Original Article

Comparison of Therapeutic Effects of 4% and 10% Purple Passion Fruit (Passiflora Edulis Sims Var. Edulis) Seeds Extract Cream with 4% Hydroquinone Cream on Epidermal Type Melasma

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Abstract

Background: Purple passion fruit seed extract (PPFSE) is rich in antioxidant and photoprotective and therefore has potential as alternative treatment for melasma.

Objective: This study aims to evaluate therapeutic effects of 4% and 10% PPFSE cream to 4% hydroquinone (HQ) cream for epidermal type melasma.

Methods: A randomized double-blind clinical trial was conducted. The study participants were divided into three groups, PPFSE cream 4%, 10% group and HQ cream 4% group. Severity of melasma was assessed with modified melasma area severity index (mMASI), melanin index (MI) with Mexameter® and Mark-Vu® skin analysis and quality of life index for melasma with melasQol at baseline, week 4, 8, and 12 for each arm

Results: A total of 38 participants were included. There was a significant reduction in mMASI, MI, and melasQol scores before and after 12 weeks of treatment across all groups (p=0.000). The difference between mMASI and melanin index before and after 12 weeks of treatment was lower in the PPFSE 4% than the HQ 4% (p<0.05).

Conclusion: PPFSE cream 10% can be a viable option for treatment of epidermal type melasma.

Keywords: Hydroquinone, Medicinal Plant, Purple passion fruit, Epidermal type melasma.

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Introduction

Melasma is an acquired, chronic hypermelanosis on the sun-exposed areas, especially the face. This condition manifests as symmetrical, brownish macules or patches with well-defined and irregular margins.[1,2] Beyond its aesthetic impact, melasma has substantial effect psychologically, detrimentally affecting quality of life, self-esteem, and social interactions. [3,4]

Hydroquinone (HQ) is a hydroxyphenolic compound that has been used since 1960 and remains the gold standard for melasma treatment. Hydroquinone inhibits the conversion of dihydroxyphenylalanine (DOPA) to melanin through tyrosinase inhibition and induces melanocyte damage by inhibiting the synthesis of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA).[1,5] However, the required long-term of HQ use and its associated side effects, particularly exogenous ochronosis, erythema, irritation, irritant or allergic contact dermatitis, and transient halo hypochromia, can make its use unappealing for some patients. Consequently, alternative treatment options are still sought.[6]

In this context of pursuing alternative treatment, it is worth to be noted that Indonesia has a long history of using natural ingredients, such as plants or fruits, as traditional medicines although research on their effectiveness and safety is still lacking.[7,8] One example of promising natural ingredient is purple passion fruit/PPF (*Passiflora Edulis Sims Var. Edulis*). Purple passion fruit seed extract (PPFSE) is rich in polyphenols, including piceatannol, scirpusin B, quercetin, and rosmarinic

acid, which can inhibit tyrosinase, as an antioxidant, and photoprotection, thus a potential candidate for melasma alternative treatment.[9-12]

Potential therapeutic efficacy of PPF is explored in several studies. An *in vitro study* of P. edulis seed extract on melanoma and fibroblast cell cultures by Matsui *et al*, reported that PPFSE has a high content of piceatannol which can increase collagen synthesis and inhibit melanogenesis.[13] Similarly, Jorge *et al*, reported PPFSE (P. edulis) significantly reduced melanin synthesis in mouse melanoma cell cultures (B16) treated with melanocyte-stimulating hormone (MSH).[14] Siti et al, compared PPFSE cream 75% with HQ cream 4% on the skin of 30 male guinea pigs exposed to ultraviolet (UV)-B light showed that PPFSE cream could prevent an increase in the amount of melanin in guinea pig skin with an effectiveness no different from HQ cream 4%.[15] Based on this finding, our study aims to evaluate therapeutic efficacy of 4% and 10% purple PPFSE (Passiflora edulis Sims var. edulis) versus 4% HQ cream on epidermal type melasma.

