COMPARATIVE TEST OF THE EFFECTIVENESS OF CEMPEDAK (Artocarpus champeden) LEAF ETHANOL EXTRACT CREAM WITH ZINC OXIDE CREAM IN DECREASING TNF-α LEVEL AND SUNBURN CELLS FROM THE EPIDERMIS OF RATS (Rattus norvegicus) EXPOSED TO ULTRAVIOLET B

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Abstract

Backgrounds: Cempedak is an endemic plant in Indonesia and its leaf has potential action as a sunscreen because it contains flavonoid compounds that have photoprotective effect because it can absorb ultraviolet. This study to prove the effect of cempedak (Artocarpus champeden) leaf extract cream compared with zinc oxide (ZnO) cream in decreasing TNF-α level and sunburn cells from the epidermis of rats (Rattus norvegicus) exposed to ultraviolet B (UVB). **Methods:** The research was an experimental study with a randomized post-test only control group design. The research subjects were 36 male wistar rats (Rattus norvegicus), which were divided into 2 groups: group I was 18 rats were given10% ZnO cream before exposured to UVB, and group II was 18 rats were given 4% Artocarpus champeden leaf extract cream applied 30 minutes before exposured to UVB. TNF-α was measured with ELISA, and sunburn cells was evaluated in histology slide from skin biopsy. The statistical analysis to compare the effect of both creams was using an independent t-test. **Results:** The mean TNF-α level in group I was lower than in group II (347.51±67.06 ng/L vs 782.38±174.44 ng/L; p<0.001). Sunburn cell were also lower in group I compared to group II (1.30±0.96 vs 2.30±0.96; p=0.024). **Conclusion:** Topical cream cempedak leaf ethanol extract (Artocarpus champeden) 4% decreased TNF-α level and sunburn cells in the epidermis of male Wistar (Rattus norvegicus) rat exposed to ultraviolet-B radiation.

Keywords: cempedak leaf, cream, flavonoid sunscreen, TNF-α, sunburn cells

1. Introduction

Now UV radiation has many effects on skin physiology, with some impacts occurring acutely while others are delayed. One of the most apparent acute effects of UV on the skin is the induction of inflammation. UVB radiation induces a cascade of cytokines, vasoactive, and neuroactive mediators in the skin, producing an inflammatory response and causing sunburn. (D'Orazio et al., 2013; Lee, Park and Hahn, 2019) These cells have been used as microscopic parameters in various studies studying the impact of UV on the skin.(Saric and Sivamani, 2016) Exposure to UV radiation of 600 mJ/cm2 optimally in 4 weeks will damage essential skin tissue, as evidenced by a high increase in proinflammatory cytokines.(Balasaraswathy et al., 2002)

Zinc oxide (ZnO) is one of the ingredients used in chemical sunscreen products, as well as antioxidants that can protect the skin from solar radiation.(Ermawati, Yugatama and Wulandari, 2020) ZnO, as in sunblock or sunscreen, functions to reflect UV radiation. In sunscreen, the percentage of zinc oxide is usually around 10% to 25%. In products such as make-up, including foundation, BB cream and facial moisturizer, it is generally lower by about 10 to 19%. The less zinc oxide is used, the shorter the window if protected.

(Schneider and Lim, 2019) Zinc oxide provides better protection against UVA (up to 380 nm) at a concentration of 5%.(Beasley and Meyer, 2010) The mechanism of protection by zinc oxide is based on the light reflection and absorption of UV light waves, which is effective at a concentration of 10%.(Cole, Shyr and Ou-Yang, 2016) Recommendation from approved ZnO with a concentration limit of up to 25%. When used as a sunscreen ingredient, ZnO filters out UVA (320-400 nm) and UVB (280-320 nm) rays from ultraviolet light.(Schneider and Lim, 2019).

