COMPARATIVE STUDY OF EFFECTIVENESS BETWEEN 20% AZELAIC ACID WITH LOW-FLUENCE 1064-NM ND:YAG PICOSECOND LASER AND 20% AZELAIC ACID ALONE IN THE TREATMENT OF MELASMA IN THAI FEMALE PATIENTS, SPLIT-FACE, PROSPECTIVE STUDY

BY

NATTHIKA KLAISUNG

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Abstract

Melasma is one of the most concerned pigmented skin conditions especially in females. It can be influenced by UV radiation, occupation, gender, and drug use. This is a split-face clinical trial that assesses the effectiveness of picosecond laser in melasma treatment combined with topical azelaic acid compared with azelaic alone. The primary outcome of this study is the Hemi-MASI score, while the secondary outcome are demographic data, physician's global assessment, patient satisfaction score, and adverse events. This study recruited twenty Thai females aged between 18 to 65 years old diagnosed with bilateral symmetrical malar-type melasma. The patients were treated with low fluence 1064-nm Nd:YAG picosecond laser three sessions every two weeks combined with topical azelaic acid twice daily on the right side of the face, whereas the left side was treated with topical azelaic acid twice daily alone for 16 weeks.

The result demonstrated that the mean Hemi-MASI score between the two sides was not statistically significantly different ($p>0.05$). The mean Hemi-MASI scores of decreases were 3.52%, 9.38%, and 19.94% on the combination side, while there were 1.93%, 7.89%, and 16.73% at the 8th week, the 12th week, and the 16th week, respectively in the topical azelaic alone side. There were no serious side effects in this study from both picosecond laser and azelaic acid, and they could be relieved without treatment.

(Total 47 pages)

Keywords: Melasma, 1064-nm Nd:YAG Picosecond Laser, Azelaic Acid

Student's Signature…….. Thesis Advisor's Signature…….....

Table of Contents

Table of Contents (continued)

List of Tables

List of Figures

Abbreviations

Abbreviation	Meaning
n	Number of patients
%	Percent
nm	Nanometer
Nd:YAG	Neodymium-doped yttrium aluminum garnet
Hemi-MASI score	Hemi-Melasma Area and Severity Index
TRP	Tyrosinase-related proteins
MITF	Microphthalmia-associated transcription factor
NO	nitric oxide
cGMP	cyclic guanylate monophosphate
ps	picosecond
mm	millimeter
J/cm^2	Joules per square centimeter
Hz	Hertz
FTU	Fingertip units
UV	Ultraviolet
SD	Standard deviation

Chapter 1

Introduction

1.1 Background and Significance of the Problems

Melasma is one of the most concerning skin problems for Thai people. Mostly the lesion will be presented with bilateral symmetrical hyperpigmented patches with irregular border and found in women more than men and dark skin type. Melasma could be found in a normal population of 1-50% (Ogbechie-Godec & Elbuluk, 2017).

There are many risk factors for melasma, for example, melasma can be found in women more than in men, being exposed to ultraviolet radiation or sunlight, pregnancy for 50-70% (Qazi et al., 2017), using oral contraceptive pills and also from genetic factors (Wu et al., 2021; Lee, 2014).

In this era, the gold standard of melasma treatment are sunlight protection and using topical hydroquinone depending on the type of melasma which the mechanism of action is Tyrosinase inhibitor but it can cause ochronosis (hyperpigmented macules with caviar-like lesion) which is rarely cured and irritant contact dermatitis (Ogbechie-Godec & Elbuluk, 2017).

Topical azelaic acid is one of the depigment agents by inhibiting Tyrosinase, a non-phenolic compound from *Pityrosporum ovale* and can inhibit DNA synthesis and mitochondrial oxidoreduction in abnormal melanocytes but not affect the normal melanocytes (Küçük, 2018). Using topical azelaic acid is one of the treatments for melasma due to it can be used in pregnant women and only affect the abnormal melanocyte.

Picosecond laser is defined as the new generation of laser with a lessened pulse width which can cause pigment fragmentation. It generates a photoacoustic effect more than a photothermal effect. The benefit of the picosecond laser is that it could decrease the surrounding tissue destruction by a lower photothermal effect than the conventional laser, for example, the Q-Switched laser. It also causes post-inflammatory hyperpigmentation less than the conventional laser. The wavelength that is usually used for picosecond laser at present is 532 nm, 755 nm, and 1064 nm. However, the evidence or research about picosecond laser and pigmented disorder is quite limited (Trivedi, Yang & Cho, 2017).

1.2 Research Objectives

To compare the effectiveness between 20% azelaic acid with low-fluence 1064 nm Nd:YAG picosecond laser and 20% azelaic acid alone in the treatment of melasma in Thai female patients as a split-face prospective study.

1.3 Research Questions / Assumptions

1.3.1 The effectiveness of 20% azelaic acid with low-fluence 1064 nm Nd:YAG picosecond laser should be better than using 20% azelaic acid alone in the treatment of melasma in Thai female patients.

1.3.2 Hemi-MASI score in 20% azelaic acid combined with low-fluence 1064 nm Nd:YAG picosecond laser facial side should be less than 20% azelaic acid alone side at the end of the study.

1.3.3 Physician's global assessment should be improved in 20% azelaic acid combined with low-fluence 1064 nm Nd:YAG picosecond laser facial side more than 20% azelaic acid alone side at the end of the study.

1.3.4 Patient satisfaction score should be improved in 20% azelaic acid combined with low-fluence 1064 nm Nd:YAG picosecond laser facial side more than 20% azelaic acid alone side at the end of the study.

1.4 Research Framework

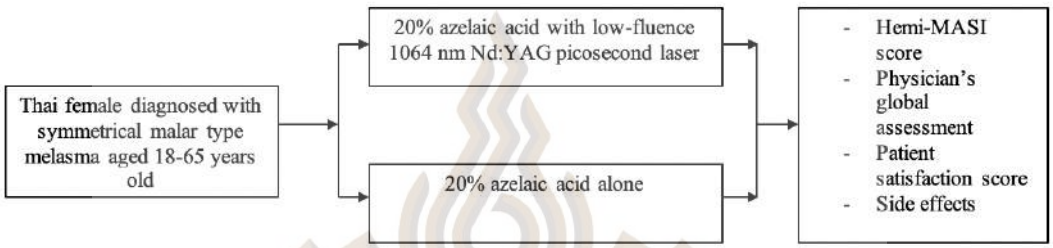

Figure 1.1 Research framework

1.5 Definition of Terms

Term 1 "Melasma" means dermatological condition presented with symmetrical irregular border hyperpigmentation macules or patches mostly on the face.

Term 2 "Azelaic acid" means 20% topical azelaic acid which has been used to treat many skin conditions, for example, acne or melasma. The mechanism of action is to inhibit DNA synthesis and mitochondrial oxidoreduction in abnormal melanocytes without affecting normal melanocytes.

Term 3 "Picosecond laser" in this study means low-fluence 1064 nm Nd:YAG picosecond laser which has a lower pulse duration than nanosecond laser. Picosecond laser will cause a photoacoustic effect more than a photothermal effect.

Term 4 "Hemi-MASI score" abbreviated from hemi-Melasma Area and Severity Index, calculated by using area of involvement (A), darkness (D), and

homogeneity of hyperpigmentation (H). Hemi-MASI = Forehead: 0.15 × A x (D+H) + Malar (each side): 0.3 × A x (D+H) + Chin: 0.05 × A x (D+H).

Term 5 "Physician's global assessment" means the overall clinical response of the disease to the treatment evaluated by physicians.

Term 6 "Patient satisfaction score" means the overall outcome of clinical response evaluated by the patients that the conditions are better or worse compared to the previous one.

Chapter 2

Literature Review

2.1 Melasma

2.1.1 General information and clinical presentation of melasma

Melasma is a skin condition presented with bilateral symmetrical irregular border with hyperpigmented macules or patches on the face (Kang et al., 2019). Mostly found in women with dark skin type. Melasma can be found in 1-50% of the normal population (Ogbechie-Godec & Elbuluk, 2017). Other areas melasma can occur are the cervical regions, arms and sternal region (Handel et al., 2014).