Methods

This pilot, phase III, randomized, double-blind clinical trial was conducted at the Center General Hospital Dr. Mohammad Hoesin Palembang between October 2022 and January 2023. The study protocol was approved by Ethics Committee of the University of Sriwijaya, South Sumatra (01/XVII.5.11/RSMH/2022). This study was done according to ethical considerations of Declaration of Helsinki and Good Clinical Practice (GCP). All subjects provided written informed consent before entering the study.

Thirty-nine females' patients aged 18-65 years with clinical diagnosis of epidermal type melasma were included. Exclusion criteria were patients who were pregnancy, breastfeeding, hormonal therapy (including hormonal contraception), and endocrine diseases. Subjects who did not apply the ingredients for 3 consecutive days or had total application of ingredients less than 11 weeks or presented with ochronosis were dropped out of the study. Ochronosis was excluded due to its dermal origin and expected lack of response to topical cream that works on epidermis.

Eligible subjects signed informed consent and were provided with three creams: 4% PPFSE, 10% PPFSE, and 4% HQ. Patients were instructed to apply one fingertip unit (FTU) of their assigned cream to the brown spots of their face every night for 12 weeks. The pharmacy held the randomization code, ensuring the patients, investigators, and clinicians were blinded to the treatment assignments. Outcomes were assessed clinically and physically in the morning, with the frequency of measurements varying as follows: the mMASI score and Mexameter® melanin index were measured at weeks 0, 4, 8, and 12, while the Mark-Vu® melanin index and melasQol score were evaluated at baseline and week 12. Side effects were assessed through physician history and physical exam, as well as, patients-completed forms.

All collected data (week 0, 4, 8, and 12) were analyzed using IBM SPSS 22. Shapiro-Wilk test was used to assess data normality. Independent T-test was performed to compare differences in mMASI score, melanin index, and melasQol for each arm of intervention. Paired T-test was done to compare of mMASI score, melanin index and melasQol before and after assigned intervention. *P* value ≤ 0.05 was considered statistically significant.

Results

There were 39 study participants initially however one patient dropped out of the study. Distribution of age in this study was shown on table 1. Majority of PPFSE 4% were aged 46-55 years (15.8%), PPFSE 10% were 36- 45 years (21.1%) and HQ 4% were 46-55 years (13.2%).

On further analysis, there was significant reduction in mMASI, melanin index, and melasQol scores before and after 12 weeks of treatment in all three groups with epidermal type melasma ($p<0.05$). Qualitative assessment showed improved appearance across all three groups of treatment as showed on figure 1 to 3. PPFSE 4% was found to have lower mMASI and melanin index compared to HQ 4% meanwhile there was no

significant difference between PPFSE 10% and HQ 4%. The only observed side effect in this study was erythema in HQ 4%, occurring in 3 out of 12 patients (25%), but only lasted for 1-2 days. This side effect however did not significantly interfere with daily activities of the participant; thus, cream application was continued. There were no reported side effects in other treatment groups. Quality of life was reportedly improved in all treatment groups, as shown by decreased melasQOL scores.

