



Effect of Purple Passion Fruit Extract Cream (Passiflora edulis Sims var. Edulis) 6% against Striae Distensae

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Abstract

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BACKGROUND: Striae distensae is a skin disorder that causes cosmetic and psychological problems. Purple passion fruit (Passiflora edulis Sims var. Edulis) is widely cultivated, especially in North Sumatra. The seeds are abundant and unused industrial waste. Purple passion fruit seeds contain piceatannol, ascorbic acid, flavonoids, resveratrol, hydroalcohols, and sterols which play a role in the repair of striae distensae through anti-inflammatory mechanisms, increase fibroblast proliferation and collagen production, increase crosslinking between collagen fibers and moisturizers.

AIM: To determine the effect of 6% purple passion fruit (P. edulis Sims var. Edulis) seed extract cream on striae distensae.

PATIENTS AND METHODS: This study is a pre-experimental clinical trial with a pretest-posttest research design on 40 patients with striae distensae. The diagnosis was confirmed by history and clinical evaluation using the Manchester scar scale before and after administration of 6% purple passion fruit extract cream at baseline, 2, 4, 6, and 8 weeks. Adverse effects were recorded during the study and satisfaction levels were assessed at the end.

RESULTS: The majority of subjects' ages ranged from 29 to 39 years (72.5%). There was a significant reduction in Manchester scar scale in striae distensae, both after being given a 6% purple passion fruit extract cream or a combination of 1% tretinoin cream for 8 weeks, with a mean reduction of 25% (p = 0.000). Striae distensae after being given 6% purple passion fruit extract cream compared to 6% purple passion fruit extract cream combined with 1% tretinoin cream, there was no significant difference (p = 0.791). From a total of 40 patients, none experienced side effects (0%). As many as 57.5% of the subjects showed a good level of satisfaction.

CONCLUSION: The use of 6% purple passion fruit seed extract cream can improve the appearance of striae distensae without side effects and the level of satisfaction is good.

Introduction

Striae distensae has a negative impact on the quality of life of a woman which is associated with the onset of stress which often leads to decreased quality of life [1]. Striae distensae is not a dangerous disease but can cause cosmetic and psychological problems in sufferers [2]. Varies, ranging from 40% to 70% in adolescents, and up to 90% in pregnant women [3], [4]. In a study conducted by Aryunisari et al. on 151 patients in Medan, it was found that 74.8% of adolescents had striae distensae [5].

Until now there is no single therapy that is completely effective in eliminating striae distensae. Several therapies have been introduced for the management of striae distensae including topical tretinoin, laser, radiofrequency, micro needling, microdermabrasion, and platelet-rich plasma [6].

Purple passion fruit (P. edulis Sims var. Edulis) is the most commonly cultivated variety in Indonesia

and its seeds are not used in the food industry and are considered unused ingredients. Ramaiya et al. found the content of ascorbic acid in P. edulis Sims var. Edulis is higher than that of other Passiflora sp [7]. Ascorbic acid functions in the maturation of cross-links between collagen, thereby preventing rupture in stretched areas [8], [9]. Gonçalves et al. studied the hydroalcoholic effect of P. edulis extract on wound healing and is associated with increased fibroblast proliferation and collagen formation [10]. In a study conducted by Soares et al., it was found that the flavonoid content in P. edulis improved wound healing by increasing fibroblast proliferation and increasing epithelialization [11]. In an in vitro study by Stipcevic et al., who administered flavonoids to fibroblast cultures, there was an increase in collagen synthesis is significant compared to placebo [12]. The benefits of purple passion fruit in the study that have been described can improve striae by repairing both the amount of collagen and the crosslink bonds between collagen.

Methods

This research was conducted after approval from the Ethics Committee of the University of North Sumatra, North Sumatra, Indonesia with registration number 555/ KEP/USU/2020. This research was conducted from December 2020 to February 2021 at the Department of Dermatology and Venereology at the University of North Sumatra hospital. This research is a pre-experimental research with a pretest-posttest research design. The patients taken in this study were forty female patients with striae distensae aged 18-50 years. Patients who were pregnant or breastfeeding and who received previous treatment of striae distensae either topically. orally, or as a procedure within the last one month were excluded from this study. If the subject does not apply the ingredients for 3 consecutive days or the total application of the ingredients is <7 weeks, the meal will be dropped out of the study.

