A COMPARISON STUDY OF THE EFFICACY BETWEEN 5% *ARTOCARPUS LAKOOCHA* HEARTWOOD EXTRACT AND 5% NIACINAMIDE CREAMS IN THE TREATMENT OF AXILLARY HYPERPIGMENTATION: A RANDOMIZED, DOUBLE-BLIND, CONTROLLED TRIAL, SPLIT-SIDE STUDY IN FEMALE PATIENTS

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MASTER OF SCIENCE
IN
DERMATOLOGY

SCHOOL OF ANTI-AGING AND REGENERATIVE MEDICINE
MAE FAH LUANG UNIVERSITY
2025

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THIS THESIS IS A PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE IN DERMATOLOGY

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THESIS APPROVAL

MAE FAH LUANG UNIVERSITY

FOR

MASTER OF SCIENCE IN DERMATOLOGY

Thesis Title: A Comparison Study of the Efficacy between 5% *Artocarpus lakoocha* Heartwood Extract and 5% Niacinamide Creams in the Treatment of Axillary Hyperpigmentation: A Randomized, Double-blind, Controlled Trial, Split-side Study in Female Patients

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ACKNOWLEDGEMENTS

I would like to express my deepest gratitude to my advisor, Asst. Prof. Dr. Anon Paichitrojjana, for his invaluable guidance, knowledge, and encouragement throughout this research. His continuous support and constructive feedback were essential to the success of this thesis. My appreciation is also extended to Assoc. Prof. Dr. Wongdyan Pandii who kindly served on my thesis committee and provided valuable feedback that shaped the direction of my research.

This study would not have been possible without the support of Mae Fah Luang University, which provided the resources necessary to conduct this study. I am also deeply grateful to my colleagues and friends for their encouragement and for making this journey more meaningful.

I would also like to acknowledge the thesis writing grant from Mae Fah Luang University, whose support contributed to the successful completion of this study.

Most importantly, I wish to express my heartfelt gratitude to my family. Their unconditional love, endless patience, and constant encouragement have been the foundation of my strength. Through every challenge and difficulty, they stood beside me with unwavering faith and support. This achievement is not mine alone but also theirs, for without their sacrifices and belief in me, this journey would not have been possible.

Additionally, I would like to thank all the participants who took part in this study. Their willingness to contribute their time and effort made this research successful.

Finally, I would like to thank myself for being patient, persevering through hardships and continuing to move forward even when the path was not easy. I am grateful for the strength I discovered within me, the courage to keep going, and the determination to achieve what once seemed impossible. This accomplishment is a reminder that with resilience and faith, I am capable of more than I ever imagined.

Sokla Chhuon

Thesis Title	A Comparison Study of the Efficacy between 5% Artocarpus lakoocha Heartwood Extract and 5% Niacinamide Creams in the Treatment of Axillary Hyperpigmentation: A Randomized, Double-blind, Controlled Trial, Split-side Study in Female Patients
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ABSTRACT

Background: Axillary hyperpigmentation is a common cosmetic concern, particularly in women. While Niacinamide is an established depigmenting agent, *Artocarpus lakoocha* (Mahad) extract has recently gained attention due to its high oxyresveratrol content, a potent tyrosinase inhibitor. However, clinical evidence in axillary hyperpigmenation remains limited.

Objective: To compare the efficacy of 5% *Artocarpus lakoocha* Heartwood Extract cream with 5% Niacinamide cream in the treatment of axillary hyperpigmentation in female patients.

Material and methods: A randomized, double-blind, split-side clinical trial was conducted in 25 female participants with 23 completers (age 20-35 years old) with Fitzpatrick's skin type III to V. One axilla was treated with 5% *Artocarpus lakoocha* Heartwood Extract cream and the contralateral side with 5% Niacinamide cream twice daily for 12 weeks. Melanin index was measured by Mexameter® MX18 at baseline, week 4, week 8 and week 12. Patient satisfaction scores were recorded by using Global Satisfaction Scores. Statistical analyses included paired t-tests and repeated-measures ANOVA.

Result: At baseline, melanin index was comparable (Mahad 302.17 ± 108.66 vs Niacinamide 299.63 ± 101.80 with $p = 0.680$). Both treatment showed significant reductions over time (Mahad -59.22, -19.60%, Niacinamide -50.79, -16.95% at week 12). Paired comparisons at week 4, 8, and 12 reveals no significant difference between

group (p = 0.103-0.306). Repeated-measures ANOVA demonstrated a significant time effect (p < 0.001), however there was a non-significant time and treatment interaction (p = 0.056). No adverse effects were observed and patient satisfaction was fairly good to good and excellent in both group.

Conclusion: Both 5% *Artocarpus lakoocha* Heartwood Extract and 5% Niacinamide creams were effective and well-tolerated for axillary hyperpigmentation. Mahad demonstrated comparable efficacy to Niacinamide, supporting its potential as a safe, natural alternative for the management of pigmentary disorders.

Keywords: *Artocarpus lakoocha*, Oxyresveratrol, Niacinamide, Axillary Hyperpigmentation

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CHAPTER 1

INTRODUCTION

1.1 Background and Rationale

As acquired pigmentation disorder, post-inflammatory hyperpigmentation arises as a sequela of inflammatory skin lesions and is recognized as one of the most common dermatologic conditions across various skin types[1].

An even and luminous complexion is widely perceived as a hallmark of beauty and youth, a standard recognized across various cultures and societies worldwide[2]. The axillary area represents a frequent site for the development of hyperpigmentation. A frequent dermatologic concern, axillary hyperpigmentation is defined by post-inflammatory hyperpigmentation at the epidermal and dermal, occurring primarily in female[3].

The etiology of axillary hyperpigmentation could be related to exposure to UV light, continuous irritation due to hair plucking, shaving, removal, the movement or stretch and contraction of axillary skin, the rubbing of clothes and physical stimulation from washing, cleansing, drying underarm, excessive sweating accompany by the consume of perfume, deodorant or antiperspirant[4].

At present, the treatment of axillary hyperpigmentation often yields unsatisfactory outcomes, posing a significant challenge in clinical practice[5]. Moreover, a universally recognized or effective treatment approach for axillary hyperpigmentation remains lacking. Initial management should focus on addressing underlying inflammatory through preventive measures such as photoprotection, stop the cause of irritation underarm, stop using perfume or antiperspirant products followed by depigmentation interventions. Various therapeutic modalities has been explored for hyperpigmentation included hydroquinone (monotherapy or combination with other compounds), mequinol, retinoids, azelaic acid, salicylic acid, chemical peels, microdermabrasion, laser therapy, other depigmenting properties such as kojic acid, arbutin, niacinamide, licorice extract, oxyresveratrol and N-acetyl glucosamine[3].

A randomized, double-blind, placebo-controlled study of topical 4% niacinamide and 0.05% desonide cream for treatment of axillary hyperpigmentation demonstrated that both of these creams are effective depigmenting properties in treating axillary hyperpigmentation in women[3].

The other study by Pichsinee Suwannarat conducted the efficiency of *Artocarpus lakoocha* Heartwood Extract in the treatment of axillary hyperpigmentation showed that this is the depigmenting properties, a good to excellent response satisfactory in women with axillary hyperpigmenation[4].

However, there is no comparative study on the efficacy between *Artocarpus lakoocha* Heartwood Extract and niacinamide in the treatment of axillary hyperpigmentation. Therefore, the main reason for this research is to study the effectiveness between these two creams for treatment of axillary hyperpigmentation.

1.2 Research Questions

1.2.1 Primary Research Question

Is the 5% *Artocarpus lakoocha* Heartwood Extract cream more effective in treatment of dark armpits than 5% niacinamide cream in female patients?

1.2.2 Secondary Research Question

1.2.2.1 Is the 5% *Artocarpus lakoocha* Heartwood Extract cream has any side effects in treatment of dark armpits than 5% niacinamide cream in female patients?

1.2.2.2 Are patient satisfactions with the use of 5% *Artocarpus lakoocha* Heartwood Extract cream in treatment of dark armpits more than 5% niacinamide cream?

1.3 Significance of the Study

The study aimed to determine the benefit of perceiving axillary hyperpigmentation treatment in female patients with all skin type using 5% *Artocarpus lakoocha* Heartwood Extract compare to 5% niacinamide cream to evaluate the therapeutic effectiveness. Furthermore, to assess patient satisfaction, potential side

effects whether which cream is qualified to be a promising treatment option as an alternative axillary hyperpigmentation treatment in the future.

1.4 Research Objectives

1.4.1 Primary Objective

To compare the efficacy defined as a degree of reduction in melanin index assessed by Mexameter, of 5% *Artocarpus lakoocha* Heartwood Extract and 5% niacinamide Creams in treatment of dark armpits

1.4.2 Secondary Objective

1.4.2.1 To compare the side effects of *Artocarpus lakoocha* Heartwood Extract and niacinamide Creams.

1.4.2.2 To compare patient satisfaction by using Patients' Satisfactory Score after using 5% *Artocarpus lakoocha* Heartwood Extract cream compared with 5% niacinamide cream.

1.5 Hypothesis

1.5.1 Primary Hypothesis

Using 5% *Artocarpus lakoocha* Heartwood Extract cream has an absolute change in decreasing melanin by more than using 5% niacinamide cream in treatment of dark armpits mesured by Mexameter MX18.

1.5.2 Secondary Hypothesis

1.5.2.1 The side effects of 5% *Artocarpus lakoocha* Heartwood Extract cream compared with 5% niacinamide cream in female patients have no difference.

1.5.2.2 By using Patients' Satisfactory Score, patient with the use of 5% *Artocarpus lakoocha* Heartwood Extract cream in treatment of dark armpits are more satisfied than those with the use of 5% niacinamide cream.

1.6 Scope of Study

The study will be conducted in female population with all skin types, healthy individuals, aged between 18-35 years diagnosed for axillary hyperpigmentation will be recruited to be treated and follow-up at Mae Fah Luang University Hospital, Bangkok. Subjects are assigned using randomization to receive treatment of 5% *Artocarpus lakoocha* Heartwood Extract cream twice daily on either left or right side of their axilla. On the contralateral side, subjects apply 5% niacinamide cream twice daily. The subjects were selected by following inclusion and exclusion criteria. Data collection and analysis will be conducted over periods of three months. Objective evaluation of an absolute change includes melanin index measured by Mexameter® MX18 comparing pre-treatment and post-treatment at 0, 4, 8 and 12 weeks. The side effects are obtained at the baseline immediately after and before treatment at week 0, 4, 8 and 12 weeks. Furthermore, at twelve weeks, patient satisfaction will be evaluated at the end of the treatment.

1.7 Conceptual Frameworks

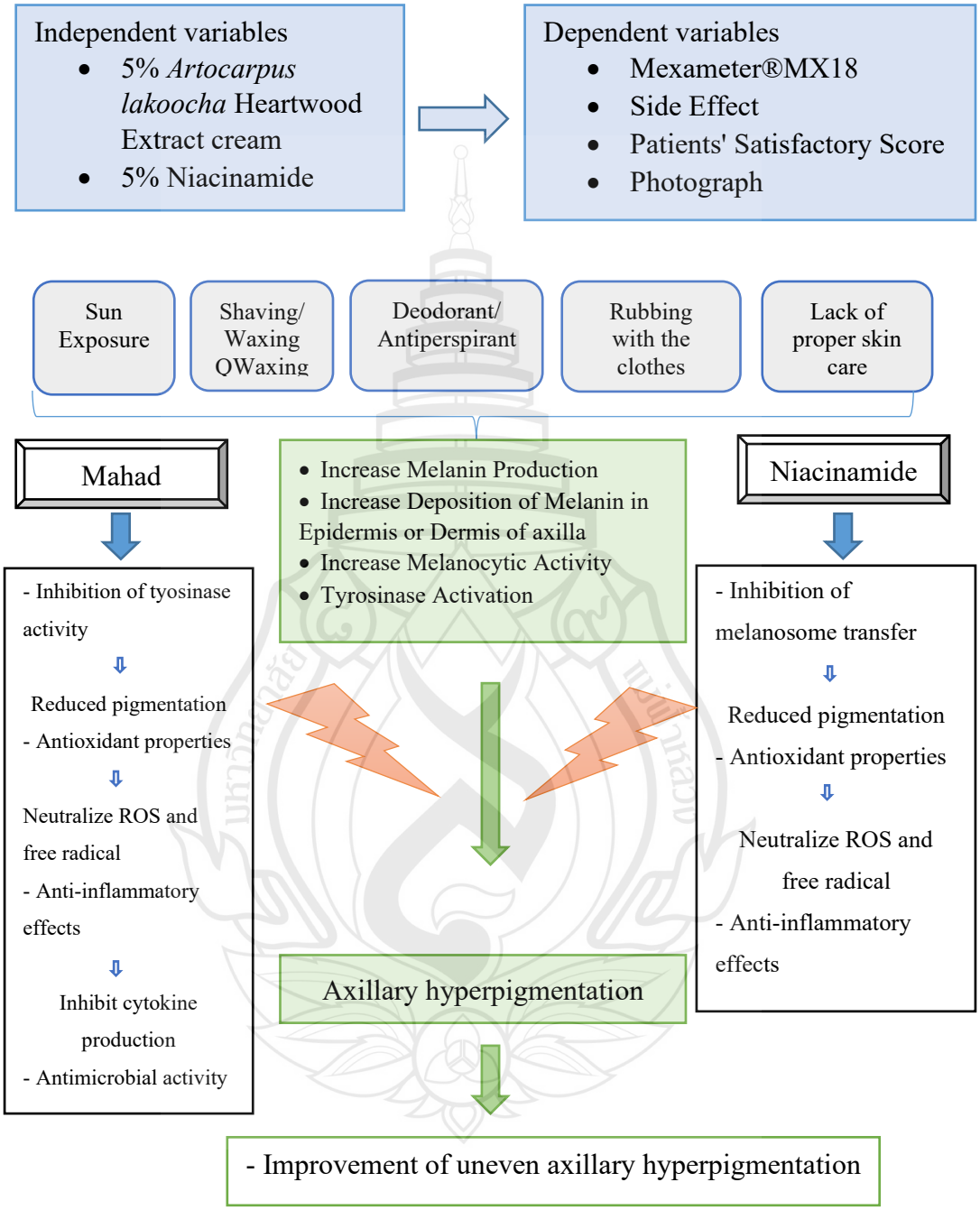


Figure 1.1 Conceptual framework

1.8 Operational Definitions

1.8.1 Axillary Hyperpigmentation

Axillary hyperpigmentation is a condition characterized by the darkening of the skin in the underarm area.

Figure 1.2 Axillary hyperpigmentation

1.8.2 Reactive Oxygen Species (ROS)

Reactive oxygen species (ROS) are molecules capable of independent existence, containing at least one oxygen atom and one or more unpaired electrons. This group includes oxygen free radicals, e.g. superoxide anion radical, hydroxyl radical, hydroperoxyl radical, singlet oxygen, as well as free nitrogen radicals. ROS show a paradoxical effect on melanocytes, both inducing depigmentation and increasing the skin pigmentation[6-7].

