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ORIGINAL ARTICLE

Test comparison of seeds and skins extract of duku's fruit (*Lansium domesticum* Corr.) against the amount of melanin pigment of skin mencit (*Mus musculus*) to prevent premature aging of the skin

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Abstract

Premature aging can occur due to excessive sun exposure which causes hyperpigmentation problems and causes brown or black patches on the skin. Duku (*Lansium domesticum* Corr.) contains flavonoids and vitamin C compounds that are effective in protecting the skin from sun exposure. This study aims to see the benefits of the extract of the seeds and peel of duku fruit (*Lansium domesticum* Corr.) On the amount of melanin pigment in the skin of mice (*Mus musculus*) as an anti-hyperpigmentation so that the dapjekal is a skin pen. Group P0 was a negative control, group P1 was exposed to sunlight for 20 days, group P2 mice were exposed to duku seed extract and then exposed to sunlight for 20 days, group P3 were exposed to duku peel and exposed to local sunlight for 20 days, P4 mice were exposed to sunlight 20 days, 21–30 days exposed to peel extract, and P5 mice exposed to sunlight 20 days, 21–30 days exposed to seed extract. The results showed that the P0 group had the amount of melanin pigment with an average of 7 grains, the P1 group: 68.4, P2 group: 26.6, P3 group: 29, P4 group: 7.2, and group P5 group: 12. The conclusion is that exposure to sunlight the amount of melanin pigment and offers the extract of the peel and seeds of duku fruit can reduce the amount of melanin pigment.

Keywords Premature aging · Sunlight · Melanin pigment · Peel of duku's extract · Seeds of duku's extract

Introduction

Aging is a natural process that occurs in all living things. This process can be associated with decreased bodily functions resulting in a decrease in the quality of life when a person reaches old age. This process can be caused by several factors, namely genetics, hormones, exposure to UV rays, and humidity. Exposure to UV light will stimulate tyrosinase enzyme activity and increase the number of melanocytes that produce melanin. As a result, the transfer of melanosome from melanocytes to keratinocytes will increase as well as melanin will increase (Sofiana et al. 2017).One of the signs of aging that interfere with appearance is the appearance of a change in skin color on the face, in the form of brown or black patches called melasma. The psychological impact of changing skin color reduces self-confidence to have social relationships with other people, many ways have been done to treat melasma, such as herbal medicines (Huda et al. 2017). Healthy skin is skin that is protected from sun exposure and prevents premature aging. Based on its structure, the skin has a natural sunscreen in the form of melanin which has an important role in protecting against ultraviolet (UV) rays (Charissa et al. 2016). Apart from being a natural photoprotective substance or sunscreen, accrding to other opinions photoprotective substance or sunscreen, according to other opinions, melanin also has a function as a colorant (pigmentation) to the skin, as a drug-binding agent, and as a modifier for some forms of heat energy and then releasing it (energy transducer) (Mamoto et al. 2009). Melanin is a

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black or blackish brown pigment. Melanin is divided into two types, namely eumelanin which produces a blackish brown color and pheomkelanin which has a reddish yellow color. The function of melanin is to protect human skin or hair from exposure to ultra violet (UV) by absorbing phosphorus and capturing free radicals (Suryaningsih and Soebono 2016). Overproduction of melanin can cause dark skin or hyperpigmentation. Exposure to UV light will stimulate tyrosinase enzyme activity and increase the number of melanocytes that produce melanin (Charissa et al. 2016). As a result, the transfer of melanosome from melanocytes to keratinocytes will increase, as well as melanin which will also increase. Excessive melanin formation and accumulation of abnormal amounts of melanin in several parts of the skin due to excessive exposure to ultraviolet radiation, will cause hyperpigmented patches which are considered an aesthetic problem (Choi and Shin 2016).

