate of *C. nutans* at 68.33% (Tu et al., 2014). Arullappan et al. (2014), demonstrated that the fraction 7 with most noteworthy enemy of microbial action, with minimum inhibitory concentration (MIC) of 1.39mg/ml against the *Bacillus cereus, Escherichia coli, Salmonella enterica Typhium and Candida albicans*.

Anti- inflammatory activity revealed with significantly reduced oedema after 3 hours in Carrageenan-induced oedema by extract, in a portion subordinate way (Wanikiat et al., 2008). Preliminary *in vivo* screening of *C. nutans* aqueous extracts have shown significant wound healing in mice models (Ramasamy, 2016). Since radical scavenging activity is also an indicator for wound healing

activity potencies, the investigator seeks to further study the efficacies of *C. nutans* solvent concentrates for wound recuperating properties

1.3 Hypothesis

It is hypothesized that the herbal ointment formulation of *C. nutans* to possess phytochemicals, wound healing properties and as well as exhibiting antioxidants properties.

1.4 Objective

1.4.1 General objective

To investigate the efficacy of *C. nutans* extracts and formulated herbal ointment on wound healing employing rat excision wound model and the underlying biochemical changes.

1.4.2 Specific Objective

1) To determine total flavonoids (TF), total phenolic compounds (TPC) and tannins (TTC) and antioxidant properties using DPPH and ABTS assays of *C. nutans* extracts.

2) To determine the efficacy of the *C. nutans* extracts on wound healing in excision wound of Sprague-Dawley rats

3) To evaluate the biochemical parameters with regards to hydroxyproline, collagen and hexosamine content on excision wounds in Sprague-Dawley rats between control groups using antiseptic Dettol cream and treatment group employing *C. nutans* herbal formulation.

4) To compare and characterize the histopathological changes of skin restoration between herbal ointment formulation of *C. nutans* and control groups in wound of Sprague-Dawley rats.

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