UNIVERSITI PUTRA MALAYSIA

EFFICACY OF EPIDERMAL GROWTH FACTOR TOCOTRIENOL RICH FRACTION CREAM FORMULATION IN DEEP-PARTIAL THICKNESS BURN IN Sprague-Dawley RATS

ASMA BINTI AHMAD ZAINI

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By

ASMA BINTI AHMAD ZAINI

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

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ASMA BINTI AHMAD ZAINI

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Chairman : Huzwah Khaza'ai , PhD
Faculty : Institute of Bioscience

Silver Sulfadiazine (SSD) is primarily used as a topical burn treatment. However, it has been reported that SSD cream can cause adverse reactions like allergy and toxicity. Thus, in this study the burn healing properties of epidermal growth factor (EGF) and tocotrienol rich fraction (TRF) formulation were evaluated. This study was conducted in four stages. The first and second stages were to evaluate the efficacy of TRF (3-5%) and EGF (A-C%) separately, meanwhile the third stage was to study the synergistic effect of both compounds in burn wound healing. *Sprague-Dawley* male rats were divided into 6 groups (n=7). The deep-partial thickness burn wounds were performed on the shaved skin with the exposure to 100°C heat for 10 second. Treatment was applied topically once daily to the burned areas for 21 days. The measurable outcomes involved rate of wound contraction, clinical evaluation, H&E staining and cellular population number. The results were analyzed for statistical significance using two-way ANOVA for microscopic study and two way repeated measure for macroscopic study. Bonferonni test was performed for the significant treatment means. The optimum dosage of both ingredients obtained was further used for the formulation of EGF-TRF cream and the synergistic effects were determined. TRF at 3% concentration showed most advanced healing indicated with better cosmetic and histopathological outcome, highest percentage of wound contraction rate at day 5, 9, 13, and 17 with 43.34±2.13, 62.87±1.74, 92.38±2.48 and 100.00±0.00 respectively, lowest count of neutrophils and macrophages. The highest dose (C%) of EGF increased the healing process indicated with better cosmetic and histopathological outcome and highest percentage of wound contraction rate at day 13 and 17 with 78.82±2.40 and 100.00±0.00 respectively. Hence, for the third stage study, A-C% EGF were mixed with 3% TRF. The best formulation was further used in the fourth stage. Microscopic changes of the collagen in the dermal layer for the optimum formulation (C% EGF + 3% TRF) was monitored. Current finding

demonstrated the C% EGF + 3% TRF treatment exhibited excellent gross appearance, highest percentage of wound contraction rate in all experimental period and full histological score as early as day 14. Microscopic evaluation demonstrated that there was a significant acceleration of the epidermal and dermal repair in C% EGF + 3% TRF. Collagen staining also showed increased fibroblast proliferation and collagen synthesis in C% EGF + 3% TRF. Combination of C% EGF + 3% TRF exhibited synergistic effects with better potential than the effects of these two compounds alone in accelerating burn wound healing. In addition, combination of EGF and TRF treatments showed better healing ability as compared to SSD. In conclusion EGF-TRF formulation is capable to accelerate the burn wound healing with better cosmetic outcome in the deep-partial thickness burn on various phase of burn wound healing.

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

EFIKASI FORMULASI EGF-TRF (FAKTOR PERTUMBUHAN EPIDERMIS-FRAKSI KAYA TOKOTRIENOL) TERHADAP TIKUS *Sprague-Dawley* YANG LUKA TERBAKAR PADA KETEBALAN SEPARA