There are currently many products on the market known as lightening creams. Topical ingredients used for antihyperpigmentation generally contain substances that inhibit melanogenesis. One of the raw materials that are often used to treat hyperpigmentation is 4% hydroquinone. The mechanism of action of this material is by inhibiting the action of the thyronase enzyme, directly damaging melanocyte cells, accelerating the degradation of melanosomes, and inhibiting the synthesis of the enzyme melanogenesis. However, long-term use of hydroquinone can cause various side effects, namely: irritation, rebound phenomenon, and ocronosis. Therefore, currently the use of hydroquinone is starting to be very limited. Based on this, it is recommended to use other skin whitening ingredients that are natural and with fewer side effects (Sofiana et al. 2017). Some of the compounds in plants that can be used as ingredients to inhibit the formation of melanin pigments (melanogenesis) are vitamin C and flavonoids. Both of these substances act as antioxidants or reducing agents in melanin synthesis, which requires a lot of oxygen. In addition, these two substances can also inhibit the change of dopa to dopakuinone (skin pigmentation process) so that it prevents the formation of melanin and can brighten the skin by renewing cells and speeding up the cell turnover process (Layuck et al. 2015).

One of the plants that can inhibit the formation of melanin pigments (skin whitening) is Duku (*Lansium domecticum* Corr.). Duku is one of the typical and endemic plants of South Sumatra and has many properties. In the health sector, duku plant extracts have various medicinal properties. Several studies have shown that duku has antimicrobial effects, other studies have also stated that duku seed extract has anti-malarial effects, anticancer effects, anti-proliferation of cells and can prevent DNA damage caused by free radicals. Duku contains glycosides, flavonoids, alkanoids, and terpenoids (Subadrant et al. 2016). In addition to having antimalarial activity, duku plants can also be used in the field of beauty such as the extract of the stem bark of the *Lansium domesticum* plant with a concentration of 25 µg/ml which can inhibit melanin production without causing toxicity after being tested on melanoma B16 cells so that it can be used as an antimelanogenesis in cosmetics, namely as a skin whitening (skin whitening cosmetics) (Hanum and Kasiamdari 2013). There is still very limited research on anti-melanogenesis which is widely produced and derived from herbs, so the researchers are interested in comparing the seed and peel extract of the duku fruit against the amount of melanin pigment in mice as an anti-premature aging of the skin. Considering the problem of aging is a very crucial problem, and the seeds and peel of the duku have not been used optimally. Moreover, the duku fruit is the mascot of South Sumatra flora. In addition, the use of chemicals to prevent aging, there are still many who use hazardous chemicals. The purpose of this study was to determine the benefits of duku seed and peel extract (*Lansium domesticum* Corr.) On the amount of melanin pigment in the skin of mice (*Mus musculus*) as an anti-hyperpigmentation so that it can prevent the aging process of the skin.

