A Comparative Study of The Efficacy Between 5% *Morinda citrifolia* Fruit Extract Cream and Placebo Cream for Treatment of Melasma

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ABSTRACT

Background: Melasma is one of the most commonly acquired hyperpigmentations that mainly affects the face. Later, natural plant extracts gain popularity for treatment of melasma due to its lesser side effects. Therefore, the researcher reviews on *Morinda citrifolia* (Noni) fruit extract which has anti-tyrosinase activity as a potential alternative.

Objective: To study the efficacy of 5% *Morinda citrifolia* fruit extract cream for the treatment of melasma.

Method: 16 volunteers were selected according to inclusion criteria. 5% *Morinda citrifolia* fruit extract cream and placebo cream were applied comparatively in split face design for 8 weeks, two times per day. Sunscreens and mild soaps were also provided. The researcher took a photograph of each patient using VISIA®. Mexameter® MX18 measurement and MASI score were evaluated by the dermatologist at baseline, 4th week and 8th week respectively. Adverse effects and satisfactory score of the volunteers were observed and evaluated by three dermatologists and recorded throughout the study.

Result: The mean of MASI score in 5% *Morinda citrifolia* fruit extract cream showed significant reduction from baseline 7.09±1.50 to 6.80±1.41 and 6.26±1.31 at 4th week and 8th week respectively with P-value <0.001 meanwhile mean of MASI score in placebo cream increased from baseline 7.26±1.79 to 7.41±1.79 and 7.60±1.69 at 4th week and 8th week respectively. The mean melanin index of 5% *Morinda citrifolia* fruit extract cream was significantly reduced from baseline 219.77±57.31 to 196.33±53.59 and 181.32±48.88 at 4th week and 8th week respectively with P-value <0.001. But the mean melanin index of placebo cream increased from baseline 223.70±65.31 to 225.41±65.38 and 228.14±67.06 at week 4th week and 8th week respectively. No adverse effects were noted throughout the study.

Conclusion: This study statistically demonstrated that 5% *Morinda citrifolia* fruit extract cream can also be used as an alternative treatment for melasma.

Keywords: Melasma, *Morinda citrifolia*, Noni fruit, mean melanin index, MASI score.

1. Introduction

Melasma is the most commonly acquired hyperpigmentations that mainly affects the face. It is much more common in women of reproductive age. The major causative factors are genetic factors, exposure to ultraviolet (UV) radiation and hormonal influences (Lee, 2015). It is characterized by irregular light to dark brown patches on the forehead, cheeks, upper lip, and chin areas of the face (Werlinger et al., 2007). The majority of patients are women and individuals with Fitzpatrick skin types IV through VI, including Hispanic, Asian, and individuals of African descent (Rodrigues and Pandya, 2015). Melasma can also be seen in women using estrogen-progesterone oral contraceptives or hormone replacement therapy and in men using estrogen derivatives (Perez et al., 2000).

It is quite challenging to treat the melasma. Fear of post-inflammatory hyperpigmentation (PIH) after inflammation inducing therapies is also a challenge (Abdallah, 2014). The depth of the pigment, aggravating factors, risk of recurrence and hormones can lead to difficulties in treating the melasma (Gupta et al., 2006).

The main goal of treatment modalities is either inhibition of melanogenesis and melanin transfer from the active melanocytes or removing pigment which is already present in epidermis and dermis (Abdallah, 2014). First-line treatment includes topical agents which inhibits melanogenesis, broad-spectrum sunscreen, and camouflage (Sheth& Pandya, 2011). Try to avoid the sun and wear protective eyewear, hats, caps and clothing for individuals who are imperative to wear sunscreen daily (Cestari et al., 2009).