Oleh

ASMA BINTI AHMAD ZAINI

Januari 2018

Pengerusi : Huzwah Khaza'ai, PhD
Fakulti : Institut Biosains

Silver Sulfadiazine (SSD) digunakan sebagai ubat sapuan utama untuk luka akibat terbakar. Walau bagaimanapun, krim SSD dilaporkan boleh menyebabkan kesan buruk seperti alergi dan toksik. Oleh itu, dalam kajian ini, sifat penyembuhan luka akibat terbakar dengan formulasi faktor pertumbuhan epidermis (EGF) dan fraksi kaya tocotrienol (TRF) dinilai. Kajian ini dijalankan dalam empat peringkat. Peringkat pertama dan kedua adalah untuk menilai kesan tindak balas dos TRF dan EGF secara berasingan, manakala tahap ketiga adalah mengkaji kesan sinergistik kedua-dua sebatian dalam penyembuhan luka terbakar. tikus jantan Sprague-Dawley dibahagikan kepada 6 kumpulan (n = 7). Luka terbakar ketebalan separa dilakukan ke atas kulit yang dicukur dengan pendedahan kepada suhu panas 100°C selama 10 saat. Rawatan diberikan secara sapuan sekali sehari pada kawasan yang terbakar selama 21 hari. Keputusan untuk ketiga-tiga peringkat ini ditentukan mengikut gabungan kadar pengecutan luka, penilaian klinikal, pewarnaan H & E dan bilangan populasi sel kulit. Data dianalisis menggunakan dua cara ANOVA untuk kajian mikroskopik dan langkah berulang ANOVA untuk data makroskopik. Ujian Bonferonni dilakukan untuk penentuan data yang signifikan. Dos yang optimum daripada kedua-dua ramuan ini telah digunakan untuk membuat rumusan krim EGF-TRF dan kesan sinergi telah ditentukan. 3% TRF menunjukkan kadar pengecutan luka yang paling tingi pada hari 5, 9, 13 and 17 dengan nilai 43.34±2.13, 62.87±1.74, 92.38±2.48 dan 100.00±0.00, bilangan neutrophil dan makrofaj yang terendah. Peningkatan dos yang responsif dapat diperhatikan dalam dos C% EGF ditunjukkan oleh hasil kosmetik yang baik, hasil histopatologi yang baik dan peratusan tertinggi kadar penguncupan luka pada hari 13 dan 17 dengan 78.82±2.40 dan 100.00±0.00 masing-masing. Oleh itu, untuk kajian peringkat ketiga, A-C% EGF telah dicampur dengan TRF 3%. Formulasi yang terbaik disiasat di peringkat keempat. Perubahan mikroskopik kolagen dalam lapisan dermal untuk formulasi terbaik telah (C% EGF + 3% TRF) dipantau. Penemuan terkini

menunjukkan rawatan C% EGF + 3% TRF menghasilkan rupa luaran luka yang baik, peratusan tertinggi untuk kadar penguncupan luka dalam semua tempoh eksperimen dan skor histologi yang penuh seawal hari 14. Penilaian mikroskopik menunjukkan bahawa terdapat akselerasi ketara pembaikan epidermis dan dermis dengan penggunaan C% EGF + 3%.TRF. Pewarnaan kolagen juga menunjukkan peningkatan proses percambahan fibroblast dan sintesis kolagen dalam kumpulan C% EGF + 3% TRF. Kombinasi C% EGF + 3% TRF menunjukkan kesan sinergi dengan potensi yang lebih baik daripada kesan kedua-dua rawatan itu secara sendirian dan rawatan lain dalam mempercepatkan penyembuhan luka terbakar ketebalan separa. Gabungan rawatan EGF dan TRF menunjukkan keupayaan penyembuhan yang lebih baik berbanding dengan SSD. Kesimpulannya, formulasi EGF-TRF mampu mempercepatkan penyembuhan luka terbakar tahap kedua di pelbagai proses tahap penyembuhan luka dan mempercepat proses penyembuhan secara langsung.