Subjects were given 6% purple passion fruit seed extract cream applied to the right and left lesions once in the morning and 0.1% tretinoin cream was applied to the left lesions once at night for 8 weeks. Furthermore, the Manchester scar scale was calculated as well as an assessment of side effects that occurred during the study period every 2 weeks (baseline, 2, 4, 6, and 8). At the final visit at week 8, the patient was asked to rate the level of satisfaction based on changes in the subject's perceived striae distensae lesion.

Data that has been collected are then processed using the Saphiro-Wilk statistical analysis to see the normality of the data. Then because the data were not normally distributed, the Wilcoxon test was continued to assess the ratio of lesions before and after administration of 6% purple passion fruit extract cream as well as to assess the ratio of lesions before and after administration of 6% purple passion fruit extract cream combined with 0.1% tretinoin cream. Furthermore, to assess the ratio between the final lesions of 6% purple passion fruit extract cream and 6% purple passion fruit extract cream combined with 0.1% tretinoin cream, the MannWhitney test was used.

Results

In this study, it was found that the majority of the age range of the study subjects was in the age range group of 29–39 years (72.5%) followed by the age range 18–28 (25%) and 40–50 (2.5%) with the youngest age being 21 years. and the oldest age is 41 years. Furthermore, in this study, the mean was 31.72 ± 4.59 (Table 1).

After the data were collected, the Shapiro-Wilk normality test was carried out which showed that

Table 1: Distribution of patients by age

Age (Years)	n	(%)
18–28	10	25
29–39	29	72.5
40–50	1	2.5
Total	40	100

the data had an abnormal distribution so that it was continued with the Wilcoxon test to assess the ratio of lesions before and after giving 6% purple passion fruit extract cream as well as to assess the ratio of lesions before and after giving purple passion fruit extract cream. 6% combined with 0.1% tretinoin cream. The median obtained before giving purple passion fruit extract cream was 12 with a minimum score of 9 and a maximum score of 15, while the median after 8 weeks of giving purple passion fruit extract cream was 9 with a minimum score of 5 and a maximum score of 11. The p-value obtained through the Wilcoxon test is <0.000 (p < 0.05) (Table 2 and Figure 1).

Table 2: Comparison of Manchester scar scale at baseline and8 weeks after administration of 6% purple passion fruit seedextract cream

Time	n	Median	Min-max	р
Baseline	40	12	9–15	0.000
8 Weeks	40	9	5–11	

Then when giving 6% purple passion fruit extract cream combined with 1% tretinoin cream, the median value was 12 with a minimum score of 9 and a maximum score of 15, while the median after 8 weeks of giving 6% purple passion fruit seed extract cream combined with tretinoin cream 1% is 9 with a minimum score of 5 and a maximum score of 12. The p value obtained through the Wilcoxon test is <0.000 (p < 0.05) (Table 3 and Figure 2).

Table 3: Comparison of Manchester scar scale at baseline and8 weeks after administration of 6% purple passion fruit extractcream combined with 1% tretinoin cream

Time	n	Median	Min-max	р
Baseline	40	12	9–15	0.000
8 Weeks	40	9	5–12	

Mann Whitney test was conducted to assess the comparison of the Manchester scar scale score on striae distensae lesions after administration of 6% purple passion fruit extract cream and after administration of 6%, purple passion fruit extract cream combined with 1% tretinoin cream for 8 weeks. The median value was 12 with a minimum score of 9 and a maximum score of 12, while the mean number of Manchester scar scale scores after 8 weeks of giving 6% purple passion fruit extract cream combined with 1% tretinoin cream was 9 with a minimum score of 5 and a maximum score of 12. The p-value obtained through the MannWhitney test is

Table 4: Comparison of Manchester scar scale afteradministration of 6% purple passion fruit extract cream with6% purple passion fruit extract cream combined with 1%tretinoin cream

Treatment	n	Median	Min-max	р
6% purple passion fruit extract cream	40	9	5–12	0.791
6% purple passion fruit extract cream combine with	40	9	5–12	
tretinoin 1% cream				

<0.000 (p < 0.05) (Table 4).