1.8.3 Antioxidant

An antioxidant refers to any molecule that protects cellular components by preventing, reducing or neutralizing oxidative damage. Alternatively, an antioxidant can be defined as a substance that either direct scavenges ROS or indirectly enhances antioxidant defense mechanisms and inhibit ROS generation[8].

1.8.4 Location

The measurement for axillary hyperpigmentation is taken from the center of the armpit, comparing with the surrounding skin within 5cm from the midpoint.

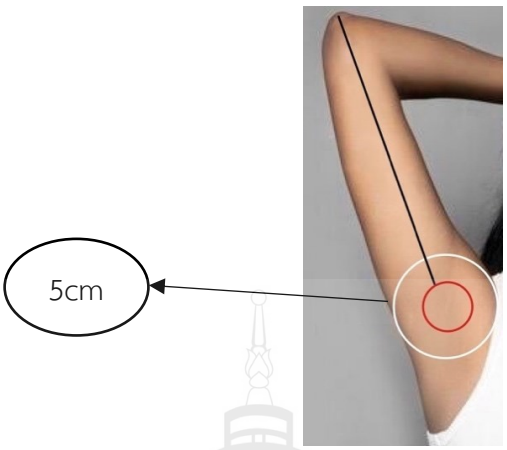


Figure 1.3 Location used in research

1.8.5 Mexameter® MX 18

The measurement made with this straightforward reflectance meter is based on how well the skin absorbs and reflects light. This device uses 16 light-emitting diodes (LEDs) arrange it in a circle to emit light at 3 distinct wavelengths: 568, 660 and 870nm, which correspond to green, red, and infrared light, respectively. The skin's reflection of light is measured using photodetector. With the help of mexameter, you can mesure the amount of light that is absorbed and reflected at wavelength in red and near-infrared for melanin and the green and red for hemoglobine[9].

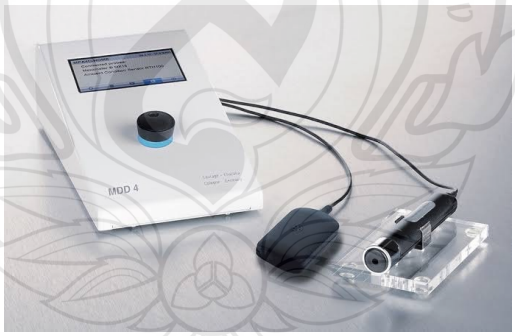


Figure 1.4 Mexameter® MX18

1.8.6 Mean Melanin Index

The lesion's melanin index is analysed using a Mexameter provided noninvasive acquisitions of skin reflectance under LED light centered at 630nm. The result is shown as 1-1000 (1 = white, 1000 = black). It is measured at the center of the lesions at the same point three times and calculated for the average value.

1.8.7 Patients' Satisfactory Score

At twelve weeks post-treatment visit (end of the study), a subjective assessment of axillary hyperpigmentation was done using a Global Satisfaction Score (from -1 to 4 numeric rating scale) as:

-1 indicates	worse
0 indicates	no improvement
1 indicates	fairly improvement (1-25%)
2 indicates	moderately improvement (26-50%)
3 indicates	good improvement (51-75%)
4 indicates	excellent improvement (76-100%)

1.8.8 Side Effects

At every visit, all side effects are recorded after each treatment at 4, 8, and 12 weeks post-treatment visit. The following side effects are:

1.8.8.1 Erythema

1.8.8.2 Pruritus

1.8.8.3 Burning

1.8.8.4 Dryness

The severity will be assessed using a 4-point-scale from:

0 indicates absent = no sign/symptom evident

1 indicates mild = sign and/or symptom clearly present but minimal awareness, easily tolerated

2 indicates moderate = definite awareness of sign and/or symptom, which is bothersome but tolerable

3 indicates severe = sign and/or symptom that is hard to tolerate, may cause interference with activities of daily living and/or sleeping

CHAPTER 2

LITERATURE REVIEW

The researcher reviewed the literature and divided it into the following topics:

1. Axillary hyperpigmentation
2. Melanocytes
3. Melanogenesis
4. Tyrosinase and Related Proteins in Melanogenesis
5. Axillary hyperpigmentation treatment modalities
6. *Artocarpus lakoocha* Heartwood Extract
7. Niacinamide
8. Related Studies

2.1 Axillary Hyperpigmentation (AH)

Axillary hyperpigmentation (AH) is a condition in which axillary skin is darken than the adjacent areas. It is common in dark-skinned individuals that can cause cosmetic concerns, especially in Asian populations[10].

2.1.1 Axillary Skin

The axillary region is recognized as a distinctive skin site in the human body [11]. In addition to numerous hair follicles and sebaceous glands, it is containing a high density of eccrine and apocrine sweat glands [12] (Figure 2.1). Studies has been conducted that the average surface area of axillary skin per axilla is approximately 116 cm2 for male and 65 cm2 for female [13]. Multiple studies have demonstrated that the general features of axillary skin differ markedly from those of other region of body. Thus, trans-epidermal water loss (TEWL) and corneosurfametry have shown reduced barrier integrity in the axilla, versus with the volar forearm [14-15]. Conversely, a recent confocal Raman study has revealed that cholesterol, ceramide 3 and lactic acid (also a component of sweat) levels are elevated, and NMF amounts lower, if compared with the forearm [16]. Moreover, studies reported that axillary cornified envelopes in the axilla

are reduced in size compared with those of the forearm, reflecting more rapid stratum corneum turnover, while corneocyte maturation remains largely comparable [11, 17]. Squamometry assessments of skin dryness have revealed that the axillary stratum corneum accumulate greater amounts of incompletely desquamated material compared with the forearm, which correlates with lower concentration of the stratum corneum chymotryptic enzyme in the outer layer of the skin[11]. A number of investigations have been examined the skin surface pH of the axilla, specifically assessing whether variation occur between genders [18-19]. The evidence is conflicting, with Burry et al. finding no sex-related differences in axillary skin surface or sweat pH once corrected for carbon dioxide loss following secretion, while Williams et al. [19] observed lower axillary skin surface pH in women compared with men, both before and after water washing. The conflicting results may be explained by differences in skin surface pH measurement techniques, and consequently the topic remain unresolved. In addition, Burry et al. also reported marked regional variation within the axilla, with higher sweat rates in the vault accounting for the observed differences from the fossa [18]. It is a though that this occurs because the eccrine duct has less time to reabsorb bicarbonate from the sweat as it travels to the skin surface [20-21]. Circadian variation has also been revealed to effect axillary skin pH with male subjects exhibiting values of pH 5.9 in the morning and pH 5.5 in the evening [22]. These findings may indicate diurnal variation in stratum corneum enzyme activity and sebum production.

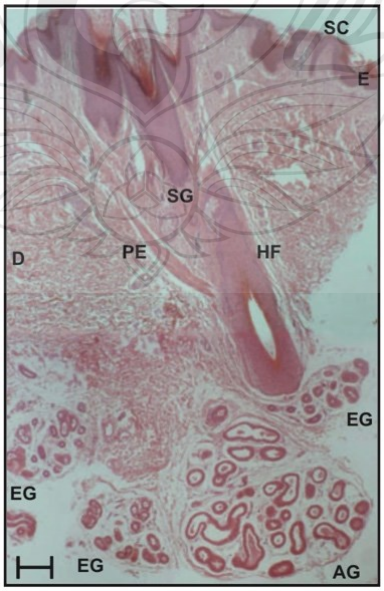


Figure 2.1 Histological section of axillary skin

2.1.2 Aetiology

Evans et al highlighted that axillary tissue exhibits distinct characteristics compared with other body tissues. Axillary tissue constitutes extra hair follicles, extra sweat glands, extra sebaceous glands, and higher transepidermal water loss values that cause weaker skin barriers. In addition, the axilla represented a flexural area susceptible to constant skin friction, chemical exposure, and repeated hair removal (shaving or plucking), factors that can injure the skin, trigger irritation, and results in post-inflammatory hyperpigmentation [4].

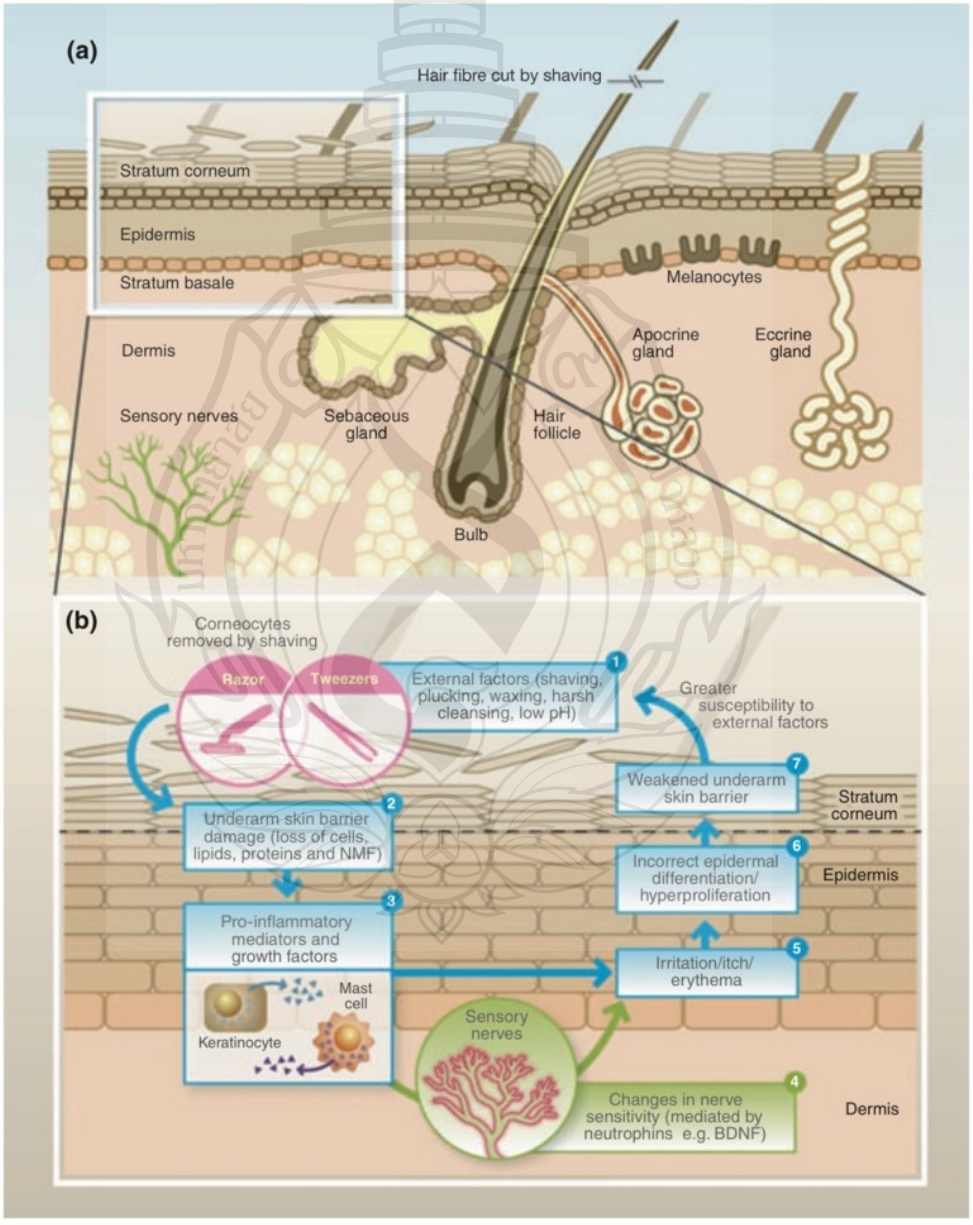


Figure 2.2 Structure of axillary skin (a) and the axillary irritation cycle (b)

2.1.2.1 The use of anti-perspirants or deodorants

For many female consumers, daily personal care involves applying of anti-perspirants and deodorants to manage wetness and unpleasant odor. These practices may lead to visible or sensory irritation and for some cases by axillary skin darkening especially among individuals with Fitzpatrick skin types III and above [24-25].

2.1.2.2 Shaving, plucking or waxing of axillary hair

Research into the effects has historically of shaving emphasized on facial skin with comparative studies on axillary skin conducted only in recent years [26-27]. Shaving induced irritation is now widely recognized as being caused by removal of the stratum corneum uppermost layer. In the case of male facial shaving, up to 20% of the material removed during the process is skin [27], and it is this which ultimately leads to the post-shaving skin dryness and flakiness associated with this area [26]. Comparable findings have now been reported for the underarm, where the average proportion of skin debris removed is even greater, at 36% [28]. Shaving of the axilla contributes by causing physical injury including cuts, nicks and a diminish smoothness of the skin, and which in turn compromises the natural barrier against external irritants [28-30]. The first observable effect of shaving is pronounced skin irritation [29-30]. Histamine iontophoresis studies reveal that this occurs in both vault and fossa sites, with neurogenic flare more common in the fossa [28]. Additionally, finding indicate that the vault adapted to repeat shaving, notably by the developing a thickened epidermis [28]. The axillary vault may show partial adaptation does not completely safeguard the skin from subsequent shaving episodes. In general, skin darkening is biochemically driven by increased melanin synthesis (melanogenesis). Histological analysis of female Filipino axillary skin demonstrated that the underarm hair plucking induce trauma associated with melanosome leakage into the dermis leading to increased pigmentation, along with infiltration of mononuclear cells and macrophages [25].

2.1.2.3 Ultraviolet Radiation Exposure

Ultraviolet exposure increases the activity of tyrosinase, the key enzyme located within the melanosomes, which are cytoplasmic vesicles of melanocytes. Tyrosinase has two primary activities. It catalyses the formation of L-DOPA from L-tyrosine and its oxidation to L-dopaquinone. Through alternative biosynthesis routes,

L-dopaquinone is then converted into either eumelanin (brown-black) or pheomelanin (red-yellow) [4].

2.1.2.4 Post-inflammatory hyperpigmentation (PIH)

According to James et al., axillary hyperpigmentation is best described as a form of mild PIH, distinguished by elevated epidermal melanin production [25, 31]. There is strong correlation between the density of epidermal pigmentation, the extent of dermal pigment and macrophage infiltration. In hyperpigmentation sites, enhance dermal melanosome release occurs, and since macrophage infiltration is linked to cytokines-mediated inflammation, a self-sustaining cycle arises in which melanocytes are stimulated to produce more pigment-filled melanosomes. Hyperpigmentation skin sites in darker-skinned panellists demonstrate melanocyte stimulation and elevated melanogenesis [25, 31-32].

2.1.2.5 Other factors

Notably, increased Body Mass Index, which promote underarm friction, together with baseline pigmentation, are both significantly to axillary darkening [33].

2.2 Melanocyte

During embryogenesis, neural crest cells, multipotent cells that migrate from the dorsal neural tube, give rise to neural tube, differentiate into neurons, glial cells, bone and cartilage cells, as well as melanocytes. Melanoblasts, the primary precursors of melanocytes, migrate via the dorsolateral pathway to colonize the hair follicles and basal layers of epidermis [34].