Commonly used agents for the treatment of melasma include hydroquinone, azelaic acid, kojic acid, glycolic acid, salicylic acid, and tretinoin. Of these treatments, hydroquinone remains the gold standard. Multiple studies suggest that combination formulations offer the best results (Werlinger et al., 2007). Even though hydroquinone is very effective and dosed at different strengths, irritant dermatitis and exogenous ochronosis can occur due to prolonged usage (Mishra et al., 2013). Additionally, many studies have addressed the safety and efficacy of chemical peels and laser/light sources for pigment reduction in melasma. Such procedures are most often considered second- and third-line therapeutic approaches (Grimes PE., 2009).

***Morinda citrifolia* (Noni) Fruit**

Morinda citrifolia L. is also known as Noni, Indian Mulberry, Ba Ji Tian, Nono or Nonu, Cheese Fruit, and Nhau. It can be found throughout the world especially in South and Southeast Asia, East Africa, the Hawaii Islands and the Caribbean. The mature fruit has a foul taste and odor (Wang et al., 2002).

Morinda citrifolia plant has been used in various combinations for herbal remedies. The fruit can be used for the treatment of oral sore, tooth decay, mouth ulcer, gingivitis, bacterial, viral and fungal infection, hemorrhoids, seizure, diabetes, hypertension and anti-inflammation (Pawlus et al., 2007).

Almost 200 phytochemicals were found from different parts of *M. citrifolia* (Singh, 2012). The chemical compositions and their concentrations depend on both the part of the plant and its country of origin. It has several advantages such as antimicrobial activity, antiseptic activity, antifungal activity, antioxidant and anti-inflammatory activity, anti-cancer activity and anti-arthritic activity. It also has anti-photo aging activity (Iloki Assanga et al., 2013). But the extract of *M. citrifolia* still does not have many reports for melasma study. Therefore, to study the efficacy of 5% *Morinda citrifolia* fruit extract cream as a treatment of melasma is the main aim of this study.

2. Objectives of the study

General Objective: To study the efficacy of 5% *Morinda citrifolia* fruit extract cream for the treatment of melasma.

Specific Objective

- Primary outcome: To compare the whitening effect of facial skin for the treatment of melasma between 5% *Morinda citrifolia* fruit extract cream and placebo cream.
- Secondary outcome:
    1. To observe the adverse effects of 5% *Morinda citrifolia* fruit extract cream in treating melasma.

To evaluate the participants' satisfaction between 5% *Morinda citrifolia* fruit extract cream and placebo cream base.

3. Materials and methods

16 volunteers were selected according to inclusion criteria after explaining the purpose of the research, process of the study, possible benefits and risks of the treatment. All volunteers participating in the study signed informed consent form. 5% *Morinda citrifolia* fruit extract cream and placebo cream were applied comparatively in split face design for 8 weeks, two times per day. Both *Morinda citrifolia* fruit extract cream and standard cream base had similar consistency, texture, color and smell. Sunscreens and mild soaps were also provided to volunteers. The researcher took a photograph of each patient using VISIA® before treatment, at 4th week and 8th week. Mexameter® MX18 measurement and MASI score were evaluated by the dermatologist at baseline, 4th and 8th weeks respectively.

Adverse effects and satisfactory score of the volunteers were observed and evaluated by three dermatologists and will be recorded throughout the study.

Sample Size Determination

The study of anti-tyrosinase property of topical 5 % *Morinda citrifolia* fruit extract on treatment of melasma has never established before. Thus, the researcher chose a similar article; a comparative study of the safety and efficacy of 75% mulberry (*Morus alba*) extract oil versus placebo as a topical treatment for melasma: a randomized double-blind placebo-controlled trial and have decided to choose the formula of one sample to show the statistically significant result on the purpose of the study (Alvin G, 2011). Mexameter readings for the mulberry group showed a significant drop from 355.56 ± 59.51 at baseline to 312.52 ± 57.03 at week 8 compared to the placebo group, whose Mexameter readings deteriorated from 368.24 ± 46.62 at baseline to 372.12 ± 44.47 at week 8.

