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Original Research Article

Differences in the Effects of *Arcangelisia flava* and *Taxus sumatrana* Extracts on Mice Skin (*Mus musculus*) ageing Induced by D-Galactose

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ABSTRACT

Arcangelisia flava (L.) Merr and *Taxus sumatrana* (Miq.) de Laub are Indonesian medicinal plants with antioxidant compounds. Antioxidant compounds play a role in inhibiting oxidative stress, thereby inhibiting ageing. This study aims to determine the differences in the effects of *Arcangelisia flava* (L.) Merr. and *Taxus sumatrana* (Miq.) De Laub extracts on the histopathology of *Mus musculus* (L.) skin ageing induced by D-galactose. It evaluates the effects of *Arcangelisia flava* (L.) Merr and *Taxus sumatrana* (Miq.) de Laub leaves on the histopathological features of D-galactose-induced ageing in mice skin. This study involved 24 mice divided into 4 groups (K-, K+, P1, and P2) of 4 animals per group. Group 1 animals (K (-)) serve as negative control received standard diet and water, Group 2 (K (+)) received standard diet, water, and D-galactose (150 mg/kg bw) intraperitoneally, Group 3 (P1) were given standard diet, water, D-galactose (150 mg/kg bw) intraperitoneally and *Arcangelisia flava* extract (750 mg/kg bw) orally, Group 4 (P2) received standard diet, water, D-galactose (150 mg/kg bw) intraperitoneally and oral *Taxus sumatrana* extract (750 mg/kg bw). The extracts were administered orally once daily for 90 days. The study results showed no significant difference (p>0.05) in the depth of the rete ridges and epidermis compared to the control. This study shows no significant difference in the effect of *Arcangelisia flava* (L.) Merr. and *Taxus sumatrana* (Miq.) De Laub extract on the histopathology of *Mus musculus* L. skin on the depth of the rete ridges and epidermis.

Keywords: Oxidative stress, ageing, histopathology, mice, *Taxus sumatrana*, *Arcangelisia flava*

Introduction

Human daily activities involving the use of machines and unhealthy lifestyles are often the reasons why many people suffer from chronic diseases that arise due to exposure to free radicals.[1] Free radicals can cause oxidative stress, necrosis, and apoptosis if their population exceeds the available antioxidant capacity.[2] Oxidative stress is a state of imbalance between the amount of free radicals and antioxidants in the body. Oxidative stress plays a significant role in the pathophysiology of degenerative diseases.[3] Intrinsic ageing of the skin occurs through three processes: decreasing the synthesis of the skin's extracellular matrix, decreasing the proliferation capacity of skin cells, and increasing the activity of enzymes degrading collagen in the dermis layer.[6] Intrinsic ageing can result in decreased fibroblast replication and thinning of the epidermis.[7] Skin ageing is also characterised by a decrease in the normal dermal papilla structure and a decrease in the height of the ridges.[8] Rete ridges (RRs) are distinct undulating microstructures located at the junction of the dermis and epidermis in mammalian skins. Rete ridges play a vital role in the skin architecture and homeostasis. They are essential in skin healing, and the ageing process caused by free radicals can be inhibited with antioxidants.[3]

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Herbal medicine is one of the choices for Southeast Asians as an alternative treatment because it is relatively cheap and easy to obtain.[7] *Taxus sumatrana* (Miq.) de Laub and *Arcangelisia flava* (L.) Merr are examples of herbal plants commonly used as medicine and contain antioxidants.[8,9] *Arcangelisia flava* (L.) Merr contains saponin, flavonoid, protoberberine alkaloid and polyphenols.[10] Flavonoids can inhibit free radicals and ageing.[11] Flavonoids can reduce reactive oxygen species (ROS) levels by neutralising free radical elements, suppressing enzymes related to forming free radicals, and triggering internal antioxidant enzymes.[12]

Taxus sumatrana (Miq.) de Laub contains a key bioactive compound, a class of diterpenes, called taxanes, a major precursor for taxol or paclitaxel (an anticancer drug) and its derivatives, which have antioxidant properties. Paclitaxel is marketed as taxol.[13] Paclitaxel can be used to inhibit the growth of cancer cells. In addition to being an anticancer agent, *Taxus sumatrana* (Miq.) also has antipyretic, anticonvulsant, and analgesic potentials.[14] Based on phytochemical tests, *Taxus sumatrana* extract contains antioxidant compounds in the form of alkaloids, flavonoids, terpenoids, and saponins.[15]

Materials and Methods

Ethical approval

This study was approved by the ethical review committee of the Faculty of Medicine, Andalas University, with No. 531 / UN.16.2 / KEP-FK / 2021.