Melanin production, a distinctive biological feature shared by various melanin producing cells like melanophores, melanocytes, and their cancerous counterparts in melanoma cells, is crucial for defining melanocyte differentiation. Within melanosomes, two distinct forms of melanin are synthesized brown-black eumelanin and yellow-red pheomelanin [34].

2.3 Melanogenesis

The melanogenesis cascade includes the collaboration between melanocytes and nearby keratinocytes, forming what's known as the epidermal melanin unit. MITF (micropthalmia-associated transcription factors) serves as the key player, guiding the activation and differentiation of melanocytes, leading to the initiation of the melanogenesis cascade, particularly evident in UV-induced tanning reactions. UV rays damage the DNA in keratinocytes, setting off a chain reaction. The damage DNA activates TP53, which then triggers the production of POMC. Proopiomelanocortin (POMC) is cleaved into serveral peptides, including α-MSH. Upon release, α-MSH binds to MC1R on melanocytes, leading to elevated intracellular cAMP. The subsequent activation of proteine kinase A (PKA), stimulates CREB transcriptional activity both through direct CREB phosphorylation and by inhibiting salt-inducible kinase (SIK), a negative regulator of CRTCs, the CREB co-activation. Activated CREB then promotes transcription of MITF-M, which in turn upregulates key pigment genes like TYR, TYRP1, DCT, and PMEL. Following synthesis, melanosomal proteins are directed to melanosomes, upon maturation, the melanosomes are subsequently transferred from melanocytes to keratinocytes, forming a shield around the nucleus to block UV light [35].

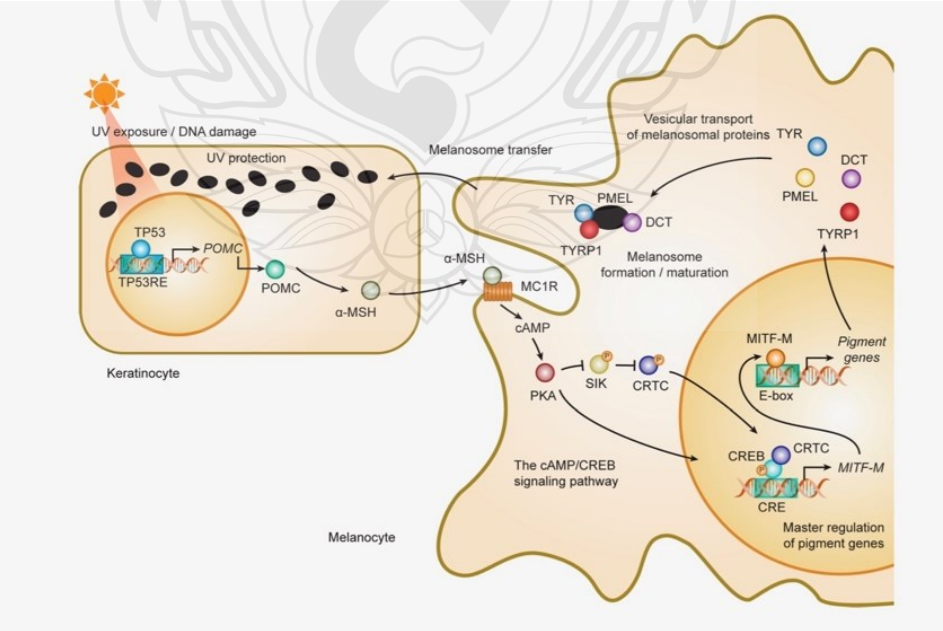


Figure 2.3 Melanogenesis cascade in human skin

2.4 Tyrosinase and Related Proteins in Melanogenesis

Tyrosinase, a di-copper oxidase widely found in various organisms, including humans, is produced exclusively by melanocytes for melanin synthesis. It undergoes glycosylation of TYR and maturation before being transported to melanosomes[36].

Melanin biosynthesis is initiated by tyrosinase, which catalyzes the conversion of tyrosine to DOPA and then to dopaquinone, the common precursors for both eumelanin and pheomelanin. Tyrosinase activity is modulated through interactions with TYRP1, TYRP2, and dopachrome tautomerase (DCT). The enzyme TYRP2 converts dopachrome into 5,6-dihydroxyindole-2-carboxylic acid (DHICA), a reaction followed by TYPR1-mediated transformation of DHICA into eumelanin pigments. In contrast, the incorporation of cysteine into dopaquinone yields cysteinyldopa, which is further converted into benzothiazine derivative, leading to pheomelanin synthesis [35].

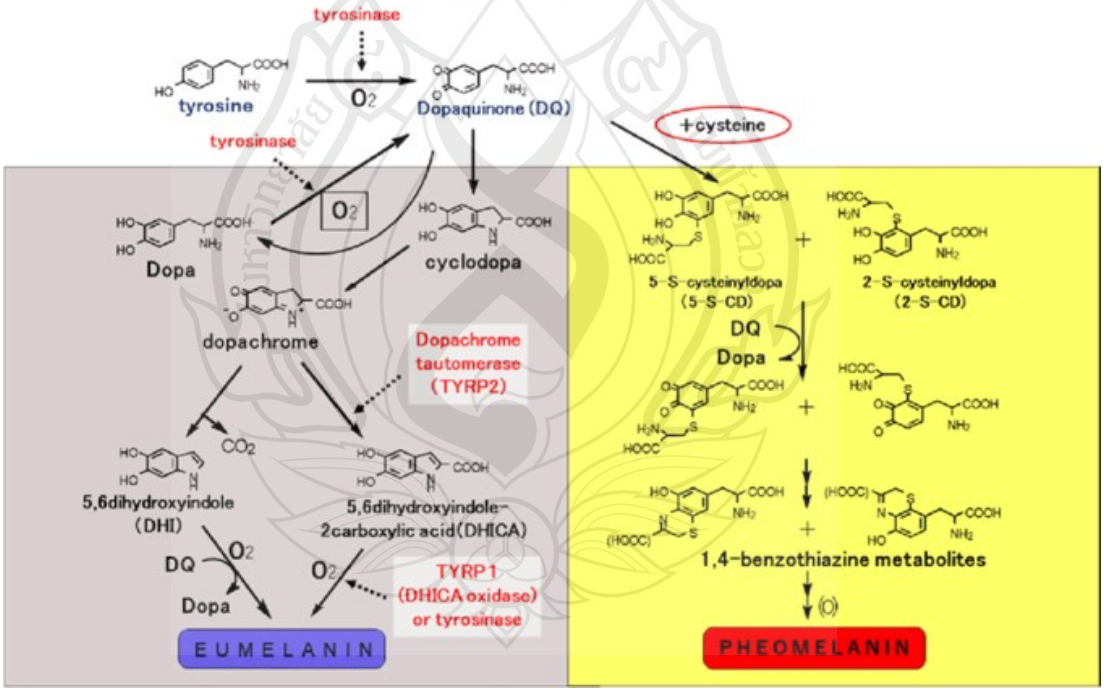


Figure 2.4 Biosynthesis pathway of eumelanin and pheomelanin

2.5 Axillary Hyperpigmentation Treatment Modalities

The treatment objective should focus on recognizing and addressing the underlying cause of hyperpigmentation along with its contributing factors. Currently, there is no established standard treatment for axillary hyperpigmentation, and available studies on its management remain limited. The condition is most often treated with topical depigmenting agents including [10].

2.5.1 Topical Agents

2.5.1.1 Hydroquinone (HQ)

Hydroquinone, 1,4-dihydroxybenzene, is a hydroxyphenolic compound known as tyrosinase inhibitor. The inhibition of tyrosinase is achieved by competitive blinding with tyrosine, the natural substrate of tyrosinase, thereby inhibiting the conversion of DOPA, thereby impeding the synthesis of melanin. Furthermore, it impedes the synthesis of DNA and RNA, promoting the degradation of melanosomes and the destruction of melanocyte. HQ has been widely recognized as the gold standard treatment for hyperpigmentation for several decades. It is available in a variety of concentrations, often from a compounding pharmacy[37].

2.5.1.2 Combination cream

Hydroquinone, 1,4-dihydroxybenzene, is a hydroxyphenolic compound known as tyrosinase inhibitor. The inhibition of tyrosinase is achieved by competitive blinding with tyrosine, the natural substrate of tyrosinase, thereby inhibiting the conversion of DOPA, thereby impeding the synthesis of melanin. Furthermore, it impedes the synthesis of DNA and RNA, promoting the degradation of melanosomes and the destruction of melanocyte. HQ has been widely recognized as the gold standard treatment for hyperpigmentation for several decades. It is available in a variety of concentrations, often from a compounding pharmacy[37].

2.5.1.3 Azelaic acid (AzA)

Because of its impact on tyrosinase, azelaic acid (1,7-heptanedicarboxylic acid), which was initially created as a topical anti-acne drug, has also been used to treat hyper-pigmentary conditions like melasma. Its mechanism of action involves the

suppression of mitochondrial enzymes and DNA synthesis, which directly causes cytotoxic effects on melanocytes[39].

2.5.1.4 Vitamin C

Vitamin C, known for its antioxidant properties, is utilized in the treatment of hyperpigmentation. Due to the instability of ascorbic acid in many topical products, stabilized derivatives like L-ascorbic acid 6-palmitate and magnesium ascorbyl phosphate are commonly consumed. The most prevalence cutaneous antioxidant is L-ascorbic acid. It neutralizes the free oxygen radicals that cause melanogenesis in the aqueous compartment[40].

2.5.1.5 Licorice Extracts

The main bioactive constituted of licorice, glabridin, is extracted from the root of the perennial plant Glycyrrhiza glabra linneva. This compound has been found to scavenge reactive oxygen species, suppresses UVB-induced pigmentation and tyrosinase activity preserve DNA synthesis, while also exhibiting anti-inflammatory properties. In vitro evidence suggests that glabridin's whitening activity is about 16 times stronger than that of hydroquinone, with additional ptential to suppress UVB induced melanogenesis [41].

2.5.1.6 Kojic acid (KA)

Produced as a metabolic byproduct of the fungi such as Acetobacter, Aspergillus, and Penicillium, kojic acid is widely recognized for its depigmentation properties. It function as a reactive oxygen species (ROS) scavenger, exerting antioxidant effects, and suppressing tyrosinase activity. Kojic acid (KA) is employed in numerous cosmetic products for skin lightening and serves as a food preservative to prevent discoloration due to browning reactions [41].

2.5.1.7 Arbutin

The compound arbutin is a hydroquinone ß-D-glucopyranoside present in serveral plants, particularly in the leaves of the bearberry, also known as Uva ursi folium. It is also present in the leaves of blueberry and cranberry plants. And randomized control trial study about arbutin shows the clinical efficacy in treating pigmentary disorder [41].

2.5.2 Chemical Peeling

Another therapeutic approach for hyperpigmentation is chemical peeling. This

procedure involves the controlled application of a chemical agent to induce a partial or complete injury to epidermis with or without involvement of dermis, resulting in exfoliation of superficial skin layers, removal of surface lesions, subsequent regeneration of new epidermal and dermal tissues. Chemical peels are divided into three groups deep peels (eg. phenol peel), medium peels (eg. 30% trichloracetic acid peel) and superficial peels (eg. alpha hydroxyl and salicylic peel). The objective of this procedure is to eliminate the outer layers of the skin uppermost layers to promote regeneration [42].

Glycololic acid is frequently used as an active ingredient in skin-lightening creams, typically at a concentration of 10%. Alpha hydroxy acid (AHA) peel is commonly used, with a range of concentrations from 20 to 70% [37,43].

Salicylic acid is a beta hydroxyl acid (BHA) peel. It has an anti-inflammatory and brightening effect that serves to decrease PIH [43].

Lactic acid peels appear to show results comparable to glycolic acid peels for patients with skin color.

Trichloroacetic acid is a chemical compound that is derived from acetic acid. TCA peels are commonly administered in various concentrations, including 15%, 25%, 50%, and 75%. When the concentration reaches 75%, it results in the destruction of the epidermis and superficial dermis, leading to re-epithelization from the epidermal adnexae. Given the potential for serious side effects such as immediate epidermal necrosis, burns, postinflammatory hyperpigmentation (PIH), and hypertrophic scars formation, it is recommended that TCA peels be administered by a qualified and experienced physician [43].

2.5.3 Laser and Light Therapies

Currently, laser and light-based therapies have become famous for treating hyperpigmentation and skin rejuvenation. The principle is based on the broad absorption spectrum of melanin, the short thermal relaxation time (TRT) of melanosomes, and the fact that longer wavelengths penetrate deeper into the skin, whereas melanin exhibits greater absorption at shorter wavelengths. However, these therapies may have adverse effects, including a paradoxical increase in pigmentation due to direct skin damage, particularly in individuals with darker skin tone (Fitzpatrick's skin type IV-VI) [44].

2.5.3.1 Intense Pulsed Light (IPL)

IPL uses a flashlamp to generate a non-coherent, high-energy, broad-spectrum light ranging from 500 to 1200nm used in many cutaneous lesions. The filters can be applied to increase target specificity. 500-550nm filters are often used for epidermal lesions, while longer wavelengths are used for deeper lesions. The utilization of a treatment should be restricted or avoided in individuals with darker skin type (Fitzpatrick skin type IV-VI) due to its ability to induce post-inflammatory hyperpigmentation (PIH) easily [43-44].

2.5.3.2 Q-Switched Neodymium-Doped Yttium Aluminum Garnet (QS-Nd:YAG) Laser

Previous research has indicated that high-fluence QS-Nd-YAG treatment was efficacious for certain individuals with fair skin but resulted in a notably elevated occurrence of unfavorable side effects among patients with skin color (30). With the longer wavelength of 1064nm QS-Nd:YAG laser causes minimal damage to the epidermis, lead to deeper skin penetration, targets dermal melanin, and heats collagen to tighten and rejuvenate the skin[45].

Currently, laser toning, which involves the delivery of low-fluence QS-Nd:YAG, is widely used. According to current beliefs, laser toning has the potential to reduce the levels of melanogenic proteins, such as α-MSH, tyrosinase, TRP-1, TRP-2, and NGF, without affecting the number of melanocytes present, despite the occurrence of hypopigmentation in the treated regions (30). According to a study by Irene Gaile C. Robredo in axillary hyperpigmentation treatment, low-fluence QS 1064nm show marked improvement in hyperpigmentation, which was sustained for as long as three months after the final treatment with no related adverse events or treatment related PIH[1].

2.5.3.3 Pulsed-Dye Laser (PDL)

Pulsed-dye laser or PDL is believed to reduce melanocyte stimulation by target vascular component in lesions. (Pigment) Utilizing the principle of selective thermolysis, these laser target hemoglobin as the chromophore, emitting visible light within the range of 585-595nm with pulse durations spanning from 0.45 to 40ms[46].

2.5.3.4 Q-switched ruby laser (QSRLs)

Q-switched ruby laser (694nm wavelength) demonstrates moderate absorption

by melanin and limited absorption by competing chromophores like hemoglobin. The rapid and intense energy delivery at this wavelength lead to fragmentation of melanosomes within keratinocytes, melanocytes, and melanophages, making well-suited for the treatment of epidermal pigmentation and dermal lesions within superficial, particularly with individuals with skin type I-II [47].