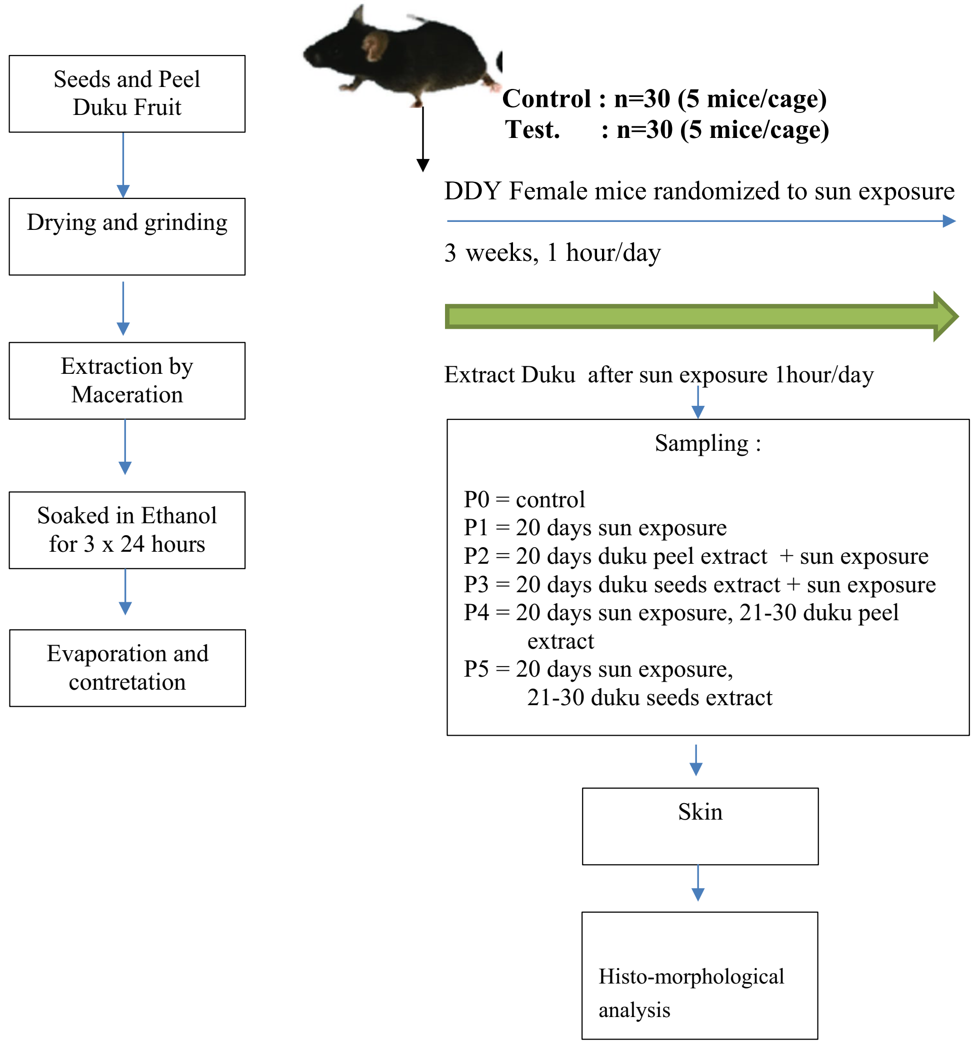
Materials and methods

This type of research is experimental which was conducted from February to March 2020 at the Palembang Health Laboratory Center and at the Animal House, Faculty of Medicine, Sriwijaya University Palembang. The subjects of this study were 30 mice divided into 6 groups. Group P0 was a negative control; P1 group of mice were exposed to sunlight for 20 days; Group P2 of mice was smeared with duku peel extract then exposed to sunlight for 20 days; Group P3 mice were smeared with duku seeds extract and then exposed to sunlight for 20 days; The P4 group of mice were exposed to sunlight and then stopped after 20 days followed by application of the duku peel extract for 30 days; and Group P5 of mice were exposed to sunlight and then stopped after 20 days followed by application of duku seed extract for 30 days (Fig. 1).

Making extracts of the seeds and peel of duku's fruit

The process of extracting the peel and seeds of the duku is carried out by the maceration method. The simplicia of the peel and seeds of the duku's fruit is soaked in 70% ethanol solvent for 3 × 24 h. Then filtered and put into a rotary evaporator to separate the extract from the solvent to produce a thick extract.

Fig. 1 Research flow chart



Maintenance of mice

A total of 30 mice in a healthy condition were kept in cages for 3 days without treatment as a process of adjusting the mice to their new environment and so that the mice did not experience stress. Mice were fed in the form of pellets and drank from a water bottle.

Determination of the length of sun exposure

Based on the research that has been done, skin darkening can occur with the provision of sun exposure for 3 weeks. Exposure for 1 h/day at 11.00–12.00 PM is believed to show changes in the basal stratum of the skin in the presence of an increase in the amount of melanin pigment produced by melanocytes.

Provision of seeds and skins extract of duku's fruit

The extract of the skin and seeds of the duku fruit is applied topically. The dose used is 1600 mg/mouse/day which is then dissolved in 1.6 ml of distilled water. The backs of mice were shaved in an area of 4 × 4 cm and then smeared with the extract of the skin and seeds of duku according to each treatment group.

Histo-morphological analysis

The amount of melanin pigment that will be calculated is the melanin pigment that appears per field of view, with a microscope (Olympus CX21) magnification of 10 × 10 and the interpretation is divided into 3 categories, namely: small (< 40 pigments), medium 40–80 pigments), and many (> 80 pigments) (Layuck et al. 2015).

The tools used are rotary evaporator, aspirator, blender, digital balance, beaker, waterbath, measuring cup, stirring rod, maceration filter, mouse cage, scalpel, preparatory glass, microscope, microscope camera, razor blade, ruler or meter, and brush. Meanwhile, the ingredients used were the skin and seeds of duku's fruit, 70% ethanol, distilled water, xylol, HE staining and silver nitrate, 10% formalin, acetone, and paraffin.

