EFFICACY AND SAFETY OF MAS062D MOISTURIZER LOTION VERSUS HYDROPHILIC CREAM IN IMPROVING THE SKIN MOISTURIZATION AND SKIN BARRIER FUNCTION AND IN XEROSIS IN THE ELDERLY: A SPLIT SITE, DOUBLE-BLINDED, RANDOMIZED, CONTROLLED TRIAL

BY

MRS. BITH SOKTEPY

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF
MASTER OF SCIENCE (DERMATOLOGY)
CHULABHORN INTERNATIONAL COLLEGE OF MEDICINE
THAMMASAT UNIVERSITY
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was approved as partial fulfillment of the requirements for
the degree of Master of Science (Dermatology)
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Thesis Title	EFFICACY AND SAFETY OF MAS062D MOISTURIZER LOTION VERSUS HYDROPHILIC CREAM IN IMPROVING THE SKIN MOISTURIZATION AND SKIN BARRIER FUNCTION AND IN XEROSIS IN THE ELDERLY: A SPLIT SITE, DOUBLE-BLINDED, RANDOMIZED, CONTROLLED TRIAL
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ABSTRACT

Xerosis is very common problem in elderly characterized by erythema, dry scaling or fissuring and either the presence or absence of pruritus which could be treated by moisturizer with anti-inflammatory ingredients without steroid to help moisturize and calm skin from inflammation. The aims of this study were to evaluate the efficacy and safety of MAS062D moisturizer lotion versus hydrophilic cream in improving the skin hydration and skin barrier function in the treatment of xerosis in the elderly. A split site, double-blinded, randomized, controlled trial was conducted in patients with mild to moderate xerosis. The patients applied MAS062D and hydrophilic cream on the assigned shins twice daily for 28days. The evaluations on each consecutive following up days (day 0, 14 and 28) were performed using clinical assessment, photography, measuring skin hydration by corneometer, transepidermal water loss (TEWL) by Tewameter and biometric assessment. Twenty four patients were included into the study of which 87.5% were female with mean age of 58.04 years and mean xerosis

severity scale (XSS) of 4.83. MAI treated side have got the same statistically significant improvement in clinical assessment by XSS with the values of hydrophilic treated side presented at 4.83 ± 0.7, 3.33 ± 0.82 and 1.83 ± 0.82 on baseline, day 14 and 28 respectively. On the following up day 14 and 28, it indicated the statistically significant decrease in TEWL values measured by tewameter of the MAI treated side (5.4 ± 3.18g/m2h) (4.83 ± 1.84 g/m2h) compared to the hydrophilic cream treated side (8.63 ± 3.92g/m2h) (8.54 ± 4.53 g/m2h) ($p<0.001$) respectively. A statistically significant increase in skin hydration on MAI treated side was remarkably seen on day 14 and 28 at (41.24 ± 6.92 a.u.) (50.49 ± 8.2 a.u.) compared to the hydrophilic treated side at (20.96 ± 6.8 a.u) (21.75 ± 8.29 a.u.) ($p<0.001$). Values of hemoglobin were shown to be statistical significant on day 14 and 28 on MAI treated side compared to hydrophilic treated side presented at (1.19 ± 0.18, 1.15 ± 0.17) and (1.24 ± 0.17, 1.26 ± 0.17) respectively. The statistically significant improvement in wrinkles have been surprisingly noticed on MAI treated side compared to hydrophilic treated side on day 28 presented at 6.37 ± 1.32 and 8.62 ± 1.68. As a result of the comparison between these two groups, it represented the statistically significant declined values of roughness texture on day 28 on MAI treated side (5.84 ± 1.47) compared to hydrophilic treated side (8.5 ± 1.98) ($p<0.001$). No serious adverse effect was observed throughout the study. Therefore, MAS062D lotion, the moisturizer with anti-inflammatory ingredients could provide the better efficacy in the treatment of xerosis in elderly than hydrophilic cream with good safety profile, leading to the new treatment option for xerosis in the elderly and also refrain from the side effects of topical steroid.

Keywords: Xerosis, Moisturizers, Anti-inflammation, Moisturizer with anti inflammatory ingredient, Treatment, Elderly

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Mrs. Bith Soktepy

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Symbols/Abbreviations	Terms
α	alpha
β	beta
κ	Kabba
MAI	Moisturizer with anti-inflammatory ingredients
XSS	Xerosis severity scale
NMF	Natural moisturizing factor
IGF-1	Insulin-like growth factor 1
MAPK	Mitogen-activated protein kinase
AP-1	Activator protein 1
MMP	Matrix metalloproteinase
EGF	Epidermal growth factor
GA	Glycyrrhetinic acid
HA	Hyaluronic acid

CHAPTER 1
INTRODUCTION

Obviously, ageing processes are the bothersome occurring in elderly. Since skin becomes aged, dry skin or so called xerosis is a very common skin disease in elderly. Xerosis is characterized by an itchy, dry, rough, fissured and scaling skin.[1] Elderly persons are noticeably vulnerable to skin barrier impairment due to a decrease or dysfunction of stratum corneum lipid which also are mainly at risk for asteatotic eczema.[1, 2] There is a reference shown that asteatotic eczema is associated with a corneodesmosome defect. Moreover, inflammation and pruritus are also signs of xerosis commonly occurring in elderly which result from an increased permeability due to perturbation of the defensive functions of the stratum corneum.[1, 3]

Treatment of xerosis principally consists of moisturizer application containing emollient, humectant, and occlusion.[4] Despite moisturizers could partially help improve the symptoms of dry skin, patients with severe pruritus and inflammation cannot be treated by only moisturizers alone. In this case, topical corticosteroids, antihistamines or phototherapy is used to additionally treat inflammation and prevent pruritus.[5]

Even though steroids are very effective in most patients, they should be used cautiously in the elderly, as the skin of elderly patients is particularly sensitive to agents causing skin atrophy and further perturbation of skin integrity.[6] Corticosteroids, which are frequently used for the treatment of severe xerosis and asteatotic eczema, have recently been shown to decrease the thickness of the stratum corneum leading to skin atrophy and striae. Furthermore, for long-term application of steroids on the face will provide a steroid rosacea and telangiectasis and if it is applied in the periorbital area, there is a chance to have a glaucoma or cataract as the adverse effects.[7]

CHAPTER 2
REVIEW OF LITERATURE

2.1 Aging of the skin

Dry skin or in another term called xerosis is treated as a concerned condition in a general population especially among elderly patients who are vulnerable to have skin barrier disruption due to a natural decrease of natural moisturizing factor and lipids.[8] It is generally known that xerosis is characterized by itchiness, roughness, scale, fissures, flaking of the skin which has lost its normal mechanical properties. Skin becomes dry when a stratum corneum has no ability to retain water and loses water remarkably faster than it is re-produced. Severe xerosis can lead to xerotic eczema or eczema craquele which certainly affects the patients' quality of life as well as annoys the routine work especially when the hands are affected.[1]

2.1.1 Skin changes in the elderly

Skin disorders are known to be very common and troublesome in the elderly. Since people age, skin has been both functionally and physiologically changed which vulnerably leads to many various skin diseases towards elderly.[9] In an aged skin, the epidermis becomes thinner and loses its regulation as well as the stratum corneum loses its ability to retain water and to maintain the skin barrier function. Since wound healing process decreases in aged skin, the dermis becomes thinner and loses its elasticity accordingly.[10] It is additionally shown that elderly is prone to have immune dysfunction which encourages the development of several autoimmune disorders such as bullous and benign mucous membrane pemphigoid paraneoplastic pemphigus and the pemphigus vulgaris.[10]

Recent studies revealed that five important proteins such as involucrin keratin 10, Heat shock protein (Hsp) 27, prealbumin, and Rho B change when skin age.[11] These five proteins are reported to be present in high density in all layer of young epidermis but these epidermal proteins are reduced as a function of age and there is an evident proving that the proteins are totally not found in some skin specimen from elderly individually.[11]

There are approximately 20% of loss of dermal thickness in the elderly individual.[12] In aged skin, it is found that the extra cellular matrixes including collagen, elastin, glycosaminoglycans and proteoglycans in the dermis are remarkably decreased as well as it is seen that there is a collagen degradation and elastin degradation which are the cause of dermal aging in elderly.[13] It is overally mentioned insulin-like growth factor 1IGF-1 is a key regulator of human skin aging hence when IGF-1 levels is dropped with age, it contributes a reduction of a skin surface lipids and thickness.[14] In overall, changes in aged skin have intrinsic aged skin and external aged skin as shown in table 2.1 and table 2.2 including aged skin associated skin disease as shown in table 2.3 and molecular mechanism in skin aging in table 2.4.

2.1.1.1 Changes in intrinsically aged skin

Table 2.1 Morphologic and functional changes in intrinsically aged skin [15]

Thinning of epidermis by 10% to 50%	Increased vulnerability, fragility
Atrophy of the stratum spinosum	Increased vulnerability, fragility
Increased heterogeneity in size of basal cells	Increased vulnerability, fragility
Decreased mitotic activity, increased duration of cell cycle and migration time	Decreased desquamation, delayed wound healing
Slow replacement of lipids	Disturbed barrier function
Flattening of the dermoepidermal junction	Decrease in surface contact area, increased risk of separation by shearing forces
Decrease and heterogeneity of melanocytes	Graying of hair, guttate amelanosis, lentigines
Decrease of Langerhans cells	Diminished cutaneous immune function
Reduction of dermis thickness, decrease of fibroblasts	Reduced strength and resiliency
Atrophy of the extracellular matrix	Reduced strength and resiliency
Reduction and disintegration of collagen and elastic fibers, deposition of exogenous substances (eg, amyloid P)	Sensitization to deformational forces, fine wrinkle formation
Reduction of cutaneous microvasculature	Reduction of cutaneous vascular responsiveness, disturbed thermoregulation and supply with nutrients
Decrease of skin appendages and their function (eg, sebaceous glands, sweat glands, apocrine glands)	Decreased lipid and sweat production, disturbed reepithelization of deep cutaneous wounds
Thinning of subcutaneous fat	Reduced insulation and energy production
Reduction of nerve endings	Disturbed sensory function

2.1.1.2 Changes in extrinsically aged skin

Table 2.2 Morphologic changes in extrinsically aged skin **[15]**

- Accumulation of abnormal elastic tissue in the dermis
- Sparse distribution of collagen fibers, increased collagen degradation
- Stellate phenotype of fibroblasts and increased biosynthetic activity
- Increased levels of dysfunctional glycosaminoglycans and proteoglycans
- Increased numbers of mast cells and neutrophils
- Flattening of the dermoepidermal junction, reduction of anchoring fibrils
- Thickening of the vascular walls of postcapillary venules and of arterial and venous capillaries, increased number of veil cells, and marked regression and disorganization of small blood vessels
- Impaired proliferation, differentiation, desquamation and apoptosis of keratinocytes
- Thickening of epidermis

2.1.1.3 Aged associated skin diseases

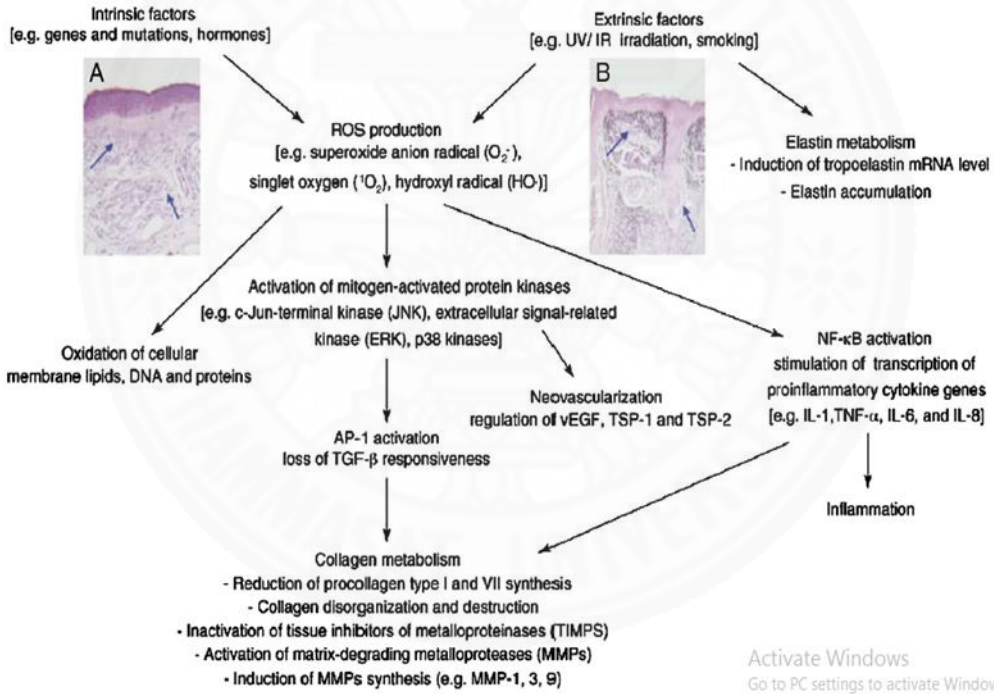
Table 2.3 Various skin diseases associated with ageing skin **[15]**

