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A Review on Antioxidant Capacity of Malaysian Herbal Plants as Potential Wound Healing Therapy and Evaluation on Consumers Acceptance Towards Herbal Cream

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Abstract: Wound healing is the result of a complex interaction of biological responses that repair damaged tissue. Emerging modern diseases have resulted in massive changes in medical treatment, with conventional treatment becoming less relevant and more expensive for modern infections. Thus, research on plant-derived compounds with therapeutic properties has been extensively studied to develop new drugs. Therefore, this study focuses on the identification of potential bioactive substances related to antioxidant in medicinal plants with wound healing abilities, including their mechanistic pathways. The Hedonic test was also used in this study to assess consumers' overall acceptability of herbal creams. For the identification of potential wound healing plants, several selected literatures were searched on electronic databases such as Research Gate, Science Direct, Google Scholar, Scopus, Academic Journal Organization, Pub Med, National Center for Biotechnology Information (NCBI) and Hindawi. The findings found that there are four antioxidant compounds that contribute to activation of Nrf2 signalling pathways and induce an antioxidant response element. These antioxidant compounds are curcumin, cinnamaldehyde, quercetin and kaempferol. All these compounds may be present in *Chromolaena odorata* (pokok kapal terbang), *Cinnamomum cassia* (kulit kayu manis), *Hibiscus rosa-sinensis* (bunga Hibiscus), *Curcuma longa* (kunyit), *Kaempferia galanga* (cekur), and *Hibiscus Sabdariffa* (roselle). Finally, an assessment of consumers' overall acceptability of herbal creams reveals a significant trend of acceptance towards herbal cream application among consumers at the range of 20 years old. The data analysis revealed that the age influenced overall acceptability. In conclusion, this research may provide insight and information regarding the potential plants and its bioactive compounds which related to antioxidant property to be utilized or incorporated in wound healing cream.

Keywords: Medicinal Plants, Wound Healing, Antioxidant, Nrf2 Pathway, Hedonic

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1. Introduction

Wounds are a major source of concern for patients and health care providers all around the world. They not only have a negative influence on patients' physical and emotional health, but they also cost them a lot of money. In 2017, approximately 6 million people worldwide suffer from chronic wounds [1]. The World Health Organization (WHO) formally recognized these global unmet needs, which the Association for the Advancement of Wound Care (AAWC) Global Volunteers strategy has brought to the forefront [2]. Therefore, progressive research on the development of new medication and treatment for wound care improved tremendously. Existing standard wound care consists of wound cleaning, debridement, application of topical antibiotics, and wound dressings. Currently, the research on plant-derived medicine for wound healing is extensively studied for its therapeutic properties and the newest fields in biomedical science [1].

Malaysia has been recorded to have abundant resources of medicinal plant that are used for both traditional medicine and beauty products [3]. Traditional medicine has utilized herbal plants as the source of medicine to treat various diseases such as fever, wounds, skin infections, diabetes, burns and insect bites, which have been passed through generations [1,3]. Phytochemical constituents in plant extracts have been reported to have pharmacological effects which is important for drug synthetization [4]. Most of crucial bioactive compounds for wound healing activity is derived from plant secondary metabolite such as alkaloids, flavonoids, terpenes, saponins, tannins, carotenoids, and phenolic compounds [4].

Numerous research and review papers have discussed the potential of phytochemical substances with antibacterial, anti-inflammatory, and antioxidant properties able to promote faster wound healing rates and improved skin health [4]. Therefore, the objective of this study is to identify potential bioactive compound related to antioxidant and its mechanistic pathways towards enhanced wound healing process. The following objective is to evaluate the consumers' overall acceptability towards herbal cream application.

2. Literature review

Wound is defined as the damage inflict on the normal epithelial structure which cause the break of skin tissue layers. A simple wound can extend from the epidermis layer to the dermis layers, but it can also reach deeper into the subcutaneous tissue, potentially increasing the severity of the damaged cells [5]. Thus, the level of severity of a wound can be categorized into three classes, which are acute, complicated, and chronic [6]. There are four stages in wound healing starting with hemostasis, inflammation, proliferation, and remodelling [7].