Results

Negative control group (P0)

The group of mice that were not given any treatment (only given food and drink) for 20 days and had their skin biopsied on the 21st day. The picture of the melanin pigment in the skin of mice found in the epidermis of mice in this group is relatively small (< 40 grains), with the amount of melanin pigment that appears as much as 19 pigments (Fig. 2).

First treatment group (P1)

The group of mice were exposed to sunlight for 1 h/day for 20 days and had their skin biopsy on day 21. The picture of mice skin melanin pigment found in the epidermis of mice in this group is relatively large (> 80 grains), with the amount of melanin pigment that appears as much as 96 pigments (Fig. 3).

Second treatment group (P2)

The group of mice that were given sun exposure for 1 h/day in 20 days after being given duku peel extract treatment 30 min before sun exposure and biopsy of their skin on the 21st day. The picture of the melanin pigment in the skin of mice found in the epidermis of mice in this group is

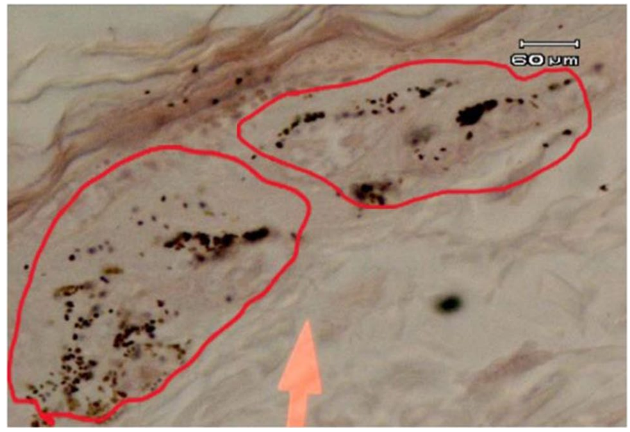


Fig. 3 Histology of skin P1, the amount of skin melanin pigment that appears in the epidermis of the mice's skin is classified as many (10 × 10 magnification, Olympus CX21)

relatively small (< 40 grains), with the amount of melanin pigment that appears as many as 27 pigments (Fig. 4).

Third treatment group (P3)

The group of mice that were given sun exposure for 1 h/day in 20 days after being given duku seed extract treatment 30 min before sun exposure and biopsy of their skin on the 21st day. The picture of mice skin melanin pigment found in the epidermis of mice in this group is classified as moderate (40–80 grains), with the amount of melanin pigment that appears as much as 42 pigments (Fig. 5).

Fourth treatment group (P4)

The group of mice who were given sun exposure for 1 h/day in 20 days was then followed by giving duku peel

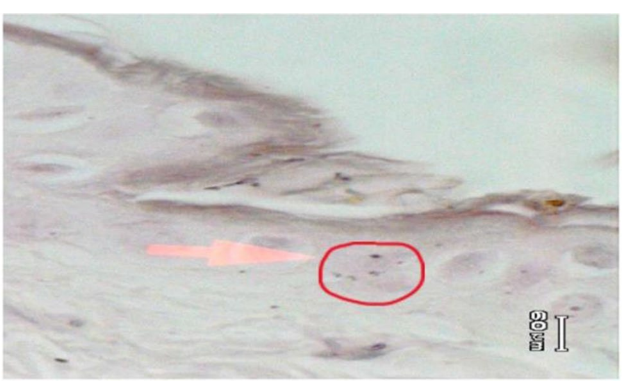


Fig. 2 Histology of skin P0, the amount of skin of melanin pigmen that appears in the epidermis of the mice's skin is classified as small (10 × 10 magnification, Olympus CX21)