Natural products are now widely researched for dermatological purposes. The wide variety of techniques currently available to investigate the skin's response to various stimuli has ushered in a new era in cosmetic and dermo-cosmetic development based on a solid understanding of the physiology of the skin and its diverse responses to disturbances from the commonly encountered environment.(Cavinato et al., 2017). Natural products are secondary metabolites produced by living organisms found in nature.(Lulan et al., 2018; Noviardi et al., 2020) The production of these metabolites is often a specific response of the producing organism to its environment, which traditional Cempedak contains alkaloids, flavonoids, phenols, saponins, terpenoids, steroids and tannins.(Anggraini, Mita and Ibrahim, 2015) Cempedak plants are known to be rich in phenolic compounds, especially in the leaves.(Hariyanto, 2017)

Cempedak leaves contain flavonoids by 75% of compounds that have antioxidant activity.(Anggraini, Mita and Ibrahim, 2015) The presence of phenolic and flavonoid compounds in cempedak leaves as antioxidants can counteract free radicals to prevent oxidation, thereby slowing down photooxidation from exposure to ultraviolet light.(Shah et al., 2016) Flavonoids are phenolic compounds as antioxidants because they can chelate metals or donate hydrogen atoms to prevent cell damage by free radicals.(Noviardi et al., 2020) Flavonoids are known as competitive Tyrosinase Inhibitorswhich has a structure similar to the tyrosinase enzyme-substrate so that they can bind directly to the active site of the tyrosinase enzyme with flavonoid bonds in copper.(Ling et al., 2010; Chan et al., 2018; Lulan et al., 2018).

Flavonoids have been shown to have antioxidant activity that can reduce hydroxy radicals caused by UVB exposure, and photoprotection effects on the number of sunburn cells in the epidermis of skin exposed to acute UVB rays are not yet known.(Ryser et al., 2014; Cavinato et al., 2017) Evidence from in vivo studies uses compete directly as a source of its active substance even though the potential antioxidant activity of A. champeden has been previously confirmed.(Ling et al., 2010; Chan et al., 2018; Lulan et al., 2018)

Cempedak leaf (Artocarpus champeden Spreng) has the potential to act as a sunscreen because it contains flavonoid compounds that have photoprotective properties so that they can absorb ultraviolet light. Cempedak leaf crude extract sunscreen profile based on % Te (per cent transmission of erythema) has protection with a concentration of 150 ppm, 200-300 ppm, and 350 ppm, respectively, while based on % Tp (per cent transmission of pigmentation) is sunblock with a concentration of 100-350 ppm.(Whenny, Rusli and Rijai, 2015; Hariyanto, 2017)

The sunscreen profile of the ethyl acetate fraction of Cempedak leaves based on % Te is standard suntan, extra protection and sunblock, with concentrations of 75 ppm, 100-150 ppm, and 200-250 ppm, respectively, while based on % Tp is sunblock with an attendance of 50-250 ppm.(Whenny, Rusli and Rijai, 2015)Ability extract as a sunscreen ingredient that must be Provides protection against erythema by absorbing less than 85% of UVB radiation and preventing pigmentation.(Ardhie, 2011)

Ability Cempedak leaf ethanol extract (Artocarpus champeden), which is a natural ingredient, has never been compared with Zinc Oxide (ZnO) sunscreen, which is a chemical compound, so the author wanted to test the effectiveness of these two ingredients against levels of TNF-αand the number of sunburn cells in the epidermis of male Wistar (Rattus norvegicus) rats exposed to ultraviolet-B radiation..

2. Methods

This research is a pure experimental study using the randomized post-test only control group design with two arms: treatment with 4% Artocarpus champeden leaf extract formulation and treatment with 10% zinc

oxide formulation. It was conducted at the Department of Pharmacology and Therapy, Faculty of Medicine, Udayana University, Denpasar, Bali. Experimental animals were maintained and treated at the Laboratory Animal Unit of the Department of Pharmacology and Therapy, Faculty of Medicine, Udayana University, Denpasar, Bali. The research was conducted at the Integrated Biomedical Laboratory Unit, Faculty of Medicine, Udayana University, Denpasar, Bali. for approximately 15 weeks. Ethical permission in this study with No. B/9/UN14.2.9/PT.01.04/2022 from the Faculty of Veterinary Medicine research ethics committee, Udayana University.

Artocarpus champeden Leaf Extract

Artocarpus champeden leaf extraction was carried out using the maceration technique described in (Damayanti, Meylina and Rusli, 2017). The steps of the maceration extraction are as follows:

1. Preparation of Simplicia: Artocarpus champeden leaves are dried without exposing them to sunlight. Drying can be accomplished with a vacuum desiccator. The wholly dried Artocarpus champeden leaves were cut into small pieces to make simplicia.
2. Maceration: Simplicia leaves of Artocarpus champeden were macerated with ethanol in a sterile and closed (airtight) container. The maceration container is then stored at room temperature in a place protected from direct sunlight and covered with aluminium foil.
3. Extraction: the macerated mixture of Artocarpus champeden leaves was separated into liquid and solid components. The liquid part was then evaporated using a rotary evaporator to obtain a crude extract of Artocarpus champeden leaves.