According to a previous study, there is a major concern arising during wound healing that involves reactive oxygen species (ROS) and reactive nitrogen species (ROS) [7]. These oxidants are called free radical that helps in molecules signalling pathways for wound healing. During inflammatory stage, oxidants are produced to aid in phagocytosis process and defending broken tissue from germs invasion [7]. However, the burst of respiratory activity through immune cells had cause overproduction of ROS, which lead to oxidative stress [7]. Oxidative stress will cause cells damage on the surrounding tissues, and it is reported to prolong inflammation phases until it become severe [7]. Prolongation of inflammation phase are cause by oxidative stress which could lead severe inflammation and impaired wound healing.

Therefore, the role of natural antioxidant agent is to regulate the oxidative stress by reducing the dangerous free radicals into harmless molecules. There are three potential mechanistic pathways available for antioxidant substances in wound healing process. These mechanisms are further described in the findings of literature study.

3. Methodology

3.1 Literature/Articles/Research Paper Selection Strategy

The identification of selected literature and articles was searched using electronic databases such as Research Gate, Science Direct, Springer Link, Molecular Diversity Preservation International (MDPI), National Center for Biotechnology Information (NCBI), Frontiers, Hindawi. The Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guidelines are used in this methodology. The total number of hits for the initial search was 116 articles. In this study, 52 articles were selected as eligible resources.

3.2 Data of Hedonic Test

In this study, the raw data of Hedonic test was obtained from the third party for analysis. Therefore, this study did not cover any procedures for collecting the responses and the construction of the questionnaire. According to the received data, there are five sample of creams provided for the sampling. The samples were labelled as; A) *Cocos nucifera* oil (Virgin coconut oil) cream, B) *Cinnamomum cassia* oil (cinnamon) cream, C) *C. odorata* (pokok kapal terbang) cream, D) *Citrus limonum* oil (Lemon) cream and E) *Cananga odorata* (Ylang-Ylang) cream.

There were 113 total of respondent and each person test two herbal creams at one time. The total count of responses for every tested herbal cream is 226 where 37 samples of cream A, 39 samples of cream B, 26 samples of cream C, 66 samples of cream D and lastly 58 samples of cream E. The screening of Hedonic Test raw data was according to the random respondent's group of age where gender is disregard. The age group consists of group 1 (6 to 12 years old), group 2 (13 to 19 years old), group 3 (20 to 29 years old), group 4 (30 to 39 years old) and lastly group 5 (40 to 49 years old).

3.3 Measure

The satisfaction was measured using Hedonic scale according to the level of satisfaction starting from 1 to 9 [8]. Respondent can measure their level of satisfaction from 'dislike extremely' to 'like extremely'.

3.3 Data Analysis

In this study, the analysis focused on two types of creams related to wound healing in descriptive statistics. Meanwhile, an ordinal logistic regression model was used to analyze the Hedonic test responses using predictive analysis. The Ordinal regression model was utilized in order to understand the relationship between one dependent variable and multiple independent variables [9]. The model approach was carried out in cumulative probabilities model [9]. The probability of responses is expressed in k category in which the k^{th} cumulative probability is calculated as following, (Eq.1). The probability for the last category is not computed because the total of the probabilities equals 1. The first $k-1$ cumulative probability have the following equations, (Eq 2).

$$P(y\ \ k) = p1 + \ldots + p\,k\,, k = 1, \ldots, K \qquad Eq.1$$

$$logit[P(y \leq k)] = ln\left(\frac{P(y \leq k)}{1 - P(y \leq k)}\right) \qquad Eq.2$$

The sequence of the responses is reflected in the cumulative probability. For a model with k response categories, it is expressed as $P(y \leq 1) < P(y \leq 2) \leq \ldots \leq P(y \leq K) = 1$. The significance value of this model is $p = 0.05$ to measure the explanatory variables for the test response in the regression model. Explanatory variables denote the test model's independent factors, which are age and sample codes. The p-value will determine the explanatory variables and response relationship through the hypotheses of the outcomes. The null hypothesis of this project was H_0: Overall acceptability and age are independent or unrelated (H_0:p=0); and H_1: Overall acceptability and age are related or dependent on each other (H_1:p≠0). All data analyses in this study were performed using MiniTab software.