2.1.2 Classification of melasma

2.1.2.1 Clinical classification

1) Centrofacial type, which is the most common type, can be found on the forehead, nose and upper lip (Figure 2.1)

2) Malar type, which can be found on the cheeks and nose (Figure 2.2)

3) Mandibular type, which can be found at the mandibular ramus (Figure 2.3)

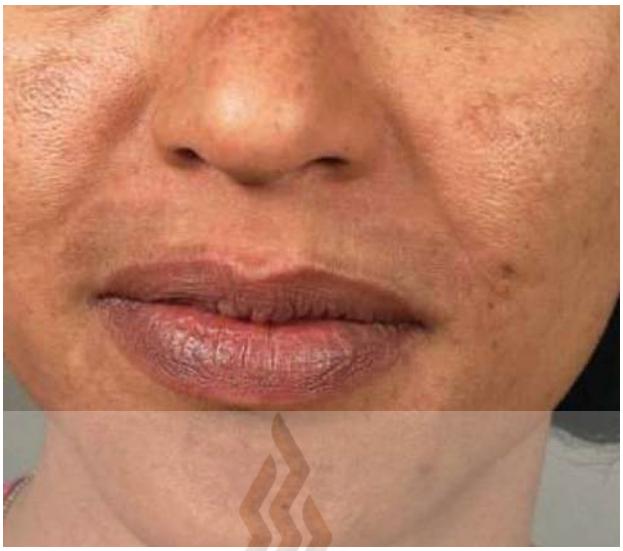

Figure 2.1 Centrofacial type melasma

Source: Bolognia, Schaffer & Cerroni, 2018

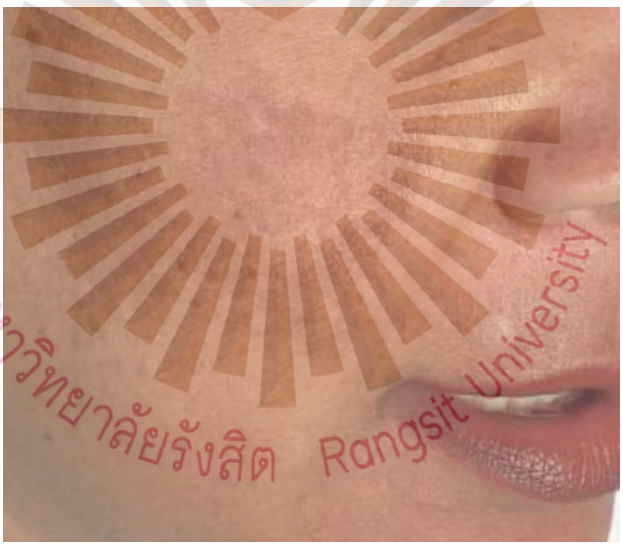

Figure 2.2 Malar type melasma

Source: Bolognia et al., 2018

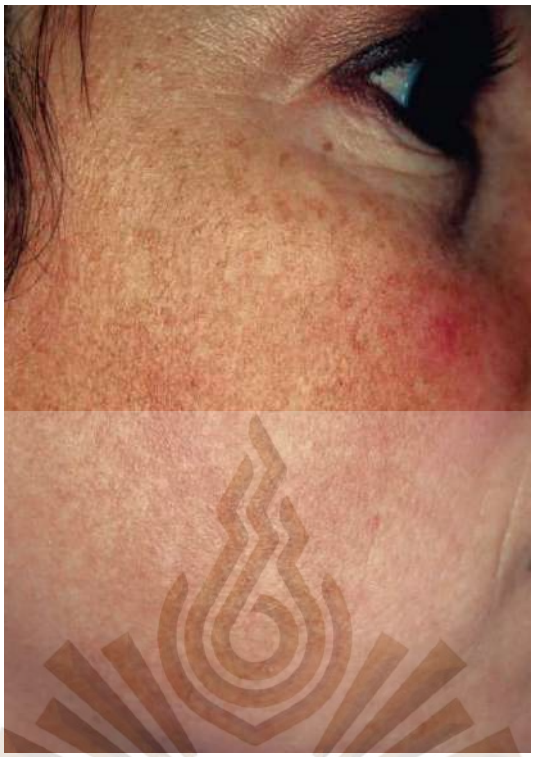

Figure 2.3 Mandibular type melasma

Source: Bolognia et al., 2018

2.1.2.2 Histological classified by using wood lamp enhancement

1) Epidermal type; all the lesions will enhance under the examination

2) Dermal type; all the lesions will not enhance under the examination

3) Mixed type; the lesion will enhance in some areas not all of the lesions

2.1.3 Pathogenesis of melasma

The pathogenesis of melasma is mainly from melanocytosis and melanogenesis (Arora, Garg, Sonthalia, Gokhale & Sarkar, 2014). The induction of nitric oxide synthase (iNOS) in keratinocytes is one of the main mechanisms in melanogenesis

(Passeron, 2013). Melasma has an enzyme that plays the main role in pathogenesis which is tyrosinase in melanogenesis together with the tyrosinase-related proteins (TRPs). Another crucial one is microphthalmia-associated transcription factor (MITF) in regulating the genes that are involved with melasma (Lee, 2015).

UV radiation is the most important factor that induces melasma. It will trigger melanogenesis on melanocytes directly and keratinocytes indirectly to deliver melanogenic factors. The direct effect of UV radiation is nitric oxide (NO) with cyclic guanylate monophosphate (cGMP) production which leads to tyrosinase and TRPs increasing as shown in Figure 2.4 (Lee, 2015). Tyrosinase plays an important role in the melanin synthesis pathway as shown in Figure 2.5 (Bolognia et al., 2018).

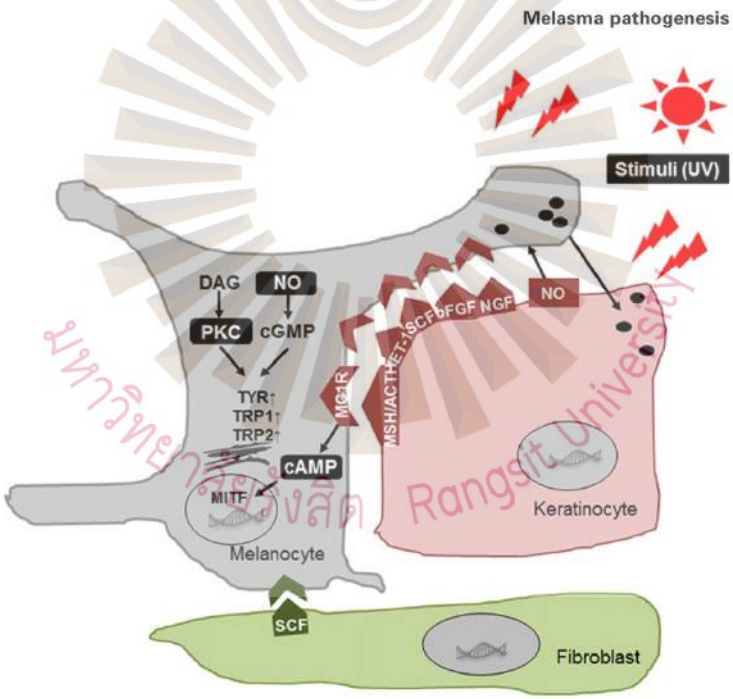

Figure 2.4 Melanogenesis pathway in melasma that involved nitric oxide, tyrosinase, and TRPs

Source: Lee, 2015

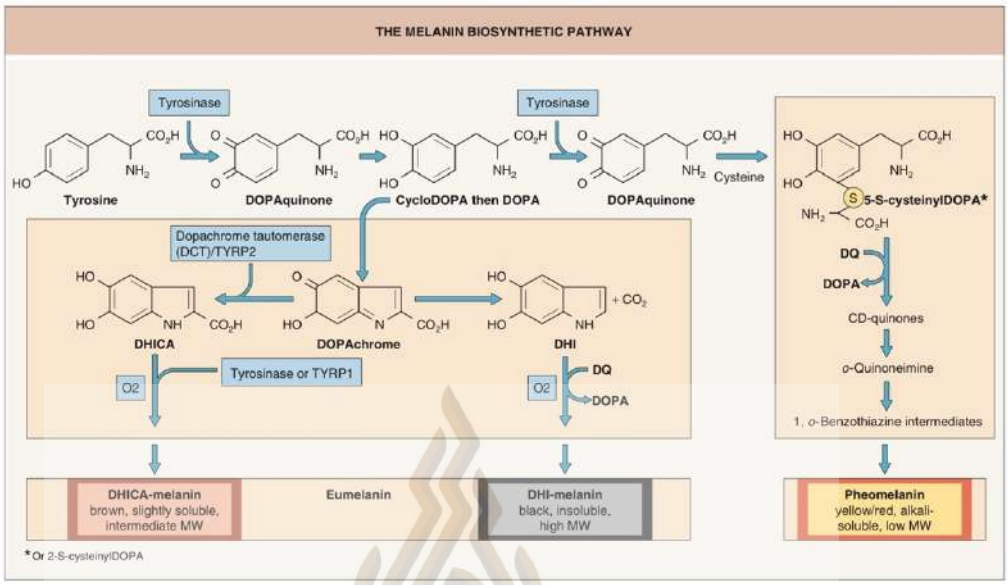

Figure 2.5 Melanin synthetic pathway including tyrosinase

Source: Bolognia et al., 2018

Another factor involved in melasma is a genetic factor. The population from Latin America and Asia tends to develop pigmentary disorders, for example, melasma more than the others (Lee, 2015).

Sex hormones are also included as a factor in developing melasma, especially estrogen and progesterone. The estrogen receptors and progesterone receptors will control the activity of estrogen and progesterone. Some who have been prescribed oral contraceptive pills which include progestin levonorgestrel reported melasma after taking the pills. Estrogen is the key factor leading to melanogenesis by triggering tyrosinase, TRP and MITF production as shown in Figure 2.6 (Lee, 2015).