Animals

Mus musculus (L.) was obtained from the Laboratory of the Faculty of Pharmacy, Andalas University. Healthy white mice (*Mus musculus*),

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male mice aged 5-8 months, weighing 25-30 g at the time of sample selection, were recruited for the study. The mice were housed in standard living conditions and followed the OECD care guidelines for experimental animals. They were allowed access to drinking water *ad libitum,* and rodent pellets and exposed to a 12-hour day/night light cycle.

Inclusion and exclusion criteria
Healthy and physically active mice with no anatomical defects that have never been used as experimental animals were recruited for this experiment.

Exclusion criteria
Mice that died during acclimatisation and treatment were excluded.
Sampling Techniques
Animals were selected randomly according to the inclusion and exclusion criteria. The independent variables in this study were the administration of *Arcangelisia flava* Merr root extract and *Taxus sumatrana* leaf extract at a dose of 750 mg/kg bw.
Experimental animal grouping
In this study, 24 mice were divided into 4 groups of 6 animals per group (Table 1).

Table 1: Experimental animal grouping

Group	Treatment
K (-)	The negative control group was given a standard feed diet and water
K (+)	The positive control group was given a standard feed diet, water, and D-galactose 150 mg/kg bw
P1	Treatment Group P1 was given a standard diet, water, D-galactose 150 mg/kg bw, and *Arcangelisia flava* (L.) Merr extract 750 mg/kg bw
P2	Treatment Group P2 was given a standard diet, water, D-galactose 150 mg/kg bw, and *Taxus sumatrana* leaf extract (Miq.) de Laub 750 mg/kg bw

Mice treatment
Before treatment, mice were acclimatised to the laboratory environment for 1 week. The weights of the mice were recorded at the beginning and end of acclimatisation. The mice were kept in cages covered with wire mesh and placed in a room with a temperature of 25±2ºC and humidity of 50±10% with sufficient light and ventilation. The animals were not exposed to direct sunlight. The mice of the ageing model group (K (+)) were administered D-galactose intraperitoneally at 150 mg/kg bw. Group P1 and P2 were given *Arcangelisia flava* (L.) Merr and *Taxus sumatrana* (Miq.) de Laub extract orally at a dose of 750 mg/kg bw, respectively and D-galactose 150 mg/kg intraperitoneally.

Data analysis
Data analysis was performed using parametric statistical tests that met the requirements, normally distributed data, and had the same variance between groups. The histopathological severity grade obtained was recorded, tabulated and analysed using a computer program with a 95% confidence interval (p = 0.05 was considered significant). A normality analysis was carried out using the Shapiro-Wilk test to determine whether the distribution of the data obtained was normal, while a homogeneity test was carried out using the Levene statistical test to determine the variance between groups. The data were further subjected to a One-Way ANOVA to compare the significance between groups. The Post Hoc Test was used for data with significant differences between groups, as indicated by a p-value <0.05. If the OneWay ANOVA test requirements could not be met, then the data was analysed using a non-parametric statistical test, the Kruskal-Wallis test. If there is a significant difference, the Mann-Whitney test was conducted to check the difference between treatment groups. The results of the data analysis are presented in a to evaluate the effect of *Arcangelisia flava* (L.) Merr and *Taxus sumatrana* (Miq.) de Laub extracts on the histological presentation of ageing mice skin.