Treatment Cream Formulation

Cream formulations for treatment were Artocarpus champeden leaf extract and zinc oxide. The formulation of the cream is carried out according to the description of (Damayanti, Meylina and Rusli, 2017). The formulation steps are as follows:

1. Weighing of the base ingredients: the basic ingredients of the cream are weighed with the formulation as described in **Table 1**
2. Preparation of cream dosage base: The components included in the oil phase, namely stearic acid, Cera alba, and liquid paraffin, were melted at 70˚C, respectively. The ingredients, including the water phase, are also melted at 70˚C, namely glycerin, TEA, methylparaben, and propylparaben, and equates while stirring until homogeneous. The oil phase is added little by a bit while still being stirred until it is homogeneously mixed, resulting in a creamy base.
3. Addition of active substances: for cream formulations for treatment with the extraction of Artocarpus champeden leaves and zinc oxide followed by the addition of active substances by **Table 1**. The base of the cream preparation is cooled to a temperature of 40˚C then the active substance, according to the table, is added slowly while still stirring so that a homogeneous cream formulation is formed.

Table 1. Composition of cream for the treatment

Component	Concentration (% wt/wt)	
	F1	F2
Leaf extract Artocarpus champeden	4	-
zinc oxide	-	10
Glycerin	5	5
Triethanolamine (TEA)	1	1
Liquid paraffin	7	7
Cera alba	3	3
Stearic Acid	4.5	4.5
Methylparaben	0.2	0.2
Propylparaben	0.3	0.3
Aquades	Up to 100 g	Up to 100 g

Test Animal Preparation

The preparation process for experimental animals includes sample selection and acclimatization of experimental animals in a living laboratory for 7 days. This process includes:

1. Thirty-six healthy male Wistar white rats, aged 12-14 weeks, weighing 200-300 grams, were placed in cages, each cage containing one rat.
2. The cage is made of a plastic container measuring 23 cm x 17 cm x 9.5 cm with a base of rice husks and a lid made of woven wire, which is strong, bite-resistant, and not easily damaged so that the animals do not easily escape.
3. The cage is lighted, placed in a room with good ventilation, sufficient light, quiet, not noisy, and the temperature is set at room temperature around 25ºC with humidity around 50%. The cage is cleaned every 3 days.
4. Mice were adapted for 7 days and given a standard diet using food brand HPS 511 and plain water for drinking.
5. Provision of food and drink on an ad libitum basis.

Giving Treatment

The process of treating and simulating tissue damage caused by UVB rays in this study took place simultaneously. UVB rays and cream administration were carried out 3 times a week, on Mondays, Wednesdays, and Fridays, for 4 weeks. In each process, UVB exposure and treatment administration are carried out as follows:

1. Cream administration: The previously prepared cream formulation was smeared on the back skin of the mice that were not covered with hair in an area of 2 x 2 cm. Administration of cream was given as much as 0.2 ml.
2. Exposure to UVB rays: Exposure to UVB rays was carried out 30 minutes after administration of the cream. UVB exposure was carried out with UVB light with a peak wavelength of 312 nm at a dose of 50 mg/cm2 for 2 minutes.

Experimental Animal Treatment

Experimental animal treatment was carried out 24 hours after the last treatment with the following steps:

1. The treatment of experimental animals was carried out by breaking the cervical vertebrae, which minimized the pain felt by the experimental animals.

2. Tissue sampling and processing: the back tissues of experimental animals that were not covered with hair and exposed to UVB rays were taken. Tissue samples were stored for two processes: 1) storage with fixation in 70%, 80%, 95%, and 100% serial ethanol. The tissue preparations were then stored in paraffin until examination.

Sunburn Cell Count Check

Examination of the number of sunburn cells was carried out by examining tissue samples under a light microscope and counting the number of sunburn cells per field of view. The stages of this inspection are as follows:

1. Tissue staining: To prepare for staining, tissue samples from experimental animals are deparaffinized. The tissue was then stained with a haematoxylin-eosin (HE) stain.
2. Microscopic examination: Histopathological changes in each section were observed using several fields of view and photographed with a light microscope with an objective magnification of 40×. The microscopic examination includes counting the number of sunburn cells.