- Common skin lesions (eg, dry skin, telangiectasia, senile purpura, freckling, lentigines, guttate hypomelanosis, stellate pseudoscars, solar comedones, colloid milia, lichen sclerosus et atrophicus)
- Benign tumors (eg, seborrheic keratoses, cherry angiomas)
- Premalignant tumors (eg actinic keratosis, Morbus Bowen, lentigo maligna)
- Malignant tumors (eg, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, cutaneous lymphomas, angiosarcoma, Merkel cell carcinoma, Kaposi sarcoma, atypical fibroxanthoma, sebaceous carcinoma, cutaneous metastases)
- Infectious diseases (eg, dermatophytosis, cellulitis, zoster)
- Bullous dermatoses (eg, bullous pemphigoid, pemphigus vulgaris)
- Autoimmune diseases (eg, contact dermatitis, atopic dermatitis, vitiligo, psoriasis, lupus erythematodes)
- Lichen simplex chronicus
- Pruritus unspecified
- Pressure ulcers, lower extremity ulcers
- Vulvodynia, glossodynia, atrophic balanitis

2.1.1.4 Molecular biology of skin aging

In aged skin, mitogen-activated protein (MAP) kinase signal transduction pathways are crucial in regulating a variety of cellular functions. It is found

that activator protein (AP-1) is a key regulator of skin aging which is biologically known to be formed by the c-Jun and c-Fos - the transcription factors of MAP kinases. AP-1 plays the important role to induce an expression of MMP and inhibits type I procollagen gene expression through breaking down TGF-α signaling pathway. It has been assumed that MAP kinases may be activated by enormous production of reactive oxygen species (ROS) that occurs with advanced age and may be triggered by extrinsic factors such as ultraviolet irradiation. An accumulation of cellular damage including oxidation of DNA which is provoked by the excessive ROS production due to both intrinsic and extrinsic factors of aging skin are able to result in mutations, oxidation of proteins leading to reduced function, and oxidation of membrane lipids resulting in reduced transport efficiency and altered transmembrane signaling as shown in Figure



2.1.

Figure 2.1 It shows the changes and signaling pathways involved in the generation of intrinsically (A) and extrinsically aged skin (B) which are major causes of an excessive production of ROS to activate MAPK (JNK, ERK, p38kinases) which downstream stimulate AP-1 to reduce collagen synthesis and induce the MMPs synthesis. Simultaneously, the excessive production of ROS also triggers accumulation of cellular damage and activates NF-κB to stimulate the transcription of proinflammatory cytokine genes (IL-1, TNF-α, IL-6 and IL-8) leading to an inflammation.[15]

2.2 Xerosis in the elderly

2.2.1 Prevalence of xerosis in elderly

Xerosis is a common skin disease in the elderly which was assessed by epidemiological studies performed in secondary care. However, the information regarding its precise prevalence and severity in the community is still limited. Epidemiological studies have shown a prevalence of xerosis in the elderly ranging from 30 to 75%.[16]

The prevalence of xerosis in senior adults is indicated 30%-75% in a long-term and cross-sectional studies and simultaneously it also shows the severity of xerosis with itch dramatically worsens with elderly.[17] Moreover another study in 2008 also reported that the prevalence of any degree of xerosis was 55.6% in the population among a total of 756 patients consisting of 43% of men with a mean age of 75.18 ± 6.9 years.[16]

The same study indicates the statistically significant association between severity of xerosis recorded by the overall dry skin score and the patients' perception of skin dryness and pruritis.[17]

2.2.2 Pathogenesis of xerosis

Stratum corneum, the outermost layer of the epidermis is the most crucial layer to mainly responsible for skin barrier function; which is composed of intercellular lipids, water and sebum to help skin moisture retention.[18] However, xerosis in aging skin is not only known to be caused by inadequate sebum production but also by the stratum corneum dysfunction primarily due to a decrease of intercellular lipids especially a deterioration of ceremide synthesis which is prone to aggravate the dry skin cycle as well as to induce the disruption of keratinocytes differentiation.[19, 20]

In xerotic skin, corneodesmosomes keep persisting and disrupt the orderly desquamation process that contribute to dry skin conditions.[1] Natural Moisturizing Factor (NMF) derived from the degradation of filaggrin plays the important role for maintaining water within the keratinocytes, hence when there is a lack of NMF and a decreased of maturation of corneocyte envelopes, they will lead to

the retention of immature corneocyte.[19] It was also found that a decline of sebum production and cutaneous ceramides due to a decrease of gonadal and adrenal androgens.[20] Moreover, a decrease of estrogen resulting from a menopause was explained to contribute in skin dryness due to loss of collagen and other ground substances in dermis.[15]

Basically the insufficiency of NMF and lipid content truly play the key important role in xerosis in skin aging. Consequently, the stratum corneum clinically forms visible and powdery flakes on a skin surface.[1, 19] However, skin xerosis in aging is multifactorial including intrinsic factor which keratinization and lipid content are changed, use of diuretics and other medications and extrinsic factor which is caused by overexposure to heaters or air conditioners. When there is a skin barrier disruption, amounts of skin surface lipids and amino acids decreased which imbalance the water holding capacity of the stratum corneum. In this aspect, xerosis can cause pruritus, which results in excoriations and risk of skin infection.[21]

2.2.2.1 Factor involved in Xerosis

Xerosis can be caused by both intrinsic aging skin and external aging skin. In intrinsic aging skin, xerosis can be aggravated by the impairment or disruption of stratum corneum barrier function leading to an abnormal ceramide synthesis and a reduction of natural moisturizing factor level. Upregulation of ceramide synthesis is prone to keep on causing dry skin cycle disrupting lipid bilayer structure, triggering dysfunctional keratinocyte lipid bilayer structure and aggravating the inflammatory response. One study has shown that the presence of low levels of fillagrin in aged skin is obviously a key role protein in the genesis of dry skin.[20]

Whereas, xerosis that is attributed to the external factors are from environmental condition such as temperature - humidity, exposure to sunlight, air conditioning, heating, some chemical agents- soaps and bath gels, lotions and perfumes, detergents, pharmacotherapy, and physical insult such as friction, abrasion and radiation.[20, 21]

(1) Intrinsic factor

Aging

As we age, our skin's predisposition towards xerosis increases. Previously believed to be due to decreased water content or sebum production that does occur in older skin, xerosis is more likely attributed to changes in the keratinization process and lipid content in the stratum corneum.[22, 23]

In aged skin, changes occur in both epidermis and dermis. The most important changes in epidermis occur in stratum corneum, which is made up of corneocyte and the intercellular substance. These age-related changes explain the elderly's susceptibility to environmental insult, their diminished Natural Moisturizing Factor (NMF) levels, and the appearance of cracking, fine white scales and wrinkling.

Natural moisturizing factors (NMFs) strongly bind water within the corneocyte. One study suggested that low levels of certain NMFs correlated with xerosis in an older adult.[24] The lipid-filled membrane of the corneocyte controls water loss. NMFs and the corneocytes thus maintain water homeostasis within the stratum corneum.

Pathogenesis of age-related changes in the skin that contribute to xerosis[21] could be summarized as (Figure 2.2)

1. Reduced water content
2. Decrease number of lipids
3. Increase number and size of corneocytes
4. Decreased size of sebaceous gland
5. Decreased size of sweat gland
6. Reduced vasculature

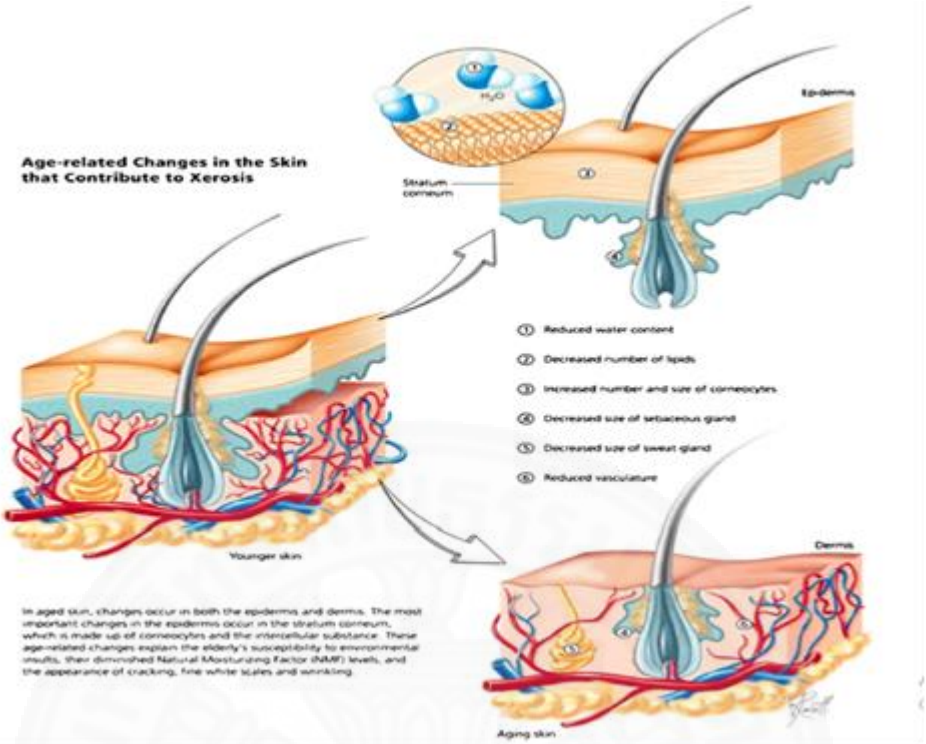


Figure 2.2: The age-related changes in the skin resulting in xerosis [21]

Genetic and Race

There exists substantial evidence to support that Black skin has a higher TEWL, variable blood vessel reactivity, decreased skin surface pH, and larger mast cell granules compared with white skin.[25, 26]

(2) Extrinsic factor

Behavioral and Environmental factors that contribute to xerosis

• Dry and/or cool ambient air (eg, air conditioners, winter seasonal changes, desert conditions)

• Harsh cleansers or soaps

• Hot water bathing: dries the skin

• Skin powders: drying agent on the skin

Chronic disease such as diabetes and chronic renal failure may cause xerosis

Medication Polypharmacy is often prevalent in older adults. Specifically, diuretics, hypercholesterolic agents, antiandrogens, and cimetidine contribute to xerosis.[22]

2.2.3 Clinical presentations of Xerosis

2.2.3.1 Xerosis and inflammation

Mild xerosis is asymptomatic, but if more pronounced, the skin conveys unpleasant sensations such as itching and stinging. Inflammation is enhanced by the release of pro inflammatory cytokines which is primarily caused by a decrease of filaggrin bringing an increase of serine protease activity activated by a decrease of SPINK5 resulting in a decrease of corneodesmosoes and a decline of lamellar body secretion leading to an impairment of integrity cohesion and permeability barrier respectively. (Figure 2.3)