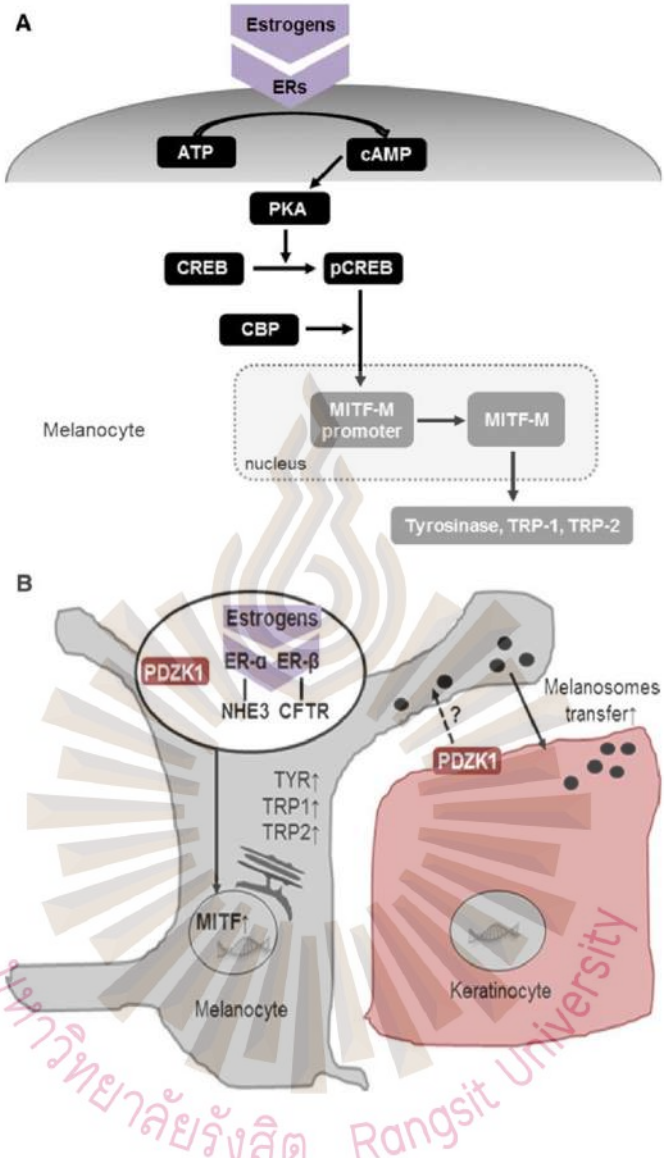

Figure 2.6 Estrogen-induced melanogenesis mechanism

Source: Lee, 2015

2.1.3 Main mechanisms for melasma treatment

2.1.3.1 Melanocyte inhibition by avoiding sunlight and other risk factors

2.1.3.2 Melanogenesis inhibition by using depigmenting agents

2.1.3.3 Chemical peeling procedure to export the melanin pigment out of the lesion

2.1.3.4 Melanin granules can be destroyed in lesions by using a laser (Küçük, 2018)

2.1.4 Treatment of melasma

2.1.4.1 Melanocyte inhibition by avoiding sunlight can be done by applying a broad-spectrum sunscreen with a sun protection factor (SPF) of at least 30. Others are wearing clothing with a long-sleeved shirt and hat (Küçük, 2018)

2.1.4.2 Using depigmenting agents to inhibit tyrosine to L-DOPA with L-Tyrosinase because L-DOPA is the rate-limiting step of melanogenesis (Küçük, 2018). These agents are divided into three groups.

1) phenolic compounds such as hydroquinone which is the current gold standard to treat melasma, kojic acid, etc.

2) non-phenolic compounds such as azelaic acid, retinoids, ascorbic acid, etc.

3) combination formulas such as Kligman's formula, triple-combination therapy, etc. (Küçük, 2018)

2.1.4.3 Using chemical peelings to remove melanin which is usually used in recalcitrant melasma patients. The response is various patients depending on melasma type, skin type, and location of melasma. It is prone to have a higher response in epidermal-type melasma and fair skin. Examples of chemical peeling agents are glycolic acid, salicylic acid, Trichloroacetic acid (TCA), tretinoin, and lactic acid (Küçük, 2018).

2.1.4.4 Prescribe systemic treatment that is claimed to have efficacy in melasma treatment is oral tranexamic acid (TA). Normally, it was used to treat menorrhagia and stop bleeding. Even though the mechanism is still not clear but there were some reports showing that oral tranexamic acid could treat melasma better than other forms of drug administration. The patient who took tranexamic acid might face

the side effects such as irregular menstruation, headache, nausea and back pain (Küçük, 2018).

2.1.5 Melasma severity assessment score

Publication about melasma scoring index in the past would use Melasma Area and Severity Index (MASI) which MASI = Forehead 0.3 x (D+H) x A + Right Malar 0.3 x (D+H) x A + Left Malar 0.3 x (D+H) x A + Chin 0.1 x (D+H) x A. A is from area of involvement that 0=no involvement, 1=1%–9%, 2=10%–29%, 3=30%–49%, 4=50%–69%, 5=70%–89%, 6=90%–100%. D is from darkness that 0=normal skin color without evidence of hyperpigmentation, 1=barely visible hyperpigmentation, 2= mild hyperpigmentation, 3=moderate hyperpigmentation, 4=severe hyperpigmentation and H is from homogeneity that 0=minimal, 1=slight, 2=mild, 3=marked, 4=severe (Pandya et al., 2006, 21-28; Hofny et al., 2017, 55-78).

Modified Melasma Area and Severity Index (mMASI) can be calculated from Forehead 0.3 x D x A + Right Malar 0.3 x D x A + Left Malar 0.3 x D x A + Chin 0.1 x D x A (Pandya et al., 2011).

Hemi-Melasma Area and Severity Index (hemi-MASI) was used when it was involved in a split-face controlled trial study starting in China. It is calculated by hemi-MASI = Forehead 0.15 x (D+H) x A + Each Malar 0.3 x (D+H) x A + Chin 0.05 x (D+H) x A. A is from area of involvement 0=0%, 1=1%–9%, 2=10%–29%, 3=30%–49%, 4=50%–69%, 5=70%–89%, 6=90%–100%, D is from darkness 0=absent, 1=slight hyperpigmentation, 2=mild hyperpigmentation, 3=marked hyperpigmentation, 4=severe hyperpigmentation and H is from homogeneity 0=minimal, 1=slight, 2=mild, 3=marked, 4=severe (Wang et al., 2014, 92-98; Hofny et al., 2017, 55-78).

2.2 Azelaic acid

2.2.1 General information of azelaic acid

Azelaic acid is extracted from Pityrosporum ovale which also can be found in cereals, rye, barley and wheat (*Azelaic Acid*, 2022). It is one of the depigmenting agents to inhibit tyrosinase. It is a non-phenolic dicarboxylic compound that only attacks abnormal melanocytes by anti-inflammatory, anti-bacterial and anti-oxidant effects. Depigment lesion is less than other drugs because it does not attack normal melanocytes (Küçük, 2018). Common side effects that can be found when applying azelaic acid are irritant contact dermatitis, dryness and erythema which can be improved within 2-4 weeks. It also can be prescribed in pregnant women due to pregnancy category B (Bolognia et al., 2018). The molecular formula of azelaic acid is $C_9H_{16}O_4$ as shown in Figure 2.7 (*Azelaic Acid*, 2022).

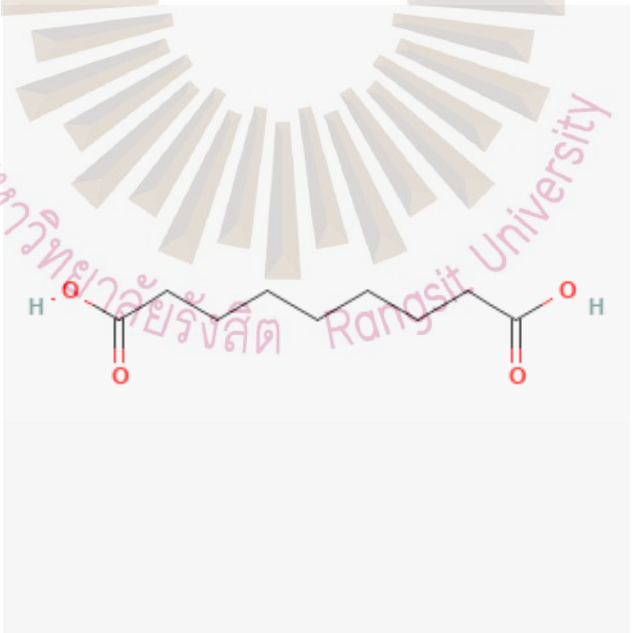

Figure 2.7 Azelaic acid chemical structure

Source: National Center for Biotechnology Information, 2022

2.2.2 Previous research about azelaic acid for treating melasma

Farshi compared the effectiveness of 20% azelaic acid with 4% hydroquinone cream by dividing subjects into two groups (fourteen persons for the azelaic acid group and fifteen persons for the hydroquinone cream group) in the 2-month duration. This study found that Melasma Area and Severity Index (MASI score) in the azelaic acid group was less than in the hydroquinone group (3.8±2.8 in the azelaic group whereas 6.2±3.6 in the hydroquinone group) statistical significantly at 95% CI = 0.03-4.9 (Farshi, 2011).

There was research comparing the effectiveness of treating melasma in Indian patients by dividing patients into three groups with twenty patients in each group. The study period was 3 months. The first group got the low-fluence 1064-nm Q-switched Nd:YAG laser. The second group got only 20% azelaic acid while the last group got both 20% azelaic acid combined with the low-fluence 1064-nm Q-switched Nd:YAG laser. The result found that these groups can reduce the Melasma Area and Severity Index (MASI score) statistically significant ($p<0.001$) from the baseline to 10.11±4.28, 9.68±3.37 and 4.94±1.67, respectively at 12 weeks (from the baseline 21.11±6.91, 15.90±5.49 and 18.73±7.5, respectively without statistically significant before treatment). A statistically significant reduction in MASI score was observed between the last group and the first group together with the last group and the second group ($p<0.05$), nonetheless, there was no statistically significant MASI score between the first and the second group ($p>0.05$) (Bansal, Naik, Kar & Chauhan, 2012).