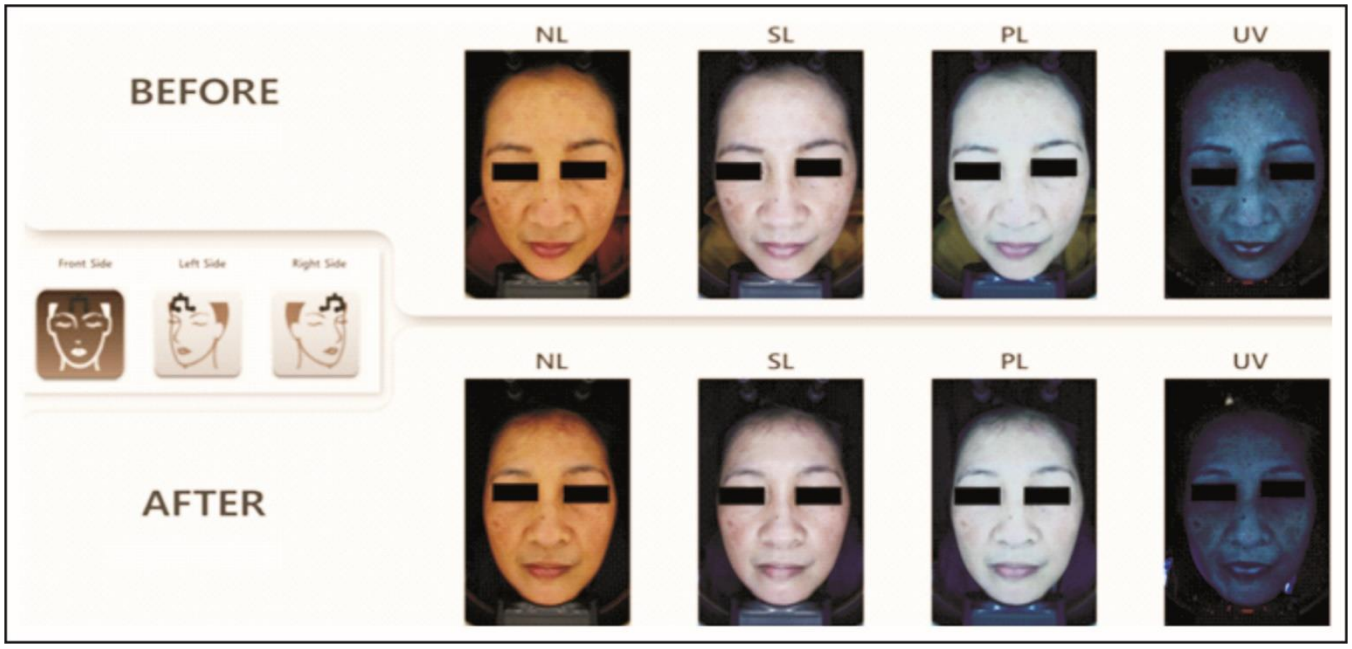

Figure 1: *Improved appearance of melasma with PPFSE cream 4%.*

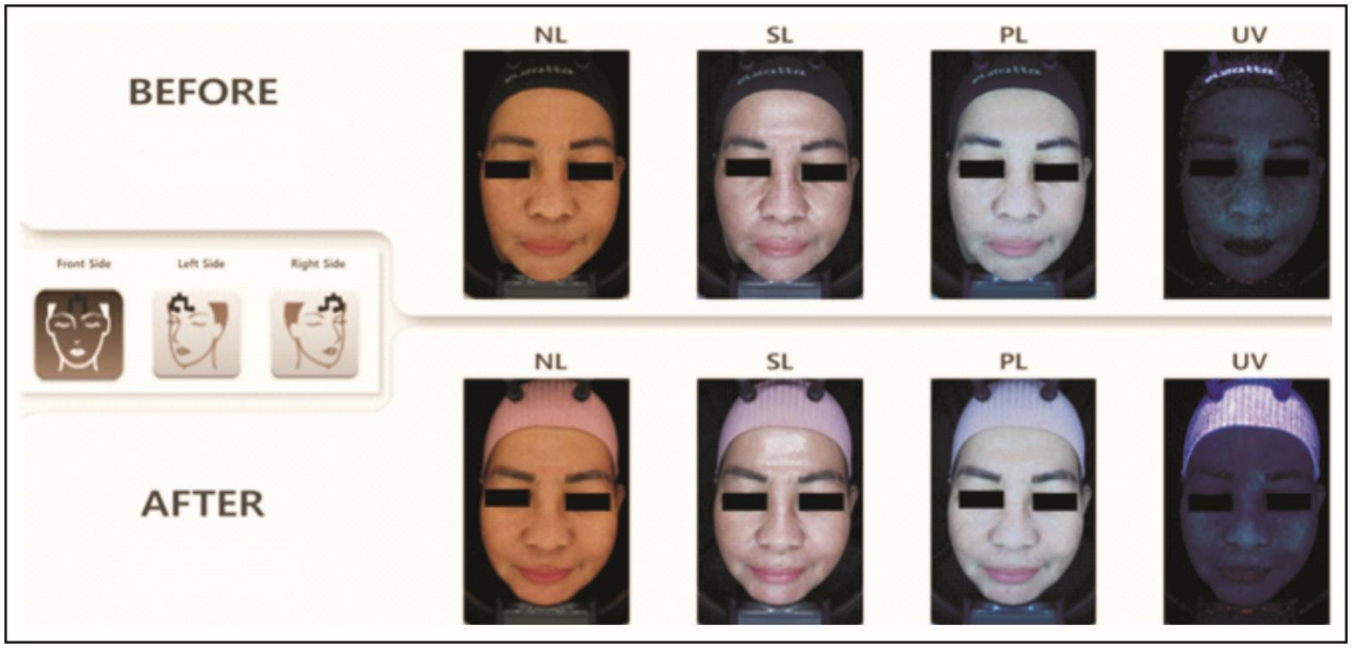

Figure 2: *Improved appearance of melasma with PPFSE cream 10%.*

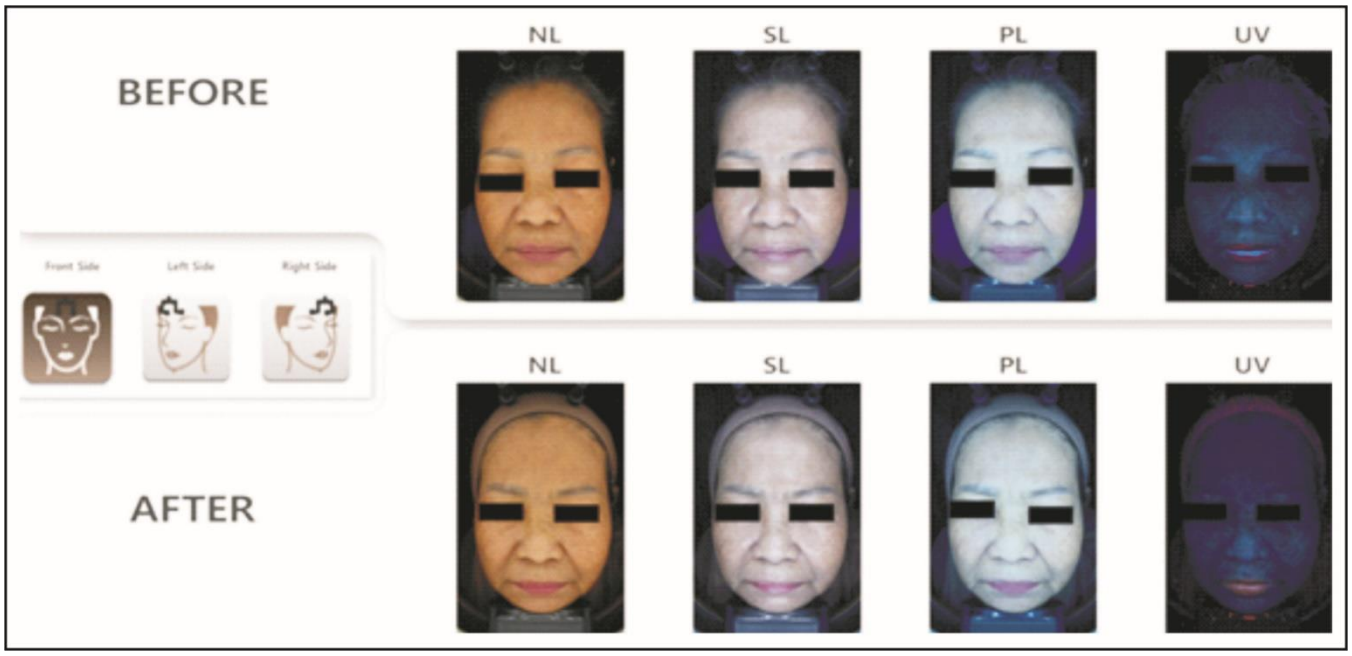

Figure 3: *Improved appearance of melasma with HQ cream 4%.*

Discussion

Our study demonstrated significant reduction in mMASI, melanin index, and melasQol scores after treatment across all three groups. These findings align with previous clinical trial by Siti et al, that found 75% PPFSE cream was as effective as 4% HQ cream in preventing UVB-induced melanin increase in 30 male guinea pig skins.[15] Mechanisms underlying our finding might be attributed to high content of piceatannol in PPFSE which inhibits melanogenesis and provide antioxidant protection from UVB exposure, also increase endogenous antioxidant activity such as glutathione. Jie et al, similarly reported a significant reduction in melanin synthesis and oxidative damage in