Different change from the baseline of 75% mulberry = 355.56-312.52 = 43.04

Different change from the baseline of placebo = 368.24-372.12 = -3.88

From the formula, $\alpha = 0.05$ (two-tailed) $Z_{0.025} = 1.96$

$\beta = 0.10$ $Z_{0.10} = 1.28$

$n_1 = 25$ $n_2 = 25$

$\sigma_1 = 57.03$ $\sigma_2 = 44.47$

$$S_p^2 = (n_1 - 1)\, S_1^2 + (n_2 - 1)\, S_2^2 / n_1 + n_2 - 2$$

$$SD^2 \text{ pooled} = [(25 - 1)\,(57.03)^2 + (25 - 1)\,(44.47)^2] / (25 + 25 - 2)$$

$$= 2613$$

$\mu_1 = 43.04, \quad \mu_2 = -3.88$

$\mu_d = 43.04-(-3.88) = 46.92$

$$n = (Z_{\alpha/2} + Z\,\beta)^2\, \sigma_d^2 / \mu_d^2$$

$$= (1.96 + 1.28)^2\, 2613 / (46.92)^2$$

$$= 12.96 \text{ or } 13 \text{ subjects}$$

Note

n = sample size per group

σ = standard deviation

μ_d = mean difference

Estimated 20% loss to follow up visit, then n = 12.96 / (1-0.20) = 16 subjects were enrolled. Thus, researcher collected 16 volunteers who willingly wanted to participate in the study.

Inclusion criteria

- Patients with bilateral epidermal or mixed melasma.
- Female, age 30 to 65 years old with Fitzpatrick skin type III-VI.
- All female of reproductive age will agree to be under the condition of acceptable form of birth control during study.
- All patients with no melasma treatment or skin laser during the last two months except for sun block.
- All subjects are willing to be involved in treatment with one time follow-up per month for three consecutive months.
- Informed consent form for benefits, risks and possible adverse effects of the treatment and photos for the publication were willingly signed by participants in the study.

Exclusion criteria

- Pregnant women
- Women who under Breastfeeding
- Women who used hormones or any medicines which can interfere the melanogenesis such as oral contraceptives, spironolactone or phenytoin.
- Being treated with hydroquinone through the last 6 months
- Being treated with tretinoin through the last 3 weeks
- Medical illness such as coagulopathy, poorly controlled diabetic mellitus, photosensitivity and immunosuppressant.
- History of poor wound healing and abnormal scarring
- Alcohol or Drug
- Active inflammatory skin disease or open wound in the treatment area
- Malignant or premalignant lesions history in the treatment area
- Concurrent treatment with any other bleaching agent
- History of strong UV exposure in some career or leisure (confounder)

Allergy to chemical compounds Morinda citrifolia fruit extract cream, standard cream base, sunscreen (SPF 50+, PA++++) and mild soap.

Discontinuation criteria

- Subject receiving treatment for melasma other than 5% *Morinda citrifolia* fruit extract cream.
- Subject who got pregnant.
- Subject who developed serious side effects or allergy from the treatment, illness, dying or accident.
- Subject who wanted to leave the program with any reasons.
- Subject who was non-cooperated the protocol or lost follow up more than 3 visits.

Equipment

Mexameter ® MX18 is a device used to measure melanin (pigmentation) and redness (erythema). The measuring principle is based on a source of light with three specific wavelengths whose radiation is absorbed by the skin and diffusely reflected. A photo detector analyses the diffuse reflection from the skin.

VISIA ® Complexion Analysis System (Canfield, Fairfield, NJ) is a clinically applicable device used to measure a patient's dyschromia. The VISIA system generates a series of photographs using standard, ultraviolet and cross polarized lighting. It also analyzes the photographs to quantify the skin complaint and count the number of lesions, such a brown spot, freckles, dilated pores, vascular lesions, acne scars and rhytides.

Statistical analysis

Participants' eligibility in this research was determined by applying inclusion and exclusion criteria and their personal information was highly confidential in data analysis.

Participants' medical record data and outcomes from this study trial conducted in Mae Fah Luang University Dermatology Clinic, were analyzed by using SPSS 18 software and Microsoft Excel 2010.