2.3 Previous research about other lasers for melasma treatment

There was research from Pakistan about low-fluence Q-switched Nd:YAG 1064 nm for thirty patients with facial melasma. They received the laser for 4 sessions with a 2-week interval with 6 mm spot size. The result showed that the Melasma Area and Severity Index (MASI score) decreased from 27.47±6.093 to 25.92±4.547 to 19.63±3.42 and 14.28±2.54 at 2, 4 and 6 weeks after the baseline, respectively (Kamal & Iftikhar, 2017).

Another split-face research from Thailand about low-fluence Q-switched Nd:YAG 1064 nm in twenty-two Thai patients with facial melasma. They were treated by the laser for 5 sessions with a 1-week interval combined with 2% hydroquinone on one side of the face and 2% hydroquinone on the other side of the face. They reported that the modified Melasma Area and Severity Index (mMASI score) was reduced. The score in laser combined with hydroquinone side was reduced from 22.3±1.8 to 20.6±1.6 at the third week after baseline and to 5.7±0.8 when the end of the study with statistically significant ($p<0.001$) while the side that received hydroquinone alone could reduce the mMASI score from 21.9±1.8 to 20.4±1.6 (5.6% reduction with $p=0.003$) after 4 weeks and to 16.6±1.4 or 24% reduction after 7 weeks (Wattanakrai et al., 2010).

There was an association between vessels and melanocytes that induce hyperpigmentation in melasma as a result of the functional vascular endothelial growth factor (VEGF) receptor. There was a research that had been noted that there was an increased expression of VEGF in altered vasculature of melasma. The gold standard for treating vessels in the lesion is Pulsed dye laser (PDL) (Kong, Suh & Choi, 2018).

The split-face trial in South Korea using Pulsed dye laser (PDL) with low-fluence Q-switched Nd:YAG 1064 nm on one side of the face compared with low-fluence Q-switched Nd:YAG 1064 nm alone on the other side was conducted in seventeen Korean women patients. The low-fluence Q-switched Nd:YAG 1064 nm was done for 9 sessions with a 1-week interval followed by Pulsed dye laser (PDL) which was done for 3 sessions immediately for the combined side at baseline, 4 weeks and 8 weeks. The result found that hemi-MASI (hemi-Melasma Area and Severity Index) in the combined side decreased statistically significantly (6.53±2.65, 5.19±2.62 and 5.07±2.58 at baseline, 9 weeks and 16 weeks, respectively) while the side that received low-fluence Q-switched Nd:YAG alone, hemi-MASI was decreased from 6.23±2.81, 5.30±2.63 to 5.33±2.584 at baseline, 9 weeks and 16 weeks respectively. However, when compared between both sides of the face, there was no statistically significant ($p=0.231$ and 0.114 at 9 weeks and 16 weeks, respectively) (Kong et al., 2018).

2.4 Picosecond laser

2.4.1 General information of picosecond laser

Picosecond laser is the new generation of laser used in many skin conditions such as tattoo removal, rejuvenation, scar and melasma (Wu et al., 2021). Picosecond laser also has a short pulse duration compared to nanosecond laser which could reduce the rate of adverse events, for example, post-inflammatory hyperpigmentation or abnormal pigmentation and collateral damage to surrounding cutaneous tissue (Kim, Jung & Park, 2021).

Picosecond laser has a pulse duration that is shorter than 1 nanosecond. The mechanism of picosecond laser in cutaneous conditions treatment are thermal lock-in and stress lock-in theory. Thermal lock-in means the particles are heated within a short period of time leading to temperature rising and vaporization (Figure 2.8). Stress lock-in indicates that mechanical stress will occur in the target particles within a short period of time rise in pressure and particle fragmentation (Figure 2.9) (Kasai, 2017).

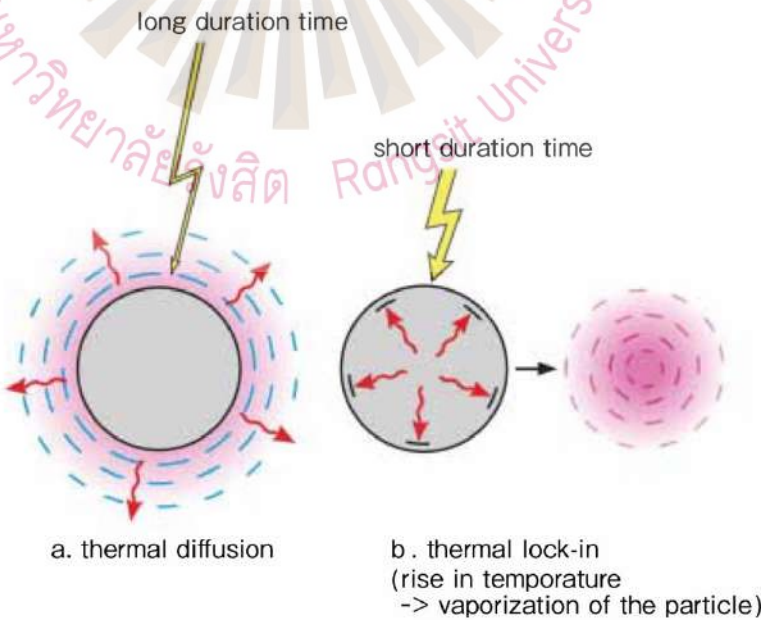

Figure 2.8 thermal lock-in phenomenon

Source: Kasai, 2017

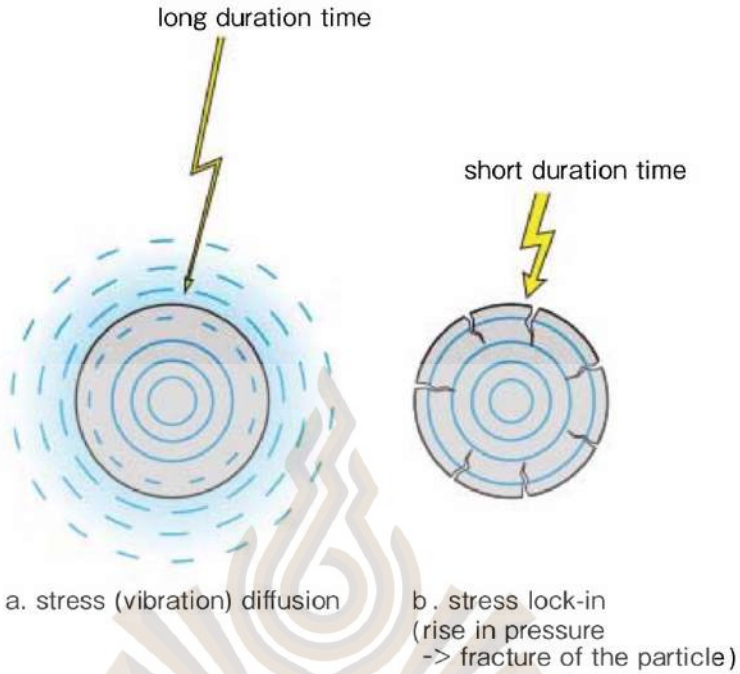

Figure 2.9 stress lock-in phenomenon

Source: Kasai, 2017

2.4.2 Previous research about picosecond laser for treating melasma

There was a split-face controlled trial studied in thirty Thai female patients comparing 1064-nm picosecond laser with 4% hydroquinone on one side of the face and 4% hydroquinone on the other side of the face. At baseline, mMASI score in the combined group was 9.46±3.4 whereas the hydroquinone group was 9.48±3.4. The result found that mMASI score at 12 weeks after baseline declined in the combined group more than another group statistically significantly (mMASI in the combined group was 3.52±1.4 while the hydroquinone group was 4.18±2.0 with $p = 0.035$). They concluded that the 1064-nm picosecond laser group with 4% hydroquinone had higher effectiveness for melasma treatment (Chalermchai & Rummaneethorn, 2018).

In South Korea, there was a case report about the efficacy of picosecond in pigmented cutaneous disorders treatment. 1 of 4 cases was diagnosed as melasma. The 38-year-old woman presented with bilateral irregular border light brown

patches on her cheeks. She got a 1064-nm picosecond laser without topical anesthesia, topical prophylactic corticosteroid and antibiotics. The spot size was 10 mm, fluence 0.3-0.4 J/cm^2, pulse rate 10 Hz. She got the laser for 12 sessions with a 2-week interval. The lesion seems faded and there are no serious side effects (Kim et al., 2021).

There was a retrospective study for pico-toning low fluence 1064-nm Nd:YAG laser in twenty-three South Korean patients from 2017 to 2020 found that after they got the laser with the parameter of 7-10 mm spot size, fluence 0.5-0.8 J/cm^2, the Modified Melasma Area and Severity Index (mMASI score) decreased from 5.1$\pm$1.4 to 2.6$\pm$0.4 at baseline and 8 weeks after finished the treatment, respectively with statistically significant ($p<0.05$). The adverse events that were found were 1 patient with erythema and 1 patient with edema (Kim, Nam, Shin and Park, 2020)

In Hongkong, there was a publication stated that twenty melasma patients who got non-ablative 1064-nm picosecond laser for 9 sessions with 4-6-week interval found that mMASI score declined from 10.8 to 2.7 and 3.6 at 6 and 12 weeks compared to the baseline ($p<0.01$) (Wong, Chan, Shek, Yeung & Chan, 2021).