Table 1: *Distribution of patients by age.*

Age (Years)	PPFSE 4% (%)	PPFSE 10% (%)	HQ 4% (%)	Total (%)
18 – 25	0	0	0	0
26 – 3 5	2 (5,3)	0	2 (5,3)	4 (10,5)
36 – 45	4 (10,5)	8 (21,1)	4 (10,5)	16 (42,1)
46 – 55	6 (15,8)	4 (10,5)	5 (13,2)	15 (39,5)
55 – 65	1 (2,6)	1 (2,6)	1 (2,6)	3 (7,9)

Table 2: ***Comparison of mMASI, melanin index and melasQol before and after administration of PPFSE 4% and HQ 4%.***

Variable	PPFSE 4%		*p*	HQ 4%		*p*
	Before	After		Before	After	
mMASI	3,54 ± 0.98	2,86 ± 0,89	0,00	3,49 ± 1,10	2,56 ± 0,99	0,00[b]
MI using Mexameter	310,69 ± 52,18	266,77 ± 49,53	0,00[b]	356,00 ± 76,68	277,0 ± 79,90	0,00[b]
MI using Mark-vu	28,00 ± 5,773	24,69 ± 5,618	0,00[d]	29,75 ± 6,001	20,92 ± 5,501	0,00[d]
MelasQol	60,08 ± 7,22	18,46 ± 6,01	0,00	59,00 ± 5,71	19,17 ± 7,13	0,00