Results and Discussions

Table 2 shows each group's average epidermis thickness (μm). It appears that group P1 (treated with 750 mg/kg bw *Arcangelisia flava* (L.) Merr root bark extract) has a lower epidermal thickness than group K- (negative control) but higher than group K+ (induced, untreated control). Group P2 (induced but treated with 750 mg/kg bw *Taxus sumatrana* leaf extract) average epidermis thickness appears higher than group K+ but lower than group K-. Table 3 shows each group's average ridge depth (μm). The result indicates that group P1 treated with 750 mg/kg bw *Arcangelisia flava* root bark extract has lower rete ridges depth than group K- (negative control) and higher than group K+ (untreated control). It also shows that group P2 (induced but treated with 750 mg/kg bw *Taxus sumatrana* leaf extract) has lower ridges depth results than groups K- and K+. Similarly, results of the differences in the effect of *Arcangelisia flava* (L.) Merr and *Taxus sumatrana* (Miq.) de Laub extracts on the Histopathology of *Mus musculus* L. skin are presented in Table 4 and figure 1. The table shows the results of the One-Way ANOVA analysis of the data to check significant differences in the research results. The data from this study were analysed using the Shapiro-Wilk test, Levene Statistic test, and One-Way ANOVA test and continued with the Post Hoc test. The Shapiro-Wilk test analysis showed a p-value > 0.05, and the Levene Statistic test showed p>0.05 in all variable groups. The results of the One-Way ANOVA test on the epidermis and ridges each sequentially obtained a value of p = 0.340 and p = 0.381, respectively, where p > 0.05 indicates no significant difference.

Table 2: Results of measurements of the average thickness of the mice epidermis

Group Treatment	Mean (μm) ±SD
K-	22.6 ± 2.5
K+	18.1 ± 4.9
P1	20.3 ± 5.8
P2	19.3 ± 4.2

Table 3: Results of measurements of the average depth of rete ridges

Group Treatment	Mean (μm) ± SD
K-	21.1 ± 5.8
K+	18.3 ± 7.7
P1	19.2 ± 4.8
P2	15.7 ± 3.5

The effects of D-galactose administration on the histopathology of mice skin was also evaluated. According to pharmacodynamic studies, animal models using D-Galactose induction include intrinsic ageing, which can increase advanced glycation end products (AGE) and reactive oxygen species (ROS).[16] The ageing process caused by D-galactose induction has been reported in various studies. Excessive doses of D-galactose induce oxidative stress through subcellular pathways, especially in brain mitochondria. D-galactose can cause mitochondrial DNA mutations, causing a decrease in DNA repair enzymes. DNA mutations lead to mitochondrial disorders, resulting in ageing. D-galactose can reduce glutathione and catalase concentrations, causing decreased ATP synthesis, mitochondrial structural damage, changes in membrane potential, and apoptosis.[17] Intrinsic skin ageing results in histological changes. Other studies have found that intrinsic ageing results in thinning of the epidermis, a reduced contact area between the dermis and epidermis due to flattening of the ridges, and a decreased ability of fibroblast proliferation.[17,18]

Table 4. Differences in the Effect of *Arcangelisia flava* (L.) Merr and *Taxus sumatrana* (Miq.) de Laub Extracts on the Histopathology of *Mus musculus* L. Skin

Group	**Average**				**P Value**
	K- Negative control	K+ Induced (untreated)	P1 Treated with 750 mg/kg bw *A. flava*	P2 Treated 750 mg/kg bw Taxus sumatrana	
Epidermis	22.6	18.1	20.3	19.3	0.381
Rete ridges	21.1	18.3	19.2	15.7	0.340

The study revealed differences in the effects of *Acangelisia flava* (L.) Merr and *Taxus sumatrana* (Miq.) de Laub extracts oral treatment on the histopathology of mice skin. Based on the results of the average measurement, it was found that the thickness of the epidermis of the P1 group treated with 750 mg/kg bw of *A. flava* was 20.3 ± 5.8 µm lower than the K- group (negative control) 22.6 ± 2.5 µm, but higher than the K+ group (induced with 150 mg/kg bw D-galactose but untreated) 18.1 ± 4.9 µm. The depth of the ridges of the P1 group was 19.2 ± 4.8 µm, lower than the K- group, 21.1 ± 5.8 µm, but higher than the K+ group, 18.3 ± 7.7 µm. *Arcangelisia flava* (L.) Merr, through its secondary metabolites, can interact with NOS (nitrogen oxide synthase), which catalyses free radicals NO (nitrogen oxide) and is pro-inflammatory to suppress the formation of NO.[5,6] Based on the average measurement results figure 1, it was found that the epidermis thickness of the P2 group (induced but treated with 750 mg/kg bw *Taxus sumatrana* leaf extract) was 19.3 ± 4.2 µm on average lower than the P1 group 20.3 ± 5.8 µm. The depth of the rete ridges of the P2 group was 15.7 ± 3.5 µm on average and lower than the P1 group 19.2 ± 4.8 µm. Research on the efficacy of *Taxus sumatrana* (Miq.) de Laub extract in preventing skin ageing is scarce in the literature. Still, based on phytochemical tests, *Taxus sumatrana (*Miq.) de Laub has antioxidants that can prevent ageing.[15] Studies suggest that the interaction between saponins and paclitaxel can inhibit proliferation, increase cell death, and potentially apoptosis.[20]