2.5.3.5 Q-switched alexandrite laser (QSAL)

The 755nm wavelength inherent in the Q-switched alexandrite laser (QSAL) is characterized by enhanced tissue penetration, displaying a diminished absorption coefficient for melanin and an extended pulse duration spanning 50-70 nanoseconds, in contrast to the Q-switched ruby laser (QSRL). This nuanced parameterization holds promise for mitigating adverse effects, particularly post-inflammatory hyperpigmentation (PIH), and proves advantageous in individuals with higher melanin concentrations, owing to its milder influence on melanosome[48].

2.6 *Artocarpus lakoocha* Hearwood Extract (Mahad)

Artocarpus lakoocha Roxb. (AL), a member of the Artocarpus species belonging to the Moraceae family, is a tropical tree widely distributed in the region of South, and Southeast Asia, covering regions such as Nepal, India, Sri Lanka, Myanmar, Southern China, Vietnam, Thailand, Malaysia and Indonesia[49].

The species is referred to by different local names: monkey jack or lakuchi in India; tampang in Malaya and as lokhat located in Thailand. The species is valued for its strong wood and edible fruits, which are regarded as having medicinal benefits. It can grow up about 20-30 meter high deciduous tree with large and leathery leaves [50].

Figure 2.5 Mahad tree

The species leaves are known to contain abundant bioactive constituents with potential thearapeutic activity [50].

Figure 2.6 Mahad with leaves and flowers

The fruits of *A. lakoocha* has revealed high concentration of flavonoids, phenols, tannins, lignins, saponins and steroids [50].

Figure 2.7 Mahad fruit

The seeds of Lakoocha are known for their purgative nature and the presence of agglutinins (ALA I and ALA II), both of which display significant high haemagglutinating activity [50].

Figure 2.8 Mahad seeds

In Thailand, an aqueous extract of *A. lakoocha* obtained by boiling the wood chips is dried to produce a brown powder referred to Puag- Haad. As a novel cosmetic component, the heartwood extract of this species has demonstrated potent *in vitro* anti-tyrosinase properties and *in vivo* efficacy in reducing melanin levels among human volunteers [51].

Figure 2.9 Heartwood of *Artocarpus Lakoocha* (Mahad)

2.6.1 Biological Effect of *Artocarpus Lacoocha* Heartwood Extract

2.6.1.1 Antioxidant Properties

Antioxidant neutralize free radicals, which are unstable chemical entities produced by the body's metabolic processes. Free radicals can cause damage to cells, but antioxidants either stop or slow this process. Antioxidants can be either synthetic or natural, with natural ones generally considered safer. Studies show that antioxidants from phytochemicals, especially polyphenols, are effective in reducing free radicals[52].

Artocarpus lakoocha heartwood extract has been shown to possesses significant antioxidant activity, primarily due to its high content of phenolic compounds including flavonoids and tannins content. Research by Panal Sitorus highlights that the high total phenolic content with alkaloids, terpenoids and organic sulfur play a critical role in neutralize free radicals, thereby preventing oxidative damage[52].

2.6.1.2 Antimicrobial activity

Based on the literature study, *Artocarpus lakoocha* including those from its leaves, bark, and wood, shows the strong antimicrobial activity which can inhibit the growth of bacteria and fungi. Tannins and flavonoids, both phenolic compounds kill bacteria by altering cell proteins, damage bacterial cell walls, precipitating proteins, and disrupting lipids cell membranes. Flavonoids target bacterial cytoplasmic membranes, affecting nutrient intake, and can form complexes with external proteins, leading to bacterial growth inhibition. Tannins damage and shrink bacterial cell walls, reducing permeability and ultimately slowing or stopping bacterial growth[52].

2.6.1.3 Anticarcinogenic effects

Artocarpus lakoocha has shown potential anti-carcinogenic activity in various studies due to the presence of bioactive compounds such as flavonoids, tannins, and phenolic compounds. These compounds exhibit antioxidant properties, which can help neutralizing free radicals that contribute to cancer development. The cytotoxic effects of *artocarpus lakoocha* extracts have been testes in vitro, revealing that they can inhibit the proliferation of cancer cells. The presence of saponins, alkaloids, and cardiac glycosides in the extracts may contribute to its anti-carcinogenic effects by inducing apoptosis in tumor cells[52].

2.6.1.4 Anti-inflammatory effects

Methanolic extracts of Artocarpus lacoocha leaves have demonstrated

dose-dependent and statically significant ($p \leq 0.05$) anti-inflammatory activity. At a dose of 200mg/kg, the extract inhibited inflammation by 64.09%, suppressing the anti-inflammatory effect of indomethacin 52.

2.6.1.5 Antinociceptive Properties

Analgesics, or pain blockers, are drug that relieve pain without causing loss of consciousness. Hydro-methanolic extracts of *Artocarpus lakoocha* wood have been shown significant analgesics effect at doses of 50-200mg/kg body weight, with not harmful to experimental animals. Nociceptive pain, which subsides as the affected area heals, can be treated with opioid analgesics, but these can lead to addiction, respiratory depression, hypotension, tolerance, and dependency. Therefore, natural compounds with antinociceptive properties are being explored as alternatives to reduce the adverse effects associated with opiods[52].

2.6.1.6 Antidiarrheal activity

The leaves of the *Artocarpus lakoocha* plant (100mg/kg) show that it has a moderate effect as an antidiarrheal. This is based on the data that were collected. Studies indicate that treatment with 200 mg/kg of the *Artocarpus lakoocha* leaf extract inhibited diarrhea by 68.11%, which is nearly equivalent to the effect produced by loperamide (71.1%). Therefore, the observed antidiarrheal effect of the extract is likely mediated by its antisecretory mechanism [52].

2.6.1.7 Neuroprotective and Hepatoprotective Properties

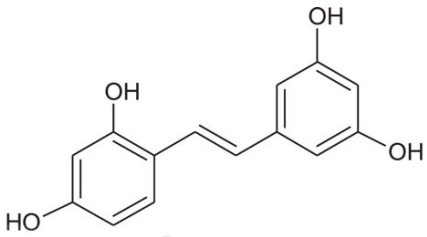
The aqueous extract of *Artocarpus lakoocha* wood shows potential for mitochondrial protection, with compounds like puaghaad and oxyresveratrol enhancing cell survival and reducing reactive oxygen species (ROS) and lipid peroxidation. Oxyresveratrol may also influence the expression of redox-sensitive antioxidant enzymes, suggesting its potential in protecting against neurodegenerative diseases[52].

In hepatoprotection studies, mice treated with paracetamol showed varying degrees of liver damage when given different doses of *Artocarpus lakoocha* methanol extract at 125 and 250 mg/kg/day, mild liver problems were observed, while no significant damage occurred at 500 mg/kg/day[52].

2.6.2 *Artocarpus lakoocha* as Inhibitor Against Tyrosinase in Melanogenesis

Artocarpus lakoocha (Mahad) composes of a potential skin-whitening agent namely Oxyresverastrol, which is a natural phenolic stilbene compound[53].

2.6.2.1 Oxyresveratrol



Oxyresveratrol (2,4,3′,5′-tetrahydroxystilbene)

Figure 2.10 Oxyresveratrol

The heartwood extract of *Artocarpus lakoocha* (Mahad) contain Oxyresveratrol, a natural phenolic stilbene that effectively suppresses tyrosinase activity, thereby interfering with the enzymatic process of melanin biosynthesis [53].

In a recent study, Sritularak et al. evaluated numerous plant species for their in vitro anti-tyrosinase potential and identified heartwood extract of *artocarpus lakoocha* as the most active inhibitor. Extraction and purification produced two major active components, oxyresveratrol and reveratrol. Of these, oxyresveratrol showed a 20 folds stronger inhibitory effect on mushroom tyrosinase and occurred in higher quantities within the extract. The reported depigmenting mechanism involved non-competitive inhibition of tyrosinase activity, distinguishing it from compounds that suppress enzyme expression or formation [54].

According to research by Surapol Natakankitkul, oxyresveratrol constitutes the major active ingredient present in the Mahad extract. In a clinical evaluation involving female volunteers, dairly application of 1% Mahad lotion in 30 females volunteers desmonstrated that daily application to the upper arms produced a statistically significant improvement over the base lotion base after 4 weeks. The average skin tone measurements of the lower arms indicated a continuous improvement in whitening effect with Mahad lotion, decreasing by 2.84% after 4 weeks and 7.64% after 6 weeks. Over the same duration, the lotion base (self-control) group demonstrated a negligible whitening effect, with skin tone values declining modestly from 0.53% after 4 weeks to 1.06% after 6 weeks. The results indicated that oxyresveratrol exerted the most pronounced whitening activity, achieving a significant effect within 28 days of application ($p < 0.05$) [55].

In a study by P. Tengamnuay, *artocarpus lakoocha* extract exhibited superior skin-whitening efficacy, significantly reducing melanin formation after just 4 weeks of treatment ($p < 0.05$), in contrast 3% kojic acid, and 0.25% licorice extract required 8 and 10 weeks to reach comparable effects. Hence, this heartwood extract shows strong potential for application as a safe, effective yet and economical skin-whitening ingredient [56].

2.6.3 Adverse Effect and Safety Profile

In terms of side effects, in all of these related studies, there are not present with skin irritation or other dermatologic complications were noticed. It considers to use as a safe and effective [55].

2.7 Niacinamide

Niacinamide chemically identified as nicotinamide or 3-pyridinecarboxamide is a physiologically active form of vitamin B3 (niacin) and is naturally present in yeast and various root of vegetables. Niacinamide, when applied topically, has desmonstrated therapeutic benefits across multiple dermatologic conditions, such as acne, rosacea, aging, atopic dermatitis, blistering disease and skin cancer prophylaxis [57]. The mechanism is believed to reversely attack hyperpigmentation by inhibiting melanosome transfer to epidermal keratinocytes through PAR-2 inhibition [58]. Since the skin tolerates niacinamide well rather than other common forms of this vitamin family (eg., nicotinic acid and its esters), niacinamide also suppresses ROS in human cells resulting in effectively reducing oxidative damage, acts as an anti-inflammatory agent in acne, prevents photoimmunosuppression and photocarcinogenesis and increase intracellular lipid synthesis [59].

As in-vitro investigation by Kim et al. identified N-nicotinoyl dopamine (NND) a synthesized derivative of niacinamide derivative, as a compound with high antioxidant potential capable of suppressing melanin formation and promote skin lightening. Nonetheless, additional clinical studies are necessary to comprehensively assess the therapeutic potential of niacinamide and NND [58].

Niacinamide has been described in many ways of dermatological practice,

including theapplication of niacinamidein isoniazid-induced pellagra, epidermalbarrier function, wound healing, acne vulgaris, cancer, blistering disorders, psoriasis, and hyperpigmentation. Also, it is involved in the cosmetic field to prevent skin aging and brighten skin tone [60].

In their publication titled "Niacinamide-Mechanisms of Action and its topical use in Dermatology", Johannes Wohlrab and Daniela Kreft elucidated the biological effects of niacinamide that are relevant in dermatology. These effects include [61] (Figure 2.10).

2.6.1 Anti-inflammatory Effect

Niacinamide plays a significant role in exerting anti-inflammatory effects, primarily by inhibiting the nuclear poly(ADP-ribose) polymerase-1 (PARP-1), which regulates the NFkB-mediated transcription. As a result, it is essential to express inflammatory mediators and adhesion molecules. Additionally, it can inhibit the expression of MHC-II and the synthesis of IL-12, TNF-alpha, IL-1 and nitric oxide.

2.6.2 Antipuritic Effect

In keratinocytes, niacinamide plays a role in the manufacture of ceramides. The stratum corneum's ability to act as a barrier is affected by increased ceramide production. Niacinamide's antipruritic properties are, therefore, primarily dependent on effects that protect the skin's barrier.

2.6.3 Lightening Effect

As mentioned above, niacinamide has the ability to inhibit keratinocyte factors, thereby causing a reversible blockage of melanosomes transfer from melanocytes to keratinocytes. Because of its individual properties distinguish it from other lightening agents, such as arbutin and kojic acid, which inhibit tyrosinase activity.

2.6.4 Antimicrobial Effect

There is evidence to support the tuberculostatic properties of niacinamide, which is achieved through the inhibition of the class III NAD-dependent deacetylase-protein family (Sir2). Additionally, niacinamide has been shown to have antiretroviral effects by inhibiting nuclear PARP.

2.6.5 Photo-protective Effect

Niacinamide has been observed to exhibit inhibitory effects on both photocarcinogenesis and the protective mechanisms against UV-induced immunosuppression.

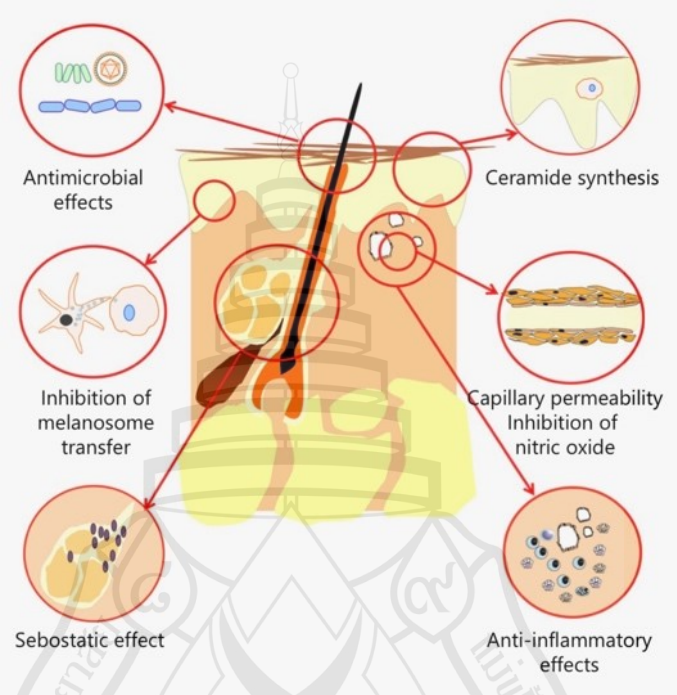


Figure 2.11 Overview of all dermatologically relevant niacinamide effects

In an in vivo experiment, Chhabra et al. demonstrated that niacinamide confers protective effects on melanocytes exposed to UVA and UVB radiation. They researcher conducted their studies using melanocytes cultured from the neonatal human skin. In the experiment, melanocytes underwent a 24 hours pretreatment with 50 μM niacinamide before being exposure to UVB radiation at a dose of 3J/cm2. Niacinamide significantly decreased the levels of both cyclobutane pyrimidine dimers (CPDs) induced by UVB penetrating deeply into epidermal basal cell layer of the skin. And 8-hydroxy-2-deoxyguanine (8oxoG) levels result from UVA, which damages DNA. Studies have shown that niacinamide enhances photoprotection by stimulating nucleotide excision repair gene expression and activating NRF-2 signaling [62].