Table 3: *Comparison of difference in mMASI, melanin index and melasQol before and after administration of PPFSE 4% and HQ 4%.*

Variable	PPFSE 4%	HQ 4%	*p*
Difference in mMASI	0,67 ± 0,13	0,93 ± 0,23	0,002[b]
Difference in MI using Mexameter	43,92 ± 15,62	79,00 ± 22,14	0,000[b]
Difference in MI using Mark-vu	3,31 ± 1,437	8,83 ± 1,801	0,000[b]
Difference in melasQol	34,23 ± 9,33	39,83 ± 6,18	0,093[b]

Table 4: *Comparison of mMASI, melanin index and melasQol before and after administration of PPFSE 10% and HQ 4%.*

Variable	PPFSE 10%		*p*	HQ 4%		*p*
	Before	After		Before	After	
mMASI	3,55 ± 1,08	2,51 ± 0,86	0,00	3,49 ± 1,10	2,56 ± 0,99	0,00 [b]
MI using Mexameter	322,69 ± 51,88	246,85 ± 36,82	0,00[b]	356,00 ± 76,68	277,0 ± 79,90	0,00[b]
MI using Mark-vu	27,61 ± 6,371	19,69 ± 6,700	0,00[d]	29,75 ± 6,001	20,92 ± 5,501	0,00[d]
MelasQol	60,08 ± 7,22	18,46 ± 6,01	0,00	59,00 ± 5,71	19,17 ± 7,13	0,00