In this study, 6% purple passion fruit seed extract cream did not cause any side effects at all in the study patients. The majority of patients given purple passion fruit seed extract had a good satisfaction level of 57.5%, followed by very good 35%, and moderate 7.5% (Table 5).

Table 5: Patients satisfaction levels on the effect of 6% purplepassion fruit seed extract cream on striae distensae

Satisfaction rate	n	%
0 (None)	0	0
1 (Minimal)	0	0
2 (Moderate)	3	7.5
3 (Good)	23	57.5
4 (Very good)	14	35
Total	40	100

Discussion

Until now, there is no single therapy that is completely effective in eliminating striae distensae [6]. This research is a preliminary study of the use of purple passion fruit seed extract for the management of striae distensae. The results of this study show that the 6% purple passion fruit seed extract cream can improve the appearance of striae distensae seen through the Manchester scar scale which has decreased the median value from baseline of 12 to 9 at week 8 so that the decrease in the median value occurs as much as 25% after use for 8 weeks. This can occur due to the presence of piceatannol, ascorbic acid, flavonoids, resveratrol, hydroalcohols, and sterols in the purple passion fruit seed extract [8], [9], [10], [13], [14], [15].

In striae distensae an inflammatory reaction occurs which determines the initial destruction of elastic and collagen fibers followed by regeneration of elastic fibers in the direction of loads generated by mechanical forces [16]. In a study conducted by Beninca *et al.*, it was found that *P. edulis* has a significant anti-inflammatory

effect by inhibiting leukocytes, neutrophils, NO and decreases macrophage inflammatory protein-2 [17]. Yamamoto *et al.* found the anti-inflammatory effect of piceatannol which can suppress the production of NO and proinflammatory cytokines produced by macrophages such as tumor necrosis factor-alpha and interleukin-6 [13]. Furthermore, Sun *et al.* There was a decrease in phospholipase A2 levels on resveratrol supplementation [18].

In the formation of striae distensae caused by steroids and glucocorticoids there is an imbalance of connective tissue and/or the dermal matrix due to the catabolic effect on fibroblast activity and decreasing collagen deposition in the dermal matrix [8], [19]. In an *in vitro* study conducted by Soares *et al.* and Stipcevic *et al.* administration of flavonoids in fibroblast culture, obtained a significant increase in collagen synthesis compared to placebo [11], [12]. Then Gonçalves *et al.* studied the effect of hydroalcoholic extract of *P. edulis* on wound healing and was associated with increased fibroblast proliferation and collagen formation.

In the striae distensae, immature collagen crosslinking occurs in the dermis, resulting in intradermal rupture [8], [9]. Ascorbic acid plays a role in collagen maturation by increasing the cross-link in the collagen triple helix. Decreased levels of ascorbic acid cause fragile cross-links in collagen fibers, causing rupture of the dermis if there is an intolerable strain. is the main substance in the formation of collagen cross-links [20].

Skin with striae distensae has lower elasticity and hydration than skin without striae distensae [21], [22]. Tanaka *et al.* who gave sterol supplementation to 64 women in Japan, found an increase in skin hydration and elasticity at the end of the study [23]. Then this study also shows that 6% purple passion fruit seed extract cream combined with 1% tretinoin can improve the appearance of striae distensae seen through the Manchester scar scale which has decreased the median value from baseline by 12 to 9 at week 8 so that a decrease in the median value occurs. as much as 25% after 8 weeks



Figure 1: Improved appearance of striae distensae with the use of 6% purple passion fruit seed extract cream; (a). before use (baseline); (b) after 2 weeks of use; (c) after 4 weeks of use; (d) after 6 weeks of use; (e) after 8 weeks of use



Figure 2: Improved appearance of striae distensae with 6% purple passion fruit extract cream combined with 1% tretinoin cream; (a). before use (baseline); (b) after 2 weeks of use; (c) after 4 weeks of use; (d) after 6 weeks of use; (e) after 8 weeks of use

of use. Apart from the high content of piceatannol, ascorbic acid, flavonoids, resveratrol, hydroalcohol, and sterols in purple passion fruit seed extract, tretinoin combined in this study has the effect of increasing collagen through stimulation of fibroblasts and inhibiting matrix metalloproteinases (MMP) activation [8], [10], [13], [15], [24], [25].