The side effects of topical niacinamide are minor and rare and include mild burning, pruritus, and erythema. Nonetheless, these side effects improve with continued use [63].

2.8 Related Studies

Recent studies mentioned the use of topical agents such as niacinamide, desonide, cyperous rotundus essential oil, *artocarpus lakoocha* heartwood extract and also lasers and energy-based devices have a great role in treatment of axillary hyperpigmentation.

One study by Robredo and Ghanam et al analyzed the observational study have shown that Q-switch Nd-YAG is clinically effective for the treatment of axillary hyperpigmentation[1].

Another study from Watinee Amornpetkul conducted a randomized, experimental, split-side controlled and assessor-blinded comparing between the use of intense pulsed light and Q-switched neodymium doped yttium aluminium garnet laser decreased mean melanin index after five treatments (week 10), and for the two groups showed no significant difference at any visit[10].

Furthermore, Castanedo-Cazares conducted 9 weeks randomized, double-blind, placebo-controlled study about topical niacinamide 4% and desonide 0.05% for treatment of axillary hyperpigmentation showed a significant colorimetric improvement was achieved in 24% of cases for niacinamide, 30% desonide, and 6% for placebo[3].

Other research article by Pichsinee Suwannarat about efficiency of *Artocarpus lakoocha* Heartwood Extraction in the treatment of axillary hyperpigmentation showed a significant drop of mean melanin index at week 12 compare with placebo[64].

Therefore, from the data mentioned above, in this study, we will use 5% *Artocarpus lakoocha* Heartwood Extraction cream compare with 5% Niacinamide cream for the study period of 12 weeks.

CHAPTER 3

RESEARCH METHODOLOGY

3.1 Study Design

Prospective study, Randomized, double-blind (both participants and assessors by another physician who is not involved in the research), in female patients, split-side comparative study.

3.2 Population Selection

The study was conducted in groups of female subjects, aged between 18-35 years old with a diagnosis of axillary hyperpigmentation.

3.3 Study Location

Mae Fah Luang University Hospital, Bangkok

3.4 Sample Size Determination

The reference data was taken from the similar research article about efficiency of *Artocarpus lakoocha* Heartwood Extraction in the treatment of axillary hyperpigmentation by Pichsinee Suwannarat[64].

Using Mexameter, the mean melanin index shows a significant drop from 328.17 $\pm$ 74.48 at week 1 to 253.90 $\pm$ 74.86 at week 12.

From the formula, $\alpha = 0.05$ (two tailed), $Z_{0.025} = 1.96$, $Z_{0.1} = 1.28$

$n_1 = 15$ $n_2 = 15$

$S_1 = 74.48$ $S_2 = 74.86$

$$\mu_1 = 253.90 \qquad \mu_2 = 328.17$$

$$Sp^2 = \frac{(n_1 - 1){S_1}^2 + (n_2 - 1){S_2}^2}{n_1 + n_2 - 2}$$

$$= \frac{(15-1)(74.48)^2 + (15-1)(74.86)^2}{15 + 15 - 2}$$

$$= 5575.60$$

$$n = \frac{2(Z_{\frac{\alpha}{2}} + Z_\beta)^2 Sp^2}{(\mu_1 - \mu_2)^2}$$

$$= \frac{2(1.96 + 1.28)^2(5575.6)}{(253.9 - 328.17)^2}$$

$$= 21.22 \approx 21$$

Where,

n = sample size

S = σ = Standard deviation

$Sp^2 = \sigma^2$ = Pooled Variance

The dropout rate is 20% was expected. Therefore, n = 25 should be recruited.

3.5 Selected Criteria

3.5.1 Inclusion Criteria

3.5.1.1 Female volunteers aged 18-35 years with skin color in the armpit area darker than skin color in the surrounding area.

3.5.1.2 Healthy individuals.

3.5.1.3 Able to follow up on treatment results at the specified time.

3.5.1.4 Willingness to provide informed consent and adhere to the study protocol.

3.5.2 Exclusion Criteria

3.5.2.1 People who have had their armpits treated with the following tools within the period of 4 weeks:

1. All types of lasers
2. Intense Pulse Light (IPL)

3. Chemical peeling

3.5.2.2 People who are being treated with drugs that affect skin color changes.

3.5.2.3 People who are pregnant or breastfeeding.

3.5.2.4 People with abnormal skin in the armpit area such as eczema, infection and cancer.

3.5.2.5 People with underlying disease that affect changes in skin color such as diabetes, cardiovascular disease and kidney disease.

3.5.2.6 People with congenital diseases that affect changes in skin color.

3.5.2.7 People who received radiotherapy or chemotherapy.

3.5.3 Criteria for Withdrawal from Research Studies (Discontinuation Criteria)

3.5.3.1 Unbearable or serious side effects occur.

3.5.3.2 Participants do not cooperate with treatment or are unable to come for follow-up.

3.6 Variables of the Study

3.6.1 Independent Variable

1. 5% Artocarpus lakoocha Heartwood Extract cream
2. 5% niacinamide cream

3.6.2 Dependent Variable

1. Mean melanin index
2. Photography
3. Side effects
4. Patient Satisfaction Score

3.7 Intervention

3.7.1 Randomization and Allocation

3.7.1.1 Eligible subjects will be assigned evaluation with Mexameter® MX18 for measuring the melanin index at the same point and calculated for the average value of every single visit at baseline (week 0), week 4, week 8 and week 12.

3.7.1.2 Eligible subjects will be performed photography, both side of the armpits (front, left and right picture) at every single visit at baseline (week 0), week 4, week 8 and week 12.

3.7.1.3 Eligible subjects will be randomized into one side using *Artocarpus lakoocha* Heartwood Extract cream and the other side using Niacinamide cream with a computer-generated randomization program.

3.7.1.4 Assign another physician who is not involved in the research to conduct the randomization. This information will be kept secret from the research participants and the assessor, are blinded to evaluate the treatment outcome until the analysis process is completed.

3.7.1.5 The physician, unrelated with the research, generated randomization sequence which randomly determined which side of eligible subjects to be treated with cream A and which side by cream B by "block randomization" and conceals the sequence in opaque envelops.

3.7.1.6 Both tubes of *Arthocarpus lakoocha* Heartwood Extract cream and Niacinamide cream are the same consistency, size, texture, smell, and color and will be enclosed in the identical packages then label with "A" and "B" respectively.

3.7.1.7 Both of these tubes contain 30g that can use for 1 month. The outside of these tubes is white color. Besides that, the texture and smell are the same.

3.7.1.8 A total of 23 numbers are assigned to represent eligible subjects. From 1 to 23 are consider whether they are even or odd numbers. Odd number participants will be received Mahad cream on the right axilla and Niacinamide cream on the left axilla and even number participants will received Niacinamide cream on the right and Mahad cream on the left.

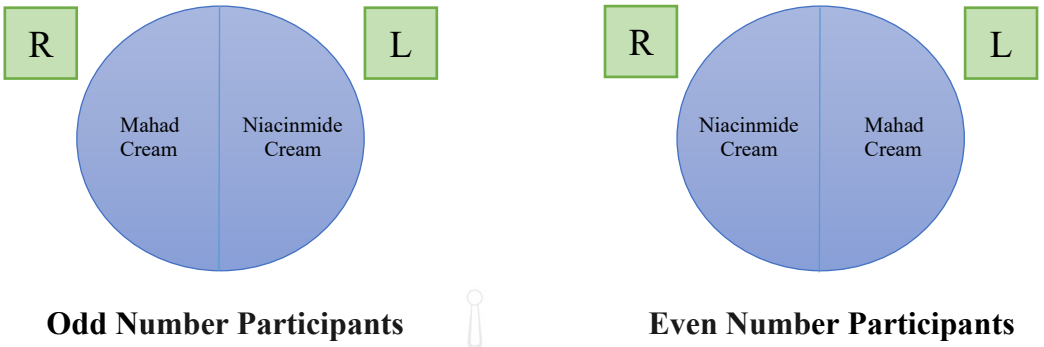


Figure 3.1 Randomization allocation diagram for split-side treatment

3.7.2 Instructions to Follow

3.7.2.1 Eligible subjects will be assigned to use daily, twice a day, after shower morning and before bed for the period of 12 weeks, followed up at baseline (week 0), week 4, week 8, and week 12.

3.7.2.2 Using the index finger with a pea-sized amount of cream, which is the precise amount of cream that comes out of the tube is one fingertip unit (FTU) weighing 0.5g is expressed in a standard 5mm diameter.

Figure 3.2 Fingertip unit amount of cream

3.7.2.3 Eligible subjects have to use their right hand to apply the cream on the left armpit and the left hand for the right armpit, without using the same hand to apply to both armpits.

3.7.2.4 If there are any side effects develop during the study time, cease using the cream, document them on the side effect form, and contact the research as soon as you can.

3.7.2.5 Eligible subjects are advised not to use any creams or other products such as skin lightning cream.

3.7.2.6 It is requested to avoid rubbing and scratching around the armpit area.

3.8 Materials and Equipment

3.8.1 Mexameter® MX18

3.8.2 5% *Artocarpus lakoocha* Heartwood Extract cream

3.8.2.1 Chemical constituents of 5% Mahad Cream

Table 3.1 Chemical constituents of 5% mahad cream

Order	Part	Ingredients	Amounts %W/W	Function
1	A	Deionized water	78.690	Solvent
2		Disodium EDTA	0.100	Chelating Agent
3	B	Carbomer	0.600	Thickener
4	C	Glycerin	3.000	Humectant
5	D	Glyceryl Stearate (and) PEG-100 Stearate	4.000	Emulsifier
6		Mineral Oil	5.000	Emollient
7		Dimethicone	1.000	Emollient
8		Polysorbate 80	0.800	Emulsifier
9		Tocopheryl Acetate	0.100	Anti-oxidant
10		Petrolatum	1.000	Emollient
11	E	Sodium Hydroxide	0.010	pH adjustor
12	F	*Artocarpus Lakoocha* Heartwood Extract	5.000	Skin conditioning
13	G	Phenoxyethanol,Chlorphenesine,Ethylhexylglycerin	0.700	Preservative

3.8.2.2 Thai FDA Registered Number

The registered number of 5% Mahad Cream is 12-1-6500037220 by Skin Intimate Company issued on 7 October 2022.

3.8.3 5% Niacinamide cream

3.8.3.1 Chemical constituents of 5% Niacinamide Cream

Table 3.2 Chemical constituents of 5% niacinamide cream

Order	Part	Ingredients	% in formula	% in material	Function	Explanation
1	A	DI water	67.700	100.000	Solvent	Clear liquid
2		Disodium EDTA	0.100	100.000	Chelating Agent	white powder
3		Carbopol 940	0.600	100.000	Thickener	white powder
4	B	Glycerin	3.000	100.000	Humectant	clear liqiud
5	C	Alcacel 170-PA-(SG)	4.000	100.000	Emulsifier	White solid
6		White Mineral Oil USP	5.000	100.000	Emollient	clear liquid
7		Dimethicone	1.000	100.000	Emollient	clear liquid
8		Polysorbate 80 USP	0.800	100.000	Emulsifier/ Solubilizer	Yellowish liquid
9		Tocopheryl Acetate	0.100	100.000	Anti-oxidant	Yellowish liquid
10		Petrolateum Jelly Markur 500	1.000	100.000	Emollient	White solid paste
11	D	Sodium Hydroxide	1.000	10.000	pH adjustor	white solid paste
		Water		90.000	solvent	clear liquid
12	E	Niacinamide	5.000	100.000	Skin conditioning	white powder
		water	10.000	100.000	solvent	clear liquid
13	G	Phenoxyethanol	0.700	65.000	Preservative	clear liquid
		Chlorphenesine				
		glycerin		25.000		
				10.000		

3.8.3.2 Thai FDA Registered Number

The registered number of 5% Niacinamide Cream is 12-1-6500036606 by Skin Intimate Company issued on 4 October 2022.

3.8.4 Informed consent form

3.8.5 Side effects assessment form

3.9 Study Procedures

The study will consist of a Screening/Baseline visit and three scheduled follow-ups. Specific activities for each follow-up are listed below:

3.9.1 Visit 1: Screening/Baseline (Week 0)

All subjects are recruited by inclusion and exclusion criteria for screening for the study. The study requirements will be reviewed during the screening, including study objectives, method, pre-and post-treatment instruction, expected benefits, possible side effects, and written informed consent.

At Screening, the investigator will:

1. Confirm the subject meets the inclusion criteria
2. Obtain a signed, written informed consent
3. Review and documentation of the subject's medical and dermatological history
4. Record any concomitant medications and therapies

Once the Screening procedures have been completed, the investigator will:

1. Perform a dermatological examination and a brief physical examination (including vital signs, height and weight)
2. Record Baseline pigmentary skin lesions
3. Perform photography of the lesions
4. Record melanin index by Mexameter® MX18
5. Randomize the subject to the number for perceiving which side of the axilla will be treated with 5% *Artocarpus lakoocha* Heartwood Extract cream or 5% Niacinamide cream by using blocked randomization.
6. Instruct the subject on how to apply the cream

7. Schedule the next visit

3.9.2 Visit 2 (Week 4) and Visit 3 (Week 8)

At these visits, the investigator will perform the same protocol as Visit 1 (Week 0), the investigator will:

1. Record side effects that occur with the subject after the treatment of Visit 1 (Week 0) and 2 (Week 4)

2. Perform photography of all subjects

3. Record melanin index by Mexameter® MX18

4. Instruct the subject on how to apply the cream

5. Schedule the next visit

3.9.3 Visit 4 (Week 12): End of Study

At this visit, the investigator will:

1. Record side effects that occur with the subject after Visit 3

2. Perform photography of all subjects

3. Record melanin index by Mexameter® MX18

4. Provide the Patient Satisfaction form to the subjects

5. Collect the tubes of 5% Artocarpus lakoocha Heartwood Extract cream and 5% Niacinamide cream

6. Complete the End of the Study and discharge the subject from the study

3.10 Data Collection

3.10.1 Mean Melanin Index

The measurement points for mean melanin index is taken from the center of the armpit, comparing with the surrounding skin within 5cm from the midpoint. Mean melanin index assessed by Mexameter®MX18 at the same point during the study at baseline (week 0), 4, 8, 12 weeks. The mean value will be recorded.

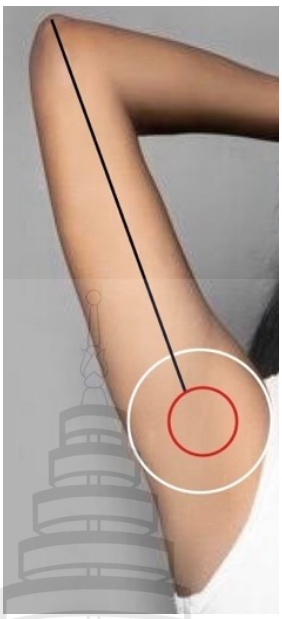


Figure 3.3 Measurement location used in research

Table 3.3 Melanin index evaluation form

Evaluation Week	**Side of the Treatment**	**Mean Melanin Index Measure by Mexameter®MX18 (1-1000)**
0 (Baseline)	Right	
	Left	
4 (After the 1st treatment)	Right	
	Left	
8 (After the 2nd treatment)	Right	
	Left	
12 (After the 3rd treatment)	Right	
	Left	

3.10.2 Patient Satisfaction Score

Patient satisfaction assessed by scoring system using Global Satisfaction Score ranging from -1 to 4 in the end of study 12 week.