Table 5: *Comparison of difference in mMASI, melanin index and melasQol before and after administration of PPFSE 10% and HQ 4%.*

Variable	PPFSE 10%	HQ 4%	*p*
Difference in mMASI	1,00 (0,80-1,70)	0,90 (0,40-1,30)	0,611[c]
Difference in MI using Mexameter	64,00 (37,00-180,00)	77,50 (53,00-125,00)	0,242[c]
Difference in MI using Mark-vu	7,92 ± 2,100	8,83 ± 1,801	0,259[b]
Difference in melasQol	41,00 (36,00-55,00)	40,50 (31,00-49,00)	0,548[c]

murine melanoma cell cultures treated with *P. Edulis* extract.[16] Matsui et al, (2010) further confirmed the inhibitory effect of piceatannol, a major component of PPFSE extract, on melanogenesis in melanoma and fibroblast cell cultures. The efficacy of PPFSE might be due to its rich polyphenols, including piceatannol, scirpusin B, quercetin, and rosmarinic acid, which can contribute to tyrosinase inhibition, antioxidant activity, and photoprotection, ultimately aiding melasma repair.[17,18]

Topical side effects of depigmentation in general are erythema, irritation, pruritus, and dryness. Hydroquinone side effects depend on the dose and duration of application. Hydroquinone side effects are irritation, erythema, irritant or allergic contact derma-titis, dryness and transient hypochromic halo. Long-term side effects of HQ include the formation of milia, post-inflammatory hyperpigmentation, and exogenous ochronosis. A study conducted by Gheisari et al, in Iran on 24 melasma patients treated with HQ 4% for 8 weeks reported side effects in the form of erythema in 3 patients (15%), irritation in 1 patient (5%), and dryness in 5 patients (25%). The side effect of this study was erythema in 3 of 12 patients (25%) in the 4% HQ group. There are no side effects of using PPFFSE cream on melasma. Dewi et al, an open-label pilot study in 2020 of 45 acne vulgaris patients reported a side effect of 10% PPFSE cream in the form of mild and temporary skin peeling in 1 patient (2.2%).[19] Aryunisari clinical trial study in 2021 on 40 striae distensae patients reported that 6% PPFSE cream could improve significant striae distensae lesions with satisfactory results without side effects.[20] The study by Lourith et al, found PPFSE was not cytotoxic even at a high concentration of 50 µg/mL.[12] Twenty subjects proved that the average irritation index was low. In this study, no side effects were found in the 4% and 10% PPFSE groups.

This research employs sound methodology but acknowledges some limitations. These include limited sample size, the hospital-based setting, and short duration (12 week) of follow-up period. Additionally, side effect that occur on research participants were evaluated by physician history and physician exam, also subjectively through patient-filled forms. While these provide valuable insights, future studies could incorporate more objective measures such as a colorimeter, spectrophotometer or laser Doppler Flowmetry.

Conclusion

The therapeutic results of the 10% PPFSE cream group did not differ significantly from those of 4% HQ group. 10% PPFSE cream can be recommended as viable option for melasma treatment. Nevertheless, further studies with larger sample sizes and longer follow-up are required to establish the safety and efficacy profile of this extract for treatment of epidermal type melasma.

Ethical Approval: This study was approved by the Ethics Committee of the University of Sriwijaya, South Sumatra vide letter no (01/XVII.5.11/RSMH/2022).

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Author's Contribution

YK: Conception & design, acquisition of data, analysis & interpretation, drafting of article.

SS: Conception & design, acquisition of data, analysis & interpretation, drafting of article, final approval of the version to be published.

TLT: Conception & design, drafting of article, revising it critically.

SAN: Conception & design, drafting of article, revising it critically.

R: Conception & design, drafting of article, revising it critically.

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