In comparison, lesions of striae distensae after administration of 6% purple passion fruit seed extract cream with after administration of 6% purple passion fruit seed extract cream combined with 1% tretinoin cream for 8 weeks. This study shows that there is no significant difference in the comparison of the two. In giving this combination there is the same mechanism both in purple passion fruit seed extract and tretinoin. Tretinoin can increase collagen through fibroblast stimulation and inhibits MMP-1 activation [24], [25]. This mechanism is in line with the high piceatannol ability in purple passion fruit seeds, namely, piceatannol can inhibit the JAK/STAT-1 pathway, thereby suppressing the expression of the MMP-1 gene in dermal fibroblasts that resulted in an increase in collagen levels [26]. Then the length of the study which was only 8 weeks appeared to have an effect on the outcome of the study. In a study conducted by Kang et al. and Rangel et al., which found significant improvement in striae distensae lesions by administering tretinoin 1%, it was carried out for 12 weeks [27].

The safety profile of purple passion fruit seed extract has been mentioned in several studies, including research by Lourith *et al.* who carried out a patch test of purple passion fruit seed extract that was proven to not cause irritation to human skin [28]. Similar to research conducted by Dewi *et al.* on patients with acne vulgaris given purple passion fruit seed extract, only one patient (2.2%) experienced side effects in the form of mild peeling [29]. In this study, 6% purple passion fruit extract cream did not cause any side effects at all in the study patients. This shows that the purple passion fruit seed extract is safe to use and well-tolerated. In a meta-analysis of striae distensae therapy conducted by Lu *et al.*, it was found that topical tretinoin had the lowest level of patient satisfaction compared to other therapies, namely 5.1% of patients who were satisfied with the results of therapy [30]. A different thing was found in the study by Hexsel *et al.*, who found that the majority of patients (66%) who were given topical tretinoin therapy were satisfied with the results of the highest patient satisfaction score of 50%, which was good [32]. Given purple passion fruit seed extract had a good satisfaction level (57.5%). Therefore, further studies with randomized controlled trial design are necessary to determine the safety and efficacy of *P. edulis Sims var. edulis* seeds extract topical application on striae distensae.

Conclusion

We found that the striae distensae lesion improved by administering 6% purple passion fruit extract cream alone or in combination with tretinoin 1%. We did not find any difference in striae distensae improvement between the administration of a single 6% purple passion fruit seed extract cream combined with 0.1% tretinoin cream. This study shows that 6% purple passion fruit seed extract has the potential to be used as a therapy for striae distensae. However, further studies are needed to compare its function and safety in the management of striae distensae.

References

1. Yamaguchi NS. Quality of life evaluation in Japanese pregnant women with striae gravidarum: A cross-sectional study. BMC Res Notes. 2012;5:450. https://doi.org/10.1186/1756-0500-5-450