4. Results and Discussion

4.1 Malaysian Herbal Plants for Wound Healing

There are six Malaysian plants chosen based on the reading from all the listed articles, which are related with wound healing ability. All of them were identified to exhibit antioxidant potency which is significant for wound healing. Phytochemicals related to antioxidant compounds were further identified according to each plant, such as *Chromolaena odorata* (quercetin, quarcetagetin, kaempferol, kaempferide, scutellarein tetramethylether); *Cinnamomum cassia* (cinnamaldehyde); *Hibiscus rosa-sinensis* (quercetin-3-diglucoside, quercetin, kaempferol); *Curcuma longa* (curcumin, demethoxycurcumin, bisdemethoxycurcumin); *Kaempferia galanga* (kaempferol, kaempferide) and *Hibiscus Sabdariffa* (chlorogenic acid, quercetin-3-rutinoside, myricetin-3-arabinogalactoside, gallic acid, kaempferol-3-glucoside).

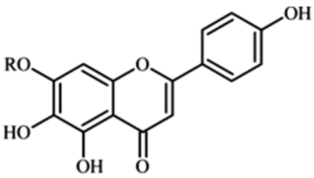
There are six potential antioxidant compounds that have been analyzed for this research paper, which include scutellarein, cinnamaldehyde, quercetin, curcumin, kaempferol and chlorogenic acid. All these compounds were found to exhibit free radical scavenging activities during wound healing. A review reported that curcumin integrated with collagen matrix with exhibits high level of peroxyl radicals scavenging activity [10]. Next is quercetin and kaempferol that belongs to the same subgroup of flavonoids, which is flavonol. Both compounds were reported to have high levels of antioxidant potency [11]. As for scutellarein, it is found that this compound could promotes angiogenesis for blood vessels regeneration coupled with high antioxidant activity [12]. While chlorogenic acid which can be found in variety of beverages present significant health benefits such as antibacterial, anti-inflammatory and antioxidant properties [13]. Lastly, cinnamaldehyde compound is reported to demonstrate strong antioxidant activity in another derivatives form compared to the natural constituent [14].

However, only four compounds, such as curcumin, cinnamaldehyde, quercetin and kaempferol, have been identified as Nrf2 activators in wound healing signal pathways, resulting in stimulation of the antioxidant response element. These selected plants are depicted in the following Table 1, while Figure 1 shows the list of potential antioxidant structural formula.

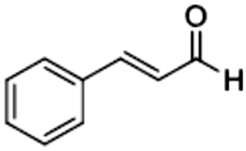
Table 1: Name and Figure of Six selected Malaysian Herbal Plants for Wound Healing

Name of Six selected Malaysia Herbal Plants for Wound Healing		
 *Chromolaena odorata* *(pokok kapal terbang)*	 *Cinnamomum cassia* (cinnamon bark)	 *Kaempferia galanga* (aromatic ginger)

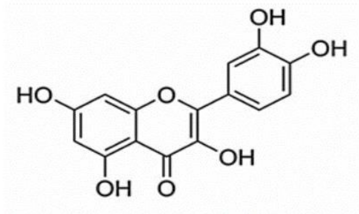
 *Hibiscus rosa-sinensis* (Hibiscus flower)	 *Curcuma longa* (turmeric)	 *Hibiscus Sabdariffa* (roselle)