Descriptive statistics are used to describe data in average mean and standard deviation if these data are continuous and with frequency and percentage if data are as counting number.

Compared base line mean melanin index of the face which was applied 5% *Morinda citrifolia* fruit extract cream and placebo cream with the treatment at week 4 and week 8 by using MX18. MASI score and mean melanin index scoring between 5% *Morinda citrifolia* fruit extract cream and placebo cream was analyzed through ANOVA test.

For doctor satisfaction by 3 dermatologists, data were described by using Fisher's exact test and find the p value between groups on 4^{th} week and 8^{th} week respectively.

Patient satisfactory score on both sides was analyzed at 8^{th} week by McNemar test and side effects were noted. Data were described by using Descriptive statistics.

The researcher did the following at significance levels of $p\text{-value}<0.05$

4. Results

General Characteristic of the Sample

According to the demographic data of the participants, mean age of the subject was 49.31±9.83 years, and there were 7 Housewife (43.7%), 2 Employee (12.5%), 2 Officer (12.5%), 1 Business owner (6.3%) and 4 others occupation (25.0%). There was no one had underlying disease, photosensitivity, take medicine regularly and food allergy. Furthermore, three subjects had history of following treatment before this study such as 2 subject who used cream and 1 laser. The ten subjects got exposed to sunlight, most of them were exposed to sunlight 30 minutes 5 subjects, more than 1 hour 3 subjects, 45 minutes and 1 hour 1 subject each. All subjects had Fitzpatrick skin type 4.

Melasma area and Severity Index (MASI)

Table 4.1 Statistical analysis of MASI score compared between 5% *Morinda citrifolia* fruit extract cream and placebo cream on Baseline, 4th and 8th week

	5% *Morinda citrifolia*	**Placebo**	**P-value[a]**
Baseline	7.09±1.50	7.26±1.79	0.580
Week 4	6.80±1.41	7.41±1.79	0.057
Week 8	6.26±1.31	7.60±1.69	0.001*
P-value[b]	<0.001*	0.118	

P-value determine by Paired t-test for between group (a) and Measure repeated ANOVA for within group (b)

* Statistically significant at the 0.05 level

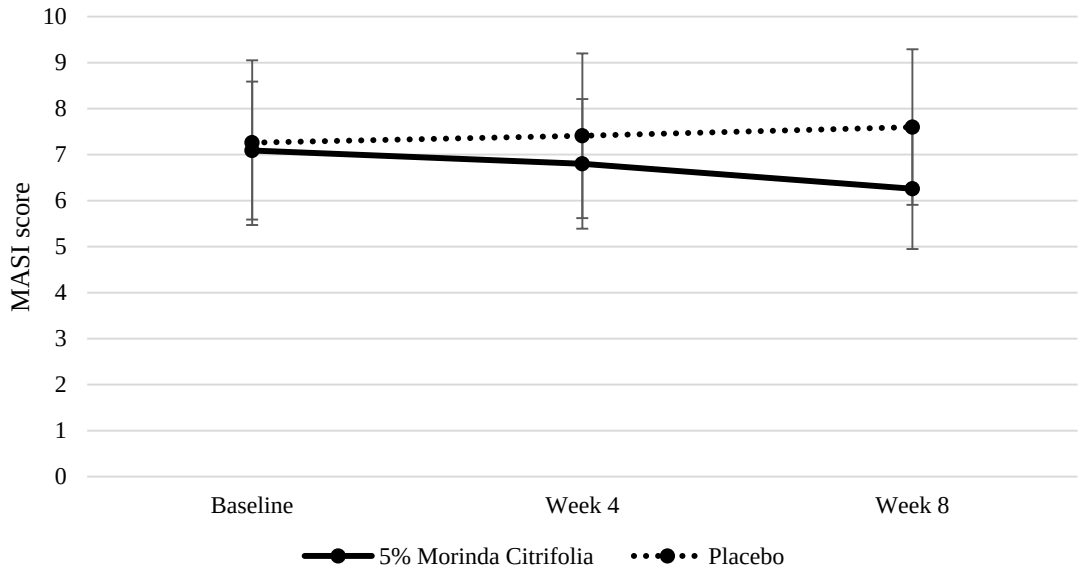

Figure 4.1 Line graph showing comparison of MASI score in each visit between 5% *Morinda citrifolia* fruit extract cream and Placebo cream