TNF-α. Level Check

The process of measuring TNF-α levels was carried out according to the procedures taught by Lee et al. (Lee et al., 2013) is as follows:

1. A total of 0.5 g of the back tissue was mixed with 2 ml of PBS pH 7.4, which had been prepared and stored in the refrigerator in an ice bath and then homogenized for 2 minutes.
2. The homogeneous mixture was centrifuged at 3000 g at 4˚C for 5 minutes.
3. The supernatant fraction was taken for the measurement of TNF-α levels.

Measurement of TNF-α levels by ELISA method: Measurements were carried out using the ELISA method, according to the instructions from the ELISA kit. The general principle of measuring TNF- levels using the ELISA method is the detection of TNF- through antibody binding, which is then detected by photospectrometry. TNF-α levels are expressed in pg/mL units..

3. Results

The The results total of rats 36 with eighteen rats per group, analysis of the characteristics data in Table 2.

Table 2
Descriptive Analysis ResultsTNF-α andTotal Sunburn Cell Per Field of View

Variable	Group	n	Mean	Standard Deviation
TNF-α (ng/L)	1	18	782.38	174.44
	2	18	347.51	67.06
Number of sunburn cells per field of view	1	18	2.30	0.96
	2	18	1.54	0.96

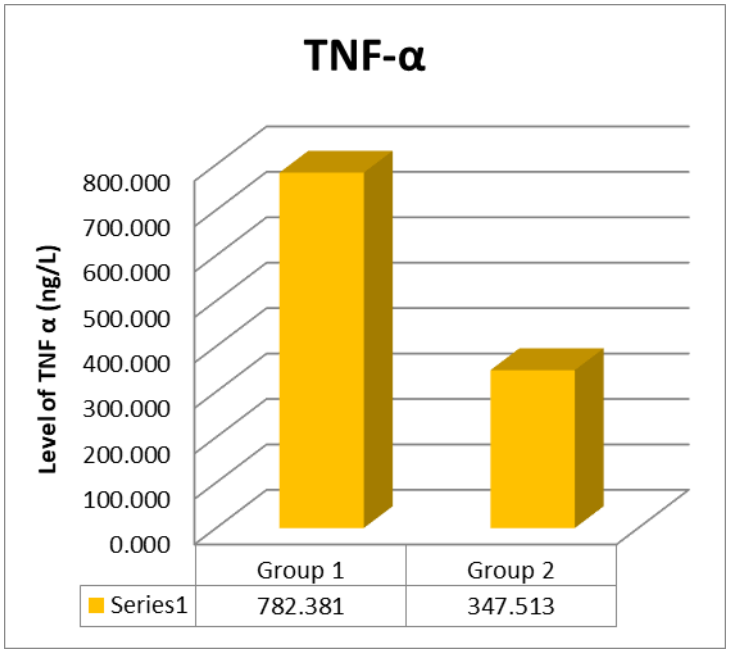

Figure 1
TNF-α. mean results

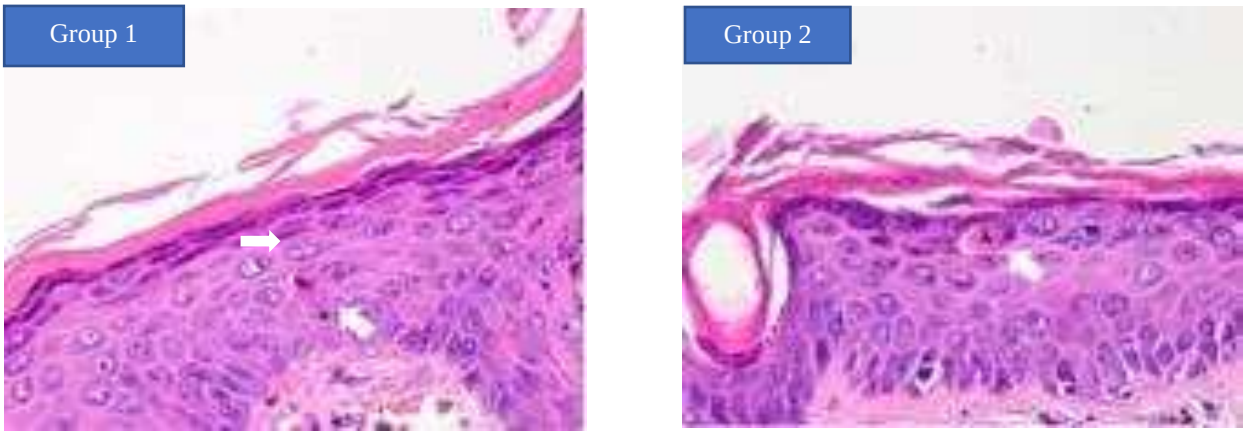

Figure 2
Histology of sunburn cells with Hematoxylin-Eosin. staining

Information :
sunburn cell: keratinocytes with pyknotic nuclei (white arrows)
Group 1: sunburn cells in the treatment group with zinc oxide (white arrow), viewed with a microscope with a magnification of 40x
Group 2: sunburn cells in the treatment group with Cempedak leaf extract
(white arrow), viewed with a microscope with a magnification of 40x

The number of sunburn cells in the Cempedak leaf extract group (Group 2) was less compared to the zinc oxide group (Group 1)

The results in table 1 show that the mean levels of TNF- in treatment group 2 are lower than in treatment group 1, with the results of 347.51±67.06 ng/L vs 782.38±174.44 ng/L and result number of sunburn cells also shows the mean of the treatment group 2lower than the treatment group 1 with the average result per field of view 1.30±0.96 vs 2.30±0.96.

In this study, a comparative analysis was performed using the unpaired T-test technique on the levels of TNF- and the number of sunburn cells in the groups given cream of cempedak leaf extract were compared to a group of rats given zinc oxide formulation **(Table 3)**

Table 3
Comparison of TNF-α and levels number of Sunburn Cells PerField of View

Variable	Group	Average±SD	n	p	95% CI
TNF-α (ng/L)	1	782.38±174.44	18	<0.001	345.34-524.39
	2	347.51 ±67.06	18		