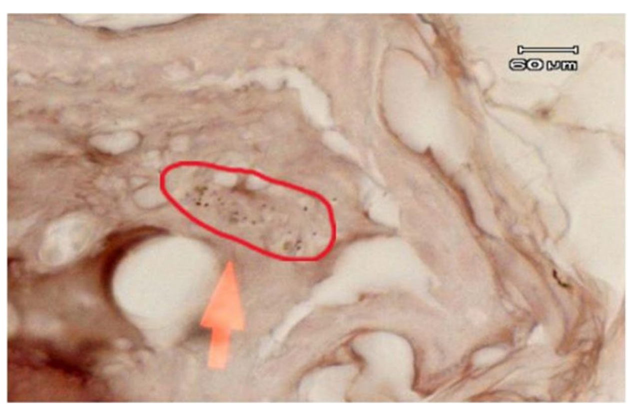


Fig. 4 Histology of the skin P2, the amount of skin melanin pigment visible in the epidermis of the mice's skin is classified as small (10 × 10 magnification, Olympus CX21)

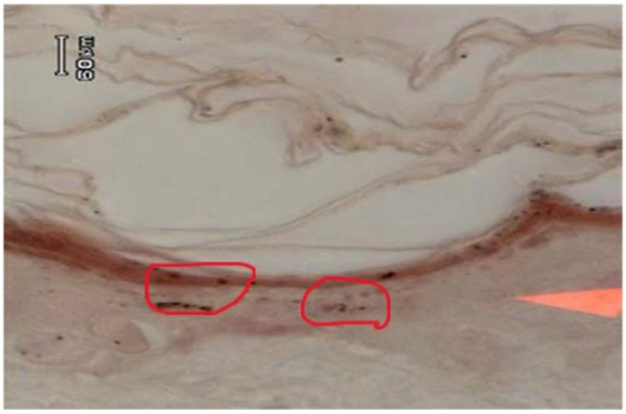


Fig. 5 Histology of the skin P3, the amount of skin melanin pigment visible in the epidermis of the mice's skin is classified as medium (10 × 10 magnification, Olympus CX21)

Fig. 6 Histology of the skin P4, the amount of skin melanin pigment visible in the epidermis of the mice's skin is classified as small (10 × 10 magnification, Olympus CX21)

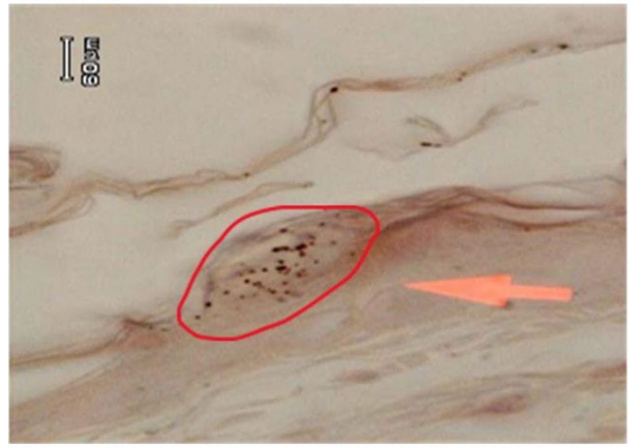


Fig. 7 Histology of the skin P5, the amount of skin melanin pigment visible in the epidermis of the mice's skin is classified as small (10 × 10 magnification, Olympus CX21)

extract on day 21 to day 30 and their skin biopsy on day 31. The picture of the melanin pigment in the skin of mice found in the epidermis of mice in this group is relatively small (< 40 grains), with the amount of melanin pigment that appears as much as 10 pigments (Fig. 6).

The fifth treatment group (P5)

The group of mice who were given sun exposure for 1 h/day in 20 days was then followed by giving duku seed extract on day 21 to day 30 and their skin biopsy on day 31. The picture of the melanin pigment in the skin of mice found in the epidermis of mice in this group is relatively small (< 40 grains), with the amount of melanin pigment that appears as much as 34 pigments (Fig. 7, Table 1).

Based on the results tained from the research that has been carried out, it can be seen that the administration of duku peel extract and duku fruit seeds has an effect on the amount of melanin pigment in the skin of mice that is treated with sun exposure. This can be seen from Fig. 8, which shows a drastic decrease in the amount of melanin pigment in the skin of mice that were not given extract (P1) and mice that were given extract application (P2, P3, P4, and P5).