According to the statistical analysis results from table 4.1 and figure 4.1, mean of MASI score in 5% *Morinda citrifolia* fruit extract cream was at baseline 7.09±1.50, 4th week 6.80±1.41and 8th week 6.26±1.31. The mean of MASI score was significantly decreased at the level of 0.05 ($p<0.001$).

For placebo cream, the results were at baseline 7.26±1.79, 4th week 7.41±1.79 and 8th week 7.60±1.69. The mean of MASI score was changed, not statistically significant ($p=0.118$).

The comparison of MASI score between 5% *Morinda citrifolia* fruit extract cream and placebo cream; it is found that mean of MASI score of 5% *Morinda citrifolia* fruit extract cream was significantly lower than MASI score of placebo cream at 8th week ($p=0.001$).

Mexameter

Table 4.2 Statistical analysis of Mexameter compared between 5% *Morinda citrifolia* fruit extract cream and placebo cream on Baseline, 4th and 8th week

	5% *Morinda citrifolia*	**Placebo**	**P-value[a]**
Baseline	219.77±57.31	223.70±65.31	0.669
Week 4	196.33±53.59	225.41±65.38	0.001*
Week 8	181.32±48.88	228.14±67.06	<0.001*
P-value[b]	<0.001*	0.076	

P-value determine by Paired t-test for between group (a) and Measure repeated ANOVA for within group (b)

* Statistically significant at the 0.05 level

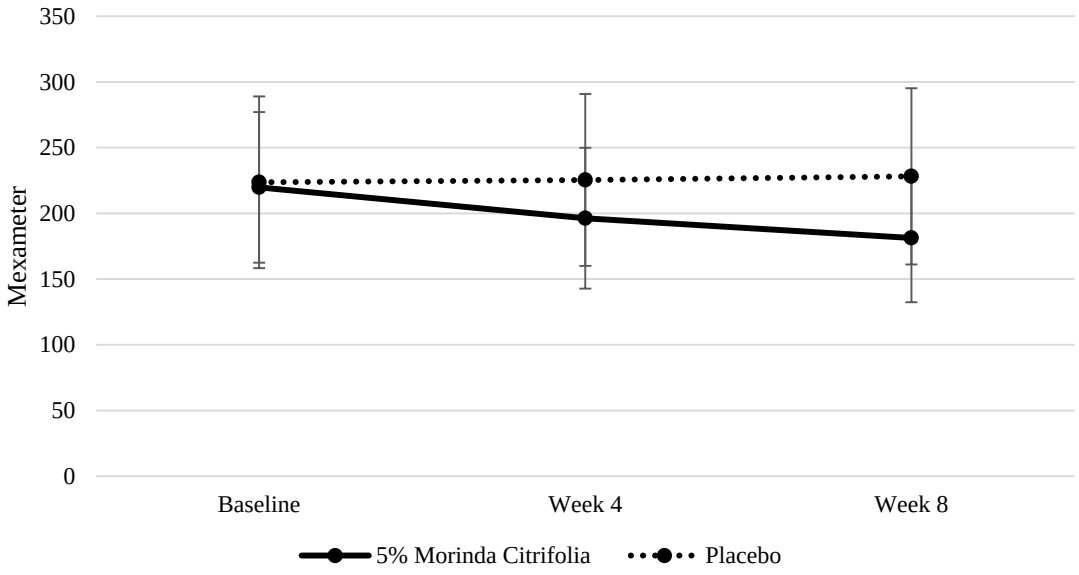

Figure 4.2 Line graph showing comparison of Mexameter score in each visit between 5% *Morinda citrifolia* fruit extract cream and Placebo cream

According to the statistical analysis results from table 4.2 and figure 4.2, mean of Mexameter score in 5% *Morinda citrifolia* fruit extract cream was at baseline 219.77±57.31, 4th week 196.33±53.59 and 8th week 181.32±48.88. The mean of Mexameter score was significantly decreased at the level of 0.05 ($p<0.001$).

