RPCPE
Review of Primary Care Practice and Education
(Kajian Praktik dan Pendidikan Layanan Primer)
Journal Homepage: https://jurnal.ugm.ac.id/rpcpe
ISSN 2613-943X (print)
ISSN 2620-5572 (online)
DOI: 10.22146/rpcpe.103175

Potential of Purple Sweet Potato Ethanol Extract (Ipomea Batata L.) to Prevent Skin Aging in Menopausal Wistar Rats

Ida Ayu Dewi Wiryanthini[1], I Wayan Gede Sutadarma[2], Ni Putu Ratih Cahaya Dewi[3], Made Dhiyo Wiweka Aryaweda[3]

[1] Department of Biochemistry/Undergraduate Medical Study Program; Faculty of Medicine; Universitas Udayana; Indonesia
[2] Department of Clinical Nutrition/Undergraduate Medical Study Program; Faculty of Medicine; Universitas Udayana; Indonesia
[3] Undergraduate Medical Study Program; Faculty of Medicine; Universitas Udayana; Indonesia

Corresponding Author:
Ida Ayu Dewi Wiryanthini: Department of Biochemistry/Undergraduate Medical Study Program, Faculty of Medicine, Universitas Udayana
Email: wiryanthini@unud.ac.id

To cite this article:
Wiryanthini IAD, Sutadarma IWG, Dewi NPRC, Aryadewa MDW. Potential of purple sweet potato ethanol extract (Ipomea Batata L.) to prevent skin aging in menopausal wistar rats. Rev Prim Care Prac and Educ. 2025;8(1):25-28.

ABSTRACT

Background: Menopause is a hypo-estrogenic condition due to decreased ovarian function, a natural thing experienced by women between the ages of 45 and 55, causing health problems on the skin, in the form of decreased collagen production so that skin elasticity decreases, and is prone to dry conditions, sagging to fine lines and wrinkles as a sign of skin aging also called Estrogen Deficient Skin (EDS). This study aims to determine the role of anthocyanin activity in purple sweet potatoes as phytoestrogens to overcome skin symptoms caused by EDS in the form of proliferation of collagen-forming cells, namely fibroblast cells in Wistar rats with a menopause model. **Method:** This research is purely experimental with the method *Post Test Only Control Group Design* which aims to determine the effect of administering purple sweet potato ethanol extract on the number of fibroblast cells in the skin tissue of Wistar rats with a menopause model. A total of 16 female Wistar rats aged 12 weeks that were bilaterally ovariectomized were divided into 2 groups, namely group P0 given 1 ml/day of distilled water, group P1 given ethanol extract of purple sweet potato at a dose of 400 mg/kg BW/day for 3 months. On the last day of treatment, the experimental animals were terminated and then skin tissue was taken to make histological preparations of Masson's Trichrome and to examine the number of fibroblast cells. **Results:** Data analysis using the Independent T test obtained significant results $p=0.00$ and Post Hoc LSD obtained significant results $p<0.05$ for all comparisons across groups. **Conclusion:** Based on these results, it can be concluded that Anthocyanin in ethanol extract of purple sweet potato can increase fibroblast cell proliferation in skin tissue of Wistar rats with a menopause model. Further research is still needed on other parameters to prove the role of Anthocyanin as a phytoestrogen to overcome EDS.

Keywords: *anthocyanins; EDS; fibroblasts; menopause; skin aging*

BACKGROUND

Skin aging is caused by intrinsic and extrinsic factors. Intrinsic factors include genetics, cell metabolism, and hormones, while extrinsic factors include ultraviolet radiation, infrared radiation, and environmental carcinogens such as air pollution. Intrinsic aging is an inevitable process and in this process the skin experiences morphological and physiological changes such as dryness, wrinkles, sagging, and the wound healing process becomes slower[1]. Skin aging due to hormonal factors, one of which is due to decreased estrogen levels in menopausal women. Menopause is a condition caused by the cessation of ovarian follicle activity which results in decreased production of the hormone estrogen[2], causes amenorrhea, the cessation of menstruation for a year or more, permanently in women. Menopause usually started around the age of 45 to 55 years, in Western populations the average age is 50 years and earlier in women in developing countries. Increasing life expectancy results in an increasing number of elderly people in the population[3]. Because life expectancy in women is longer than in men, the age of menopause tends to remain the same, thus increasing the number of postmenopausal women in society[4]. The world's menopausal population is expected to increase to 1.2 billion by 2030[5].