Number of sunburn cells per field of view	1	2.30±0.96	18	0,024	0.10-1.41
	2	1.30±0.96.	18		

The results in Table 3 show a significant difference in the TNF levels in the two groups, with $p < 0.05$. J number of sunburn cells per field of view in both groups also found a significant difference, $p < 0.05$.

4. Discussion

Giving Artocarpus champeden leaf extract 4%show rate of lower TNF-α compared to 10% Zinc Oxide

The results showed that the administration of the 4% Artocarpus champeden leaf extract formulation hadrateLower TNF-α compared to 10% Zinc Oxide, which was statistically significant with $p < 0.001$. UVB exposure induces an inflammatory response and produces inflammatory mediators in the skin that have an immunosuppressive effect. UVB irradiation causes increased blood flow and vascular permeability, resulting in oedema, erythema, hyperplastic response, activating cyclooxygenase-2 (COX-2) and higher production of prostaglandin (PG) metabolites.(Pal et al., 2016) Prostaglandins are small molecules derived from arachidonic acid produced by the action of COX-2 on arachidonic acid. Almost immediately after UV exposure, keratinocytes secrete platelet-activating factors. This substance increases the expression of COX-2 and the production of PGE2, the most active PG metabolite produced from arachidonic acid. It is well known that PGE2 regulates various aspects of inflammation and the function of different immune cells. PGE2 has been identified as a mediator of inflammation through the promotion of local vasodilation and activation of neutrophils, macrophages, and mast cells during the early stages of inflammation.(Prasad and Katiyar, 2017) Activation of the cyclooxygenase (COX-2) and lipoxygenase enzyme systems due to UV exposure also increases the production of proinflammatory leukotrienes further.(Rittié and Fisher, 2015; Zegarska et al., 2017; McDaniel, Farris and Valacchi, 2018).

After sun exposure, inflammatory reactions in the skin and other cell types such as monocytes, macrophages, lymphocytes, and vascular endothelial cells also occur due to upregulation of the nuclear factor-κB (NF-B) pathway. This signalling pathway causes epidermal keratinocytes to release primary proinflammatory cytokines, one of which is TNF-α.(Lopes and Mcmahon, 2016; McDaniel, Farris and Valacchi, 2018)

In vitro studies using human keratinocytes found that UVB or TNF-α. mediated suppression of nuclear

translocalization in activated NF-B from mouse fibroblasts; can cause a decrease in the expression of essential fibroblast growth factor, MMP, and COX-2 and increase procollagen production.(Bashir, Sharma and Werth, 2009; Lee, Park and Hahn, 2019)