Table 3.4 Patient satisfaction evaluation form

Evaluation Week		Satisfaction Score					
Week 12	Axilla	-1	0	1	2	3	4
		(worse)	(no improvement)	(1-25%)	(26-50%)	(51-75%)	(76-100%)
	Right						
	Left						

3.10.3 Side Effects Evaluation

Table 3.5 Side effects evaluation form

Evaluation Week	Side of the treatment	Side effects from the first treatment			
		Erythema	Pruritus	Burning	Dryness
4	Right	• Absent	• Absent	• Absent	• Absent
		• Mild	• Mild	• Mild	• Mild
		• Moderate	• Moderate	• Moderate	• Moderate
		• Severe	• Severe	• Severe	• Severe
	Left	• Absent	• Absent	• Absent	• Absent
		• Mild	• Mild	• Mild	• Mild
		• Moderate	• Moderate	• Moderate	• Moderate
		• Severe	• Severe	• Severe	• Severe
8	Right	• Absent	• Absent	• Absent	• Absent
		• Mild	• Mild	• Mild	• Mild
		• Moderate	• Moderate	• Moderate	• Moderate
		• Severe	• Severe	• Severe	• Severe
	Left	• Absent	• Absent	• Absent	• Absent
		• Mild	• Mild	• Mild	• Mild
		• Moderate	• Moderate	• Moderate	• Moderate
		• Severe	• Severe	• Severe	• Severe

Table 3.5 (continued)

Evaluation Week	Side of the treatment	Side effects from the first treatment			
		Erythema	**Pruritus**	**Burning**	**Dryness**
12	Right	• Absent • Mild • Moderate • Severe	• Absent • Mild • Moderate • Severe	• Absent • Mild • Moderate • Severe	• Absent • Mild • Moderate • Severe
	Left	• Absent • Mild • Moderate • Severe	• Absent • Mild • Moderate • Severe	• Absent • Mild • Moderate • Severe	• Absent • Mild • Moderate • Severe

Note Side effect assessment level describes:

1. Absent
2. Mild = has few side effects, does not affect daily life
3. Moderate = has moderate side effects, affecting daily life but it doesn't need treatment
4. Severe = has severe side effects, affecting daily life must be treated

Table 3.6 Data collection

	Baseline	**4th Week**	**8th Week**	**12th Week**
Mexameter	√	√	√	√
Photography	√	√	√	√
Patient Satisfaction Score				√
Side effects		√	√	√

3.11 Data Analysis

3.11.1 Descriptive Data Analysis

3.11.1.1 Qualitative data calculated as a frequency and percentage:

1. Gender
2. Occupation
3. Side effects
4. Patient Satisfaction

3.11.1.2 Quantitative data calculated as a mean with standard deviation (for normal distribution data) and median (for non-normal distribution data):

1. Age
2. Melanin index (measured by Mexameter® MX18)

3.11.2 Inferential Statistics

3.11.2.1 Primary hypothesis

To compare melanin decreasing between using 5% *Artocarpus lakoocha* Heartwood Extract cream and 5% niacinamide cream in treatment of dark armpits measured by Mexameter MX18 resulted in different time points from baseline compared with week 4, 8, and 12 visits by using repeated measure ANOVA to compare continuous data between 2 sides

3.11.2.2 Secondary hypothesis

1. To compare the side effects of 5% *Artocarpus lakoocha* Heartwood Extract cream and 5% niacinamide cream using Mc Nemar's test

2. To compare patient satisfaction after the use of 5% *Artocarpus lakoocha* Heartwood Extract cream and 5% niacinamide cream measured by Global Satisfaction Score (-1 to 4 numeric rating scale) resulted in at least a scale of 3 (good improvement or excellent improvement) between two sides after 12 week visit by using Mc Nemar's test

All of these are calculated with a significance level of a p-value < 0.05.

Statistical Package for the Social Sciences (SPSS) for window version 23.0 is used for statistical analysis.

3.12 Ethical Consideration

All protocols of the study have been approved by the human research committee at Mae Fah Luang University and this study was conducted by following the guideline of Good Clinical Practice (GCP). The researcher has completed Good Clinical Practice and the Human Research Ethics training course. Volunteers will experience enhanced levels of confidence when they are aware that the rights, safety, and welfare of study subjects are respected in accordance with ethical norms.

For general understanding, considerations were as follows.

3.12.1 An evaluation and approval of the research by an ethics committee.

3.12.2 Volunteers completely understood the objective, methodology, and possible side effects of the research.

3.12.3 Prior to participating in the study, volunteers provided their informed consent by signing a consent form. Individuals have the option to depart at any given moment without incurring any negative consequences.

3.12.4 In the event of the occurrence of a problem, the researcher assumed responsibility and fully helped the volunteers.

3.12.5 This research was free of charge.

3.12.6 All data provided was held in strict confidentiality. The researcher replaced the file names of the patients' pictures with serial numbers, ensuring that both the names and the numbers were identical.

3.12.7 During the course of the research, serious adverse events were reported to the ethics committee.

CHAPTER 4

RESULTS

This comparative study for efficacy between 5% *Artocarpus lakoocha* Heartwood Extract cream and 5% Niacinamide cream in female patients was reviewed and approved by Mae Fah Luang University Ethics Committee on Human Research in compliance with international guidelines. Approval date March 18, 2025. The researcher started conducting the study on 2nd May 2025 to 9th August 2025. The study is a prospective, randomized, double-blind, controlled trial, split-side study with 25 subjects enrolled.

The study was conducted at Mae Fah Luang University Hospital, Bangkok. The duration was 12 weeks through the end of the study. All subjects received 4 treatments monthly at baseline, week 4, 8 and 12. The side effects were obtained at 4, 8, and 12 weeks of treatment. And patient satisfaction was evaluated at 12 weeks of treatment.

4.1 General Characteristics of the Sample

23 of the 25 subjects completed the treatment protocol and were follow up through the end of the study. The patient demographics data are summarized in Table 4.1.3 subjects withdrew from the study because they had scheduling conflicts and could not follow the follow-up plan. The average age of participants was 28.9 ± 3.5 years, ranging from 20 to 35 years, divided into age 20-25 with 3 subjects and 25-35 with 20 subjects. All participants were female. Regarding occupation, 8 subjects (34.8%) were student and 15 subjects (65.2%) were employees. In term of Fitzpatrick skin type, the majority were type IV (69.6%), followed by type III (17.4%) and type V (13%). None of the participants had underlying disease and all of them with normal body mass index (BMI). The diagnosis of axillary hyperpigmentation was based on clinical features by physician.

Table 4.1 Patient demographics (n=23)

Variable	Overall
Age (years)	
Mean (SD)	28.9 (3.5)
20-25 years, n	3
25-35 years, n	20
min-max	20-35
Occupation, n (%)	
Student	8
Employee	15
Fitzpatrick skin type, n	
Type III	4
Type IV	16
Type V	3

4.2 Clinical Evaluation

4.2.1 Melanin Index

The researcher assessed the melanin index using Mexameter® MX18 at the center of the lesion of axillary prior to treatment. The measurement was taken three times at the same point, and the average value was calculated at each visit, which included baseline, week 4, 8 and 12. The mean and standard deviation of the two sides presented in Table 4.2 and Figure 4.1 were compared.

Table 4.2 Statistical analysis of mean melanin index of *Artocarpus lakoocha* heartwood extract cream and niacinamide cream at baseline, follow-up 4th, 8th and 12th week (n=23)

	5% *Artocarpus lakoocha* Heartwood Extract cream	**5% Niacinamide cream**	**p-value**
Baseline	302.17 ± 108.66	299.63 ± 101.80	0.680
4th week	276.11 ± 101.86	283.49 ± 100.41	0.103
8th week	254.82 ± 94.21	263.70 ± 95.85	0.143

Table 4.2 (continued)

	5% *Artocarpus lakoocha* Heartwood Extract cream	**5% Niacinamide cream**	**p-value**
12thweek	242.95 ± 90.29	248.84 ± 93.16	0.306
P-value	< 0.001	< 0.002	0.056

Note Data were analyzed by two-way, with repeated measure ANOVA

The data presented in Table 4.2 indicates a statistical analysis of mean melanin index values for both 5% *Artocarpus lakoocha* Heartwood Extract cream and 5% Niacinamide cream from baseline to the 4th, 8th and 12th weeks of treatment among 23 participants. At baseline, the mean melanin index was comparable between the two treatment sides, indicating no significant difference. Additionally, a progressive decline in melanin index was observed in both groups throughout the 12th week study period, reflecting a gradual improvement in axillary hyperpigmentation. The side treated with 5% *Artocarpus lakoocha* Heartwood Extract cream shows decrease from 302.17 ± 108.66 at baseline to 242.95 ± 90.29 at week 12, with p-value of < 0.001, indicating a significant improvement over time. Similarly, the side treated with 5% Niacinamide cream decreased from 299.63 ± 101.80 at baseline to 248.84 ± 93.16 at week 12, with p-value of 0.002, also demonstrating a statically significant reduction. When comparing the two treatments directly (Mahad vs Niacinamide), the time and treatment interaction was not significant with p-value was 0.056, indicating that although both treatments effectively reduced pigmentation over time, their depigmenting effects were comparable, with no clear superiority of one treatment over the other.

Table 4.3 Mean difference melanin index measured by Mexameter® MX18 in 5% *Artocarpus lakoocha* heartwood extract and 5% niacinamide cream

Comparison between time periods	**5% *Artocarpus lakoocha* (Mean diff.± SD)**	**p-value**	**5% Niacinamide (Mean diff.± SD)**	**p-value**
Baseline - Week 4	-26.06 ± 3.2	< 0.001	-16.15 ± 2.18	< 0.001
Baseline - Week 8	-47.35 ± 5.88	< 0.001	-35.93 ± 4.49	< 0.001
Baseline - Week 12	-59.22 ± 6.32	< 0.001	-50.80 ± 4.65	< 0.001
Week 4 - Week 8	-21.29 ± 3.54	< 0.001	-19.78 ± 3.27	< 0.001

Table 4.3 (continued)

Comparison between time periods	5% *Artocarpus lakoocha* (Mean diff.± SD)	p-value	5% Niacinamide (Mean diff.± SD)	p-value
Week 4 - Week 12	-33.15 ± 3.96	< 0.001	-34.65 ± 3.76	< 0.001
Week 8 - Week 12	-11.87 ± 2.1	< 0.001	-14.87 ± 2.81	< 0.001

Note Multiple comparison by Bonferroni method

According to the multiple comparison analysis results from Table 4.3, the mean melanin index in the *Artocarpus lakoocha* group at week 4 was significant lower compared to baseline (MD = -26.06, $p < 0.001$). Similarly, reductions were observed at week 8 (MD = -47.35, $p < 0.001$) and week 12 (MD = -59.22, $p < 0.001$), all statistically significant at the 0.05 level. Pairwise comparisons further showed progressive decreases between week 4 and week 8 (MD = -21.29, $p < 0.001$), week 4 and week 12 (MD = -33.15, $p < 0.001$), and week 8 and 12 (MD = -11.87, $p < 0.001$). Additionally, for Niacinamide group, the mean melanin index also decreased significantly over time. At week 4, the reduction compared to baseline was significant (MD = -16.15, $p < 0.001$), with further decreases at week 8 (MD = -35.93, $p < 0.001$), and week 12 (MD = -50.80, $p < 0.001$). Additional comparisons demonstrated significant reduction between week 4 and week 8 (MD = -19.78, $p < 0.001$), week 4 and week 12 (MD = -34.65, $p < 0.001$), and week 8 and 12 (MD = -14.87, $p < 0.001$).

4.3 Patient Satisfaction Scores

Patient Satisfaction assessed by using Global Satisfaction Score ranging from -1 t 4 (worse to 76-100% improvement) between two sides of armpit after 12 weeks of the visit. Overall, at 12 weeks, both 5% *Artocarpus lakoocha* Heartwood Extract cream and 5% Niacinamide cream showed no significant differences ($p = 1.000$) in patient satisfaction (Table 4.3)

Table 4.4 Patient satisfaction scores at week 12th of treatment

Patient Satisfaction	5% *Artocarpus lakoocha* Heartwood Extract cream	5% Niacinamide cream	p-value
	n	n	
-1 (worse)	0	0	1.000
0 (no improvement)	0	0	
1 (fairly 1-25% improvement)	7	6	
2 (Moderate 26-50% improvement)	8	8	
3 (Good 51-75% improvement)	8	7	
4 (Excellent 76-100% improvement)	0	2	

Note McNemar test comparison of the percentage satisfaction between the two treatments.
"Minimal Satisfied" (-1 to 2), "Satisfied" (3 to 4)

Table 4.5 Regrouped patient satisfaction score at week 12 of treatment (n = 23)

Patient Satisfaction	5% *Artocarpus lakoocha*	5% Niacinamide cream	p-value
	n	n	
Minimal satisfied	15	14	1.000
Satisfied	8	9	

Note Value presents as number. "Minimal Satisfied" (-1 to 2) include worse, no improvement, or fairly improvement and moderate improvement (1-50%). "Satisfied" (3 to 4) includes good and excellent improvement (51-100%).
McNemer test comparison between Mahad and Niacinamide.

This table 4.5 presents the regrouped patient satisfaction scores at week 12 of treatment with 5% *Artocarpus lakoocha* and 5% Niacinamide cream. In the Mahad group, 15 participants were classified as minimal satisfied (worse to moderate improvement with ≤ 50%), while 8 participants were satisfied (Good to Excellent

improvement > 50%). Similarly, in the Niacinamide group, 14 participants were minimal satisfied, whereas 9 participants were satisfied. Statistical analysis using McNemer test revealed no significant difference in satisfaction levels between the two treatments (p = 1.000). These finding indicate that both agents provided comparable levels of patient-perceived improvement in axillary hyperpigmentation.

4.4 Side Effects

There were no any side effect symptoms reported by any of the 23 participants throughout 12 weeks clinical trial duration of using both 5% *Artocarpus lakoocha* Heartwood Extract cream and 5% Niacinamide cream. The result reveals that it does not induce dryness, redness, burning or itching during the study period. Furthermore, no participants discontinued or withdrew from the study due to adverse effects, confirming the favorable safety and tolerability profiles of both topical agents for axillary application.

CHAPTER 5

DICUSSION AND CONCLUSION

5.1 Discussion

Hyperpigmentation in the axilla is a common dermatologic concern, particularly in women[3], and is often associated with friction, hair shaving, plucking, removal, obesity, hormonal influences, UV exposure, the use of antiperspirant, deodorant, perfume or post-inflammatory hyperpigmentation[4]. Currently, there is no gold standard treatment for axillary hyperpigmentation[3]. Only we have to prevent by avoiding friction, or discontinuing the use of any perfume or deodorant that may worsen the pigmentation, and various therapeutic options for hyperpigmentation have been explored, including the use of skin lightening such as hydroquinone, mequinol, retinoids, azelic acid, kojic acid, niacinamide, licorice extract and etc[3]. Since this condition can negatively affect quality of life, confidence, and cosmetic satisfaction, effective yet treatment is clinically valuable.