For placebo cream, the results were at baseline 223.70±65.31, 4th week 225.41±65.38 and 8th week 228.14±67.06. The mean of Mexameter score was changed, not statistically significant ($p=0.076$).

The comparison of Mexameter score between 5% *Morinda citrifolia* fruit extract cream and placebo cream; it is found that mean of Mexameter score of 5% *Morinda citrifolia* fruit extract cream was significantly lower than Mexameter score of placebo cream at 4th and 8th week ($p=0.001$ $p<0.001$, respectively).

Patients' Satisfaction on 8th week

Table 4.3 Statistical analysis of Patients' Satisfaction on 8th week compared between 5% *Morinda citrifolia* fruit extract cream and Placebo cream

	5% *Morinda citrifolia*	**Placebo**	**P-value**
≤ 2 (Less than or equal to moderately satisfied)	8 (50.0%)	15 (93.7%)	0.016*
> 2 (Very/extremely satisfied)	8 (50.0%)	1 (6.3%)	

P-value determine by McNemar 's test

* Statistically significant at the 0.05 level

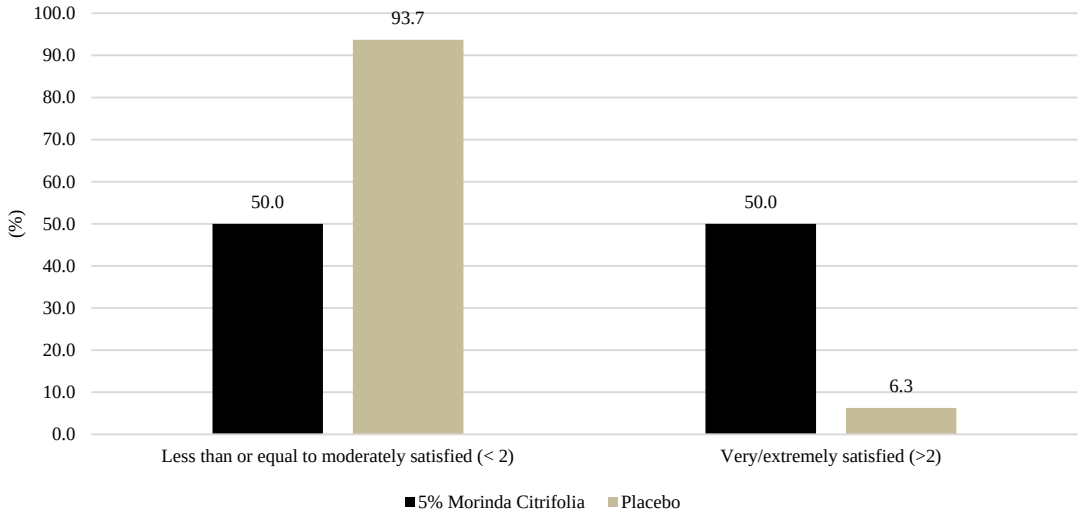

Figure 4.3 Bar chart revealing the percentage of patients' satisfaction score of 5% *Morinda citrifolia* fruit extract cream and placebo cream

According to the statistical analysis results from table 4.3 and figure 4.3 showed patients' satisfaction score on 8th week, the results showed that in 5% *Morinda citrifolia* fruit extract cream were very/extremely satisfied (>2 score) 50% and less than or equal to moderately satisfied (≤ 2 score) 50%. For placebo cream, most of the subject rated less than or equal to moderately satisfied (≤ 2 score) 93.7% and very/extremely satisfied (>2 score) 6.3%, respectively. The comparison of patients' satisfaction score between 5% *Morinda citrifolia* fruit extract cream and placebo cream showed that statistically significant difference (p=0.016).