Cempedak leaf extract is known to have potent antioxidant activity with an IC50 concentration of 20.416 ppm so that at low concentrations, it can prevent the formation of reactive Oxygen Species (ROS) and decreased TNF-α. This is due to the active compounds contained in it through two main mechanisms: the acquisition of flavonoid compounds, phenols and tannins that function as antioxidants and as competitive inhibitors of tyrosinase.(Hakim, 2017; Wang et al., 2018) Flavonoids as metal ion chelators with adjacent hydroxyl and/or ketone and phenol sides as scavenger antioxidants remove one hydrogen atom from the hydroxyl group so that reactive Oxygen Species (ROS) is not formed.(Lulan et al., 2018) Prevention Reactive Oxygen Species (ROS) formed due to exposure to ultraviolet B light to the skin can reduce TNF- through the NF-κB. Pathway.(McDaniel, Farris and Valacchi, 2018) Mechanism illustration scheme Cempedak leaf ethanol extract provides a photoprotective effect decreased TNF-α in **Figure 3.**

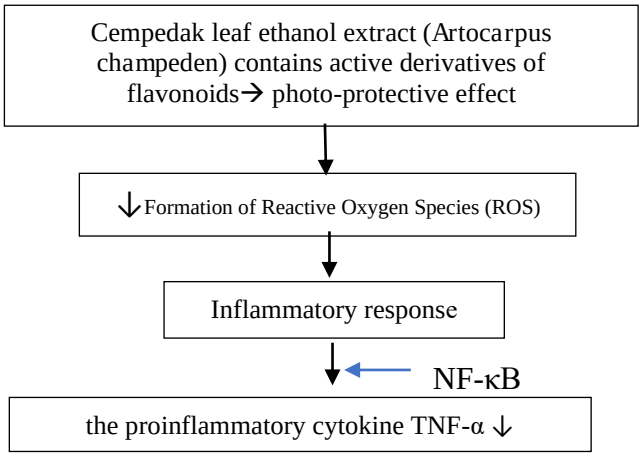

Figure 3
Mechanism illustration scheme Cempedak leaf ethanol extract provides a photoprotective effect decreased TNF-α

Giving Artocarpus champeden leaf extract 4%showed a lower number of sunburn cells compared to the administration of 10% Zinc Oxide.

The results showed that the administration of the 4% Artocarpus champeden leaf extract formulation had several sunburn cells lower than Zinc Oxide at 10%, which was statistically significant with p 0.024. These results are from research conducted by Damayanti et al. Photoprotective effect of Artocarpus champeden against ultraviolet light with preparations containing Artocarpus champeden leaf extract at a protection concentration of 4%; there was a decrease in the formation of sunburn cells compared to the control, namely the topical formulation without Artocarpus champeden leaf extract.(Damayanti, Meylina and Rusli, 2017)

The ability of Artocarpus champeden leaf extract to protect rat skin from the appearance of sunburn cells after exposure to UVB rays is because they contain secondary metabolites of phenols and flavonoids. Almost all groups of phenolic compounds and flavonoids are reported to have photoprotective abilities because they can absorb UV radiation.(Cetinkaya et al., 2017) The absorption of UV rays by flavonoids will cause changes

in the structure of these flavonoids (**Figure 4**).

The mechanism of flavonoids in protecting the skin from UV exposure is by absorbing UV rays that penetrate the skin. Flavonoids have a structure in the form of conjugated double bonds so that almost all flavonoids can act as chromophores. Flavonoids will absorb UV light and cause electron excitation from the ground state to orbitals with higher energy.(Reichrath, 2014; Noviardi et al., 2020) When rats were irradiated with UVB lamps, the flavonoids in the extract as well as in the cream formula would absorb UVB rays that exposed the mice's skin, and when the electrons returned to their original state, the UVB rays that were absorbed would then be emitted but with much less energy.(Chan et al., 2018) By flavonoids, most of the power of UVB rays is converted into heat energy, which is harmless to the skin.(Whenny, Rusli and Rijai, 2015) This mechanism will further inhibit or minimize the appearance of erythema due to exposure to UV rays.(Halimatussa'diah, Fitriani and Rijai, 2014) Flavonoids can reduce oxidative stress and mitochondrial dysfunction in DNA damage.(Panche, Diwan and Chandra, 2016) Flavonoids are also thought to have anti-inflammatory activity acting on the arachidonic pathway(Wang et al., 2018). Flavonoids can inhibit the expression of COX-2 so that the synthesis of prostaglandins such as PGI2 and PGE2, which play an essential role in the pathogenesis of erythema induced by UV light will also be inhibited.(Cetinkaya et al., 2017)