Discussion

UV radiation causes pigmentation in several ways, namely increasing the work of melanogenic enzymes, damaging DNA that will stimulate melanogenesis, increasing the transfer of melanosomes to keratinocytes, and dendritic activity of melanocyte cells. UV radiation can trigger the occurrence of ROS which in turn trigger the release of NO, protein kinase, melanocyte stimulating hormone (MSH), and prostaglandin E2 (PGE2) which can stimulate the process of melanogenesis. Melanocytes can be defined as cells that possess the unique capacity to synthesize melanins within melanosomes. Factors related to melanin production within melanocytes can be divided into three groups as: structural proteins of melanosomes, enzymes required for melanin synthesis, and proteins required for melanosome transport and distribution (Yamaguchi et al. 2007). This study was aimed to evaluate the effectiveness of duku fruit extract in preventing the increase of melanin in mice skin exposed to sun.

In the negative control group (P0), the average value of the number of melanin pigments was relatively low, namely 19 pigments (number of pigments < 40 grains). Whereas in the first treatment group (P1), namely the group of mice treated with sun exposure for 1 h/day for 20 days and their skin biopsied on the 21st day without giving the extract, showed the results with the highest average value compared

Table 1 The number of melanin pigment granules on the skin of the control and treatment groups mice

Group of mice	Amount of pigment	Classification	Category	Information	Average amount of pigment
P0					
1	3	< 40	Small		**7**
2	4	< 40	Small		
3	5	< 40	Small		
4	**19**	**< 40**	**Small**		
5	4	< 40	Small		
P1					
1	83	> 80	Many		**68.4**
2	**96**	**> 80**	**Many**		
3	82	> 80	Many		
4	81	> 80	Many		
5	–	–	–	Died	
P2					
1	45	40–80	Medium		**26.6**
2	**27**	**< 40**	**Small**		
3	32	< 40	Small		
4	29	< 40	Small		
5	–	–	–	Died	
P3					
1	42	40–80	Medium		**29**
2	49	40—80	Medium		
3	29	< 40	Small		
4	25	< 40	Small		
5	–	–	–	Died	
P4					
1	5	< 40	Small		**7.2**
2	**10**	**< 40**	**Small**		
3	12	< 40	Small		
4	9	< 40	Small		
5	–	–	–	Died	
P5					
1	5	< 40	Small		**12**
2	**34**	**< 40**	**Small**		
3	12	< 40	Small		
4	9	< 40	Small		
5	–	–	–	Died	

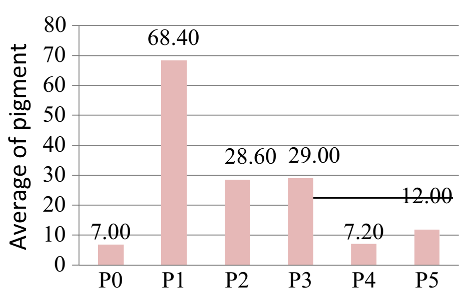


Fig. 8 Average amount of melanin pigment

to other treatment groups with the number of melanin pigments is quite large, namely as many as 96 pigments (total pigments > 80 grains). This occurs because the treatment of sun exposure affects the increase in the work of the tyrosinase enzyme, thereby increasing the rate of melanin pigment production and its accumulation in keratinosid (Mamoto et al. 2009). Sun exposure will cause an increase in the activity of the tyrosinase enzyme, which catalyzes the hydroxylation reaction of tyrosine to dihyroxy-phenylalanine (DOPA) and oxidation of DOPA to Dopaquinone, resulting in increased production of the pigment melanin in the skin (Yonathan et al. 2016). UV damage leads to inflammation, and neutrophil infiltrate activates NAD(P)H oxidase, generating ROS that alter the production of keratinocytic cytokines (Oresajo et al. 2010; Freitas et al. 2015). Generation of UV induced free radicals in the skin develops oxidative stress when it exceeds the ability of natural defense: the only skin protection systems are antioxidant enzymes and melanin, the first line of defense against DNA damage (Addor 2017). DNA absorbs ultraviolet light, whose energy can break its molecular bonds; most of these breaks are repaired by enzymes present in the nucleus itself, however the remaining damages generate mutations that lead to neoplasia (Katiyar and Mukhtar 2001). The induced UV inflammatory process also favors the increase of melanogenesis (Sarkar et al. 2014).