In Vietnam, there was research conducted in twenty female melasma patients after receiving 1064-nm Nd:YAG picosecond laser with 8-mm spot size, fluence 0.6-0.8 J/cm^2 for at least 8 sessions followed by 3 sessions of dual toning of 1064-nm Nd:YAG picosecond laser together with micropulsed mode Nd:YAG 1064 laser with 15-mm spot size, 0.35 ms, 2.6 J/cm^2, repetition rate of 10 Hz. This concluded that MASI score reduced from 16.24$\pm$4.88 to 15.12$\pm$4.69 (7.44$\pm$4.41% reduction) after completed 3 sessions of dual toning and reduced to 9.7$\pm$3.86 (35.15$\pm$13.51% reduction) after completed 8 sessions of dual toning and 40.17$\pm$12.14% reduction from baseline (Hai, 2021).

In Taiwan, there was a study comparing the efficacy of melasma treatment between picosecond alexandrite laser with diffractive lens array and topical triple combination cream (fluocinolone acetonide 0.01%, 4% hydroquinone and 0.05% tretinoin). Twenty-nine female patients were divided into three groups. The first group

(n=9) got picosecond laser 3 sessions with a 4-week interval. The second group (n=11) got picosecond laser 5 sessions with a 4-week interval. The last group got topical triple combination cream for 8 weeks and tapered until the end of this study. The result showed that MASI score improved statistically significantly in all groups at 12 and 20 weeks after the baseline with 53%, 38%, and 50% improvement at 20 weeks in the first, second and last group, respectively (Wang, Li, Zang, Li & Sophie, 2020).

Chapter 3

Research Methodology

This research is a split-face, non-randomized clinical trial, prospective study to compare the effectiveness between 20% azelaic acid with low-fluence 1064-nm Nd:YAG picosecond laser and 20% azelaic alone for melasma treatment in Thai female patients.

3.1 Population and Samples

3.1.1 Samples

The samples of this study will include Thai female patients diagnosed with bilateral symmetrical melasma at the face aged 18-65 years old at the Institute of Dermatology, Bangkok, Thailand.

The sample size was calculated from two dependent means formula

$$n = \frac{(z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2 \sigma^2}{\Delta^2} \quad (3\text{-}1)$$

n = sample size with $\alpha = 0.05$, $\beta = 0.20$

Z at $1-\alpha/2$ when $\alpha = 0.05 = 1.959964$

Z at $1-\beta$ when $\beta = 0.20 = 0.841621$

Δ = difference of standard deviation between group A and B which the maximum of the difference was 21.11-15.9 = 5.21

σ = standard deviation of Melasma Area and Severity Index which σ = 6.91 from Bansal C, et al. A Comparison of Low-Fluence 1064-nm Q-Switched Nd:

YAG Laser with Topical 20% Azelaic Acid Cream and their Combination in Melasma in Indian Patients. J Cutan Aesthet Surg. 2012 Oct;5(4):266–72.]

$$n = \frac{(1.96+0.84)^2\,(6.91)^2}{(5.21)^2} = 14$$

Because some subjects may drop out of the research, the sample sizes were increased based on a dropout rate of 30%.

$$n^* = \frac{n}{(1-R)},\ n^* = \frac{14}{(1-0.3)}$$

$$n = 20$$

In conclusion, the sample size would be twenty patients.

3.1.2 Inclusion criteria

1) Thai female patients
2) Aged 18-65 years old
3) Diagnosed with bilateral symmetrical malar type melasma at the face
4) Can be able to attend and willing to be a subject in this study including being able to give a consent

3.1.3 Exclusion criteria

1) Taking oral contraceptive pills or receiving hormone replacement
2) In the period of pregnancy or lactation
3) Have underlying disease of autoimmune diseases such as SLE
4) Have underlying disease of thyroid diseases
5) Allergy to azelaic acid or preservatives in topical melasma treatment
6) Have a laser treatment on the face within 6 months before the study

7) Using topical melasma treatments such as kojic acid, hydroquinone, alpha arbutin and whitening agents within 4 weeks before the study

8) Treated melasma by chemical peeling agents within 3 months before the study

9) Using tranexamic acid or vitamin C within 3 months before the study

10) Taking or applying retinoid within 12 months before the study

11) Having an active asthma

12) Having a history of using antiepileptic drugs

13) Having skin infections or any other skin disease, for example, allergic dermatitis, cellulitis, erysipelas, herpes simplex and herpes zoster infection on the face

3.2 Research Instruments

The instruments consist of case record form (CRF), low fluence 1064-nm Nd:YAG picosecond laser (Picoway®, Candela), VISIA® skin analysis equipment, 20% azelaic acid cream 30 g, Skin intelligence soap, Skin intelligence SPF 30 sunscreen 30 g and 0.05% betamethasone valerate 15 g

3.2.1 Case record form

1) case record form at baseline for patients' background such as age, underlying disease, allergy history, history of melasma treatment or any drug uses and also Fitzpatrick skin type.

2) case record form to record hemi-MASI evaluated by three dermatologists at baseline, 8 weeks, 12 weeks and 16 weeks.

3) case record form to record the physician's global assessment evaluated by three dermatologists at 8 weeks, 12 weeks and 16 weeks.

4) case record form to record patient satisfaction scores at 8 weeks, 12 weeks and 16 weeks.

5) case record form after receiving picosecond laser treatment consisted of the parameter being used at baseline, 2 weeks and 4 weeks.

6) case record form after receiving picosecond laser treatment if there are any side effects at baseline, 2 weeks, 4 weeks, 8 weeks, 12 weeks and 16 weeks.

3.2.2 Low fluence 1064-nm Nd:YAG picosecond laser (Picoway®, Candela)

The parameter of laser for this research is pulse width 450 ps, spot size 8-10 mm, fluence 0.4-0.8 J/cm^2, repetition rate 5 Hz

3.2.3 VISIA® skin analysis equipment (Figure 3.1)

Used to take a photograph of patients at baseline, 8 weeks, 12 weeks and 16 weeks to compare the clinical of melasma after treatment by laser and azelaic acid.

Figure 3.1 VISIA® skin analysis equipment

Source: Canfield Scientific, 2022

3.2.4 20% Azelaic acid cream 30 g

Patients have to apply 20% azelaic acid cream on the area of melasma on both sides of the face twice daily until the end of the study except on the day that they got the laser treatment.

3.2.5 Skin Intelligence soap

Patients' faces will be cleaned with skin intelligence soap before the laser treatment.

3.2.6 Skin Intelligence SPF 30 sunscreen 30 g

Patients have to apply Skin intelligence SPF 30 sunscreen on the whole face for a week before the study and every day once daily until the end of the study along with avoiding the sunlight.

3.2.7 0.05% betamethasone valerate 15 g

0.05% betamethasone valerate is prepared if any side effects occur in any patients such as erythema or burning sensation.

3.3 Data Collection

3.3.1 Announcement and enrollment process of this research

This study will be announced by posters at the Institute of Dermatology, Bangkok, Thailand and electronic posters on social media platforms explaining the inclusion criteria, the objective of the study, the number of subjects and the duration of the research.

3.3.2 The informed consent process

3.3.2.1 Enroll the twenty Thai female patients that fulfill the inclusion criteria

3.3.2.2 Inform consent about the general information about melasma, the research procedure, the risk and benefit of the intervention, and the adverse events that could happen in this study including giving the patient information sheet to the subjects. The informed consent form will be signed by the subjects who are willing to participate in this study.

3.3.3 History taking and physical examination process

3.3.3.1 Subjects will have diagnosis confirmation with melasma by physical examination.

3.3.3.2 History taking by case record form including patients' background data, for example, age, underlying disease, allergy history, history of melasma treatment, pregnancy or lactation, any drug uses especially anticonvulsants drug, any current skin infections, Fitzpatrick skin type (Figure 3.2) and baseline hemi-MASI score. The subjects also have to take a photograph with VISIA® skin analysis equipment to compare before and after the intervention.

Fitzpatrick skin type		
Skin type	**Skin features**	**Tanning ability**
I	Pale white skin, blue/ green eyes, blond/red hair	Always burns, does not tan
II	Fair skin, blue eyes	Burns easily, tans poorly
III	Darker white skin	Tans after initial burn
IV	Light brown skin	Burns minimally, tans easily
V	Brown skin	Rarely burns, tans darkly easily
VI	Dark brown or black skin	Never burns, always tans darkly

Figure 3.2 Fitzpatrick skin type

Source: Ullah & Vishrolia, 2021

3.3.4 Intervention process

3.3.4.1 Preparing patients' faces by avoiding sunlight 2 weeks before the study and applying Skin Intelligence SPF 30 sunscreen for 2 fingertip unit (2 FTU) on the whole face once daily a week before the study and throughout the study period of 16 weeks.

3.3.4.2 For the right side of the face, all subjects will be treated by low fluence 1064-nm Nd:YAG picosecond laser (Picoway®, Candela) with the laser parameter pulse width 450 ps, spot size 10 mm, fluence 0.4-0.8 J/cm^2, repetition rate 8 Hz. The interval is 2 weeks and 3 sessions on the right side of the face. Subjects' faces will be cleaned with Skin Intelligence soap before laser. The endpoint of the laser is mild erythema.

The patients have to apply 20% azelaic acid cream twice daily to the melasma on the right side of the face the day they do not get treated by the laser. The amount of the azelaic cream should not exceed 0.5 FTU/side/times depending on the size of melasma throughout the study period.

3.3.4.3 For the left side of the face, patients have to apply 20% azelaic acid cream twice daily to the melasma on the left side of the face the day they do not get treated by the laser. The amount of the azelaic cream should not exceed 0.5 FTU/side/times depending on the size of melasma throughout the study period.