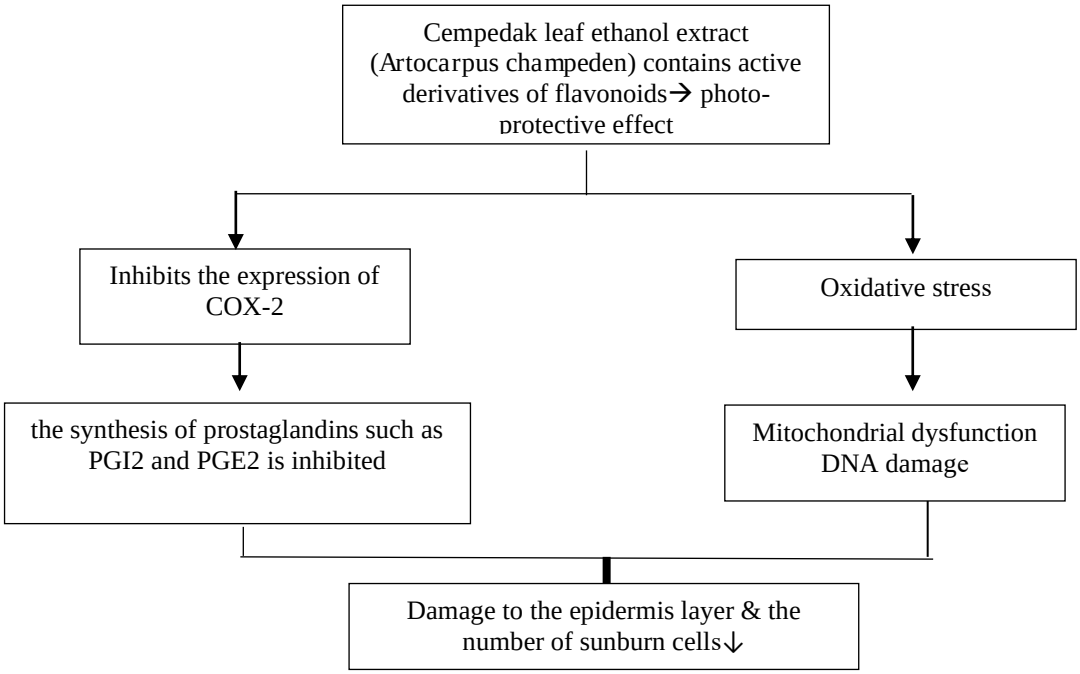

Figure 4
Mechanism illustration leaf ethanol extract provides a photoprotective effect to number on sunburn cells.

Photoprotective effect of extract creamcempedak leaves

Cempedak leaves have been widely used by the community traditionally, one of which is to treat skin diseases.(Izzi et al., 2012; Whenny, Rusli and Rijai, 2015) This study proves that cempedak leaf extract cream can have a good photoprotection effect on the skin. This can be seen from low TNF-α and the number of sunburn cells little.

It is hoped that with these benefits, cempedak leaf extract cream can be an alternative in photoprotective

therapy that can help improve a person's quality of life and self-confidence. Further research needs to be done to determine the side effects of cempedak leaf extract both physically and mentally in vivoas well as in clinical trials.

In this study, only one dose was given, so the difference in the effectiveness of different doses and doses of cream toxicity was unknown. No studies were conducted with negative controls, so they could not be compared with normal rats..

Conclusions

The Based on the results of this study, it was concluded that:

1. TNF- levels of rat epidermis (Rattus norvegicus) exposed to ultraviolet-B radiation in rats receiving cream of ethanol extract of cempedak (Artocarpus champeden) leaves were lower than those receiving zinc oxide (ZnO) formulation.
2. The number of sunburn cells in the epidermis of rats (Rattus norvegicus) exposed to ultraviolet-B radiation in the group of rats receiving cream of ethanol extract of cempedak (Artocarpus champeden) leaves less than those receiving zinc oxide (ZnO) formulation.

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Conflicts of Interest: none

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