Furthermore, in the second treatment group (P2), namely the group of mice that were treated with sun exposure 1 h/day in 20 days after being given duku peel extract treatment 30 min before sun exposure and biopsy of their skin on the 21st day showed yield of melanin pigment production with an average value that is classified as small, namely as many as 27 pigments (total pigment < 40 grains). Then in the third treatment group (P3), namely the group of mice that were treated with sun exposure 1 h/day in 20 days after being given the duku seed extract application for 30 min before sun exposure and their skin biopsied on the 21st day showed the results of the production of melanin pigments with an average value that is classified as moderate, that is, the number between 40 and 80 grains. These results indicate a decrease in the amount of melanin pigment compared to the first treatment group (P1) which was included in the many category. This shows the role of giving duku fruit peel extract 30 min before the exposure treatment, namely as an inhibitor of the process of melanin pigment formation.

The peel of the duku fruit contains polyphenol compounds in the form of flavonoids which can inhibit the melanogenesis process and prevent an increase in the amount of melanin pigment in the epidermis of the skin (Sofiana et al. 2017). Flavonoids are natural polyphenolic compounds that have the ability to depigment the skin by directly inhibiting tyrosinase activity in the melanogenesis process (Charissa et al. 2016). The role of flavonoids as an inhibitor of the melanogenesis process occurs through the bonds formed between these flavonoid compounds and the tyrosinase enzyme. The bond that is formed is what causes the weakening of the catalytic properties of the tyrosinase enzyme so that it reduces its effectiveness in catalyzing the hydroxylation reaction of tyrosine to DOPA and the oxidation of DOPA to Dopaquinone (the reaction of forming melanin pigments) (Yamaguchi et al. 2007).

P4, namely the group of mice treated with sun exposure 1 h/day for 20 days and continued with duku peel extract application on day 21 to day 31 and a biopsy of the skin on day 31 shows the results of the production of melanin pigments with an average value that is classified as small, namely as many as 10 pigments (total pigments < 40 grains). This proves that the application of duku peel extract for 10 days after sun exposure treatment (on the 21st day) has a role in helping to accelerate the reduction of the amount of melanin pigment in the skin. In addition, the decrease in the amount of melanin pigment in the third treatment group (P3) could also be caused by the physiological processes of the skin after stopping sun exposure (Yamaguchi et al. 2007). *Lansium domesticum* Corr. has good antioxidant activity properties, the two main actions of defenses that antioxidants can provide are in relation to preventing the formation of free radicals or neutralizing the radicals already generated (Cheeseman and Slater 1993). Epidermal antioxidant capacity is much higher than the dermal: catalase, glutathione peroxidase and glutathione reductase systems were higher in the epidermis than in the dermis-both the lipophilic antioxidants (tocopherol, ubiquinol 9, etc.) and the hydrophilic ones (ascorbic acid and glutathione). The stratum corneum contains both hydrophilic and lipophilic antioxidants. Vitamins C and E, as well as glutathione (GSH) and uric acid, were found. Use of antioxidants in the prevention and repair of ultraviolet photodamage is widely studied, being the most known and used indication. Association of antioxidant molecules, from vitamins to phytoextracts, in photoprotectors and moisturizers with appeal against aging, is frequent (Burns et al. 2013; Schroeder and Krutmann 2010).

Antioxidants are substances that can delay or prevent the formation of free radical reactions (peroxides) in the oxidation of lipids, DNA or proteins (Burns et al. 2013). Several compounds from natural ingredients such as glycosides, flavonoids, alkaloids, several types of terpenoids, lansid acid, dukunolid, and lancioside acid have potential as antioxidants (Hanum et al. 2018). Phytochemical test results showed that the active compounds contained in duku seeds were terpenoids and flavonoids. Terpenoid compounds or flavonoids in duku seed extract are able to reduce free radicals such as superoxide anions and hydrogen peroxide (Klungsupya et al. 2015; Techavuthiporn 2018; Abotaleb et al. 2020).