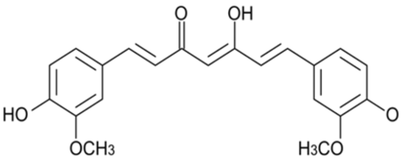
Scutellarein



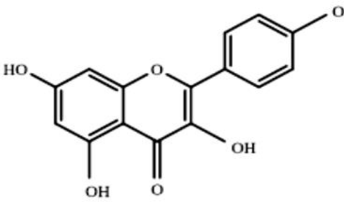
Cinnamaldehyde



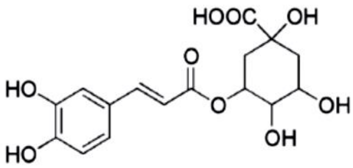
Quercetin



Curcumin



Kaempferol



Chlorogenic acid

Figure 1: List of Potential Antioxidant Structural Formula

4.2 Nrf2 Activation

Nuclear factor erythroid 2 (NFE-2)-related factor 2 (Nrf2) is a transcription factor that helps stimulating the antioxidant defence system and regulate excessive ROS generation [15]. In some cases, Nrf2 deficiency may hinder normal wound healing process as the expression of antioxidant cannot suppress the accumulation of ROS [15]. During normal wound healing process, Nrf2 is naturally induced when the cells are under high level of oxidant stress [15]. However, in low level stress condition, Nrf2 will be directed to proteasomal degradation by binding protein called Keap1 [15]. The role of Nrf2 is to stimulate antioxidant response element (ARE) through the transcription of gene inside nucleus. The results are the expression of enzymatic antioxidant such as superoxide dismutase (SOD), peroxiredoxin (PRDX), glutathione peroxidase (GPX) and catalase [15].

4.3 Regulated-Protein Kinases Signalling Pathways

Another possible pathway to activate the Nrf2-antioxidant response element (ARE) is through the protein-mediated enzymes. The structure of protein kinases consists of phosphorylate tyrosine, threonine, and serine residues which is sensitive under oxidative conditions. According to Huang H. C. et al (2000), protein kinases C (PKC) is found to regulate phosphorylated Nrf2 in response to Nrf2 impaired conditions. Meanwhile, in mitogen-activated protein kinases (MAPKs) pathways, the signalling pathways for Nrf2 is triggered under oxidative condition due to serine and threonine sensitivity [16]. Therefore, these protein kinases mediated the stimulation of Nrf2 for further redox modulation in wound healing.

4.5 Potential Mechanism of Nrf2 activation through Selected Antioxidant Substances

The activation of the Nrf2 signalling pathway can be found through the stimulation of natural compound activators. The findings of this research have found that curcumin, cinnamaldehyde, quercetin and kaempferol activate Nrf2 expression during wound healing [17,18,19] Therefore, this allows immediate redox modulation of ROS production during the inflammation phase. Nrf2 will be released from the Keap1 binding and proceed to transcribe the ARE genes in the nucleus. As a result, the expression of enzymatic antioxidative such as superoxide dismutase (SOD), catalase, glutathione peroxidase (GPX), and peroxiredoxin (PRDX) will be deployed to regulate oxidative damage. Curcumin and quercetin are found to stimulate protein-kinases pathways as one of the possible Nrf2 translocation for condition such as Nrf2 deficiency. Table 2 shows the potential role of selected antioxidant substances as Nrf2 signalling pathway and Figure 2 depicts the potential mechanistic pathway of selected natural antioxidant activators. Curcumin, cinnamaldehyde, quercetin, and kaempferol were to be found acted as Nrf2 activator through the intracellular of wound healing where it induced Nrf2 to transcript ARE genes and expressed enzymatic antioxidant as oxidative redox modulation. However, chlorogenic acid and scutellarein was not discovered yet as Nrf2 activators for wound healing due to most study focused on neurodegenerative impact.

Table 2: Potential Role of Selected Antioxidant Substance in Nrf2 Signalling Pathway

Compounds	Role in Nrf2 Pathway	Model
Curcumin	MAPK-Nrf2 Activator	Diabetic-Induced mice
Cinnamaldehyde	Nrf2 Activators	Diabetic-Induced mice
Quercetin	MAPK-Nrf2 Activator	Atopic dermatitis (AD)
Kaempferol	Nrf2/HO-1	Vascular injury
Chlorogenic acid	NA	NA
Scutellarein	NA	NA