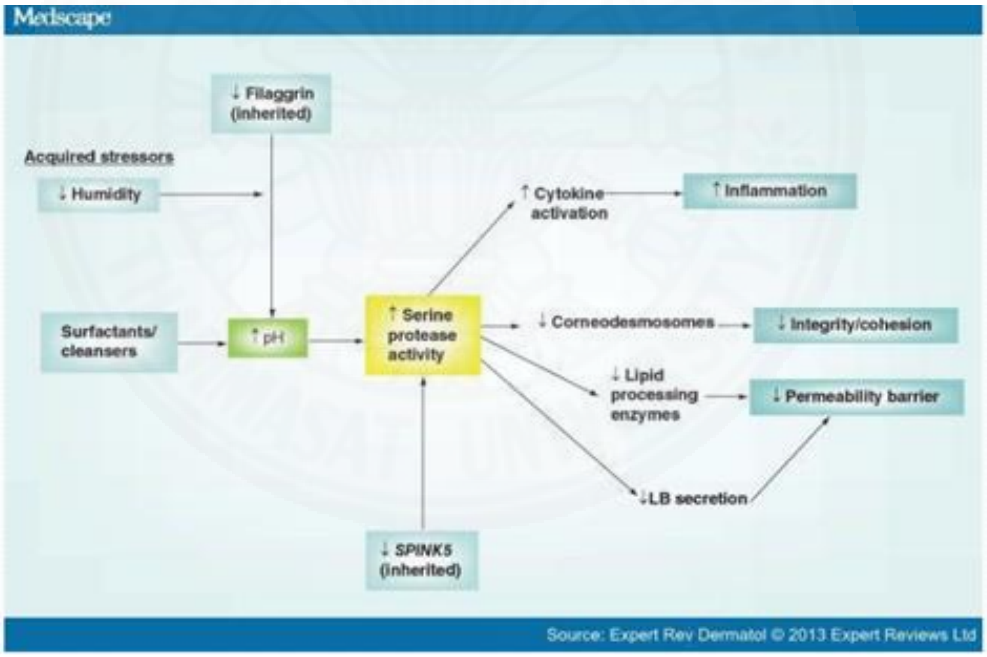
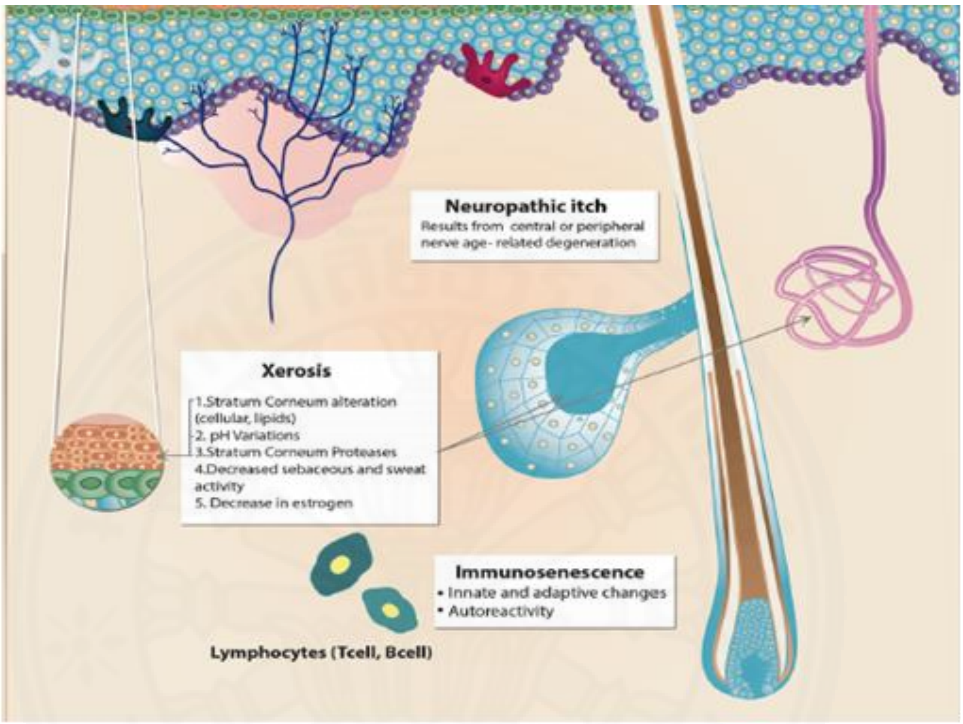


Figure 2.3 shows the cascade of how a decrease of fillagrin affects to cause an inflammation.[27]

2.2.3.2 Xerosis and pruritus

Pruritic skin diseases especially xerosis are the most common skin problem in the elderly.[1, 28] There are approximately up to 38% of elderly patients having got generalized pruritus.[28] Pruritus is a common problem in the

elderly. Pruritus is defined as a perceived itching sensation. Itch is induced by the effects of cutaneous histamine and are mediated specifically only by the peripheral nervous system.[1] Moreover, aging can contribute to itch via skin barrier disruption, immunosenescene and neuropathic changes as shown in Fig 2.4.[29] Scratching is



evoked by itching and respond to itch to produce an inflammatory response which can lead to other secondary infection diseases.[1] Managing xerosis and maintaining moist skin with emollients, humectants, occlusive and anti-inflammatory agent are extremely beneficial to prevent these complications.

Figure 2.4 Skin in elderly that may lead to chronic itch [29]

2.2.3.3 Clinical feature of xerosis

Xerosis first arises on the shins. Later it may spread to the thighs, proximal extremities and trunk, but spares the face and neck as well as the palms and soles. It develops insidiously over many years, whereas asteatotic eczema often has a more subacute to acute onset. Xerotic skin is dry, dull, with fine bran-like scales which may be released as powdery clouds when patients take off their stockings.

If more advanced, the skin exhibits a criss-cross pattern of superficial cracks and fissures of the horny layer (“crazy-paving”, eczema craquelé,

"dried riverbed") and appears pink to light red in color. The skin becomes rough, and may develop an appearance similar to ichthyosis vulgaris ("pseudo-ichthyosis"). In more advanced stages that would develop into asteatotic eczema, there is a dull erythema as well as oozing, crusting and abundant excoriations; disseminated nummular lesions are frequently seen. Vesiculation and lichenification are not regular features except when irritant or allergic contact dermatitis is superimposed. (Figure 2.5)

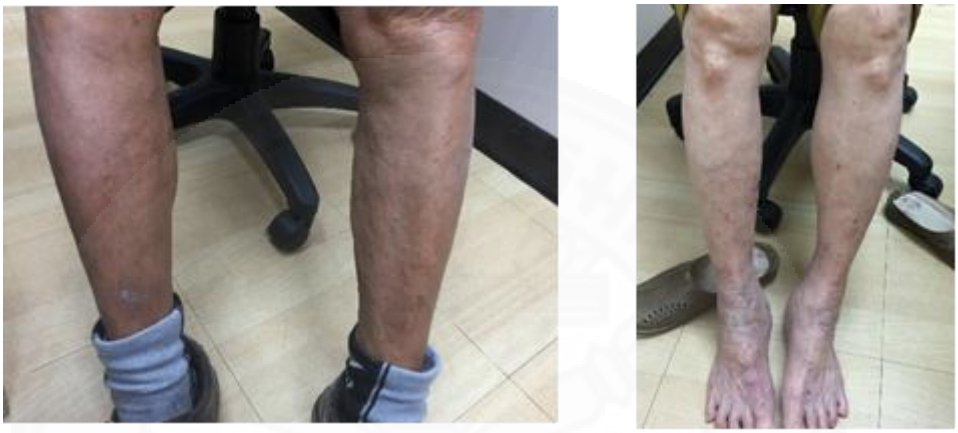


Figure 2.5 shows confluent scaly erythematous patches and plaque with dry skin change occupying both lower extremities in the elderly patients.

2.2.4 Management of Xerosis

Interventions that may improve xerosis and related pruritus include [21, 30]

- Use of mild cleansers – Traditional soaps (eg, Ivory, Dial, Irish Spring, Zest) alkalinize the skin and can cause damage to the natural skin moisture barrier, thereby worsening xerosis and aggravating pruritus. Synthetic detergent (syndet) cleansers or other mild cleansers are preferred. Syndet cleansers typically have a low pH that approximates the normal acidic pH of the skin. They tend to be less irritating than traditional soaps and may optimize skin barrier function.[31-33] In addition, there is some evidence to suggest that serine proteases involved in the pathogenesis of pruritus are inhibited by low pH agents.[34]
- Routine use of skin moisturizers Daily use of moisturizers, which contain substances that promote epidermal hydration, include
- Humectants such as glycerin, lactic acid, or topical urea and/or

• Occlusive such as petrolatum and mineral oil substances that reduce water loss from the skin and/or

• Emollients substance that acts like natural moisturizing factors (NMFs) that strongly bind water within the coenocyte,

The use of moisturizer is a crucial component of xerosis management.[24, 35] Moisturizers and/or occlusive should be applied immediately after bathing and gentle drying of the skin.

Thicker, greasier products tend to be more effective for maintaining skin moisture, but may be perceived as uncomfortable or unsightly by some patients. Greasier preparations may be better accepted by patients for use at bedtime.

• Avoidance of excessive and aggressive skin washing.

Excessive washing can worsen dry skin, particularly when hot water is used to bathe. Lukewarm or warm water is preferable for bathing, and patients should be instructed to avoid aggressive scrubbing of the skin.

• Use of a humidifier increasing the relative humidity of indoor air during the winter may be beneficial for patients who are prone to xerosis.

In addition, low pH topical agents may be of further benefit through their reduction in activity of serine proteases such as mast cell tryptase, which is known to activate protease-activating receptor 2 (PAR2) on skin nerve fibers. This notion stems from recent studies suggesting serine proteases, via PAR2 located on C fiber terminals, may play an important role in mediating pruritus.[34] In patients who develop eczema as a result of xerosis, moderate potency topical corticosteroids can be used in combination with moisturizers.

2.3 Moisturizers for the treatment of Xerosis

2.3.1 Moisturizers

Moisturizers are bland oily substances that are applied to the skin by rubbing. They are used to replace natural skin oils, to cover tiny fissures in the skin, and to provide a soothing protective film. They may, thus, slow evaporation of the skin's moisture by maintaining hydration, and improving the appearance and tactile properties of dry and aging skin.[24]

Scientifically, the moisturizing treatment involves a 4-step process:

- Repairing the skin barrier
- Increasing water content
- Reducing TEWL
- Restoring the lipid barriers' ability to attract, hold and redistribute water.[24]

Moisturizers have three main types consisting of occlusive, emollients, and humectants with individual mechanism as follows:

- Occlusive physically block TEWL in the stratum corneum. Petrolatum is the most popular and effective occlusive in the moisturizers followed by lanolin, mineral oil and silicones such as dimethicone.[35, 36] (Table 2.4)
- Emollients smoothen the skin by filling spaces between skin flakes with droplets of oil, and are not usually occlusive. They may help hold oil and water in the stratum corneum when there is the combination of emollients with an emulsifier.[24, 37] (Table 2.4)
- Humectants enhance skin hydration by attracting water from the dermis to the epidermis and water from the external environment to the skin.[24] (Table 2.4)

Table 2.4 Groups of moisturizing substances that are based on their theoretical mechanism of action.[24]

Class Action	Mechanism of Ingredients	Exmaple	Indication	Indication Side Effects
I. Occlusive	Physically block TWEL	Petrolatum Lanolin Mineral Oil Silicones Zinc Oxide	Xerosis - Atopic Dermatitis Prevention of Irritant Contact Dermatitis	Messy, Cosmetically Unacceptable, Folliculitis, (Mineral Oil) Comedogenic Contact Dermatitis,(Lanolin)
II. Humectants	Attract water to stratum corneum (transepidermal)	Glycerin Sorbital Urea Alpha hydroxy acids Sugars	Xerosis Ichthyosis Skin Rejuvenation?	Irritation (Urea, Lactic Acid)
III. Emollients	Smooth Skin by filling spaces between skin flakes, with droplets of oil	Cholesterol Squalene Fatty Acids	Decrease skin roughness	Not always effective
IV. Protein Rejuvenators	Claim rejuvenate skin by replenishing essential proteins in skin	Collagen Keratin Elastin	Skin Rejuvenation?	Unlikely to work Protein too large to cross epidermis Contact reactions

2.3.2 Summary of moisturizers in treatment of xerosis in elderly

Table 2.5: A systematic review of the treatment of xerosis in elderly with various moisturizers.[4]