3.3.5 Follow-up process

The follow-up process will be done at 8 weeks, 12 weeks and 16 weeks after the baseline.

3.3.5.1 Hemi-MASI and physician's global assessment will be evaluated by three dermatologists who are not involved in this study. Hemi-MASI and

physician's global assessment will be analyzed by intraclass correlation coefficient (ICC) to determine the inter-rater reliability. ICC will be accepted at 0.7 and above.

The mean hemi-MASI score will be calculated at baseline, 4 weeks, 8 weeks and 12 weeks after laser completion (at 8 weeks, 12 weeks and 16 weeks after the baseline). The mean hemi-MASI score will be compared between two sides of the face before and after the treatment at 8 weeks, 12 weeks and 16 weeks after the baseline.

Furthermore, the mean physician's global assessment will also be calculated from a 5-point Linkert scale (5 = strongly improved, 4 = moderate to strongly improved, 3 = moderately improved, 2 = slightly improved and 1 = not improved or worsen) and the primary data will be described as descriptive data at 4 weeks, 8 weeks and 12 weeks after laser completion (at 8 weeks, 12 weeks and 16 weeks after the baseline) from the photograph of patients taken by VISIA® skin analysis equipment.

Patient satisfaction scores will be graded by the patients at 4 weeks, 8 weeks and 12 weeks after laser completion (at 8 weeks, 12 weeks and 16 weeks after the baseline). Patients will answer with a 5-point Linkert scale (5 = strongly improved, 4 = moderate to strongly improved, 3 = moderately improved, 2 = slightly improved and 1 = not improved or worsen).

3.3.5.2 Sides effects that could occur from the laser will be asked from the patients such as post-inflammatory hyperpigmentation, post-inflammatory hypopigmentation, swelling, blistering, erythema and burning sensation along with side effects that could be caused by azelaic acid such as burning sensation, pruritus, erythema and dryness at the day they got three sessions of picosecond laser and at 4 weeks, 8 weeks and 12 weeks after laser completion (at 8 weeks, 12 weeks and 16 weeks after the baseline).

Table 3.1 Process of the research

Assessment and procedure	Week 0 (visit 1)	Week 2 (visit 2)	Week 4 (visit 3)	Week 8 (visit 4)	Week 12 (visit 5)	Week 16 (visit 6)
Physical examination	✓					
History taking and answer case record form	✓					
Photograph by VISIA®	✓			✓	✓	✓
Hemi-MASI	✓			✓	✓	✓
Picosecond at melasma on right side of face	✓	✓	✓			
Physician's global assessment				✓	✓	✓
Patient satisfaction scores				✓	✓	✓
Side effects assessment	✓	✓	✓	✓	✓	✓

3.4 Data Analysis

The data will be analyzed and reported by a statistic program such as SPSS or Stata.

3.4.1 General information and side effects will be reported as descriptive data: frequency, percentage, mean and standard deviation.

3.4.2 Hemi-MASI and physician's global assessment will be evaluated by three dermatologists who are not involved in this study. Hemi-MASI and physician's global assessment will be analyzed by intraclass correlation coefficient (ICC) to determine the inter-rater reliability. ICC will be accepted at 0.7 and above.

The mean hemi-MASI score will be calculated at baseline, 4 weeks, 8 weeks and 12 weeks after laser completion (at 8 weeks, 12 weeks and 16 weeks after the baseline). The mean hemi-MASI score will be compared between two sides of the face before and after the treatment at 8 weeks, 12 weeks and 16 weeks after the baseline. The hemi-MASI change will be analyzed by using a multilevel model.

3.4.3 Physician's global assessment and patient satisfaction score will be analyzed and reported in descriptive data as percentage and frequency. Moreover, the physician's global assessment will be calculated to find the mean of this data and reported as descriptive data.

Basically, the p-value < 0.05 will be accepted as statistically significant.

Chapter 4

Research Results

4.1 Demographic data

Demographic data in this study include age, underlying disease, and Fitzpatrick skin type.

Table 4.1 Demographic data including age, underlying disease, and Fitzpatrick skin type (n=20)

Demographic data	Results
Age, mean (standard deviation; SD), years	48 (8)
- range, years	31-60
Underlying disease	
- allergic rhinitis, n (%)	3 (15%)
- hypertension, n (%)	3 (15%)
- dyslipidemia, n (%)	1 (5%)
- gastritis, n (%)	1 (5%)
- thalassemia trait, n (%)	2 (10%)
- none, n (%)	13 (65%)
Fitzpatrick skin type	
- type III, n (%)	9 (45%)
- type IV, n (%)	11(55%)

4.2 Hemi-MASI score

The mean Hemi-MASI score is calculated at baseline, 4 weeks, 8 weeks, and 12 weeks after laser completion (at 8 weeks, 12 weeks, and 16 weeks after the baseline). The mean Hemi-MASI score is compared between two sides of the face before and after the treatment at 8 weeks, 12 weeks, and 16 weeks after the baseline.

The results show that the hemi-MASI score between two sides of the face is not statistically significant. The hemi-MASI is lower in picosecond with the azelaic side but with no statistically significant ($p>0.05$) shown in Table 4.2 and Figure 4.1.

Table 4.2 The mean hemi-MASI score and standard deviation

	Picosecond with azelaic side	Azelaic side	p-value
Baseline	5.115 ±1.819	5.450±1.903	0.559
8th week	4.935±1.764	5.345±1.815	0.457
12th week	4.635±1.742	5.020±1.800	0.481
16th week	4.095±1.829	4.538±1.871	0.437

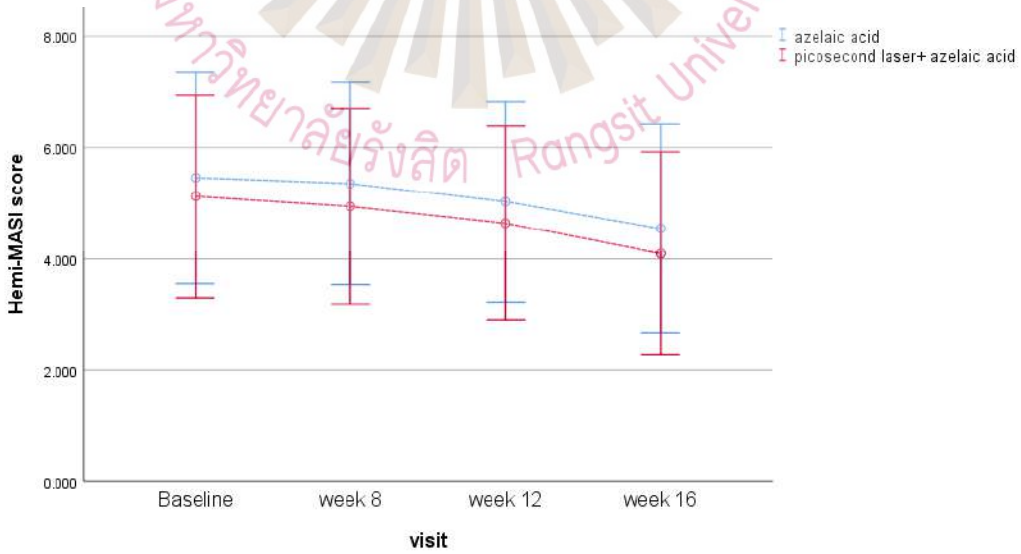

Figure 4.1 Mean Hemi-MASI score between two sides of the face at baseline, 8th week, 12th week, and 16th week

Even though the mean Hemi-MASI score is not statistically significant it is lower in the combination side. The mean Hemi-MASI reduction is 3.52%, 9.38%, and 19.94% at the 8th, 12th, and 16th week, respectively on the combined side while there are 1.93%, 7.89%, and 16.73% at 8th week, 12th week and 16th week, respectively in the topical azelaic alone side.

The p-value of the mean Hemi-MASI when compared between baseline and 8th, 12th, and 16th week are 0.744, 0.384, and 0.064 in the combined side respectively whereas there are 0.854, 0.450, and 0.109 respectively in the topical azelaic side as shown in Table 4.3 which means it is not statistically significant in both sides.

Table 4.3 P-value compared between baseline and 8th week, 12th week, and 16th week

	Picosecond with azelaic side	Azelaic side
8th week	0.744	0.854
12th week	0.384	0.450
16th week	0.064	0.109

4.3 Physician's global assessment

The physician's global assessment was evaluated by using photographs of melasma patients on each visit, they were assessed and compared by three dermatologists who were not involved in the study.

The mean physician's global assessment will also be calculated from a 5-point Linkert scale (5 = strongly improved, 4 = moderate to strongly improved, 3 = moderately improved, 2 = slightly improved and 1 = not improved or worsen) and the primary data will be described as descriptive data at 4 weeks, 8 weeks and 12 weeks after laser completion (at 8 weeks, 12 weeks and 16 weeks after the baseline) from the photograph of patients taken by VISIA® skin analysis equipment.

The mean physician's global assessment (mean PGA) from three dermatologists are 1.55±0.60, 1.85±0.67, and 2.25±0.72 out of 5 with ICC = 0.627 indicating moderate reliability (Koo & Li, 2016) at the 8th, 12th, and 16th, respectively on the combined side while the mean PGA are 1.20±0.41, 1.65±0.59 and 2.15±0.75 at the 8th, 12th, and 16th week, respectively on the azelaic side as demonstrated in Table 4.4. The descriptive data of physician's global assessment are shown in Table 4.5, 4.6, and 4.7.