PMid:22905939

- Bertin C. Lopes DA. Nkengne A. Roure R. Stamatas GN. Striae 2. distensae distensae are characterized by distinct microstructural features as measured by non-invasive methods in vivo. Skin Res Technol. 2014;20(1):81-6. https://doi.org/10.1111/srt.12088 PMid:23865630
- Cho S, Park E, Lee D, Li K, Chung J. Clinical features and risk 3 factors for striae distensae distense in Korean adolescents. J Eur Acad Dermatol Venereol. 2016;20(9):1108-13. https://doi. org/10.1111/j.1468-3083.2006.01747.x PMid-16987267
- Korgavkar K, Wang F. Striae distensae during pregnancy: 4. Areview of topical prevention. Br J Dermatol. 2015;172(3):606-15. https://doi.org/10.1111/bjd.13426 PMid-25255817
- Aryunisari CG, Putra IB, Jusuf NK. The relationship between 5 age of menarche with Sriae among female students. Bali Med J. 2020;9(1):400-3. https://doi.org/10.15562/bmj.v9i1.1734
- Lokhande AJ, Mysore V. Striae distensae treatment review and 6 update. Indian Dermatol Online J. 2019;10(4):380-95. https:// doi.org/10.4103/idoj.idoj 336 18 PMid:31334056
- Ramaiya SD, Bujang JS, Zakaria MH, Kinga WS, Sahrira MA. 7. Sugars, ascorbic acid, total phenolic content and total antioxidant activity in passion fruit (Passiflora) cultivars. J Sci Food Agric. 2013;93(5):1198-205. https://doi.org/10.1002/jsfa.5876 PMid:23027609
- Schuster S. The cause of striae distensae distensae. Acta Derm 8. Venereol. 1979;59(85):161-9.

PMid:294092

- El-Khalafawy GM. Comparative Study Between Intense Pulsed 9. Light "IPL" and Pulsed Dye Laser in the Treatment of Strie Distensae (Thesis). Cairo: National Institute of Laser Enhanced Sciences; 2013.
- 10. Filho AG, Torres OJ, Campos AC, Filho RT, de Almeida Rocha LC, Thiede A, et al. Effect of Passiflora edulis (passion fruit) extract on rats' bladder wound healing: Morphological study. Acta Cir Bras. 2006;21(2):1-8. PMid:17117271
- 11. Soares RD, Campos MG, Ribeiro GP, Salles BC, Cardoso NS, Ribeiro JR, et al. Mice, development of a chitosan hydrogel containing flavonoids extracted from Passiflora edulis leaves and the evaluation of its antioxidant and wound healing properties for the treatment of skin lesions in diabetic. J Biomed Mater Res A. 2020;108(3):654-62. https://doi.org/10.1002/jbm.a.36845 PMid:31747098
- 12. Stipcevic T, Piljac J, Berghe DV. Effect of different flavonoids on collagen synthesis in human fibroblasts. Plant Foods for Human Nutr. 2006;61(1):27-32. https://doi.org/10.1007/ s11130-006-0006-8

PMid:16642409

- Yamamoto T, Li Y, Hanafusa Y, Yeh YS, Maruki-Uchida H, 13. Kawakami S, et al. Piceatannol exhibits anti-inflammatory effects on macrophages interacting with adipocytes. Food Sci Nutr. 2017;5(1):76-85. https://doi.org/10.1002/fsn3.366 PMid:28070318
- Middleton E, Kandaswami C. Effects of flavonoids on immune and 14. inflammatorycellfunctions.BiochemPharmacol1992;43(6):1167-79. https://doi.org/10.1016/0006-2952(92)90489-6 PMid:1562270
- 15. Coutinho DS, Pacheco MT, Frozza RL, Bernardi A. Antiinflammatory effects of resveratrol: mechanistic insights. Int J Mol Sci. 2018;19(6):1812. https://doi.org/10.3390/ijms19061812 PMid:29925765

- 16. Cordeiro RC, Zecchin KG, Moraes AM. Expression of estrogen, androgen, and glucocorticoid receptors in recent striae distense. Int J Dermatol. 2010;49(1):30-2. PMid:20465607
- 17. Beninca Z, Montanher AB, Zucolotto SM, Schenkel SP, Frode TS. Evaluation of the anti-inflammatory efficacy of Passiflora edulis. Food Chem. 2007;104:1097-105. https://doi. org/10.1016/j.foodchem.2007.01.020
- Sun S, Zhang M, Yang Q, Shen Z, Chen J, Yu B, et al. 18. Resveratrol suppresses lipoprotein-associated phospholipase A2 expression by reducing oxidative stress in macrophages and animal models. Mol Nutr Food Res J. 2017;61(10):1-33. https:// doi.org/10.1002/mnfr.201601112