NA=not available

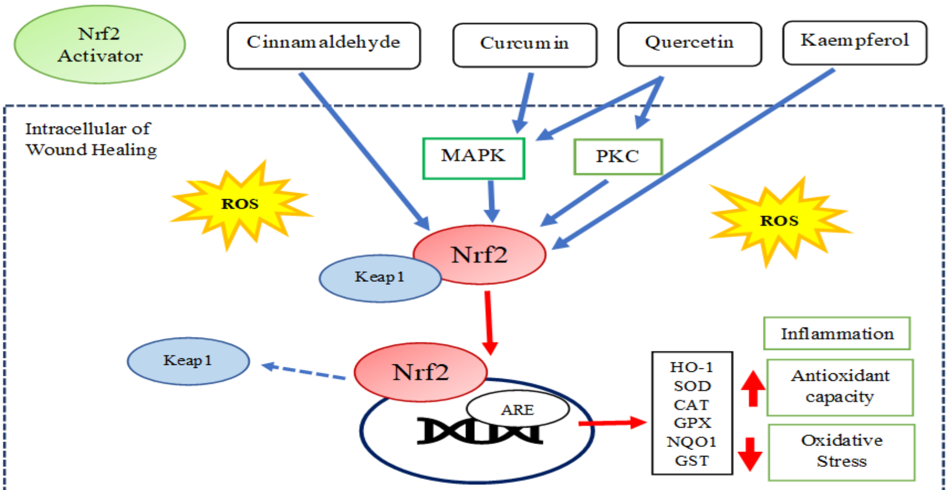


Figure 2: Potential Mechanistic Pathway of Selected Antioxidant Substances in Nrf2 Activation of Wound Healing

4.6 Evaluation on the Acceptance of Consumers towards Herbal Cream

The total responses for each sample were recorded as shown in Table 3. It must be noted that the total of respondents consists of 113 individuals. Each person sampled two creams at one time. The total responses count was 226. The results show that the cream D piqued the interest of consumers, as evidenced by the 66 tested samples.

Table 3: Total of Responses

Sample Code	% Tested Sample	N=226
A	16	37
B	17	39
C	12	26
D	29	66
E	26	58

Table 4: Performance of Ordinal Logistic Model

(Between the Response Variable and Predicted Probabilities)

Sample Code	% Concordant	%Discordant	%Ties	Somers' D	Goodman-Kruskal Gamma	P=value
Group 1	76.6	2.6	20.8	0.74	0.93	0.001
Group 2	47.1	30.7	22.1	0.16	0.21	0.832
Group 3	58.8	20.5	20.6	0.38	0.48	0.000
Group 4	57.1	24.1	18.9	0.33	0.41	0.254
Group 5	49.4	30.8	29.8	0.29	0.41	0.590

According to Table 4, the ordinal regression model analysis computed the p=value for each group of age variables in order to determine the test hypotheses. The p-value for Group 1 is p=0.001. Thus, this model of group 1, null hypothesis is rejected as overall acceptability and age are related or dependent on each other. The p-value $\leq$ 0.05 hence it can be concluded that group 1 test model is statistically significant. Group 2 has p-value of 0.832 which is larger than significance value of the test model, 0.05. Thus, this model of group 2, null hypothesis is not rejected as overall acceptability and age are independent or unrelated.

The p-value of group 3 is p=0.000. The significance value of the test model remained the same which is 0.05. It is concluded that the p-value of group 3 is less than the significance value of the test model, 0.05. Thus, this model of group 3, null hypothesis is rejected as overall acceptability and age are related or dependent on each other. Next is the p-value of group 4 is p=0.254. The significance value of the test model remained the same which is 0.05, thus null hypothesis of group 4 is not rejected where (H_0: p=0), the overall acceptability and age can be independent or unrelated. The p-value of group 5 is p=0.590 which is higher than 0.05, thus, this model of group 5 null hypothesis is not rejected where, (H_0: p=0), the overall acceptability and age can be independent or unrelated.

Somers' D (S-delta) and Goodman-Kruskal Gamma (K-gamma) value indicate the performance of the predictive model using the differential percentage between three pairs of results which were concordant, discordant and tied. Each interpretation of value is dependent on the percentage of concordant. For group 1 summary of predictive measurement in Table 4, the value of S-delta is 0.74 and K-gamma is 0.93 which indicates strong performance of this model for group of age 6 to 12. Therefore, this test model was relevant for group 1. For group 2 summary of predictive measurement, the value of S-delta is 0.16 and K-gamma is 0.21 which indicates the low concordant percentage affect the predictive performance of this model for group 2. In the summary of group 3 predictive measurement, the value of S-delta is 0.38 and K-gamma is 0.48 which indicates the moderate concordant percentage differences. Therefore, this model test performance was relevant to be used for group 3. The summary of group 4 predictive measurement, the value of S-delta was 0.33 and K-gamma was 0.41 which indicated a moderate concordant percentage difference due to low differential value between concordant and discordant pairs. Therefore, this model test showed acceptable predictive performance used for group 4. As for the summary of group 5 predictive measurement, the value of S-delta was 0.29 and K-gamma was 0.41, which indicated a moderate concordant percentage difference. Therefore, this model test showed acceptable predictive performance to be used for group 5. This concluded that the test model of group 5 was reliable.