Dermatologist's evaluation

Table 4.4 Statistically analysis of dermatologist evaluation score compared between *Morinda citrifolia* fruit extract cream and placebo cream on 4th and 8th week.

Improvement	Week 4		Week 8	
	5% Morinda citrifolia	**Placebo**	***5% Morinda citrifolia***	**Placebo**
100% =				
Excellent	-	-	-	-
75% = Good	-	-	-	-
50% = Moderate	5	-	9	-
25% = Fair	11	10	7	12
0 = No change	-	6	-	4
(-1) = Worse	-	-	-	-

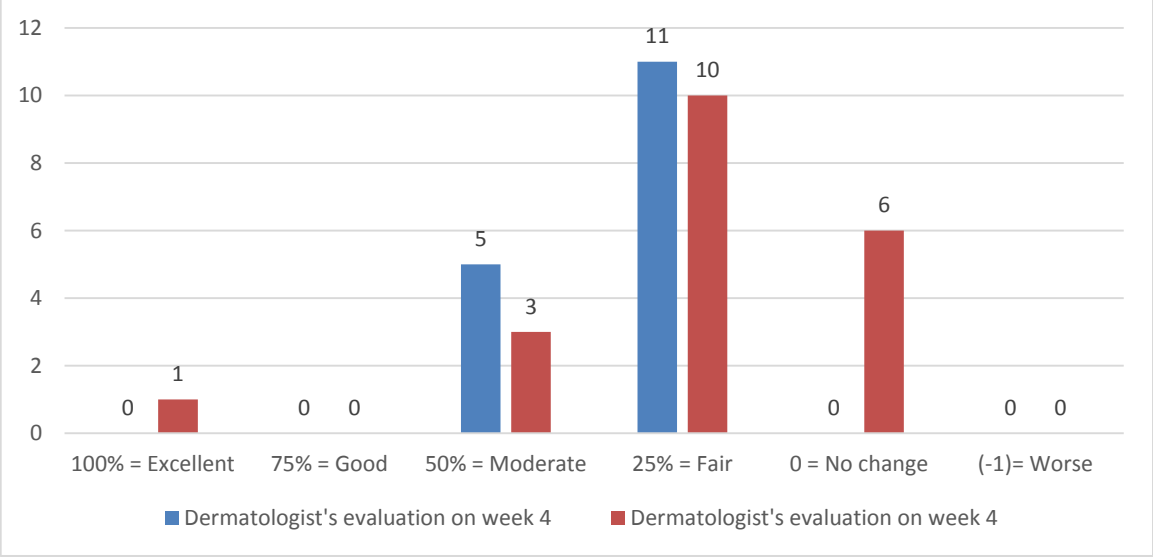

Figure 4.4 Column chart reveals the dermatologists' evaluation scoring of 5% *Morinda citrifolia* fruit extract cream and placebo cream on 4th week