Furthermore, in the fifth treatment group (P5), namely the group of mice that were treated with sun exposure for 1 h/day for 20 days then followed by giving duku seed extract on day 21 to day 30 and a biopsy of their skin on day 31 indicates that melanin production is decreasing, namely by the amount less than 40 and some melanin pigments appear to be scattered. The content of flavonoids is thought to affect the amount of melanin pigment. Duku fruit contains flavonoid compounds, where flavonoid bonds with copper and their antioxidant effects are reported to play a role in inhibiting the action of the tyrosinase enzyme and also working at the end of the oxidative pathway of melanogenesis so that it can reduce hyperpigmentation (Charissa et al. 2016). Antioxidants are substances that combine to neutralize reactive oxygen species preventing oxidative damage to cells and tissues (Preedy 2012). The cutaneous antioxidant system consists of enzymatic and non-enzymatic substances. Among enzymatic antioxidants, glutathione peroxidase (GPx), catalase (CAT) and superoxide dismutase (SOD) can be highlighted (Kohen et al. 1997). Non-enzymatic or low molecular weight antioxidants also contribute to the maintenance of cellular redox balance. Here some hormones are grouped such as estradiol and, melatonin, as well as some vitamins, such as E and C (Kvam and Dahle 2003). Apart from the flavonoid content, the skin of the duku fruit also contains vitamin C which can also function as depigmentation on the skin. This depigmentation of the skin by vitamin C occurs due to the ability of vitamin C to convert eumelanin (dark oxidized melanin) into feomelanin (melanin is oxidized to a pale color) so that it can brighten skin tone. In addition, vitamin C can also brighten or treat hyperpigmentation in the skin by renewing cells and speeding up the cell turnover process in the skin (Yonathan et al. 2016).

Flavonoids have antioxidant effects through two mechanisms. The first mechanism is that flavonoids inhibit enzymes responsible for the production of superoxide anions, hydroxyl radicals and SOR, such as xanthine oxidase, protein kinase C, cyclooxygenase, lipoxygenase, microsomal monooxygenase, glutathione s-transferase, mitochondrial succinyxidase and NADH oxidase. The second mechanism is that with a low redox potential, flavonoids can thermodynamically reduce free radicals such as superoxide, peroxyl, alkoxyl and hydroxyl radicals by donating a hydrogen atom to form a stable quinone structure (Klungsupya et al. 2015). The difference in GSH and MDA levels caused by various doses of duku seed extract given needs to be observed. Duku seed extract at a dose of 100 mg/kg weight of mice had a higher antioxidant effect than the 200 mg/kg weight of mice or 300 mg/kg weight of mice (Sallam et al. 2021).

This is possible because the dose is the optimal dose of flavonoids or flavonoids terpenoids contained in duku peel extract. Another study regarding the benefits of duku, namely duku peel extract with 50% ethanol solvent and partitioned with ethyl acetate has high antioxidant potential. In addition, this fraction also has a genoprotective effect by reducing DNA damage caused by H2O2 radicals (Klungsupya et al. 2015; Manosroi et al. 2012; Fadhilah et al. 2021). The antioxidant effect of duku seed extract was optimal at a dose of 100 mg/kg weight of mice and decreased at a dose of more than 100 mg/kg. This indicates that the ethanolic extract of duku seeds follows the hormesis pattern. Hormesis is a term in toxicology that describes a dose–response phenomenon that has the characteristics of stimulation at low doses and inhibition at high doses and produces an inverted U-shaped dose curve (Bergman et al. 2019; Lubis et al. 2022).

Conclusion

Extract Duku can reduce the amount of melanin pigment in the skin of mice. Duku is typical of Indonesian plant contains flavonoid compounds, where flavonoid bonds with copper and their antioxidant effects are reported to play a role in inhibiting the action of the tyrosinase enzyme and also working at the end of the oxidative pathway of melanogenesis so that it can reduce hyperpigmentation.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13596-022-00651-5.

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Authors contributions All the five authors reviewed the paper and contributed in developing the content.

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Declarations

Ethical statement Study ethics this research was conducted according to ethical standards for the use of animals for scientific purposes. The research protocol obtained an ethical review from the Faculty of Public Health, University of Sriwijaya with registration number: 219/UN9.1.10/KKE/2020.

Conflict of interest Delima Engga Maretha has no conflict of interest. Dini Afriansyah has no conflict of interest. Dewi Susilo Wati has no conflict of interest. Mashuri Masri has no conflict of interest. Ade Rizky Dwiyanti has no conflict of interest. Muhammad Ifham Hanif has no conflict of interest. Slamet Wardoyo has no conflict of interest.

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