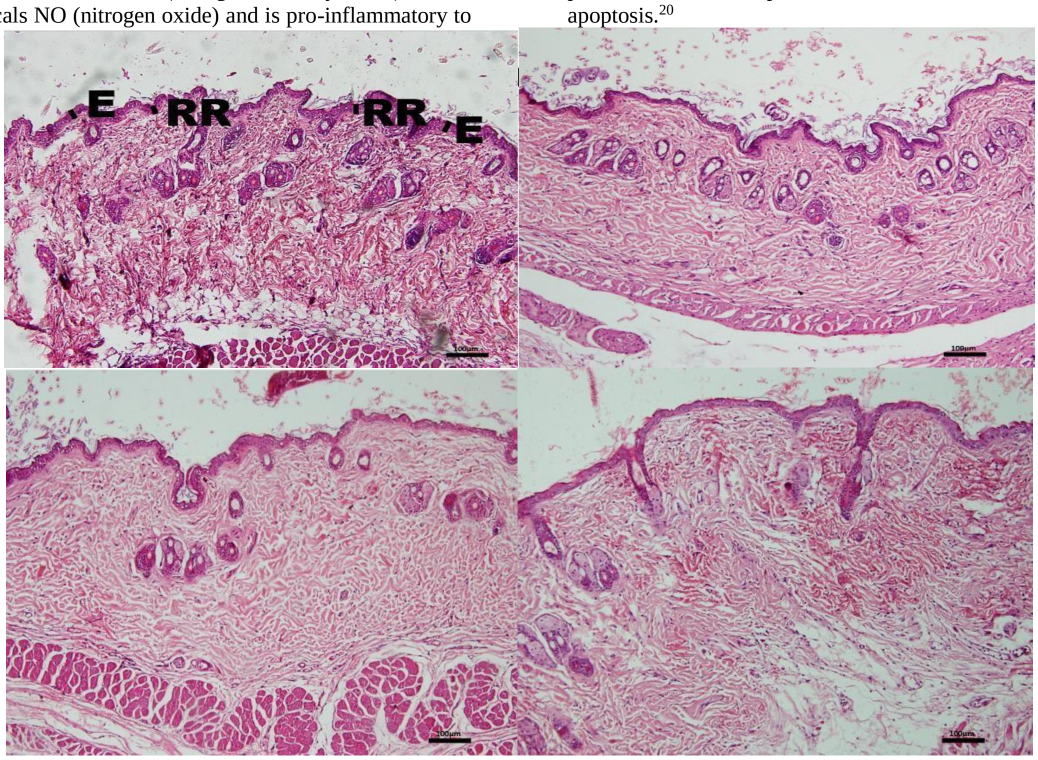

Figure 1: A, B, C, D are histopathological descriptions of Mice skin with 10x magnification in the groups in sequence (K-, K+, P1, P2).

Conclusion

It could be concluded that the effectiveness of antioxidants contained in *Arcangelisia flava* (L.) Merr is better than *Taxus sumatrana* (Miq.) de Laub based on histological images of epidermis thickness and ridges depth. The data analysis results showed no significant difference ($p>0.05$) between the effects of the extracts. There is a need for further research to evaluate the effect of *Arcangelisia flava* and *Taxus sumatrana* extract as an anti-ageing agent on animals and their development as cosmetics products.

Conflict of interest

No conflicts of interest are disclosed by the authors.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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