PMid:28608449

- 19. Cordeiro RC, Moraes AM. Striae distense: Physiopathology. Surg Cosmet Dermatol. 2009;1(3):137-40.
- 20. Levene CI, Shoshan S, Bates CJ. Ascorbic acid and collagen synthesis in cultured fibroblasts. Ann NYAcad Sci 1975;258:288-306. https://doi.org/10.1111/j.1749-6632.1975.tb29289.x PMid:173226
- Lourith N. Kanlavavattanakul M. Antioxidant activities and 21 phenolics of Passiflora edulis seed recovered from juice production residue. J Oleo Sci. 2013;62(4):235-40. https://doi. org/10.5650/jos.62.235 PMid:23535311
- 22 Cho C, Cho E, Kim N, Shin J, Woo S, Lee J, et al. Biophysical properties of striae rubra and striae alba in human skin: Comparison with normal skin. Skin Res Technol. 2019;25(3):283-8. https://doi.org/10.1111/srt.12645 PMid:30345576
- Tanaka MA, Yamamoto YB, Misawa EA, Nabeshima KA, 23 Saito MA, Yamauchi KA, et al. Effect of aloe sterol supplementation on skin elastisity, hydration and collagen score: A 12 weeks doble blind, randomized, controlled trial. Skin Pharmacol Physiol 2016;29(6):309-17. https://doi. org/10.1159/000454718 PMid:28088806
- 24. Kang S. Topical tretinoin therapy for management of early striae. J Am Acad Dermatol. 1998;39(2 Pt 3):90-2. PMid:9703132
- 25. Kang S, Kim KJ, Griffiths CE, Wong TY, Talwar HS, Fisher GJ, et al. Topical tretinoin (retinoic acid) improves early stretch marks. Arch Dermatol. 1996;132(5):519-26. https://doi. org/10.1001/archderm.1996.03890290053007 PMid:8624148
- 26 Matsui Y, Sugiyama K, Kamei M, Takahashi T, Suzuki T, Katagata Y. Extract of passion fruit (Passiflora edulis) seed containing high amounts of piceatannol inhibits melanogenesis and promotes collagen synthesis. J Agric Food Chem. 2010;58(20):11112-8. https://doi.org/10.1021/jf102650d PMid:20822151
- Rangel O, Arias I, Garcia E, Lopez-Padilla S. Topical tretinoin 27. 0.1% for pregnancy-related abdominal striae: An open-label, multicenter, prospective study. Adv Ther. 2001;18(4):181-6. https://doi.org/10.1007/bf02850112 PMid 11697021
- 28. Lourith N, Kanlayavattanakul M, Chingupitak J. Development of sunscreen products containing passion fruit seed extract. Braz J Pharm Sci. 2017;53(1):e16116. https://doi.org/10.1590/ s2175-97902017000116116
- Dewi NK, Putra IB, Jusuf NK. Passion fruit purple variant 29 (Passiflora edulis Sims var. edulis) seeds extract 10% cream in acne vulgaris treatment: An open-label pilot study. Int J Dermatol. 2020;59(12):1506-12. https://doi.org/10.1111/ijd.15178
- 30. Lu H, Guo J, Hong X, Chen A, Zhang X, Shen S. Comparative

effectiveness of different therapies for treating striae distensae: A systematic review and network meta-analysis. Medicine. 2020;99(39):39-46. https://doi.org/10.1097/md.00000000022256 PMid:32991422

31. Hexsel D, Soirefmann M, Porto MD, Schilling-Souza J, Siega C, Dal'Forno T. Superficial dermabrasion versus topical tretinoin on

early striae distensae: A randomized, pilot study. Dermatol Surg. 2014;40(5):537-44. https://doi.org/10.1111/dsu.12460 PMid:24612027

 ParkKY,KimHK,KimSE,KimBJ,KimMN.Treatmentofstriaedistensae using needling therapy:Apilot study.Dermatol Surg 2012;38(11):1823-8. https://doi.org/10.1111/j.1524-4725.2012.02552.x
PMid:22913429