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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:

Huzwah Khaza'ai, PhD
Senior Lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Razana Md Ali, PhD
Senior Lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

ROBIAH BINTI YUNUS, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

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Signature: _____
Name of Chairman of Supervisory Committee: Dr. Huzwah Khaza'ai

Signature: _____
Name of Member of Supervisory Committee: Dr. Razana Md Ali

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LIST OF ABBREVIATIONS

ECM	Extracellular matrix
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
GPX	Glutathione peroxidase
GRB 2	Growth factor receptor-bound protein two
GTP	Guanosine-5'-triphosphate
GTPase	Guanosine-5'-triphosphatase
H&E	Hematoxylin and eosin
H_2O_2	Hydrogen peroxide
HDLs	High-density lipoproteins
hEGF	Human epidermal growth factor
MAP	Mitogen-activated protein
MDA	Malondialdehyde
MMP	Matrix metalloproteinase
NADPH	Nicotinamide adenine dinucleotide phosphate
O_2	Oxygen
PDGF	Platelet-derived growth factor
PUFA	Polyunsaturated fatty acids
ROS	Reactive oxygen species
SOD	Superoxide dismutase
SSD	Silver sulfadiazine
VLDLs	Very low density lipoprotein

α-TTP	Alpha tocopherol transport protein

CHAPTER 1

INTRODUCTION

1.1 Background of study

Burns are the fourth most common type of trauma worldwide which results in limb deformity, large amount of expenditure in health care, and trauma in both physical and psychological status of an individual (Lazarus et al., 1994). According to the World Health Organization (WHO), 238,800 individuals died due to fire-related burn in the year 2000 (Orgill & Ogawa, 2013)(Orgill and Ogawa, 2013; Afify et al., 2012). Annually, about 2 million people are wounded, 80 000 warded, and 6,500 fatalities due to burn wound in the United States. As in Malaysia, incidence rates of burn is 31, 176 cases per year. The remodeling of damages skin initiated by edema, skin inflammation and scar formation. Poor wound management and delayed progress of wound healing will lead to keloid, hypertrophic, non-raised and contracture scar (Tavares Pereira et al., 2012). Incidence rates of hypertrophic scarring is up to 91% for burn injury (Gauglitz et al., 2011). These consequences have an impact on the psychological and social behaviour of an individual (Clouatre et al., 2013). Skin-related complications also significantly reduced the ability of an individual to move by causing joint contracture, pain from inflammatory mediators and the worst case is that it could leads to deformation from severe scarring (Orgill & Ogawa, 2013).

The damage of epithelial part of the skin exposed the wound area unprotected (Enoch & Leaper, 2005). Generally, pathophysiology and management of burn and normal wound healing is similar and divided into four different but intersecting stages: hemostasis, inflammation, proliferation and remodeling. Physiologically, wound can heal by regeneration and reparative process. Successful tissue regeneration is the ideal form of healing process giving good cosmetic and functional results. On the other hand, in reparative process specialized tissue is replaced with collagen and result in a loss of functional and cosmetic outcome. The reparative events are generally preceded by hemostatic and inflammatory phenomena which may in turn influence the final result of wound healing (Orgill and Ogawa, 2013). It was suggested by Hsu and Mustoe (2010) that a proper technique to optimize the healing process is by reducing the inflammation, increasing tissue regeneration, minimizing tissue destruction and providing a moist environment on the wound area. There are four different classes of burn namely; superficial, superficial partial thickness, deep partial thickness and full thickness burn. However, the main concern in burn unit is infection that will trigger the other complications in healing burn wound. In deep partial-thickness burn, the patients have a high risk to develop into a full-thickness burn (Chan., et al 2002). Hence, it is a critical requirement to create a better treatment for deep-partial thickness burn.

The goal of wound care is to heal wounds in the shortest time with minor pain and scarring. It is concluded that antibacterial formulation can prevent infection from bacteria, nevertheless, they can hinder healing cells from proliferating during wound healing followed by delayed in wound closure. Silver sulfadiazine (SSD) is a standard topical treatment for burn but could cause adverse side effects upon long term usage. In addition, most current therapeutic approaches for burn healing treatment can also cause scar formation and disfigurement (Aarabi et al., 2007). They are different functions of wound healing formulation in a market. The active ingredients and properties were depending on their main function; whether to clean, to protect, to keep in good condition or to change the appearance.