Study	NHMRC Level	Population	Sample Size (n male)	Intervention/active ingredients tested	Study duration	Outcome measurements	Inclusion Criteria	Study results	Mean values/ Effect size
Nash [30]	IV	M/F, 12 – 87 years	75 (NR)	20% urea cream	7 months	Clinical scoring	UTD	Significant improvement after treatment	N/A
Hopp and Sundberg [27]	III-1	M/F, 60 +yrs	60 (NR)	Alpha-Keri (oil) vs Keri-lotion * (both containing lanolin, mineral oil and emulsifiers) vs water soak vs control	12 days	Questionnaire, Dryness Scale, Panel evaluation	UTD	Water soak + Keri-lotion was superior to other combinations	Mean difference 1.16 ($P < 0.05$)
Brenner [25]	IV	M/F, 53 – 97 years	10 (7)	12% ammonium lactate	14 days	7-point Dry Skin Grading Scale	UTD	Significant improvement after treatment	N/A
Sitkin et al. [29]	III-2	Sex NR, 24 – 85 years	55 (NR)	12% ammonium lactate vs no therapy	8 weeks	Overall Dryness Severity Score, Physician Global Improvement of Improvement/Worsening	≥ Moderate bilateral dryness	12% ammonium lactate superior to no treatment	Mean difference 0.98 ($P < 0.05$)
Jennings et al. [33]	III-3	M/F, 22 – 86 years	70 (34)	5% salicylic acid + 10% urea vs 12% ammonium lactate	28 days	Xerosis severity scale, Tenderness Scale, VAS	Mild-moderate bilateral xerosis	No significant difference between treatments	Mean difference 0.1 ($P = 0.15$)
Uy et al. [28]	III - 2	Sex NR, 13 – 72 years	57 (NR)	12% ammonium lactate vs liposome – based emollients (petrolatum, paraffin)	28 days	Clinical grading scores	≥ Moderate bilateral dryness and/or hyperkeratosis	No significant difference between treatments	N/A
Ademola et al. [2]	III-2	M/F, 18 – 65 years	25 (NR)	40% urea cream vs 12% ammonium lactate	28 days	Evaporimeter (roughness), Corneometer (dryness), D-Squame (scales), VAS	≥ Grade 2 xerosis Free of cutaneous disease	40% urea cream superior	Effect size 0.19 (95% CI: −0.47 to 0.84)
Jennings et al. [36]	III-3	M/F, 26 – 83 years	35 (10)	10% lactic acid vs 12% ammonium lactate	28 days	Xerosis severity scale, Tenderness Scale, VAS	Mild-moderate bilateral xerosis	No significant difference between treatments, patients preference for 10% lactic acid	Mean difference 0.1 ($P = 0.9$)
Pham et al. [7]	III-2	M/F, age NR	40 (22)	10% urea +4% lactic acid vs placebo vehicle	28 days	Xerosis Assessment Scale	≥18 years Type 1 or 2 diabetes Mild-moderate bilateral xerosis	10% urea +4% lactic acid superior to placebo vehicle	N/A
Baird [20]	III-3	M/F, age NR	30 (14)	10% urea cream vs 25% urea cream	6 weeks	Customised equipment measuring skin electrical resistance	Type 1 or 2 diabetes Bilateral dry skin	25% urea cream superior to 10% urea cream	Effect size 0.27 (95% CI: −0.24 to 0.78)
Jennings et al. [37]	III-3	M/F, 18 +yrs	41 (NR)	Lanolin cream vs 12% ammonium lactate	28 days	Xerosis severity scale, Tenderness Scale, VAS	Moderate-severe bilateral xerosis	No significant difference between treatments	N/A
Baker and Rayman [21]	III-3	M/F, 40 – 74 years	26 (12)	10% urea foam vs 'patient's regular creams' (aqueous cream, Diprobase and Linguentum)	14 days	5-point scale for dryness, flexibility and callus formation	Type 1 or 2 diabetes Neuropathic Bilateral xerosis	10% urea foam superior to patient's existing creams	Effect size −2.33 (95% CI: −2.99 to −1.59)
Quatresooos et al. [19]	III-2	Female, 55 – 62 years	30 (0)	Chitin – Glucan vs placebo vehicle + glycerol	35 days	Moisture Accumulation Test (MAT)	Menopausal women Type 1 or 2 diabetes Mod – severe xerosis	Chitin-Glucan superior to placebo vehicle, equal result to glycerol yet longer-lasting	Mean difference of 60 points
De Souza and De Atencio [18]	IV	M/F, 20 – 50 year	40 (NR)	10% urea cream	28 days	Clinical scoring, VAS, Hydrometer, Skin pH	20 – 50 yo 'Normal' body weight Type 1 or 2 diabetes	Significant improvement after treatment	Mean difference of 5.4
Baalham et al. [4]	III-3	Female, age NR	15 (0)	Paraffin vs Paraffin + 10% urea	14 days	Digital moisture monitor	Adult Free of cutaneous disease Bilateral xerosis	Paraffin + 10% urea superior	Effect size 0.87 (95% CI: 0.1 to 1.59)
Garrigue et al. [8]	II-2	M/F, 18 – 75 years	54 (24)	Pedimed * (urea, lactic acid, paraffin) vs placebo vehicle	28 days	Xerosis Assessment Score (XAS), D-Squame Corneometer	M / F 18 – 25 Type 1 or 2 diabetes Mod – severe xerosis	Pedimed * superior to placebo vehicle	18% difference between groups ($P < 0.05$)
Grossman et al. [1]	IV	M/F, 41 – 70 year	12 (6)	35% urea foam	28 days	Clinical grading score, Global assessment score	≥18 years Xerosis diagnosis as per Global Assessment Score	Significant improvement after treatment	N/A
Papanas et al. [22]	II-2	M/F, age NR	20 (10)	10% urea foam vs no treatment	14 days	Corneometer	Type 2 diabetes	10% urea foam was superior to no treatment	Effect size 1.25 (95% CI: 0.55 to 1.9)
Ciammaichella et al. [23]	II-2	M/F, age NR	54 (29)	5% urea cream vs no treatment	28 days	Microangiopathy, Ultrasound, Partial $O_2 + CO_2$ pressures, VAS scale	Diabetes - Insulin treated Stable control Defined neuropathy	5% urea cream superior to no treatment	N/A
Dykes [24]	III-3	Female, 22 – 64 years	25 (0)	25% urea cream vs unspecified urea cream	14 days	Clinical photo scores, Corneometer	18+ years old Visibly dry feet Otherwise healthy	25% urea cream more effective than unspecified urea cream	Effect size −0.26 (95% CI: −0.83 to 0.35)
Federici, Federici and Milani [17]	II-2	M/F, 40 – 75 years	40 (16)	Urea, arginine and carnosine cream vs glycerol cream	28 days	Dryness Area Severity Index (DASI score), VAS score	40 – 75 years Mod – severe xerosis Type 2 diabetes	Urea, arginine and carnosine cream superior	Mean difference −0.8
Loden, von Scheele and Michelsen [3]	III-3	M/F, 21 – 86 years	50 (25)	15% alphahydroxy acid + 15% urea cream vs healthy controls	14 days	Trans-epidermal water loss (TEWL), Clinical scores, VAS	UTD	15% alphahydroxy acid + 15% urea significantly improved skin condition in both symptomatic and healthy samples	N/A

2.3.3 Studied moisturizer: Efficacy of MAS063DP and MAS062D

MAS063DP and MAS062D, a nonsteroidal cream, has been efficacious in several open-label and vehicle-controlled studies in adults with atopic dermatitis (AD) and contact dermatitis [38, 39] and also in a multicenter, randomized, placebo-controlled study evaluating the efficacy and safety of MAS063DP in infants and children with mild to moderate AD.[40]

2.3.3.1 MAS063DP is a hydrolipidic cream and lotion that helps maintain a healthy epidermal barrier while providing symptomatic relief of pruritus. Ingredients include glycyrrhetinic acid (GrA), vitis vinifera, (grapevine extract), and telmestine. GrA 2%, the active metabolite in licorice root extract, shows anti-inflammatory and antipruritic activity and has been shown to block the degradation of endogenous cortisol through inhibition of 11-B-hydroxysteroid dehydrogenase.[41] Additionally, GrA has been demonstrated to potentiate cutaneous hydrocortisone activity.[42] The standardized vitis vinifera (grapevine) extract in MAS063DP has antioxidant and antiprotease activity, which may help protect against breakdown of the epidermis.[43] Telmestine also has antiprotease action and inhibits elastase, collagenase, and matrix metalloproteinase, which are expressed at high levels in patients with AD.[44] Finally, hyaluronic acid in the emollient helps to moisturize the epidermis and restore barrier function.[45]

Product ingredients MAS062D is the product in which some key ingredients, together with oil in water emulsion are mixed. The key ingredients are Vitis vinifera, vitamins C and E, telmesteine, hyaluronic acid (sodium hyaluronate), glycyrrhetinic acid and Butyrospermum parkii (shea butter). The other ingredients include aqua, ethylhexyl palmitate, pentylene glycol, arachidyl alcohol, behenyl alcohol, arachidyl glucoside, glyceryl stearate, PEG-100 stearate, butylene glycol, capryloyl glycine, bisabolol, carbomer, ethylhexylglycerin, piroctone olamine, sodium hydroxide, allantoin, DMDM hydantoin, disodium EDTA, and propyl gallate and ceteth 20, only in lotion formulation. These compounds are all combined to form the moisturizer with occlusive, humectant and emollient effect. Moreover, MAS062D contains many anti- inflammatory ingredients as summarized in table 2.6.[46]

Table 2.6 Summary of the ingredients of MAS062D and Hydrophilic cream

	Occlusion	Humectant	Emollient	Preservative	Active Ingredients
MAI	Shea butter	Pentylene glycol, Capryloyl glycine, Sodium hyaluronate	Glyceryl stearate, Behenyl alcohol	Pentylene glycol, Butylene glycol	Vitis Vinisfera Telmesteine HA Glycyrrhetinic acid
Hydrophilic cream	Cetyl alcohol, Stearic acid	Propylene glycol		Propyl pareben	

Product Safety The safety and tolerability profile of MAS063DP is similar or better than that met during the use of topical corticosteroids or TCIs.[47, 48] The most frequently systemic AEs reported in all studies were fever, cold and upper respiratory infections (Table 2.7),[38, 39, 44, 46] while the most frequently reported side effects related to the medication were moderate contact dermatitis or burning, erythema and stinging upon application.

Considering that more than 90% of patients assigned to MAS063DP who did not present any adverse events were willing to continue treatment [38, 39] and therefore showed a very high compliance as they also deemed the study cream even more effective than some previous treatments, the risk–benefit ratio definitively shifts towards the beneficial effects shown in the efficacy measurements.

MAS062D lotion has received marketing authorization in the USA and the EU as a medical device and is manufactured and controlled the quality by Sinclair Pharma Srl, Milano, Italy. The investigators will repackage into the clean, sun-protected bottles and advise the participants to keep the bottles in the room temperature and keep away from sun light.

Table 2.7 Showed adverse events in 4 studies [5, 6, 16, 17]

Table 2. Adverse events encountered during the four studies considered.

	Common		Influenza		Rash		Upper respir. infect./bronchitis		Itching		Sinusitis		Hematoma		Burning upon application		Fever		Stinging		Severe adverse events requiring hospitalization
	M	V	M	V	M	V	M	V	M	V	M	V	M	V	M	V	M	V	M	V	
Aramovits *et al.* [34]	++	++	+	+	+	++	+	-	+	++	+	-	+	-	+	-			-	-	-
Boguniewicz *et al.* [37]	-	++	++	++	-	-	-	++	-	-	-	-	-	-	++	++	+	+	++	-	+
Patrizi *et al.* [35]	No specific adverse events were reproducible																				
Belloni *et al.* [36]	No observered or reported adverse events were recorded in either patients' group																				

M: MASO63DP; V: Vehicle; * = MASO60.
- Absent; +: < 5% pts; ++: > 5% pts.

2.3.4 Comparative moisturizer

2.3.4.1 Hydrophilic cream base

Hydrophilic cream base is the moisturizer with semi-liquid and oil in water formula, commonly used to treat many skin diseases including xerosis. This moisturizer has both occlusive and humectant effect. The ingredients include cetyl alcohol, stearic acid (occlusive), propylene glycol (humectant) and propyl paraben. The study product (Hydrophilic cream base) is produced and controlled the quality by pharmacy department of King Chulalongkorn hospital. The investigators will repackage into the clean, sun-protected bottles and advise the participants to keep the bottles in the room temperature and keep away from sun light.

Therefore, the role of moisturizer is crucial to prevent and also treat xerosis condition. Moreover, the moisturizer with anti-inflammatory ingredient without steroid would be beneficial to prevent and treat the inflammation that may be caused from both intrinsic factor and extrinsic factors such as excoriation from pruritus, irritation from environment and bathing behavior in order to prevent the inflammation that would result in further dermatitis. In addition, the anti-inflammatory effect without steroid would also prevent and avoid topical steroid adverse effect.