In descriptive statistic, the frequency of overall acceptability scale was tabulate in Table 5 according to the group variables. The data had summarized the total acceptance towards all five cream samples in each group. In Figure 3, the overall acceptability received the highest value of 34 moderate favorability from group 3, which consists of respondent at the age between 20 to 29 years old. The trend was followed by 31 'like very much' in favorability also from group 3. Thus, these results concluded that a significant trend of acceptance towards herbal cream application among consumers in 20's.

Table 5: Frequency of Overall Acceptability scale for all Samples

	Frequency								
Variables	**Dislike extremely**	**Dislike very much**	**Dislike moderately**	**Dislike slightly**	**Neither like or dislike**	**Like slightly**	**Like moderately**	**Like very much**	**Like extremely**
Group 1	2	4	0	0	1	0	2	1	4
Group 2	2	3	1	1	2	2	1	6	12
Group 3	3	2	7	11	15	20	34	31	12
Group 4	0	1	0	2	2	3	3	11	2
Group 5	1	2	0	0	1	1	2	11	4

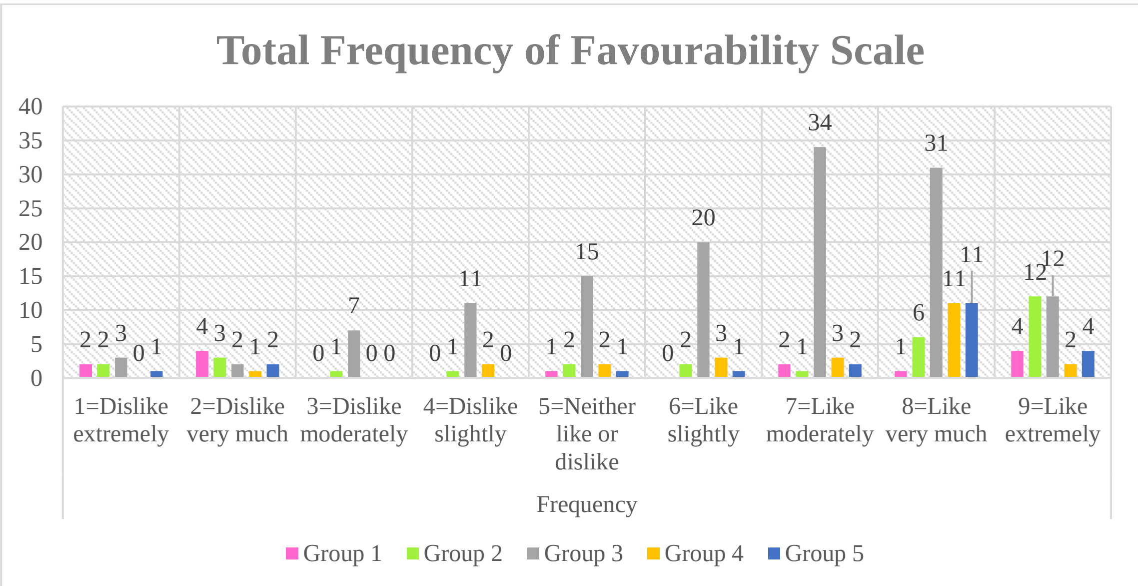


Figure 3: Total Frequency of Favourability Scale

5. Conclusion

The present study has successfully identified four antioxidant compounds among six selected Malaysian herbal plants as Nrf2 activators for oxidative regulation in wound healing. The collection of articles and research papers was obtained by using multiple electronic databases. This study also found that consumers between the ages of 20 until 29 were the most accepting of the use of herbal creams. It is also recommended that the antioxidant compounds of scutellarein and chlorogenic acid should be studied for their effects on Nrf2 through an *in vitro* cell-based assay.

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