Vitamin E composed of eight different isoforms, four tocopherol and four tocotrienol. The difference is that tocotrienol has an unsaturated phytyl tail at carbon number 3,7 and 11 whereas tocopherol possess saturated isoprenoid side chain. These eight forms of vitamins E have different biological activity. It is well establish that vitamin E has the ability to prevent the lipid oxidation and can act as antioxidant molecules to scavenge reactive oxygen species (ROS). The action of vitamin E in accelerating wound repair is increasingly welcomed. However, much of the present work on wound healing has focused on α -tocopherol. It has been proven that tocotrienols have higher antioxidant activity than the tocopherols and it possess a few medicinal properties that are not present in tocopherol (Zingg, 2007). These characteristic are due to the presence of three double bonds on the hydrophobic side chain of tocotrienol (Sen et al., 2010).Therefore, vitamin E in the form of tocotrienol is highly welcomed and should lead to the development of strategies aimed specifically in reducing ROS produced upon burn injury.

Due to the importance of cellular proliferation during burn wound healing, any treatment that can increase the mitogenic effect of healing cells is highly desirable. Each of the phases in wound healing is controlled and regulated by cytokines called growth factors. Primary function of growth factors in wound healing is as mitogen, angiogenic and chemoattractant to command the progression of healing stages. Currently, cytokines have a limited role in clinical practice. The only growth factor currently available commercially is platelet-derived growth factor (PDGF). Wound healing managed with exogenous growth factors has been beneficial on the healing process. However, all of these studies were focused on the healing ability of vitamin E and growth factor as individual compound. By far, there are no experimental reports on the study of the healing ability of the combination of tocotrienol-rich fraction (TRF) and epidermal growth factor (EGF). Therefore it is of current interest to study on the interaction of TRF and EGF on deep partial thickness burn wound. In concert with combining antioxidant properties of TRF and mitogenic properties of EGF, increase ability of wound healing is expected. In this regards, reduced inflammation and increase cellular proliferation in wound healing could be achieved and eventually offered an alternative in topical based therapy.

1.2 Problem statement

One of the major culprit in burn injury is the presence of oxygen radicals that can form chain reaction of lipid peroxidation. Increase free radicals will result in longer inflammation which may cause the wound to lock into chronic state and resulting in delayed wound healing. Fortunately, protection againts oxidative stress can be provided by radical scavenger compund such as vitamin E which can help to arrest the chain propagation. Vitamin E usually used in topical formulation, such as in wound healing and cosmetic products. Nevertheless, most vitamin E skin care products contain only alpha-tocopherol and synthetic alpha-tocopheryl acetate, which involve hydrolyzation during absorption to demonstrate its activity (Henegouwen et al., 1995). Other factor that will delayed wound healing include minimal re-epithelialization and minimal cellular proliferation. Increased cellular proliferation can be provided by cytokines and growth factor. EGF can exert a powerful mitogenic effect particularly on epithelial cells and fibroblasts. These two cells are responsible for regeneration and collagen production of the skin. Therefore in this study, the synergistic effect of both TRF and EGF in burn wound healing were evaluated.

1.3 Research objective

1.3.1 General objective

To elucidate the burn wound healing efficacy of EGF-TRF formulation in *Sprague-Dawley* rats.

1.3.2 Specific objectives

1. To evaluate the macroscopic and histopathological changes of burn wound healing treated with different concentration of TRF and EGF separately upon wound healing.
2. To investigate the synergistic effect between the optimum concentration of TRF mix with three different concentration of EGF separately upon wound healing activity via macroscopic and histopathological changes.
3. To compare and identify the best combination formulation for burn wounds.
4. To monitor the dermal collagen changes of the best treatment formulation at specific time of healing.

1.4 Hypothesis

EGF-TRF formulation is efficient in treating deep-partial thickness burn.

1.5 Significance of the study

Silver sulfadiazine (SSD) is a standard topical treatment for burn but could cause adverse side effects upon long term usage. SSD can cause allergy and toxicity. It is concluded that antibacterial formulation can prevent infection from bacteria, nevertheless, they can hinder healing cells from proliferating during wound healing followed by delayed in wound closure. So, it is important to find safer and effective treatment without any toxicity effect and aimed at promoting the stage of wound healing with better cosmeceutical outcome.

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