The decrease in estrogen hormone is associated with a decline in skin health and condition, called Estrogen Deficient Skin (EDS) including loss of collagen, elastin, fibroblast function, vascularization and increased activity of matrix metalloproteinase (MMPs) enzymes, resulting in cellular and extracellular degradation causing dry, scaly skin, wrinkles, atrophy, impaired wound healing, decreased antioxidant capacity, decreased attractiveness and psychological health resulting in aging of the skin[4,6]. Estrogen or estradiol hormone is a steroid hormone synthesized from cholesterol, synthesized in the ovaries in premenopausal women and peripheral tissues in postmenopausal women. Estrogen Receptors (ERs) α and β are estrogen hormone receptors that are often found in the skin, have the same affinity for estradiol[3] with ERβ being more widely distributed in the skin than Erα[7]. ERα and ERβ

expression levels decline from the perimenopausal years onwards as women enter a state of estrogen deficiency[8].

In intrinsic skin aging, the epidermal layer thins, causing the contact area between the dermis and epidermis to reduce, which in turn decreases the exchange of nutrients to the epidermis. As a result, the skin becomes more prone to abrasion and tearing after minor trauma. The proliferative capacity of basal cells also decreases. In the dermal layer, the number of mast cells and fibroblasts is lower compared to youthful skin, and this also applies to collagen fibers and elastin fibers. The production of type 1 procollagen in aging skin decreases due to reduced TGF-β/Smad signaling and a decline in connective tissue growth factors. Fibroblasts are responsible for synthesizing connective tissue components such as collagen, elastin, fibronectin, microfibrillar proteins, and laminin. They also regulate the secretion of enzymes that control the balance of connective tissue production, such as lysyl oxidase, matrix metalloproteinases (MMPs), and tissue inhibitors of metalloproteinases (TIMPs)[1].

The skin is influenced by the hormone estrogen. Collagen, a fibrous protein, is the main component of the dermis, and when combined with elastin, it helps maintain the skin's elasticity and flexibility. These features decrease during menopause, when the dermis loosens and the skin surface becomes wrinkled and saggy. Matrix metalloproteinases (MMPs) degrade extracellular matrix (ECM) proteins, such as collagen and elastin, while tissue inhibitors of MMPs (TIMPs) inhibit this activity[9]. Estrogen regulates the metabolism of ECM components. As estrogen levels decrease during menopause, there is a reduction in ECM components such as collagen, hyaluronic acid, and elastin. To address skin aging during menopause, caused by decreased estrogen levels or Estrogen Deficient Skin (EDS), hormone replacement therapy (HRT) in the form of estrogen administration is used[10]. Although systemic HRT can improve the signs of EDS, various risks—especially endometrial hyperplasia or cancer[11]—and concerns about an increased risk of breast and ovarian cancer prevent its use for treating skin disorders[12]. Since maintaining youthful skin is highly desired by the majority of today's population[13], research evaluating approaches to reversing menopausal skin changes through alternative medicine and topical therapies has expanded[14].

Phytoestrogens are chemical compounds derived from plants that have estrogenic effects on animals. These include isoflavones, lignans, coumestans, and resveratrol, which are found in many foods. One of the most studied phytoestrogens is the flavonoid group. The structural similarity of flavonoids to estrogen allows them to bind to and activate estrogen receptors on target cells. Several phytoestrogens have been identified as binding to both types of estrogen receptors, ERβ and ERα. Binding of phytoestrogens to these receptors induces the expression of estrogen-responsive genes and triggers cell proliferation. Phytoestrogens are classified as selective estrogen receptor modulators (SERMs) due to their ability to bind to receptors and produce estrogen-like effects[15]. Anthocyanins in blackcurrants (Ribes nigrum L., Grossulariaceae) are flavonoids whose structure is similar to flavanones and isoflavones. They have been shown to exhibit estrogenic activity both in vitro and in vivo[10,16]. Supplementation with anthocyanins from grapes has been shown to improve memory in ovariectomized female rats, an effect thought to be due to the phytoestrogen activity of anthocyanins[17].