Artocarpus lakoocha Heartwood Extract, rich in oxyresveratrol, has been extensively studied as a potent tyrosinase inhibitor. Previous study by Pichsinee Suwannarat conducted the efficiency of *Artocarpus lakoocha* Heartwood Extract in the treatment of axillary hyperpigmentation reported a significant reduction in melanin index after 12 weeks treatment and this is the depigmenting properties, a good to excellent response satisfactory results[4]. In this present study, the reduction in melanin index after 12 weeks of treatment with 5% *Artocarpus lakoocha* Heartwood Extract cream showed a comparable trend, suggesting that the depigmenting efficacy observed is consistent with previous findings. This supports the role of oxyresveratrol as a potent natural tyrosinase inhibitor contributing to melanin suppression and improvement of axillary hyperpigmentation.

Previous studies have reported that topical niacinamide is an effective agent for reducing hyperpigmentation through inhibition of melanosome transfer to keratinocytes. Hakozaki et al. demonstrated that a 5% niacinamide formulation

significantly decreased depigmentation after 8 weeks of treatment, with visible improvement in the skin brightness. Similarly, Bissett et al. reported that niacinamide not only reduced pigmentation but also improved skin texture and barrier function[60]. In this present study, the improvement in melanin index after 12 weeks of treatment with 5% niacinamide cream is consistent with these findings, confirming its role as a safe and effective depigmenting agent for axillary hyperpigmentation[3].

This study is the comparative, for efficacy between 5% *Artocarpus lakoocha* Heartwood Extract cream and 5% Niacinamide cream in the treatment of axillary hyperpigmentation in female patients. It is a prospective, randomized, double-blinded split-side study with 25 subjects enrolled and 23 subjects are completed all sessions of treatment. 2 subjects withdrew from the study due to scheduling conflicts, preventing them from adhering to the follow-up plan. The majority were aged 25 to 35 years (87%), with a smaller proportion aged 20 to 25 years old (13%). Most participants were Fitzpatrick skin type IV (70%), followed by type III (17%) and type V (13%). In terms of occupation, 65% were employees and 35% were students. These demographics reflect the typical population affected by axillary hyperpigmentation, predominantly young adult females with intermediate to dark skin phototypes. We recorded mean melanin index, side effect at every visit and patient satisfaction at the end of follow-up period (week 12).

Mean melanin index at baseline was comparable between Mahad side (302.17 ± 108.66) and Niacinamide side (299.63 ± 101.80) with no significant difference ($p = 0.680$). Both treatments demonstrated progressive improvement over time. By week 12, the mean melanin index decreased by -59.22 (-19.6%) on Mahad-treated side and 50.79 (-16.95%) on Niacinamide-treated side. With-in group analysis confirmed significant reductions over time for both agents ($p < 0.001$ for Mahad, $p < 0.002$ for Niacinamide). However, paired comparisons at each time point did not reveal significant difference between the two-sides. Repeated measures ANOVA confirmed a significant main effect of time ($p < 0.001$), indicating that both treatments consistently reduced pigmentation across the study period. While the main effect of treatment was not statistically significant, the time with treatment interaction ($p = 0.056$). This borderline value suggests a potential trend toward differential effects between Mahad and Niacinamide over time, which may become clearer in studies with a larger sample size

or longer follow-up to confirm whether the observed trend represents a true clinical difference.

Patient satisfaction scores paralleled the objective findings of melanin index reduction. The majority of participants reported fairly to moderate improvement in axillary hyperpigmentation at the end of week 12. Although, Mahad-treated side showed a slight greater mean reduction (-19.6%) compared with Niacinamide side (-16.95%), this 3% difference did not reach statistical significance. Nevertheless, such a numerical difference may still be clinically relevant, as even small improvements can influence how patients perceive treatment benefits. Overall, the consistency between objective outcomes and subjective satisfaction supports the effectiveness of both Mahad and Niacinamide in managing axillary hyperpigmentation.

Importantly, no adverse effects such as erythema, burning, pruritus or dryness were reported throughout the study on either treatment side. This finding indicates that both 5% Mahad and 5% Niacinamide cream were well-tolerated. The absence of this side effects is noteworthy, as 5% Niacinamide, despite its common use, has been associated in some study by Rofte, H.M, reported with mild burning, itching and redness[63]. Similarly, plant extracts such as *Artocarpus lakoocha* may carry a potential risk of sensitivity due to their natural polyphenolic compounds. The lack of such effects in the present study reinforces the favourable safety profile of both agents and supports their suitability for long-term use in managing axillary hyperpigmentation.

The comparable improvement observed between *Artocarpus lakoocha* (Mahad) and Niacinamide in this study may be attributed to their distinct yet complementary mechanisms of action in melanin suppression. Mahad, rich in oxyresveratrol, acts primarily as a potent tyrosinase inhibitor, directly interfering with the enzyme responsible for melanin synthesis. In contrast, Niacinamide exerts its depigmenting effect by blocking melanosome transfer from melanocytes to keratinocytes through PAR-2 inhibition, thereby reducing visible pigmentation rather than melanin formation itself. Consequently, both agents act at different stages of the pigmentation pathway, Mahad at the level of melanin production and Niacinamide at the level of pigment transfer which may explain the comparable reduction in melanin index and patient satisfaction despite their mechanistic differences. The slightly greater reduction observed with Mahad could reflect its stronger enzymatic inhibition effect, though the

lack of statistical significance suggests that both treatments achieve clinically meaningful yet similar outcomes in axillary hyperpigmentation. These results confirm that both Mahad and Niacinamide are effective and well-tolerated topical agents for axillary hyperpigmentation. Mahad showed a slightly greater mean reduction compared to Niacinamide, but the difference did not reach a statistical significance.

5.2 Conclusion

In summary, both 5% *Artocarpus lakoocha* Heartwood Extract cream and 5% Niacinamide cream significantly improved axillary hyperpigmentation with no notable adverse effects after 12 weeks of treatment. Mahad demonstrated a slighter greater mean melanin index reduction compared with Niacinamide, however, the difference did not reach statistical significant. These findings suggest that Mahad is non-inferior to Niacinamide and may serve as a potential alternative treatment option rather than a proven superior agent. Nevertheless, larger and long-term studies are warranted to confirm the durability of these effects and to further evaluate long-term safety beyond the 12-week study period.

5.3 Suggestions

The results suggest that 5% *Artocarpus lakoocha* Heartwood Extract cream, a natural botanical preparation, may serve as an effective and safe alternative to Niacinamide in the management of axillary hyperpigmentation. Both treatments were tolerated without significant adverse effects, reinforcing their suitability for use in sensitive areas such as axillae.

5.4 Limitations

In this study, the small sample size of 25 participants, with 23 completing, may have limited the ability to subtle differences between treatments. In addition, the duration of follow-up was 12 weeks, which is insufficient to determine long-term efficacy, durability of response, or recurrence after discontinuation of therapy. Moreover, the study population included only female participants, most of them were Fitzpatrick skin types III to V. And, the pigmentation assessed solely using Mexameter® MX18, which provides objective melanin index values however does not capture histological or molecular changes.

5.5 Future Studies

In future studies, Mahad may be regarded as a promising natural option alongside Niacinamide, serving as an alternative rather than a full replacement. Moreover, a larger of patients should be recruited, more diverse populations, incorporating both male and female participants and a wide range skin phototypes, to enhance the generalizability of findings. Longer follow-up periods are also recommended to better evaluate long-term outcomes and the risk of relapse. In addition, comparison with gold standard depigmenting agents, such as hydroquinone, would provide valuable benchmarks. Furthermore, mechanistic investigations, including histological and biochemical analyses such as melanin granules or tyrosinase expression, are recommended to clarify the biological pathways involved in pigment reduction.

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APPENDIX A

INFORMED CONSENT FORM

หนังสือแสดงความยินยอมเข้าร่วมการวิจัย

ข้าพเจ้า _____ ตัดสินใจเข้าร่วมการวิจัยเรื่อง "การศึกษาเปรียบเทียบประสิทธิผลระหว่างสารสกัดจากมะหาด (Artocarpus lakoocha Heartwood Extract 5%) และครีมวิตามิน B3 ไนอะซินาไมด์ (Niacinamide 5%) ในการรักษาภาวะผิวคล้ำบริเวณรักแร้ ในผู้ป่วยเพศหญิง ด้วยวิธีการทดลองแบบสุ่ม แบบปกปิดสองทาง (A Randomized, Double-Blind, Controlled Trial)" ซึ่งข้าพเจ้าได้รับข้อมูลและคำอธิบายเกี่ยวกับการวิจัยนี้แล้ว และได้มีโอกาสซักถามและได้รับคำตอบเป็นที่พอใจแล้ว ข้าพเจ้ามีเวลาเพียงพอในการอ่านและทำความเข้าใจข้อมูลในเอกสารให้ข้อมูลสำหรับผู้เข้าร่วมการวิจัยอย่างถี่ถ้วน และได้รับเวลาเพียงพอในการตัดสินใจว่าจะเข้าร่วมการวิจัยนี้

ข้าพเจ้ารับทราบว่าข้าพเจ้าสามารถปฏิเสธการเข้าร่วมการวิจัยนี้ได้โดยอิสระ และระหว่างการเข้าร่วมการวิจัย ข้าพเจ้ายังสามารถถอนตัวออกจากการวิจัยได้ทุกเมื่อ โดยไม่ส่งผลกระทบต่อการดูแลรักษา หรือสิทธิที่ข้าพเจ้าพึงมี

โดยการลงนามนี้ ข้าพเจ้าไม่ได้สละสิทธิใด ๆ ที่ข้าพเจ้าพึงมีตามกฎหมาย และหลังจากลงนามแล้ว ข้าพเจ้าจะได้รับเอกสารข้อมูลและขอความยินยอมไว้จำนวน 1 ชุด

ลายมือชื่อผู้เข้าร่วมการวิจัย _____ วัน-เดือน-ปี _____

(_____)

..... (กรณีที่ผู้เข้าร่วมการวิจัยอ่านหนังสือไม่ออกแต่ฟังเข้าใจ) .....

ข้าพเจ้าไม่สามารถอ่านหนังสือได้ แต่ผู้วิจัยได้อ่านข้อความในเอกสารข้อมูลและขอความยินยอมนี้ให้แก่ข้าพเจ้าฟังจนเข้าใจดีแล้ว ข้าพเจ้าจึงลงนามหรือพิมพ์ลายนิ้วมือของข้าพเจ้าในหนังสือนี้ด้วยความเต็มใจ

ลงนาม/พิมพ์ลายนิ้วมือผู้เข้าร่วมการวิจัย _____ วัน-เดือน-ปี _____

(_____)

ลายมือชื่อผู้ขอความยินยอม _____ วัน-เดือน-ปี _____

(นพ. ชกลา ชวน)

คำรับรองของพยานผู้ไม่มีส่วนได้เสียกับการวิจัย (กรณีที่ผู้เข้าร่วมการวิจัยอ่านหนังสือไม่ออกแต่ฟังเข้าใจ)

ข้าพเจ้าได้อยู่ร่วมในกระบวนการขอความยินยอมและยืนยันว่า ผู้ขอความยินยอมได้อ่าน/อธิบายเอกสารข้อมูลให้แก่ _____ ซึ่งผู้มีชื่อข้างต้นมีโอกาสซักถามข้อสงสัยต่าง ๆ และได้ให้ความยินยอมเข้าร่วมการวิจัยโดยอิสระ หลังจากรับทราบข้อมูลที่มีอยู่ตรงตามที่ปรากฏในเอกสารนี้แล้ว

ลายมือชื่อพยาน _____ วัน-เดือน-ปี _____

(_____)

ลายมือชื่อผู้แทนโดยชอบธรรม/ผู้ปกครอง_____ วัน-เดือน-ปี _____

(_____)

APPENDIX B

CASE RECORD FORM

DO NOT PUBLISH INFORMATION

RESEARCH PROFILE (CONFIDENTIAL)

ID:……..……Date……

General information (only official)

1. Name: ……
2. Age:…….years
3. Participants Identification Code: ……
4. Address:……
5. Tel: ……
6. Email:……

PATIENT ASSESSMENT FORM

Melanin Index evaluation form

Date.....

Evaluation Week	Side of the Treatment	Mean Melanin Index Measure by Mexameter®MX18 (1-1000)
0 (Baseline)	Right	
	Left	

Date.....

Evaluation Week	Side of the Treatment	Mean Melanin Index Measure by Mexameter®MX18 (1-1000)
4 (After the 1st treatment)	Right	
	Left	

Date.....

Evaluation Week	Side of the Treatment	Mean Melanin Index Measure by Mexameter®MX18 (1-1000)
8 (After the 2nd treatment)	Right	
	Left	

Date.....

Evaluation Week	Side of the Treatment	Mean Melanin Index Measure by Mexameter®MX18 (1-1000)
12 (After the 3rd treatment)	Right	
	Left	

Patient Satisfaction Score

Patient satisfaction assessed by scoring system using Global Satisfaction Score ranging from -1 to 4 in the end of study 12 week.

Patient Satisfaction Evaluation form

Date.....

Evaluation Week	Satisfaction Score						
Week 12	Axilla	-1 (worse)	0 (no improvement)	1 (1-25%)	2 (26-50%)	3 (51-75%)	4 (76-100%)
	Right						
	Left						

Side effects Evaluation

Side effects evaluation form

Date.....

Side effect assessment level describes:

- Absent
- Mild = has few side effects, does not affect daily life
- Moderate = has moderate side effects, affecting daily life but it doesn't need treatment
- Severe = has severe side effects, affecting daily life must be treated

Evaluation Week	Side of the treatment	Side effects from the first treatment			
		Erythema	Pruritus	Burning	Dryness
4	Right	• Absent • Mild • Moderate • Severe	• Absent • Mild • Moderate • Severe	• Absent • Mild • Moderate • Severe	• Absent • Mild • Moderate • Severe
	Left	• Absent • Mild • Moderate • Severe	• Absent • Mild • Moderate • Severe	• Absent • Mild • Moderate • Severe	• Absent • Mild • Moderate • Severe

Other symptoms (please specify).....

.....

Date.....

Side effect assessment level describes:

- Absent
- Mild = has few side effects, does not affect daily life
- Moderate = has moderate side effects, affecting daily life but it doesn't need treatment
- Severe = has severe side effects, affecting daily life must be treated

Evaluation Week	Side of the treatment	Side effects from the first treatment			
		Erythema	Pruritus	Burning	Dryness
8	Right	• Absent • Mild • Moderate • Severe	• Absent • Mild • Moderate • Severe	• Absent • Mild • Moderate • Severe	• Absent • Mild • Moderate • Severe
	Left	• Absent • Mild • Moderate • Severe	• Absent • Mild • Moderate • Severe	• Absent • Mild • Moderate • Severe	• Absent • Mild • Moderate • Severe

Other symptoms (please specify).....