2.4 Measurement techniques for xerosis

2.4.1 Subjective assessment

2.4.1.1 Clinical assessment

All clinical assessments such as redness, thickness, pruritus, lichenification, hyperpigmentation, edema, dermatitis were scored on a 4-point scale that was ranked as follows: 0 = none, 1 = mild, 2 = moderate and 3 = severe. The Investigator global assessment (IGA) and Subject global assessment (SGA) were scored on a 6-point scale: 5 = Worse, 4 = No improvement, 3 = Slight improvement, 2 = Moderate improvement, 1 = Excellent improvement, 0 = Clear.[49]

2.4.1.2 Xerosis severity score

Xerosis Severity Scale is a scale to measure the grade of xerosis dividing to mild, moderate and severe with different scores defined with clinic features respectively as shown in table 2.8.[49] Xerosis severity scale (XSS) is a scale to measure and evaluate the severity of xerosis by scoring from grade 1 to 6 depending on the clinical features in an accordance with the criteria set of each grade. Moreover the XSS could be classified as the severity as following mild (for XSS score 0: normal skin, 1: dusty appearance, occasional minute skin flakes and 2: generalized dusty appearance, many minute skin flakes), moderate (for XSS score 3: defined scaling with flat borders and 4: well-defined heavy scaling with raised borders, shallow fissures) and severe (for XSS score 5: large scale plates, fissures and 6: large scale plates, deep erythematous fissures).

Table 2.8 Xerosis Severity Scale presented by Rogers et al.[49]

Mild	0	Normal skin
	1	Dusty appearance, occasional minute skin flakes
	2	Generalized dusty appearance, many minute skin flakes
Moderate	3	Defined scaling with flat borders
	4	Well-defined heavy scaling with raised borders, shallow fissures
Severe	5	Large scale plates, fissures
	6	Large scale plates, deep erythematous fissures

2.4.2 Objective assessment

2.4.2.1 Biophysical skin parameters

(1) Transepidermal water loss (TEWL) measurement (Tewameter)

The skin acts as a barrier preventing organism from loss of essential components such as ions, water, and serum protein. The past couple of decades have seen the development of various noninvasive methods for the in vivo investigation of the skin. Beyond its structural components stratum corneum encompasses the passage of water and electrolytes from the viable epidermis and the active and passive transport of exogenous substances.[50]

The most prominent in vivo parameter for the evaluation of epidermal permeability barrier function is called transepidermal water loss (TEWL). It is comprised by the insensible perspiration which is based on the diffusion of body water through the stratum corneum. TEWL measurements can be used to assess the inside-out barrier as well as to indirectly predicting the influence of topically applied substances and pharmaceutical compounds at the skin surface. Minimizing thermal sweating, consequently, is crucial for quantifying TEWL under basal condition.

TEWL measurement consists of three methods: the unventilated-chamber (closed method), the ventilated-chamber method, and the open-

$$\frac{dm}{dt} = -D \cdot A \cdot \frac{dp}{dx}$$

chamber method. Open-chamber method does not involve with the microclimate and the skin is not occluded at all; it is an useful tool for both single and continuous measurements of the evaporative loss from the skin surface. The measuring concept behind the open-chamber devices is Fick's diffusion law that is revealing the mass per cm^2 to be transported in a defined period of time and calculated by the formula:

A = surface in m^2

m = water transported (g)

t = time (h)

D = diffusion constant = (0.0877 $g/m^2/h$ mmHg)

P=vapor pressure of the atmosphere (mmHg)

x = distance from skin surface to point of measurementt (m)

Density gradient is measured indirectly by two pairs of sensors (temperature and relative humidity) and is analyzed by a microprocessor. After computer calculation the TEWL is displayed in g/m2 /h. All methods could be influenced by the microclimatic changes near the skin surface. Hence, the measurements must be performed in acclimatized rooms with controlled air temperature and relative humidity without direct airflow into the test field. Practical aspects in performing the TEWL measurement include:

- Perform measurements in an acclimatized room with temperature 18–21 °C and relative humidity of 40–60 %
- Allow sufficient acclimatization time of the study volunteers from 20–30 min prior to the first measurement.
- Avoid direct airflow and direct light at the test site.
- Circadian rhythm: perform measurements at the same daytime and season and measurements during summer is prohibited
- Consider inter- and intra-individual variability in TEWL when calculating the size of the study population.
- Allow an equilibration time of about 20s until a steady state is reached due to the heating of the sensors.
- Allow for the vapor remnants in the probe to dry after each measurement (second), when performing repeated measurements.
- Perform at least two consecutive measurements of neighboring areas of each test site but avoiding the measure from the exactly same site due to possible occlusion.
- Place the probe perpendicular to the skin surface applying a minimal stable pressure.
- Leave the probe dry.

- The interval from the last product (cosmetic, topical drug) application should be at least 12 h; otherwise the occlusion effect of the product itself or its remnants is measured instead of its effects on the epidermal barrier properties.
- The interval from the last skin cleansing should be at least 2–4 h.

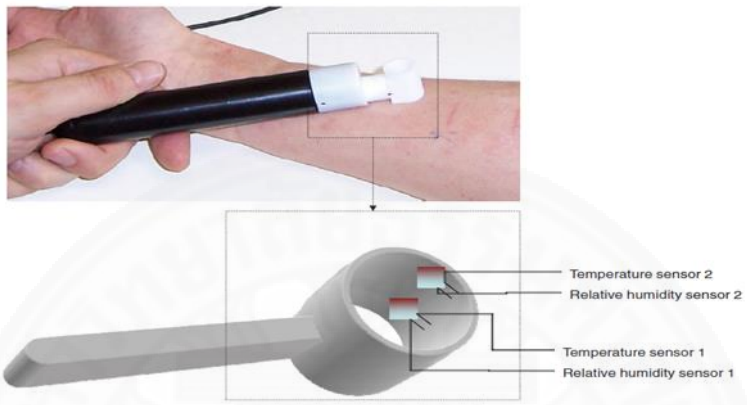


Figure 2.6 TEWL measurement and a schematic overview of the open-chamber device measuring probe.[50]

Table 2.9 Influence of individual and environment related variables on the measurement of transepidermal water loss (TEWL).[50]

Variable		Influence on TEWL measurement
Individual related	Age	+
	Gender	-
	Race/ethnicity	-/+
	Anatomical site	+
	Skin temperature	+
	Sweating	+
	Intake of vasoactive substances (drugs, caffeine, nicotine)	+
Environment related	Air convection	+
	Ambient temperature	+
	Humidity	+
	Direct light	+
	Season	+
	Circadian rhythms	+

Used symbols: “+” influencing, “–” no influence, “+/–”controversial data

Passive diffusion of water measurement vaporized through the skin.[1] This diffusion flow can be expressed in terms of vapor pressure gradient. Without the presence of sweating, the amount of water vapor that passes the stratum corneum by passive diffusion is indicated. Enormous amounts of water is produced by sweat glands, which evaporates. With the same concept, measuring TEWL can quantify this diffusion of water vapor by sweating.

(2) Corneometer

The Corneometer CM 825 (Courage & Khazaka Electronic GmbH) is presented in Figure 2.7 and was used to evaluate the stratum corneum water content. The measurement was based on high frequency (0.9–1.2 MHz) capacitance measurement of a dielectric medium. The main unit through one of four input channels attached the probe of the Corneometer. The small probe (length 11 cm), which is presented in Figure 2.8, comprising a series of gold metal tracks is known to be functioning as capacitor plates. Electrically, these plates were isolated. Electrons flowed from one plate over the terminal to the other after connecting a supply point to the capacitor. The quantity of charge that was stored by the capacitor, was referred to as the capacitance. [51] Because of its frequency-dependence, this capacitance was the fault electrical capacitance in the usual engineering sense.[52] Most materials between the capacitor plates would rise up the capacitance compared with that of a vacuum due to their higher dielectric constant. This meant that an alteration of the amount of water in the measured skin leading to proportional changes in capacitance measurements.[53] For protection of the fragility of gold tracks, a very thin glass layer covered the probe head. All data of the Corneometer were demonstrated in arbitrary units (a.u.), ranged from 0 to 120 a.u. A value of 0 a.u. defined no water, a value of 120 a.u. represented fully soaked. The values were in linear relation to the water contents.[53] (Table 2.10)

Figure 2.7 The MPA5 the main unit of Corneometer 825

Figure 2.8 The probe of the Corneometer 825

Practical aspects in performing the Corneometer measurement include:

- The measurement of water content must be performed in a room at a temperature of 20-23°C and a relative humidity of 40-60%.
- At least 2 h after applying moisturizers or other skin care products.
- The instrument acclimatization is needed for at least 20 min and was turned on about 15 min before the performance.
- The measurements on the calf were done in prone position.
- The test sites were covered nothing during the acclimatization. Each site was wiped very tidily with a dry tissue to remove superficial oil. Test sites with abundant skin hair were not allowed for the performance.

Table 2.10 The various value of AU shown after the measurement on the different areas at the temperature 20-23°C and the humidity 40-60%

	Forehead, t-zone, scalp, eyelid, temple, corner of the mouth, upper body parts, back, neck (arbitrary units)	Arms, hands, legs, elbows (arbitrary units)
Very dry	<50	<35
Dry	50-60	35-50
Sufficiently moistured	>60	>50

(3) Biometric assessment Antera

The Antera facial scanning was obtained in a bid to evaluate the following parameters; hemoglobin (erythema), melanin, wrinkles and skin texture.

Figure 2.9 The Antera 3D facial scan device

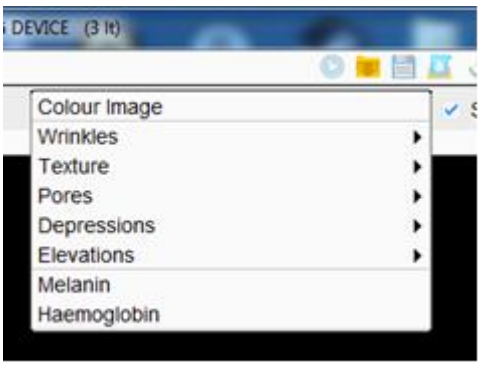
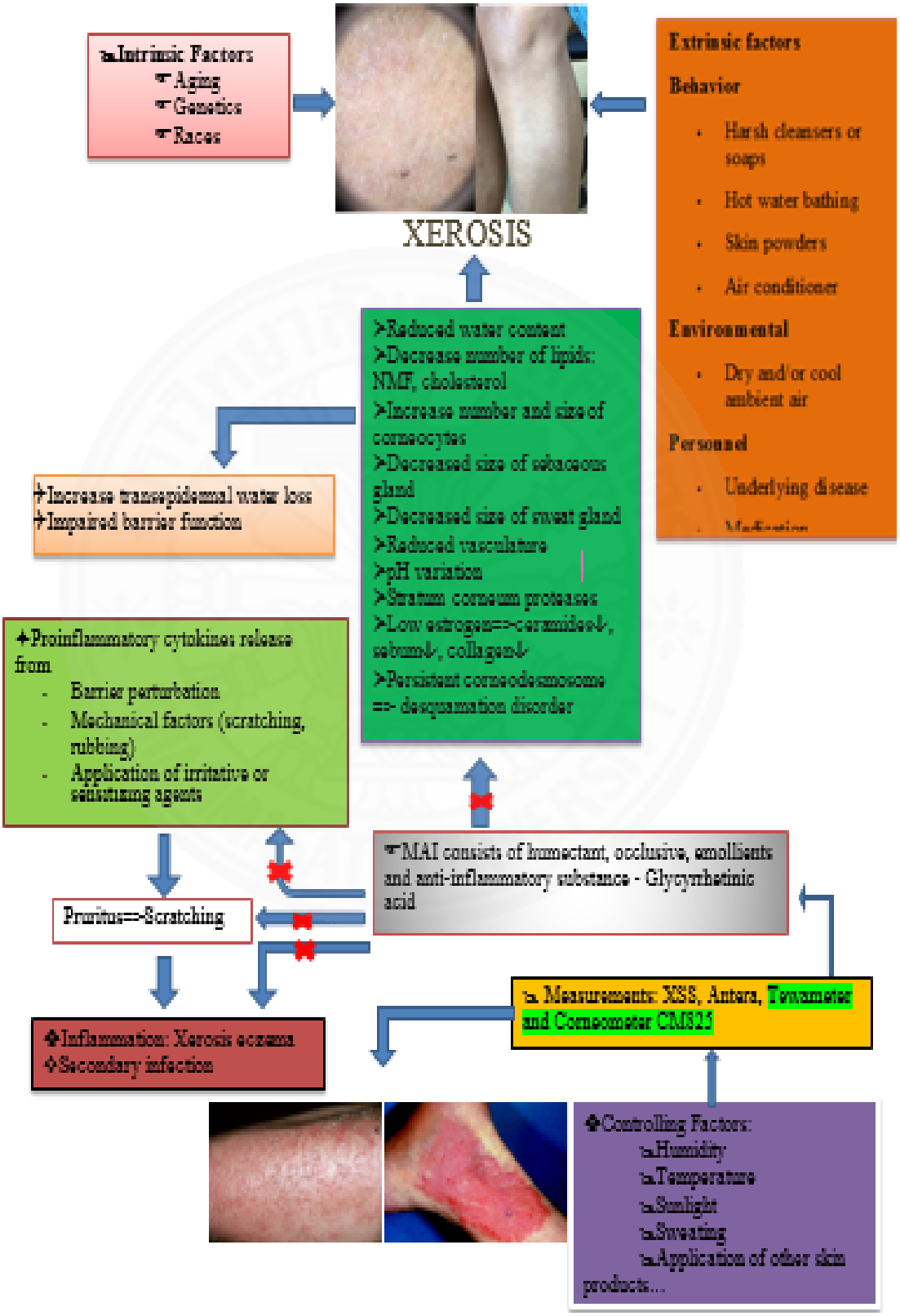


Figure 2.10 The parameter provided in the Antera 3D program

2.5. Conceptual Framework



CHAPTER 3
RESEARCH METHODOLOGY

3.1. Objectives

3.1.1. Primary Outcome

To determine the efficacy of MAS062D lotion compare with hydrophilic cream by applying twice daily for 28days in the treatment of xerosis by skin hydration measurement by skin capacitance value, measured by corneometer 825.