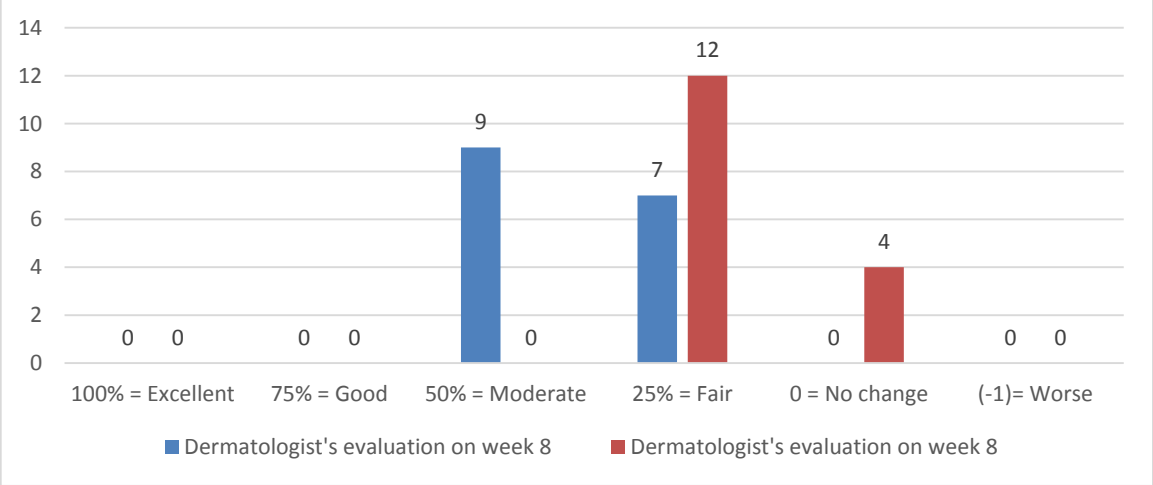

Figure 4.5 Column chart reveals the dermatologists' evaluation scoring of 5% *Morinda citrifolia* fruit extract cream and placebo cream on 8th week

As described in Table 4.4 and Figure 4.4 and 4.5, 5% of *Morinda citrifolia* fruit extract cream and placebo cream applied on 4th week were evaluated by dermatologists and more than half of the volunteers improved fairly on 5% *Morinda citrifolia* fruit extract cream side while nearly half of those showed fair improvement on placebo cream side. Five volunteers showed moderate improvement on the 5% *Morinda citrifolia* fruit extract cream side. As for placebo cream side, three volunteers improved moderately, ten of those improved fairly and 6 of those didn't change anything at all.

On 8th week of evaluation, the difference between two creams was seen clearly. For 5% *Morinda citrifolia* fruit extract cream side, nine volunteers started to show moderately improvement and seven of them showed fair improvement. Meanwhile on the placebo cream side, four volunteers were still the same with no changes and twelve of those showed fair improvement.

5. Discussion

Melasma is the most common facial hyperpigmentation which results in a cosmetic disfigurement with psychological impact causing important quality of life issues (Tzouveka, 2014). Since hyperpigmentation is mainly through the process called melanogenesis, we can reduce it by inhibiting the enzyme tyrosinase, the rate limiting step in the synthesis. Topical creams with plant active compounds that have anti-tyrosinase effect become consumer demand as they can reduce pigmentation. Therefore, in this study, we used 5% *Morinda citrifolia* fruit extract cream to evaluate whether it has anti-tyrosinase activity or not.

We can be seen the effectiveness of 5% *Morinda citrifolia* fruit extract cream starting from the 4th week to the end of the study in term of both MASI score and mean melanin index. The result from repeated ANOVA test was p value <0.001. Moreover, both dermatologist and volunteers were satisfied the result.

The other side of the face treated with placebo cream showed no significant improvement. The result from repeated ANOVA test was p value = 0.080. According to this result, it can be clearly seen that *Morinda citrifolia* fruit extract cream has better efficacy than placebo cream. Therefore, it can be concluded that 5% *Morinda citrifolia* fruit extract cream has anti-tyrosinase activity to a certain extent since there was significant improvement in melasma.

6. Conclusion

In conclusion, the study showed that 5% *Morinda citrifolia* fruit extract cream can reduce pigmentation over an 8-week of period. Therefore, 5% *Morinda citrifolia* fruit extract cream is effective and safe for the treatment of melasma. No serious side effects and complications were found during the study period although high concentration of *Morinda citrifolia* fruit extract cream was used. But since the study period is limited (only eight weeks), long term complications should be monitored by doing the research for a longer period of time.

Limitation

In this study, since the sample size was small and the duration of the study period was too short, there might be some difficulties in interpretation of the results and unable to predict long term complications. All volunteers are Fitzpatrick type IV so that we need to study further to know whether it is effective in darker skin types or not.

Suggestion

The data from this research can be used in the future to continue the study on melasma with different concentration of *Morinda citrifolia* extract cream. And it can be also used as a database for further research about skin whitening agent. The use of noni fruit extract cream can be advantages to correct other aesthetic conditions so it should be studied more (e.g., anti-aging serum, sunscreen).

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