Purple sweet potato (Ipomoea batatas L.) cultivated in Bali has the potential to act as a phytoestrogen due to its relatively high anthocyanin content. Administration of ethanol extract from purple sweet potato has been shown to prevent fatty degeneration of the liver in menopausal model animals, an effect thought to be due to the phytoestrogen activity of purple sweet potato[18]. This study aims to better understand the mechanism of ethanol extract from purple sweet potato tubers as a phytoestrogen in treating EDS in Wistar rats with a menopause model. The study focuses on increasing fibroblast cell proliferation, which in turn will enhance the production of ECM, particularly dermal collagen.

RESEARCH METHODS

Pure experimental research with methods *Post Test Only Control Group Design* was conducted on 16 female Wistar rats, aged 12 weeks, with body weights ranging from 180-250 grams, that had undergone bilateral ovariectomy. The study was conducted at the Integrated Biomedical Laboratory of the Faculty of Medicine, Udayana University. The rats were divided into two groups, each consisting of 8 rats. Group P0 (control) was administered 1 ml of aquades per day, while Group P1 (treated) received 400 mg/kg body weight per day of purple sweet potato ethanol extract for 3 months. After the treatment, the rats were sacrificed, and their skin tissue was collected for the preparation of skin slides using Masson's Trichrome staining.

The purple sweet potato extract was prepared at the Post-Harvest Medicinal Plant Processing Center (P4TO) in Bali, located in Rendang, Karangasem. The purple sweet potatoes were sourced from plantations in Rendang, Karangasem, Bali, then ground and macerated using 96% ethanol solvent in a 1:5 ratio of purple sweet potato powder to solvent. The process lasted for 3x24 hours, with daily stirring for 15 minutes. After 3x24 hours, the filtrate was filtered and evaporated using a rotary evaporator, resulting in 280 grams of concentrated purple sweet potato extract. The anthocyanin content was 82.99 mg/100 grams, flavonoid content was 3,438.42 mg/100 grams, and Vitamin C content was 12.127 mg/100 grams of extract.

Comparison between groups was made by microscopic examination to observe the number of fibroblast cells. Fibroblasts were counted using a binocular microscope (Olympus CX41) at 400x magnification and an Optilab Pro camera. The count was performed across three fields of view, and the number of fibroblasts per field was recorded. Descriptive statistics were used to provide an overview of the fibroblast data, including the mean, standard deviation, minimum, and maximum values. Since the data was normally distributed, it was analyzed using a parametric independent T-test. The variable tested was the mean number of fibroblasts between the groups after treatment, followed by a Post Hoc test using the Least Significant

Difference (LSD) method. The data were analyzed using SPSS version 20 for Windows.

RESULTS AND DISCUSSION

Deviation (SB), minimum value and maximum value of the research data. The results of the descriptive analysis of fibroblast cells in each research group are presented in Table 1.

Table 1. Results of descriptive analysis of fibroblast cell variables

Variables	Group	Average	SB	Minimum	Maximum
Fibroblast Cells (cells)	Control (P0)	30.29	6.18	21.33	38.33
	Treatment (P1)	44.00	4.48	38.67	51.33

SB = Standard Deviation

The average number of fibroblast cells in group P0 was 30.29 and group P1 was 44.00 (Figure 1). The difference in the average number of fibroblast cells in each treatment group was tested using the independent T test because the data were normally distributed ($p>0.05$) and homogeneous ($p>0.05$). The significance analysis using the independent T test showed a p value = 0.000, which means that the average number of fibroblast cells in both groups after treatment was significantly different ($p <0.05$).