The median of the physician's global assessment for the combined side is 3, 3, and 3 whereas the topical azelaic side is 2, 3, and 3 at the 8th, 12th, and 16th week, respectively as shown in Figure 4.2.

Table 4.4 The mean physician's global assessment at 8th week, 12th week, and 16th week

	Week	Mean ± SD
Picosecond laser with Azelaic	8	1.55±0.60
	12	1.85±0.67
	16	2.25±0.72
Azelaic acid	8	1.20±0.41
	12	1.65±0.59
	16	2.15±0.75

Table 4.5 Physician's global assessment score at 8th week from baseline

Assessor	score	Picosecond laser with azelaic n, (%)	Azelaic acid n, (%)
1	1	13 (32.5%)	13 (32.5%)
	2	7 (17.5%)	7 (17.5%)
2	1	10 (25%)	14 (35%)
	2	9 (22.5%)	6 (15%)
	3	1 (2.5%)	0 (0%)
3	1	8 (20%)	10 (25%)
	2	10 (25%)	10 (25%)
	3	2 (5%)	0 (0%)

Table 4.6 Physician's global assessment score at 12th week from baseline

Assessor	score	Picosecond laser with azelaic acid n, (%)	Azelaic acid n, (%)
1	1	10 (25%)	13 (32.5%)
	2	10 (25%)	5 (12.5%)
	3	0 (0%)	2 (5%)
2	1	4 (10%)	10 (25%)
	2	13 (32.5%)	10 (25%)
	3	3 (7.5%)	0 (0%)
3	1	5 (12.5%)	4 (10%)
	2	10 (25%)	5 (12.5%)
	3	5 (12.5%)	1 (2.5%)

Table 4.7 Physician's global assessment score at 16th week from baseline

Assessor	score	Picosecond laser with azelaic acid n, (%)	Azelaic acid n, (%)
1	1	7 (17.5%)	10 (25%)
	2	12 (30%)	7 (17.5%)
	3	1 (2.5%)	3 (7.5%)
2	1	1 (2.5%)	4 (10%)
	2	10 (25%)	12 (30%)
	3	9 (22.5%)	4 (10%)
3	1	2 (5%)	2 (5%)
	2	6 (15%)	5 (12.5%)
	3	8 (20%)	10 (25%)
	4	3 (7.5%)	3 (7.5%)
	5	1 (2.5%)	0 (0%)

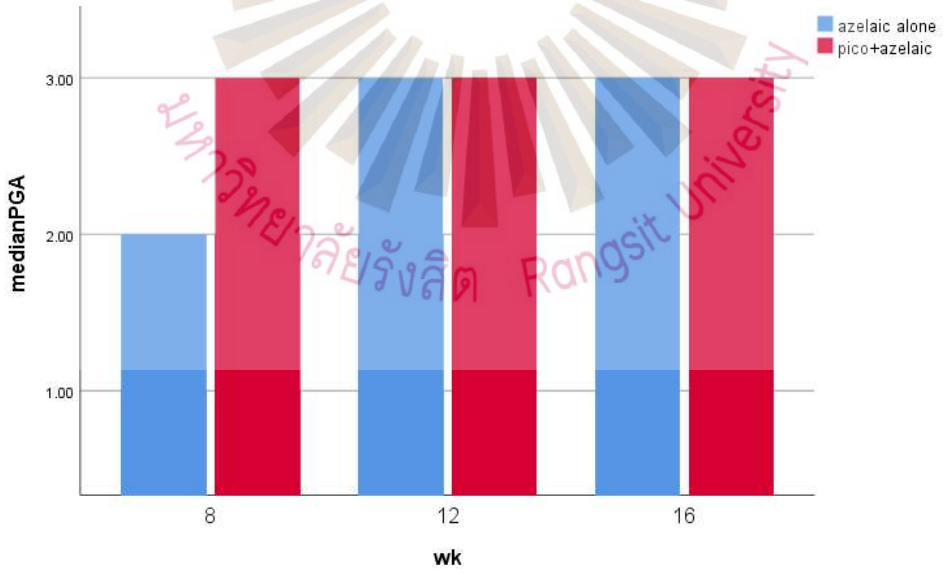

Figure 4.2 Median physician's global assessment between two sides of the face at 8th week, 12th week, and 16th week

4.4 Patient satisfaction score

Patient satisfaction scores will be graded by the patients at 4 weeks, 8 weeks, and 12 weeks after laser completion (at 8 weeks, 12 weeks, and 16 weeks after the baseline). Patients will answer with a 5-point Linkert scale (5 = strongly improved, 4 = moderate to strongly improved, 3 = moderately improved, 2 = slightly improved and 1 = not improved or worsened).

For the picosecond combined with azelaic acid side, the patient satisfaction score shows that at the 8th week, the score was mostly graded at score 4 followed by scores 3, and 5 respectively. At the 12th week, the score was mostly graded at score 4 followed by scores 5, and 3 respectively. At the 16th week, the score was mostly graded at score 4, followed by scores 5, and 3 respectively which are shown in Table 4.8.

For the azelaic acid side, the patient satisfaction score shows that at the 8th week, the score was mostly graded at score 3 followed by scores 4, 2, and 5 respectively. At the 12th week, the score was mostly graded at score 3 and 4, followed by scores 2, and 5 respectively. At the 16th week, the score was mostly graded at score 4, followed by scores 3, and 2 respectively which are shown in Table 4.8.

The mean patient satisfaction score is 4±1, 4±1, and 4±1 at the 8th, 12th week, and 16th week, consecutively on the picosecond laser with azelaic side whereas on the azelaic side, there is 3±1, 4±1, and 3±1 at the 8th, 12th week, and 16th week, consecutively as shown in Table 4.9.

Table 4.8 Patient satisfaction score at 8th week, 12th week and 16th week from baseline

Patient satisfaction score	Picosecond laser with azelaic acid			Azelaic acid alone		
	8th week	12th week	16th week	8th week	12th week	16th week
1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
2	0 (0%)	0 (0%)	0 (0%)	2 (5%)	2 (5%)	2 (5%)
3	6 (15%)	1 (2.5%)	1 (2.5%)	10 (25%)	8 (20%)	6 (15%)
4	12 (30%)	12 (30%)	14 (35%)	7 (17.5%)	8 (20%)	12 (30%)
5	2 (5%)	7 (17.5%)	5 (12.5%)	1 (2.5%)	2 (5%)	0 (0%)

Table 4.9 The mean patient satisfaction score at 8th week, 12th week, and 16th week

	Week	Mean ± SD
Picosecond laser with azelaic acid	8	4±1
	12	4±1
	16	4±1
Azelaic acid	8	3±1
	12	4±1
	16	3±1

4.5 Side effects

Data about side effects are collected from both azelaic acid and picosecond causes. They are collected after three sessions of laser including at 8th week, 12th week, and 16th week.

The patients' side effects were burning and stinging sensations from azelaic acid for 5 patients (12.5%) at the 2nd week, 1 patient (2.5%) at the 4th week, 1 patient (2.5%) at the 8th week, and 1 patient (2.5%) at the 12th week. These side effects faded when the time passed by and the patients claimed that the severity of the symptoms are minimal to mild and resolved without using any treatment.

From picosecond laser, the patients developed the side effect of erythema for 4 patients (10.5%) at the 2nd week and 1 patient (2.5%) at the 4th week. The symptoms are relieved after cold compression for five minutes, after that, the erythema was improved. The erythema severity was graded as mild erythema.

Chapter 5

Conclusion and Recommendations

5.1 Conclusion

Melasma is multifactorial and is influenced by many factors such as gender, UV exposure, oral contraceptive pills, and ethnicity (Lee, 2015). The first choice of treatment for melasma is UV protection and topical agents such as hydroquinone, kojic acid, azelaic acid, etc. (Küçük, 2018). For this study, we compared two sides of the face using a picosecond laser combined with topical azelaic acid and azelaic acid alone.

Due to the mechanism of the picosecond laser, it has a shorter pulse duration when compared to the conventional laser, and also claimed that it has a photoacoustic effect more than a photothermal effect on the target component which leads to fewer side effects of hyperpigmentation and surrounding tissue injury (Kim et al., 2021; Kasai, 2017).

From this study, the age of female malar-type melasma patients ranged from 31-60 years old with Fitzpatrick skin types III and IV. The results show that the mean Hemi-MASI score between the two sides is not statistically significantly different ($p>0.05$).

The percentage of mean Hemi-MASI reduction are 3.52, 9.38, and 19.94 at the 8^{th} week, 12^{th} week, and 16^{th} week, respectively on the combination side, on the other hand, there are 1.93, 7.89, and 16.73 at 8^{th} week, 12^{th} week, and 16^{th} week, respectively in the topical azelaic alone side.

The mean physician's global assessment scores are 1.55±0.60, 1.85±0.67, and 2.25±0.72 on the combined side while there are 1.20±0.41, 1.65±0.59, and 2.15±0.75

out of 5 on the topical azelaic acid side at the 8th week, 12th week, and 16th week, respectively. However, the patient satisfaction score is higher when compared to the physician's global assessment with a similar score between the two sides. For the side effects, there is no serious complication in this study.

The safety profile of this study is satisfying and beneficial because the severity of side effects from both low fluence 1064-nm Nd:YAG picosecond laser and azelaic acid is very mild, for example, mild burning sensation, and mild erythema. The serious side effects such as dyspigmentation are not found in this research.