.....

Date.....

Side effect assessment level describes:

- Absent
- Mild = has few side effects, does not affect daily life
- Moderate = has moderate side effects, affecting daily life but it doesn't need treatment
- Severe = has severe side effects, affecting daily life must be treated

Evaluation Week	Side of the treatment	Side effects from the first treatment			
		Erythema	Pruritus	Burning	Dryness
12	Right	• Absent • Mild • Moderate • Severe	• Absent • Mild • Moderate • Severe	• Absent • Mild • Moderate • Severe	• Absent • Mild • Moderate • Severe
	Left	• Absent • Mild • Moderate • Severe	• Absent • Mild • Moderate • Severe	• Absent • Mild • Moderate • Severe	• Absent • Mild • Moderate • Severe

Other symptoms (please specify).....

.....

APPENDIX C

CLINICAL EVALUATION

Table C1 Mean melanin index of 5% *Artocarpus lakoocha* heartwood extract cream and 5% niacinamide cream at baseline, 4th week, 8th week and 12th week

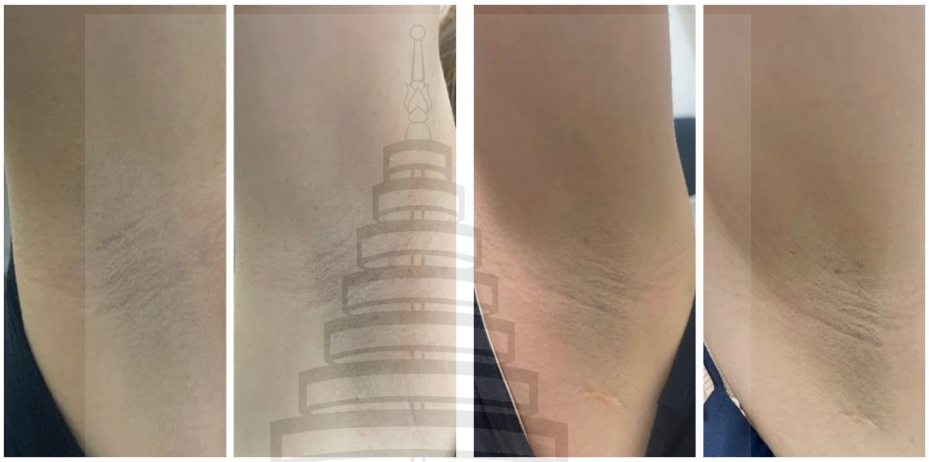
ID	5% *Artocarpus lakoocha*				5% Niacinamide			
	Baseline	4th week	8th week	12th week	Baseline	4th week	8th week	12th week
1	166.67	164.0	157.33	145.33	181.67	178.64	170.0	162.0
2	540.0	486.67	466.67	432.67	459.67	429.33	387.33	354.33
3	335.67	320.0	308.0	300.0	381.67	374.0	369.33	329.0
4	235.67	194.33	180.33	173.67	191.33	188.0	184.33	168.0
5	354.67	339.0	335.0	296.33	364.33	362.33	347.33	335.33
6	281.67	258.0	220.0	211.0	262.33	255.33	203.33	201.0
7	317.67	282.67	241.67	234.67	324.67	302.0	254.33	242.67
8	275.33	257.33	248.0	235.67	280.0	267.33	251.67	247.33
9	503.67	452.67	388.33	369.33	479.33	454.67	445.0	434.0
10	306.0	246.67	204.33	200.67	247.0	230.67	226.67	215.67
11	278.0	252.67	240.0	235.67	285.0	261.0	250.0	245.67
12	277.0	259.67	234.33	230.67	284.0	264.67	249.67	245.67
13	181.0	178.33	161.67	155.33	180.0	161.67	143.33	132.67
14	292.33	261.67	256.67	243.0	289.0	282.67	257.33	245.67
15	237.67	221.33	204.67	200.33	251.0	240.67	229.33	224.67
16	261.33	228.33	217.67	209.33	264.67	254.33	245.0	193.33
17	206.33	189.33	179.67	151.67	186.67	178.33	171.67	150.33
18	269.0	242.33	223.67	215.33	276.0	259.67	226.67	220.33
19	558.33	536.0	490.0	478.67	571.0	549.33	496.0	490.0
20	135.33	107.67	99.67	90.33	168.67	121.33	91.33	89.0
21	330.0	310.67	309.0	305.0	346.67	323.33	305.0	282.0
22	239.33	234.0	215.33	210.67	267.0	246.33	239.67	230.33
23	367.33	327.33	279.0	262.67	350.0	334.67	321.0	284.33

Table C2 Patient's satisfaction score at 12th week for 5% *Artocarpus lakoocha* heartwood extract cream and 5% niacinamide cream

ID	5% *Artocarpus lakoocha*	5% Niacinamide
1	2	4
2	2	3
3	3	2
4	2	3
5	3	1
6	3	2
7	2	4
8	1	1
9	1	2
10	1	1
11	3	3
12	2	3
13	3	3
14	1	1
15	3	3
16	1	2
17	1	1
18	3	2
19	1	2
20	2	1
21	2	2
22	3	3
23	2	2

APPENDIX D

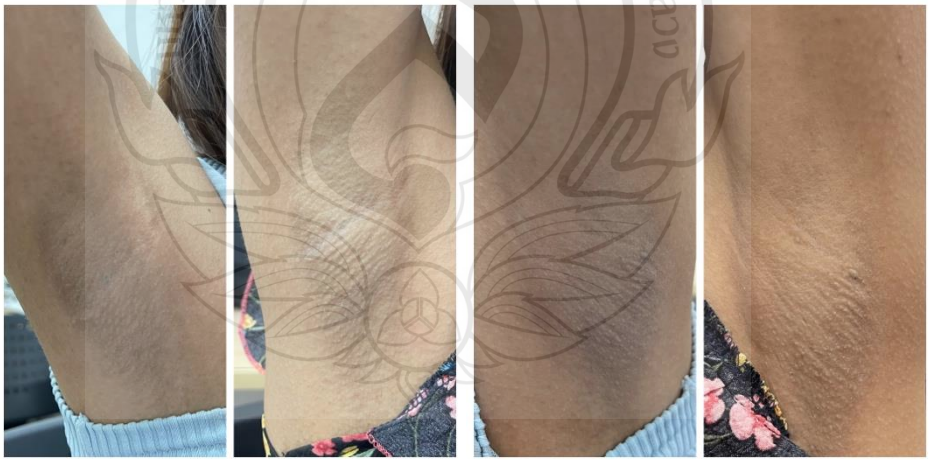
STANDARDIZED PHOTOGRAPHS OF SUBJECTS



Before (Right) **After (Left)**

(Mahad) **(Niacinamide)**

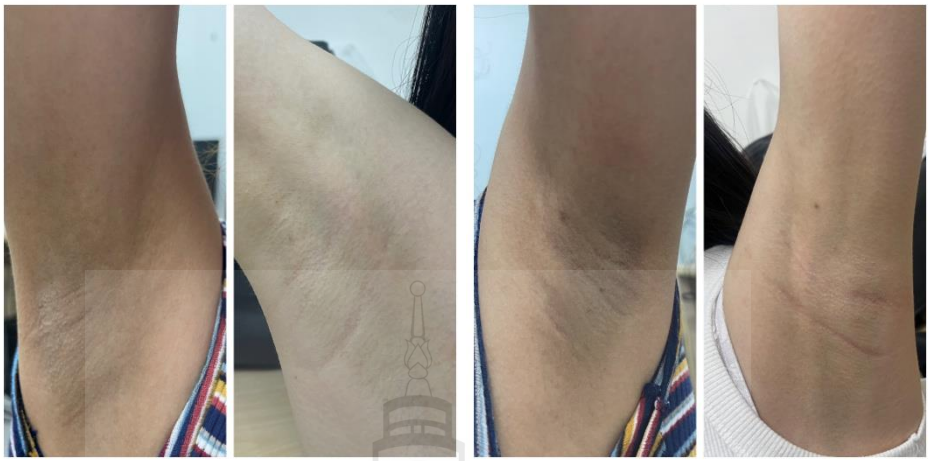
Figure D1 Photos of subject showing before and after 12th week result



Before (Right) **After (Left)**

(Mahad) **(Niacinamide)**

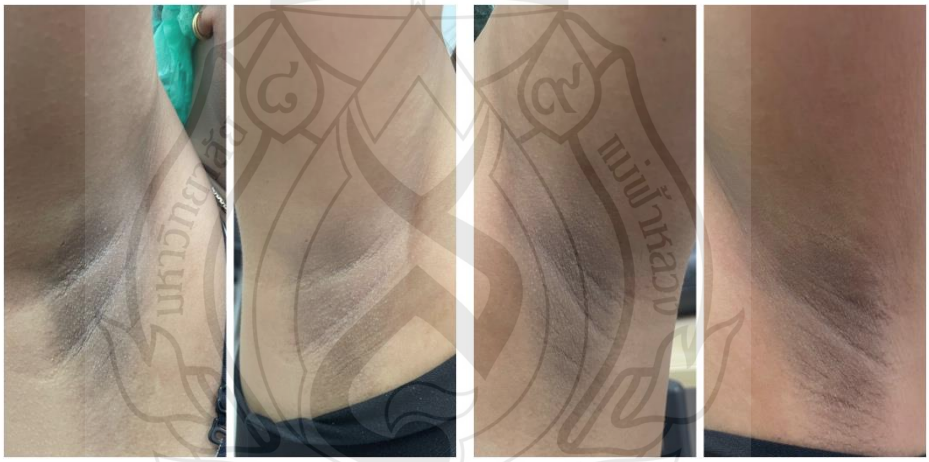
Figure D2 Photos of subject showing before and after 12th week result



Before (Right) **After (Left)**

(Niacinamide) **(Mahad)**

Figure D3 Photos of subject showing before and after 12th week result



Before (Right) **After (Left)**

(Niacinamide) **(Mahad)**

Figure D4 Photos of subject showing before and after 12th week result

APPENDIX E

FIGURES

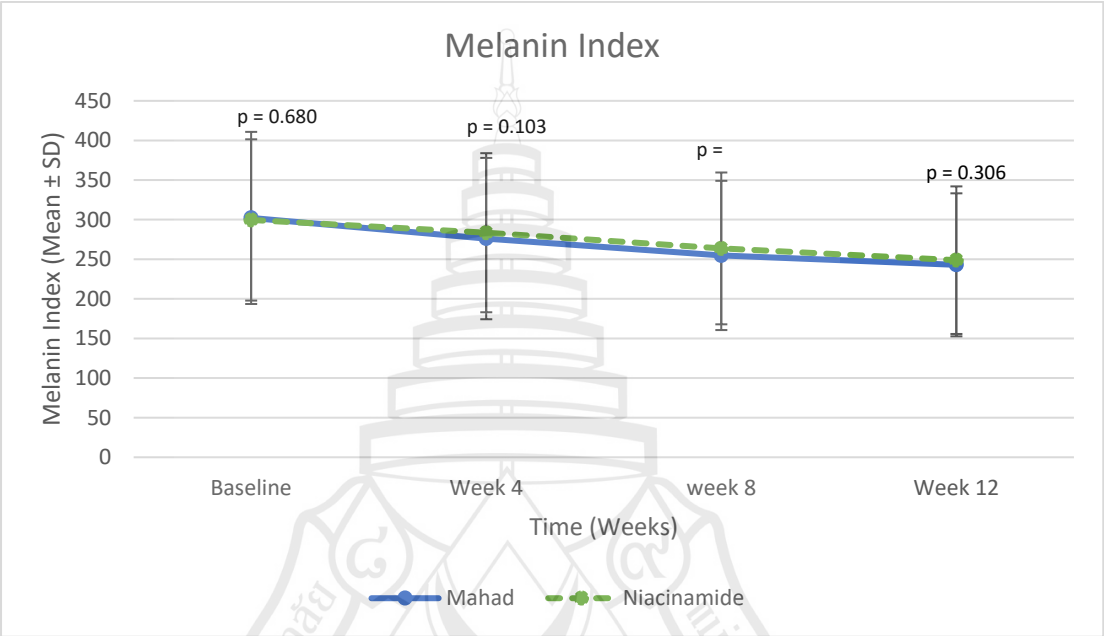


Figure E1 Mean melanin index (mi) measured by Mexameter® at baseline, week 4, week 8, and week 12 for both treatment groups 5% *Artocarpus lakoocha* heartwood extract and 5% niacinamide cream

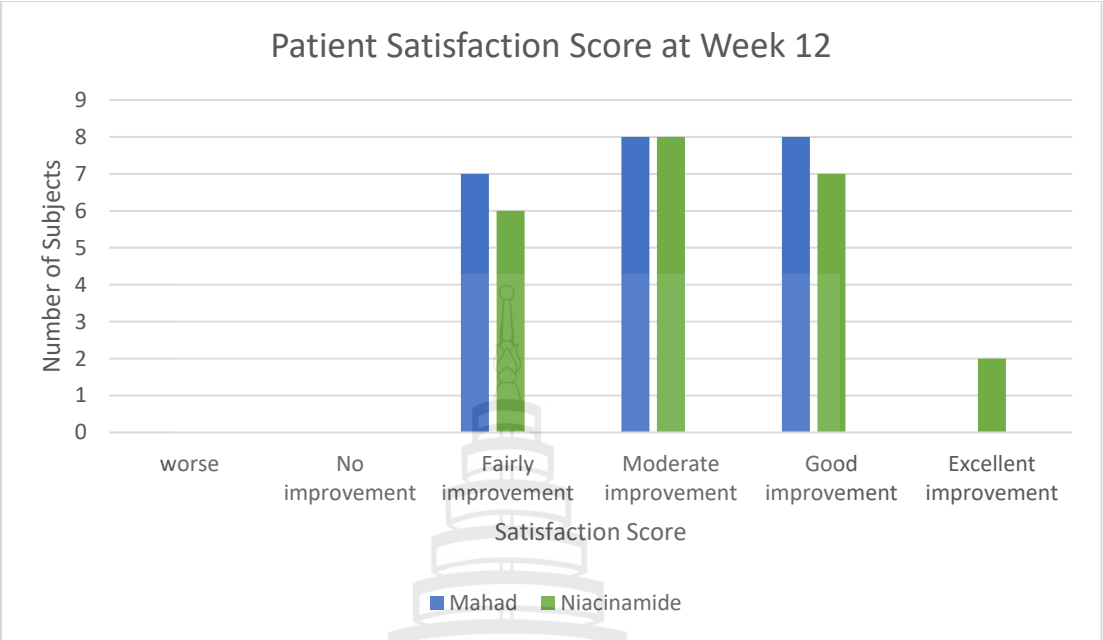


Figure E2 Bar chart displaying patient satisfaction score at week 12 comparing Mahad and Niacinamide groups

APPENDIX F

MATERIAL

Figure F1 Photos revealing 5% *Artocarpus lakoocha* heartwood extract cream and 5% niacinamide cream

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2022 Medical Doctor Degree
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