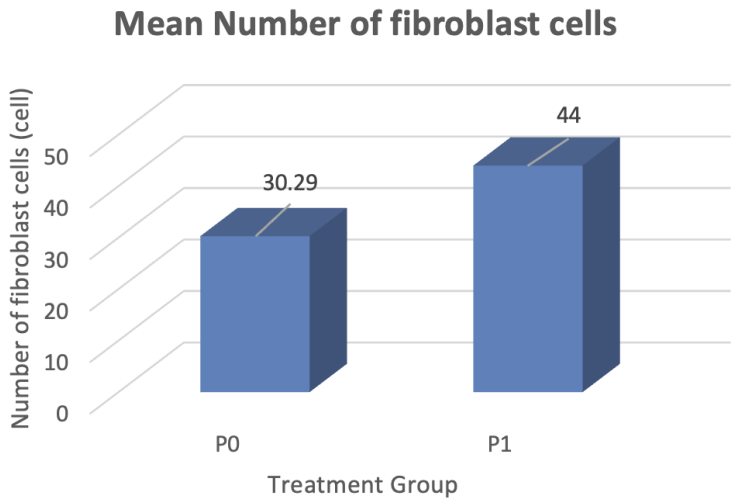

Figure 1. Mean number of fibroblast cells

The results of this study show that the average number of fibroblast cells after treatment in the two groups differed significantly, where a significant increase in the number of fibroblast cells occurred in the treatment group which was given 400 mg/kg BW/day of purple sweet potato ethanol extract and the control group which was given 1 ml/day of distilled water for 3 months as presented by **Figure 2**. The increase in the number of fibroblast cells in the purple sweet potato ethanol extract group is in line with research conducted by Moraes et al. in 2009[19] where topical administration of the antioxidant genistein increases the number of fibroblasts, although it does not match the administration of the hormone estrogen in improving skin aging. The increase in the number of fibroblast cells is related to the bioactive compounds contained in purple sweet potatoes, one of which is flavonoids. Flavonoid content can increase the expression of Insulin Like Growth Factor-1 (IGF-1) and Transforming Growth Factor- β1 (TGF-β1) receptors as mediators of fibroblast proliferation and collagen synthesis[20].

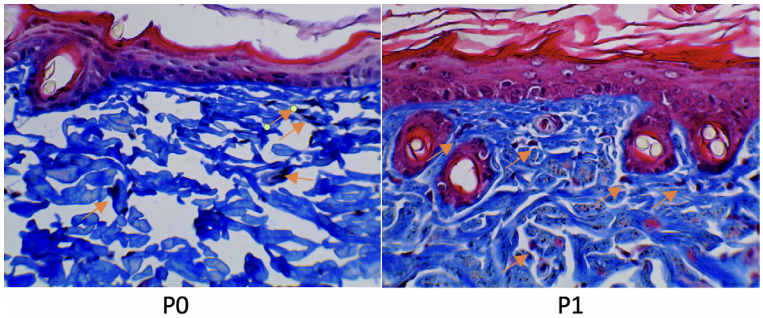

Figure 2. Fibroblast cells of group P0 and P1 in Masson's Trichrome staining

This study examined the potential of purple sweet potato in increasing the formation of fibroblast cells that will produce ECM, especially dermal collagen, so that it can prevent skin aging caused by conditions of decreased estrogen levels or EDS.

The results of this study indicate that giving ethanol extract of purple sweet potato 400 mg/kg BW/day gave significant increase in fibroblast number compared to control group, so it can be concluded that ethanol extract of purple sweet potato is able to increase fibroblast cell number for collagen production and prevent skin aging in EDS. Anthocyanin and Flavonoid content in purple sweet potato is able to increase fibroblast cell number in dermis of Wistar rat skin model of menopause, but it needs to be proven through further research to find out how purple sweet potato mechanism is able to increase fibroblast cell number in Wistar rat model of menopause.

In this study, only the parameter of the number of fibroblast cells was assessed, so it is still necessary to examine other parameters to further determine the ability of purple sweet potato ethanol extract to stimulate growth factors so as to increase collagen production in the skin's dermis tissue.

CONCLUSIONS

Administration of purple sweet potato ethanol extract has the effect of increasing the number of fibroblast cells in the dermis of female Wistar rats in a menopause model so that it can increase collagen synthesis in skin tissue. It is hoped that further research can be carried out on the non-genomic working mechanisms of Anthocyanins to prevent skin aging.

ACKNOWLEDGMENTS

The author would like to thank the Research and Community Service Unit (UP2M) of the Faculty of Medicine, Research and Community Service Institute (LPPM), Udayana University for the 2023 Study Program Excellent Research (PUPS) grant to complete this research.

Ethical Approval

This research has received ethical approval from the Ethics Commission of the Faculty of Medicine, Udayana University, Bali with number 1752/UN14.2.2.VII.14/LT/2023 before the research was carried out.

Conflicts of Interest

There is no conflict of interest in this research.

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