The patient satisfaction score is higher on the combined side in compared with the topical azelaic side. The mean patient satisfaction score of the picosecond laser combined with azelaic acid is 4±1 whereas the topical azelaic side is 3±1.

5.2 Recommendations

In future research, the researcher can adapt the protocol by engaging more samples of patients. Moreover, a variety of parameters in terms of number of sessions, interval, fluence, spot size, and mode of the laser which are non-fractional or fractional modes can be adjusted to conduct the new protocol.

The future researcher can also provide the protocol of treatments by using a low fluence picosecond laser with other topical melasma medications such as kojic acid, ascorbic acid, glycolic acid, etc. Additionally, the researcher can adapt the picosecond laser combined with topical medications to treat other pigmented diseases.

References

Arora, P., Garg, V., Sonthalia, S., Gokhale, N., & Sarkar, R. (2014). Melasma update. *Indian Dermatology Online Journal*, *5*(4), 426. https://doi.org/10.4103/2229-5178.142484

Bansal, C., Naik, H., Kar, H. K., & Chauhan, A. (2012). A Comparison of Low-Fluence 1064-nm Q-Switched Nd: YAG Laser with Topical 20% Azelaic Acid Cream and their Combination in Melasma in Indian Patients. *Journal of Cutaneous and Aesthetic Surgery*, *5*(4), 266–272. https://doi.org/10.4103/0974-2077.104915

Bolognia, J., Schaffer, J., & Cerroni, L. (2018). *Dermatology* (4th Edition). Elsevier.

Canfield Scientific. (2022). *Visia Redefining the Vision of Skin Care*. Retrieved from https://www.canfieldsci.com/imaging-systems/visia-complexion-analysis/

Chalermchai, T., & Rummaneethorn, P. (2018). Effects of a fractional picosecond 1,064 nm laser for the treatment of dermal and mixed type melasma. *Journal of Cosmetics and Laser Therapy,* 20(3)*, 134-139. https://doi.org/10/1080/14764172.2017.1376098*

Farshi, S. (2011). Comparative study of therapeutic effects of 20% azelaic acid and hydroquinone 4% cream in the treatment of melasma. *J Cosmet Dermatol*, *10*(4), 282–287. https://doi.org/10.1111/j.1473-2165.2011.00580.x

Hai, L. (2021). Dual Toning Method with the Combination of Picosecond and Microsecond Nd:YAG in Refractory Melasma Unresponsive to Picosecond Alone. *J Cutan Aesthet Surg*, *14*(1), 101–106. https://doi.org/10.4103/JCAS.JCAS_30_20

References (Cont.)

Handel, A. C., Miot, L. D. B., & Miot, H. A. (2014). Melasma: A clinical and epidemiological review. *Anais Brasileiros de Dermatologia*, *89*(5), 771–782. https://doi.org/10.1590/abd1806-4841.20143063

Hofny, E. R. M., Abdel-Motaleb, A. A., Ghazally, A., Ahmed, A. M., & Hussein, M. R. (2017). Melasma. *Archives of Biological and Biomedical Research*, *1*(1), 55-78.

Kamal, T., & Iftikhar, U. (2017). Low-fluence Q-switched neodymium-doped yttrium aluminum garnet (1064nm) laser for the treatment of facial melasma in local population. *Journal of Pakistan Association of Dermatologists, 27*(2), 5.

Kang, S., Amagi, M., Bruckner, A., Enk, A., Margolis, D., McMichael, A., & Orringer, J. (2019). *Fitzpatrick's Dermatology* (9th Edition). McGrawHill education.

Kasai, K. (2017). Picosecond Laser Treatment for Tattoos and Benign Cutaneous Pigmented Lesions. *Nippon Laser Igakkaishi*, *37*(4), 440–446. https://doi.org/10.2530/jslsm.jslsm-37_0033

Kim, D. G., Nam, S. M., Shin, J. S., & Park, E. S. (2020). Effectiveness of the Pico-toning Technique for the Treatment of Melasma with a Low Fluence 1,064-nm Nd:YAG Laser in Asian Patients. *Medical Lasers*, *9*(2), 166–171. https://doi.org/10.25289/ML.2020.9.2.166

Kim, J. H., Jung, S. E., & Park, Y. H. (2021). Efficacy of a laser with a pulse duration of 300 ps in skin rejuvenation and treatment of pigmentation disorders in Asians: A series of four cases. *Journal of Cosmetic and Laser Therapy*, 1–4. https://doi.org/10.1080/14764172.2021.2016846

References (Cont.)

Kong, S. H., Suh, H. S., & Choi, Y. S. (2018). Treatment of Melasma with Pulsed-Dye Laser and 1,064-nm Q-Switched Nd:YAG Laser: A Split-Face Study. *Annals of Dermatology*, *30*(1), 1. https://doi.org/10.5021/ad.2018.30.1.1

Koo, T. K., & Li, M. Y. (2016). A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *Journal of Chiropractic Medicine*, *15*(2), 155–163. https://doi.org/10.1016/j.jcm.2016.02.012

Küçük, O. S. (2018). Current Treatment Approaches for Melasma. *Bezmialem Science*, 54–62. https://doi.org/10.14235/bs.2018.1155

Lee, A.-Y. (2014). An updated review of melasma pathogenesis. *Dermatologica Sinica*, *32*(4), 233–239. https://doi.org/10.1016/j.dsi.2014.09.006

Lee, A.-Y. (2015). Recent progress in melasma pathogenesis. *Pigment Cell And Melanoma Research*, *28*(6), 648–660. https://doi.org/10.1111/pcmr.12404

National Center for Biotechnology Information (2023). *PubChem Compound Summary for CID 2266, Azelaic Acid.* Retrieved November 29, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Azelaic-Acid.

Ogbechie-Godec, O. A., & Elbuluk, N. (2017). Melasma: An Up-to-Date Comprehensive Review. *Dermatology and Therapy*, *7*(3), 305–318. https://doi.org/10.1007/s13555-017-0194-1

References (Cont.)

Pandya, A., Berneburg, M., Ortonne, J.-P., & Picardo, M. (2006). Guidelines for clinical trials in melasma: Guidelines for clinical trials in melasma. *British Journal of Dermatology*, *156*, 21–28. https://doi.org/10.1111/j.1365-2133.2006.07590.x

Pandya, A. G., Hynan, L. S., Bhore, R., Riley, F. C., Guevara, I. L., Grimes, P., Nordlund, J. J., Rendon, M., Taylor, S., Gottschalk, R. W., Agim, N. G., & Ortonne, J.-P. (2011). Reliability assessment and validation of the Melasma Area and Severity Index (MASI) and a new modified MASI scoring method. *Journal of the American Academy of Dermatology*, *64*(1), 78-83.e2. https://doi.org/10.1016/j.jaad.2009.10.051

Passeron, T. (2013). Melasma pathogenesis and influencing factors - an overview of the latest research: Melasma pathogenesis and influencing factors. *Journal of the European Academy of Dermatology and Venereology*, *27*, 5–6. https://doi.org/10.1111/jdv.12049

Qazi, I., Dogra, N. K., & Dogra, D. (2017). *Melasma: A Clinical and Epidemiological Study*, *4*(10), 3.

Trivedi, M. K., Yang, F. C., & Cho, B. K. (2017). A review of laser and light therapy in melasma. *International Journal of Women's Dermatology*, *3*(1), 11–20. https://doi.org/10.1016/j.ijwd.2017.01.004

References (Cont.)

Wang, X., Li, Z., Zhang, D., Li, L., & Sophie, S. (2014). A Double-Blind, Placebo Controlled Clinical Trial Evaluating the Efficacy and Safety of a New Skin Whitening Combination in Patients with Chloasma. *Journal of Cosmetics, Dermatological Sciences and Applications*, 04(02), 92–98. https://doi.org/10.4236/jcdsa.2014.42014

Wang, Y. -J., Lin, E. -T., Chen, Y. -T., Chiu, P. -C., Lin, B. -S., Chiang, H. -M., Huang, Y. -H., Wang, K. -Y., Lin, H. -Y., Chang, T. -M., & Chang, C. -C. (2020). Prospective randomized controlled trial comparing treatment efficacy and tolerance of picosecond alexandrite laser with a diffractive lens array and triple combination cream in female asian patients with melasma. *Journal of the European Academy of Dermatology and Venereology*, *34*(3), 624–632. https://doi.org/10.1111/jdv.15934

Wattanakrai, P., Mornchan, R., & Eimpunth, S. (2010). Low-Fluence Q-Switched Neodymium-Doped Yttrium Aluminum Garnet (1,064 nm) Laser for the Treatment of Facial Melasma in Asians. *Dermatologic Surgery*, *36*(1), 76–87. https://doi.org/10.1111/j.1524-4725.2009.01383.x

Wong, C. S. M., Chan, M. W. M., Shek, S. Y. N., Yeung, C. K., & Chan, H. H. L. (2021). Fractional 1064 nm Picosecond Laser in Treatment of Melasma and Skin Rejuvenation in Asians, A Prospective Study. *Lasers in Surgery and Medicine*, *53*(8), 1032–1042. https://doi.org/10.1002/lsm.23382

References (Cont.)

Wu, D. C., Goldman, M. P., Wat, H., & Chan, H. H. L. (2021). A Systematic Review of Picosecond Laser in Dermatology: Evidence and Recommendations. *Lasers in Surgery and Medicine*, *53*(1), 9–49. https://doi.org/10.1002/lsm.23244

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