3.1.2. Secondary Outcome

To determine the efficacy of MAS062D lotion compare with hydrophilic cream base, applying twice daily for 28days in the treatment of xerosis by improving the skin barrier function and moisturizing the skin in elderly demonstrated by measuring

a. improving the skin barrier function and moisturizing the skin in elderly demonstrated by measuring transepidermal water loss (TEWL)
b. Xerosis Severity Scale (XSS)
c. Investigator's global assessment (IGA)
d. Patient's self-assessment
e. Dermatology Life Quality Index (DLQI)

To determine the safety of MAS062D lotion compare with hydrophilic cream base applying twice daily for 28days in the treatment of xerosis in elderly.

3.2. Study design

Experimental: A Split Site, Double-blinded, Randomized Controlled Trial

3.3. Target population

Patients aged 50-70 years with xerosis on legs who attend the OPD at TTMH.

3.4. Sampling method

Inclusion Criteria	Exclusion Criteria
• Male or female aged more 50-70 years old. • Fitzpatrick skin Types III to V • Mild to moderate xerosis score ranged from 2-4 on both shins using XSS • The dry skin on both legs had not received prior topical medication for at least 3days. • Willingness and ability to comply with the requirements of the protocol.	• Skin infections, inflammation, photosensitive dermatoses, psoriasis or any concomitant skin disease at the site of treatment • Received oral steroid and topical calcineurin inhibitor and topical steroid within 4 weeks prior the research. • Taking any medicines that could impair skin dryness such as Isotretinoin, anticholigenic drugs • Received phototherapy within 4weeks prior the study. • Suspected allergy to any ingredients in the cream used in the research. • Presence of evidence indicating likely poor compliance with the protocol.

Inclusion / Exclusion Record form

Do you have these symptom	Yes	No	Detail
1. Age 50 to 70 years			
2. Underlying disease			
3. Current daily Drug use			
4. Prior treatment of dry skin within 4weeks			
5. Received oral steroid or topical calcineurin			

inhibitor within the past 4weeks			
6. Suspected allergy to any component of MAS062D			
7. History of receiving phototherapy 1month before a research			

3.5 Sample size calculation

Sample size was calculated from the proposed efficacy of the MAS062D that will be better than hydrophilic cream from the improvement of the corneometer value for 25% from the previous study the alpha error for 20% and 95% CI.[49]

n= (〖1.96〗^2×0.25× (1-0.25))/〖0.2〗^2

n=20

Drop off rate 20% = 4 person so the final sample size is 24

(Lwanga S. K. And Lemeshow S. 1991.Sample Size Determination in Health Studies. World Health Organization.)

3.6. Preparation of research subjects

a. Subjects will be selected to enroll in the study according to the selection criteria

b. Details in the information sheet will be informed to all subjects

c. The subjects will sign an inform consent form for participation in the study

d. The information of the subject will be recorded

3.7. Intervention

- Three days before study, patients will be instructed to refrain from using any cream, lotion or any ointment.
- Patients bathe and wash legs two times a day by using a gentle soap from Pan Rajdhevee Group to prepare the skin before starting a research (wash out period).

• Both MAS062D and hydrophilic cream are randomly divided into the 50ml bottles with label “A” and label “B” .

• Patients are told to randomly apply a teaspoon (5ml) of bottle “A” on one shin using the right hand and a teaspoon of the bottle “B” on an opposite shin using the left hand for 28days by coming to follow up once a week followed by taking pictures, measuring skin hydration by corneometer and TEWL by Tewameter on each consecutive following up days (D0, D14, D28).

• The patients will be called to follow up about the side effect of the creams and the improvement of the xerosis condition on D7.

• To ensure the compliance, the patients must be told to return the bottles to every visit to measure the amount of lotion and cream to assess whether they use proper amount for the treatment during a study.

3.8. Procedure

• Before each treatment at day 0, 14, 28 standardize digital photograph and measurement of skin dry dryness by XSS, corneometer and tewameter will be performed.

• Measure skin hydration, TEWL day 0, 14, 28 before beginning of each treatment session.

• Xerosis Severity Score will be evaluated at day 0, 14, 28.

• Measuring skin hydration is to measure the amount of water in the stratum corneum with a corneometer by controlling the room temperature to approximately 21-25 degree celcius in this study because it is done in a tropical country.

• Measuring TEWL is to measure water loss in stratum corneum by Tewameter in a room temperature approximately 25 degrees celcius.

• Patients apply MAS062D on right shin and hydrophilic cream on left shin for 28days by coming to follow up once per two week followed by taking pictures, measuring skin hydration by corneometer and TEWL by Tewameter on each consecutive following up days (D0, D14, and D28).

3.9. Post-operative care

• The researcher will evaluate the patients during and post-treatment about their discomfort and other side effects of the lotions on day 7.

• Other topical products on the treated site will not be allowed during the protocol.

3.10. Outcome measurement

Assessment /day	3days before	Day 0	Day 7	Day 14	Day28
Avoid using cream on the shin 3days prior a study					
Consent form for TM					
Fill in the questionnaire					
Take pictures with digital camera					
Skin assessment by dermascopy					
TEWL measurement					
Skin hydration measurement					
Use the lotions to apply on a skin					
Report satisfactory					
Report side effect					
Data Analysis and report result					

3.11. Data collection

The data was collected in the paper document, text file, and imaging file in the computer in every visit of the follow up. The case record form was used in this study to collect all the patients' demographic data.

3.12. Data analysis

The sample size of subjects was calculated according to the equivalence randomized trial. Means SDs expressed all of the measured values that were summarized using a descriptive statistical technique. ANOVA test was used to measure changes in the XSS, electrical capacitance, TEWL and Antera assessment between treatment subjects at baseline, day 14 and 28. Wilcoxon signed ranks test was also used to measure the differences in the IGA, SGA and pruritus grade at day 14 and 28. In all cases, statistical significance was defined as $p < 0.005$.

CHAPTER 4
RESULTS AND DISCUSSION

4.1 Patients demographic data

A total of twenty-four subjects (3 males and 21 females) with xerosis were included and successfully completed the study. The majority of the subjects (87.5%) were female, with a mean ± SD age of 58.04 ± 6.93 years. It shows that there are 16 subjects (66.7%) with a past history of xerosis. Moreover, as the history of the treatment in xerosis indicated in the table below, there are 2 subjects (8.3%) applying the topical medication, while there are 2 subjects (8.3%) taking oral medication and 9 subjects (37.5%) applying cream as the treatment of choice in xerosis.

The demographic data shows 12 patients (50%) without and 12 patients (50%) with underlying diseases such as 37.5% hypertension, 16.7% diabetes, 4.2% stroke, 20.8% hyperlipidemia, 8.3% thyroid disease, 4.2% cancer meanwhile there are no any patients with cardiovascular disease and ischemic heart disease as the underlying diseases.

There are 23 patients with 95.8% who don't smoke, 0% of patients used to smoke and only 1 patient about 4.2% currently smoke.

Moreover, there are 12.5% of patients who drink alcohol occasionally and approximately 87.5% do not drink alcohol at all.

In this data also revealed 54.2% of patients haven't used any medications so far while there are 12.5% of patients having taken diabetes drug, 25% of patients having taken hypertension drug, 20% of patients having taken dyslipidemia drug, 4.2% of patients having taken diuretic drug and 12.5% for others.

Additionally, the data of family history also demonstrated that there are 17.7% of family members who have got xerosis including 4.2% are mothers, 8.3% are brothers, and 4.2% are sons and daughters. (Table 4.1)

Table 4.1 Patients demographic data

Variable	N	%
Sex		
Male	3	(12.5%)
Female	21	(87.5%)
Age (years)	58.04 ± 6.93	59 [43, 73]
Underlying disease		
No	12	(50%)
Yes	12	(50%)
• Diabetes	4	(16.7%)
• Hypertension	9	(37.5%)
• Dyslipidemia	5	(20.8%)
• Ischemic Heart disease	0	(0%)
• Stroke	1	(4.2%)
• Cardiovascular disease	0	(0%)
• Thyroid disease	2	(8.3%)
• Cancer	1	(4.2%)
Smoking		
no	23	(95.8%)
past	0	(0%)
present	1	(4.2%)
Alcohol		
no	21	(87.5%)
Occasionally drink	3	(12.5%)
Routine	0	(0%)
Other diseases	11	(45.8%)
Past history of drug reaction	3	(12.5%)
Routine drugs		
• no	13	(54.2%)
• Anti-Diabetes drugs	3	(12.5%)

Variable	N	%
• Anti-hypertensive drugs	6	(25%)
• Anti-dyslipidemia drugs	5	(20%)
• Anti-diuretic drugs	1	(4.2%)
• Others	3	(12.5%)
Eczema	6	(25%)
Duration (months)	96.75 ± 175.55	12 [3, 360]
Treatment		
• Topical medication	0	(0%)
• Oral medication	0	(0%)
• Cream	1	(4.2%)
• Topical medication and cream	1	(4.2%)
Xerosis	16	(66.7%)
Duration (months)	11.71 ± 0.76	12 [10, 12]
Treatment		
Topical medication	2	(8.3%)
Oral Medication	2	(8.3%)
Cream	9	(37.5%)
Family history for Atopic dermatitis		
No	20	(83.3%)
Father	1	(4.2%)
Sister	3	(12.5%)
Brother	1	(4.2%)
Family history for xerosis		
No	20	(83.3%)
Mother	1	(4.2%)
Brother	2	(8.3%)

Variable	N	%
Son and daughter	1	(4.2%)

Values presented as mean ± SD, median [min, max] and n (%).

For the risk factors of xerosis leading to xerosis includes taking bath more than 10 minutes (15subjects; 62.5%), taking bath more than 2times/day (13subjects; 54.2%), taking bath with warm water (8subjects; 33.3%) and staying in a room with air conditioner more than 6 hours per day (9subjects; 37.5%). Also using cream (10subjects; 41.7%), using bath soap (23subjects; 95.8%) and using talcum powder (13subjects; 54.2%). (Table 4.2)

Table 4.2 Risk factors of xerosis

Risk factors of xerosis	N	%
Take bath more than 10 minutes	15	(62.5%)
Take bath more than 2times/day	13	(54.2%)
Take bath with warm water	8	(33.3%)
Stay in a room with air conditioner more than 6 hours per day	9	(37.5%)
Others	1	(4.2%)
Treatment cream	10	(41.7%)
Use bath soap	23	(95.8%)
Use talcum powder	13	(54.2%)
Feeling dry skin	20	(83.3%)
Itchy	14	(58.3%)
Desquamation	10	(41.7%)
Scaly skin	6	(25%)
Red skin	6	(25%)
Skinny	6	(25%)

Pain	2	(8.3%)
Itches that disturb daily life	6	(25%)
Itches that disturb sleeping	7	(29.2%)

Values presented as mean ± SD, median [min, max] and n (%).

Moreover, there are 20 subjects who have got the sensation of dry skin following by some clinical signs such as itchy (14; 58.3%), desquamation (10; 41.7%), scaly skin (6; 25%), red skin (6; 25%), skinny (6; 25%), Pain (2; 8.3%), itches that disturb daily life (6; 25%), itches that disturb sleeping (7; 29.2%). (Table 4.3)

Table 4.3 Symptoms of xerosis

Symptoms of xerosis	N	%
Feeling dry skin	20	(83.3%)
Itchy	14	(58.3%)
Desquamation	10	(41.7%)
Scaly skin	6	(25%)
Red skin	6	(25%)
Skinny	6	(25%)
Pain	2	(8.3%)
Itches that disturb daily life	6	(25%)
Itches that disturb sleeping	7	(29.2%)

Values presented as mean ± SD, median [min, max] and n (%).

4.2 Xerosis severity scale measurement

Xerosis severity scale (XSS) is a scale to measure and evaluate the severity of xerosis by scoring from grade 1 to 6 depending on the clinical features in an accordance with the criteria set of each grade.[49] Moreover the XSS could be classified as the severity as following mild (for XSS score 0: normal skin, 1: dusty appearance, occasional minute skin flakes and 2: generalized dusty appearance, many minute skin flakes), moderate (for XSS score 3: defined scaling with flat borders and 4: well-defined heavy scaling with raised borders, shallow fissures) and severe

(for XSS score 5: large scale plates, fissures and 6: large scale plates, deep erythematous fissures) [54].

The improvement of XSS on MAI treated side was distinctively observed. The mean XSS of MAI treatment decreased significantly for 4.83 ± 0.7, 3.33 ± 0.82 and 1.83 ± 0.82 at baseline, day 14 and 28, respectively ($p<0.001$). (Figure 4.1)

Coincidently, hydrophilic treated side also have got the same statistically significant improvement with the values of MAI treated side presented at 4.83 ± 0.7, 3.33 ± 0.82 and 1.83 ± 0.82 on baseline, day 14 and 28 respectively. (Figure 4.1)

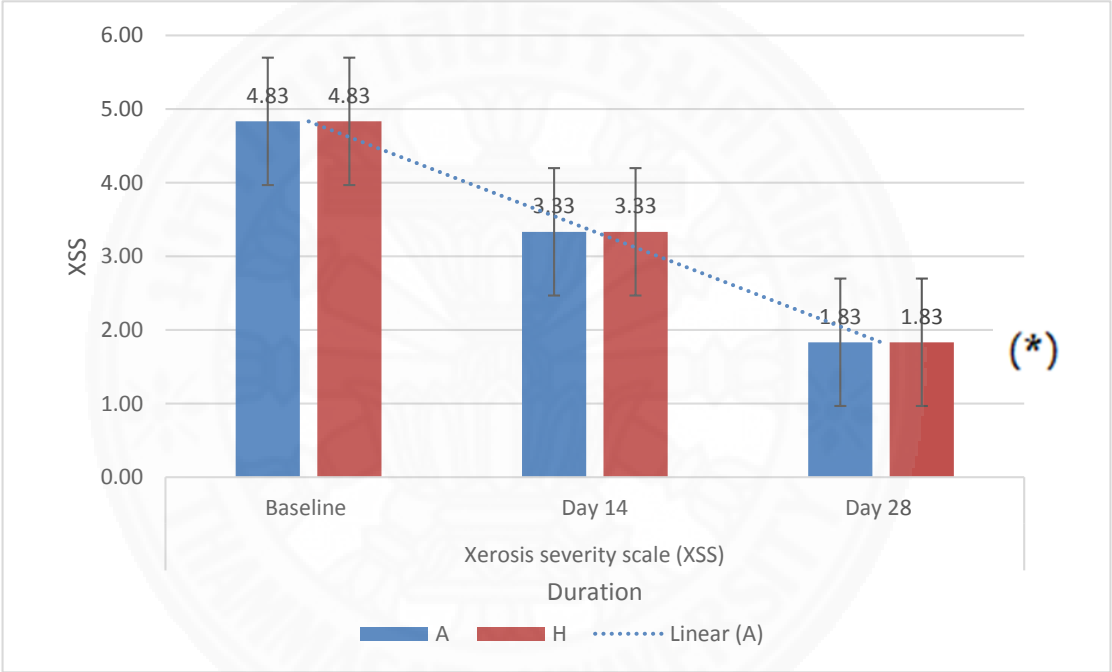


Figure 4.1. Xerosis Severity Scale (XSS) on MAI and hydrophilic cream treated side (*$p<0.001$, A: MAI, H: Hydrophilic cream)

Basically, the baseline values between MAI and Hydrophilic cream were exactly the same at 4.83 ± 0.7 respectively with the statistical insignificance ($p=1.000$).

On day 14th and day 28th also showed the same insignificant values between MAI and Hydrophilic cream at 3.33 ± 0.82 on day 14th and 1.83 ± 0.82 on day 28th respectively with P value =1.000.

Additionally, on baseline there was no any subjects with mild xerosis but there were 3subjects (33.3%) with moderate xerosis and 16subjects (66.7%) to be

treated with both MAI and hydrophilic cream. On Day 14, after treatment with both MAI and hydrophilic cream, the same number of subjects with severe xerosis statistically significant decreased from 16persons 66.7% on baseline to only 2persons 8.3% and finally to 0person on the day 28. It was observed that after treatment with MAI and Hydrophilic cream, there was the same statistically significant decrease in number of subjects with moderate xerosis from 19 persons 79.2% on day 14 to 4 persons on day 28. However due to the statistically significant decrease in patients with severe and moderate xerosis, the same numbers of patients with mild xerosis were revealed to increase from 0person 0% on baseline to 3persons 12.5% on day 14 and finally rise to 20persons 83% on day 28 respectively after the treatment with MAI and Hydrophilic cream. So it means there was no any remarkably different improvement in these 3 grades of xerosis as a comparison between these 2agents. (Table 4.4)

Table 4.4 Xerosis Severity Scale and Clinical Severity Grading of MAI and Hydrophilic treated side

	MAI	Hydrophilic **Cream**	**p-value**
Xerosis severity scale (XSS)			
Baseline	4.83 ± 0.7	4.83 ± 0.7	1.000
Day 14	3.33 ± 0.82	3.33 ± 0.82	1.000
Day 28	1.83 ± 0.82	1.83 ± 0.82	1.000
p-value, day 14	<0.001*	<0.001*	
p-value, day 28	<0.001*	<0.001*	
Clinical severity Grading			
Baseline			
Mild	0 (0%)	0 (0%)	1.000
Moderate	8 (33.3%)	8 (33.3%)	
Severe	16 (66.7%)	16 (66.7%)	
Day 14			
Mild	3 (12.5%)	3 (12.5%)	1.000
Moderate	19 (79.2%)	19 (79.2%)	
Severe	2 (8.3%)	2 (8.3%)	
Day 28			

Mild	20 (83.3%)	20 (83.3%)	1.000
Moderate	4 (16.7%)	4 (16.7%)	
Severe	0 (0%)	0 (0%)	
p-value, day 14	<0.001*	<0.001*	
p-value, day 28	<0.001*	<0.001*	

Values presented as mean ± SD. P-value corresponds to paired t test.

As a result, for the XSS measurement, it could be concluded that both MAI and Hydrophilic cream have provided the same improvement of treatment equally in terms of clinical features by using XSS to evaluate on baseline, day 14 and day 28. (Figure 4.2 and 4.3)

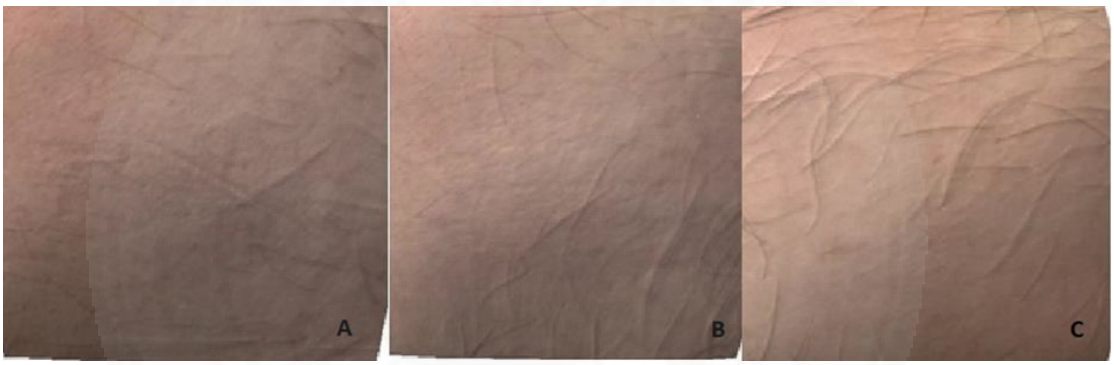


Figure 4.2. Clinical presentation of MAI treated side on baseline, day 14 and day28

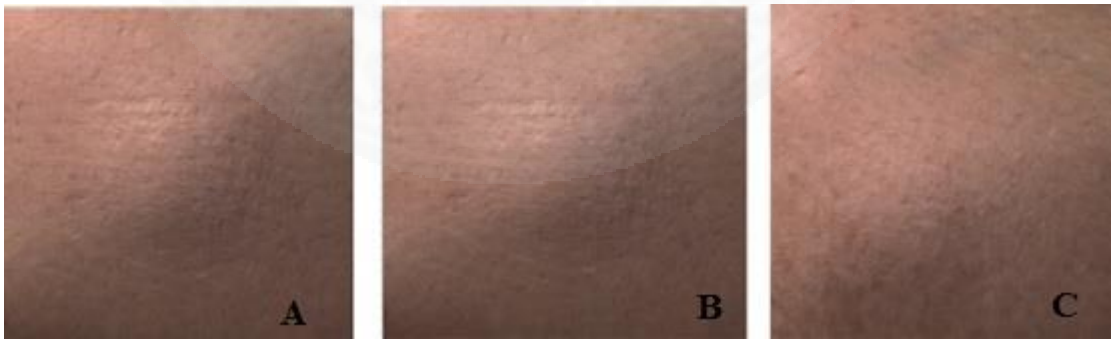


Figure 4.3. Clinical presentation of hydrophilic treated side on day 0, 14 and 28

4.3 Clinical assessments by blinded dermatologist (Table 4.5)

All clinical assessments by blinded dermatologist included dryness, smoothness and moist were scored on a 5-point scale that was ranked as follows:: 0 = No improvement, 1 = Slight improvement, 2 = Mild improvement, 3 = Moderate improvement, 4 = Excellent improvement. [49]

Dryness on MAI treated side The improvement of clinical assessment in MAI treated side was remarkably noticed with a significant improvement of dryness from day 14 (1.25 ± 0.44) compared with day 28 (0.96 ± 0.46) (P=0.005).

Smoothness on MAI treated side While smoothness showed the significantly better results on day28 (3.58 ± 0.58) compared with day14 (3.04 ± 0.36) ($p<0.001$).

Moist on MAI treated side Simultaneously, it also indicates the statistically noticeable improvement of moist on day 28 (3.75 ± 0.44) compared with day14 (2.85 ± 0.65) ($p<0.001$) as shown in Figure 2.

Dryness on hydrophilic cream treated side The improvement of clinical assessment in hydrophilic cream treated side was remarkably noticed with a significant improvement of dryness from day 14 (2.13 ± 0.8) compared with day 28 (1.63 ± 0.71) ($P<0.001$).

Smoothness on Hydrophilic cream treated side While smoothness showed the significantly better results on day28 (3 ± 0.66) compared with day14 (2.75 ± 0.53) (p=0.011).

Moist on hydrophilic cream treated side Simultaneously, it also indicates the statistically noticeable improvement of moist on day 28 (2.58 ± 0.72) compared with day14 (2 ± 0.66) ($p<0.001$) as shown in Figure 3.

Table 4.5 Clinical assessments by blinded dermatologist

	MAI	Hydrophilic Cream	p-value
Scratching, Baseline	1.08 ± 0.28	1.04 ± 0.2	0.328
Hyperpigmentation, Baseline	1.17 ± 0.48	1.17 ± 0.48	1.000
Dermatitis, Baseline	1.08 ± 0.28	1.17 ± 0.38	0.162
Dryness			
Day 14	2.13 ± 0.8	1.25 ± 0.44	<0.001*
Day 28	1.63 ± 0.71	0.96 ± 0.46	<0.001*
p-value, day 14 vs. day 28	0.005*	<0.001*	
Smoothness			
Day 14	3.04 ± 0.36	2.75 ± 0.53	0.005*
Day 28	3.58 ± 0.58	3 ± 0.66	<0.001*
p-value, day 14 vs. day 28	<0.001*	0.011*	
Moist			
Day 14	2.85 ± 0.65	2 ± 0.66	<0.001*
Day 28	3.75 ± 0.44	2.58 ± 0.72	<0.001*
p-value, day 14 vs. day 28	<0.001*	<0.001*	

Values presented as mean ± SD. P-value corresponds to Wilcoxon signed ranks test

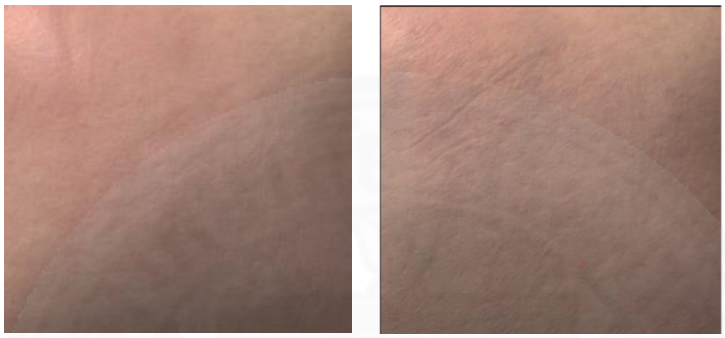
According to the comparison between these 2 groups, on baseline day, it showed an unremarkable value of scratching between MAI treated side 1.08 ± 0.28 and hydrophilic treated side 1.04 ± 0.2 without the statistically significant p-value. In this case, the value of hyperpigmentation at baseline was shown the same on both MAI treated side 1.17 ± 0.48 and hydrophilic treated side 1.17 ± 0.48. Whereas dermatitis at baseline was proved to have got a very similar value between MAI treated side 1.08 ± 0.28 and hydrophilic treated side 1.08 ± 0.28 without a statistical significance.

Dryness between MAI and Hydrophilic treated side However, on day 14 and 28, it indicated a better improvement of dryness with a statistical significance ($p<0.001$) on MAI treated side compared to hydrophilic treated side presented at (2.13 ± 0.8, 1.63 ± 0.71) and (1.25 ± 0.44, 0.96 ± 0.46) respectively. (Figure 4.4 and 4.5)

Smoothness between MAI and Hydrophilic treated side Moreover, the values of smoothness was also shown to have statistically significant improvement ($p<0.001$) on day 14 and 28 of MAI treated side compared to hydrophilic treated side

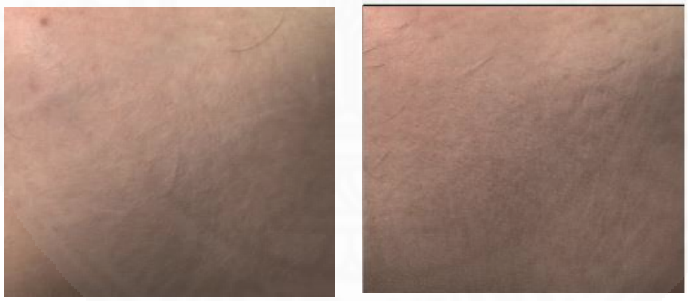
presented at (3.04 ± 0.36, 3.58 ± 0.58) and (2.75 ± 0.53, 3 ± 0.66) respectively. (Figure 4.4 and 4.5)

Moist between MAI and Hydrophilic cream Simultaneously, it also illustrated the statistically significant increase of moist ($p<0.001$) on day 14 and 28 of MAI treated side compared to hydrophilic treated side presented at (2.85 ± 0.65, 3.75 ± 0.44) and (2 ± 0.66, 2.58 ± 0.72) respectively. (Figure 4.4 and 4.5)



MAI treated side **Hydrophilic treated side**

Figure 4.4 The comparison of clinical presentation of MAI and hydrophilic treated sides on day 28



MAI treated side **Hydrophilic treated side**

Figure 4.5 The comparison of clinical presentation of MAI and hydrophilic treated side on day 14

4.4 Biophysical skin parameter assessment

4.4.1 Transepidermal water loss (TEWL) measurement

For the TEWL measurement, the baseline values of each side of shin with MAI and hydrophilic cream didn't show the any statistical significance presented at 8.87 ± 10.11 and 9.25 ± 10.14 g/m^2h, respectively.

On the following up day 14, it indicated the statistically significant decrease in TEWL values measured by tewameter of the MAI treated side (5.4 ± 3.18g/m2h) compared to the hydrophilic cream treated side (8.63 ± 3.92g/m2h) (P<0.001).

Whereas on day 28, the comparison between MAI and hydrophilic treated sides illustrated a more statistically significant decrease of TEWL values (4.83 ± 1.84 g/m2h) of MAI treated side than a hydrophilic cream treated side (8.54 ± 4.53 g/m2h) (P<0.001). (Figure 4.6)

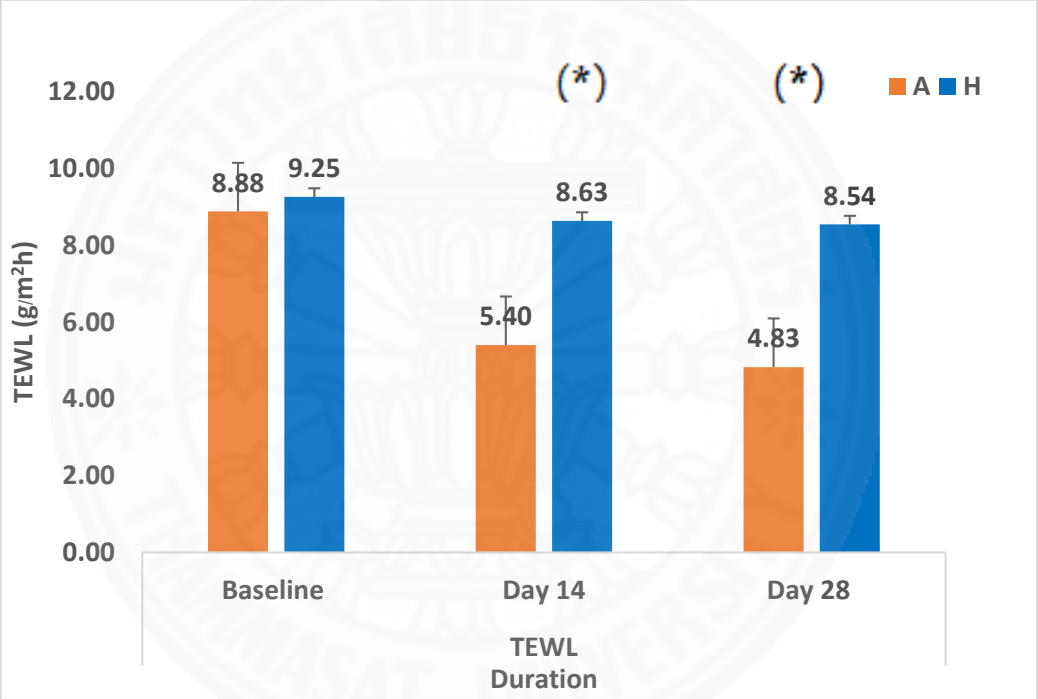


Figure 4.6 The values of TEWL of MAI and Hydrophilic treated sides measured by Tewameter on baseline, day 14 and day 28, respectively

However, the values of TEWL of MAI treated side was expressed to remarkably decrease from baseline, day 14 (p=0.111) and day 28(p=0.056) presented at 8.87 ± 10.11, 5.4 ± 3.18 and 4.83 ± 1.84 respectively without any statistical significance. (Table 4.6)

Simultaneously, on hydrophilic treated side also didn't show the statistical significant value of TEWL even though it showed a gradual decline from baseline, day 14 and day 28 presented at 9.25 ± 10.14, 8.63 ± 3.92(p=0.754), 8.54 ± 4.53(p=0.748) respectively. (Table 4.6)

In summary, it totally concluded that there was a statistically significant decrease in TEWL of MAI treated side on day 14 and day 28 compared to the hydrophilic treated side but there was no any statistical significant drop in TEWL of either MAI or hydrophilic treated side alone on both day 14 and 28. (Table 4.6)

Table 4.6 The values of TEWL (g/m2h) of MAI and Hydrophilic treated sides measured by Tewameter on baseline, day 14 and day 28, respectively (*p<0.001, A: MAI, H: Hydrophilic cream)

TEWL (g/m2h)	MAI	Hydrophilic Cream	p-value
Baseline	8.87 ± 10.11	9.25 ± 10.14	0.793
Day 14	5.4 ± 3.18	8.63 ± 3.92	<0.001*
Day 28	4.83 ± 1.84	8.54 ± 4.53	<0.001*
p-value, day 14	0.111	0.754	
p-value, day 28	0.056	0.748	

Values presented as mean ± SD. P-value corresponds to paired t test.

4.4.2 Skin hydration measurement

From the skin hydration measured by corneometer, it illustrates a statistically significant increase of skin hydration measured by corneometer from 26.86 ± 7.94, 41.24 ± 6.92 and 50.49 ± 8.2 a.u. from baseline, d14, d28 respectively on the MAI treated side with P-value<0.001. (Table 4.7)

It also indicated the statistically significant decrease of skin hydration on the hydrophilic treated side presented at 25.84 ± 5.1, 20.96 ± 6.8 (p=0.002) and 21.75 ± 8.29 (p=0.050) from baseline, day14 and day 28 respectively. According to this data, it obviously proved that there was no any significant improvement in terms of skin hydration after using hydrophilic cream. (Table 4.7)

Table 4.7 The values of skin hydration measured by corneometer (a.u.) on MAI and hydrophilic treated side on baseline, day 14 and day 28, respectively. (*p<0.001, A: MAI, H: Hydrophilic cream)

Corneometer (a.u.)	MAI	Hydrophilic Cream	p-value
Baseline	26.86 ± 7.94	25.84 ± 5.1	0.480
Day 14	41.24 ± 6.92	20.96 ± 6.8	<0.001*
Day 28	50.49 ± 8.2	21.75 ± 8.29	<0.001*
p-value, baseline vs. day 14	<0.001*	0.002*	
p-value, baseline vs. day 28	<0.001*	0.050	

Values presented as mean ± SD. P-value corresponds to paired t test.

Moving onto the comparison between MAI and hydrophilic treated side, it illustrated that the baseline values of each side of shin are not statistically different from each other presented at 26.86 ± 7.94 and 25.84 ± 5.1 a.u., respectively. (Figure 4.7)

A statistically significant increase in skin hydration on MAI treated side was remarkably seen on day 14 at 41.24 ± 6.92 a.u. compared to the hydrophilic treated side at 20.96 ± 6.8 a.u. (p<0.001). (Figure 4.7)

Moreover, on day 28, a dramatic increase of skin hydration on MAI treated side was observed to be statistically significant at 50.49 ± 8.2 a.u. compared to the hydrophilic cream treated side at 21.75 ± 8.29 a.u. (p<0.001) (Figure 4.7)

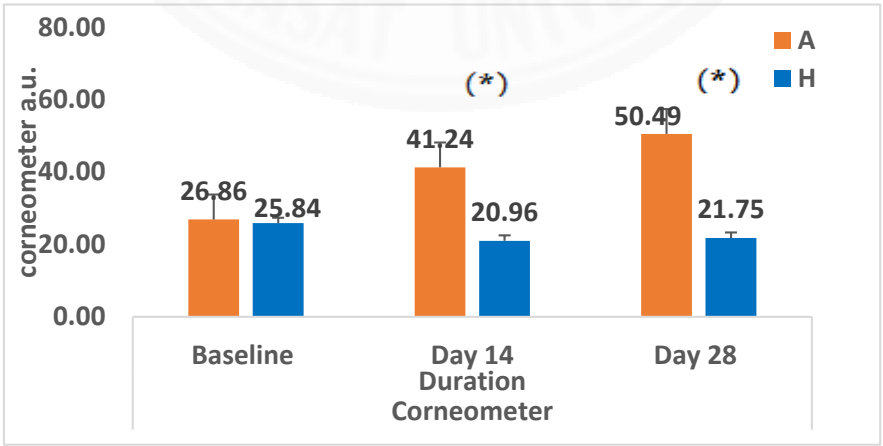


Figure 4.7 The values of skin hydration measured by corneometer (a.u.) on MAI and hydrophilic treated side on baseline, day 14 and day 28, respectively. (*p<0.001, A: MAI, H: Hydrophilic cream)

According to the result of TEWL measurement and corneometer shown in the table, it was obviously seen that MAI provided a better improvement in terms of skin hydration measured by corneometer than a TEWL measured by tewameter on both day 14 and 28 with a statistical significant p value <0.001.

4.5 Biometric evaluation (Table 4.8)

4.5.1 Hemoglobin (Erythema index)

The Biometric assessment using Antera 3D camera measurement showed a decrease of hemoglobin on the MAI treated side, reflecting the erythema from inflammation of the skin for 1.2 ± 0.16, 1.19 ± 0.18 and 1.15 ± 0.17 at baseline, day14 and 28, respectively and the result appeared to be statistically significant on day 28 (p=0.039). (Figure 4.8)

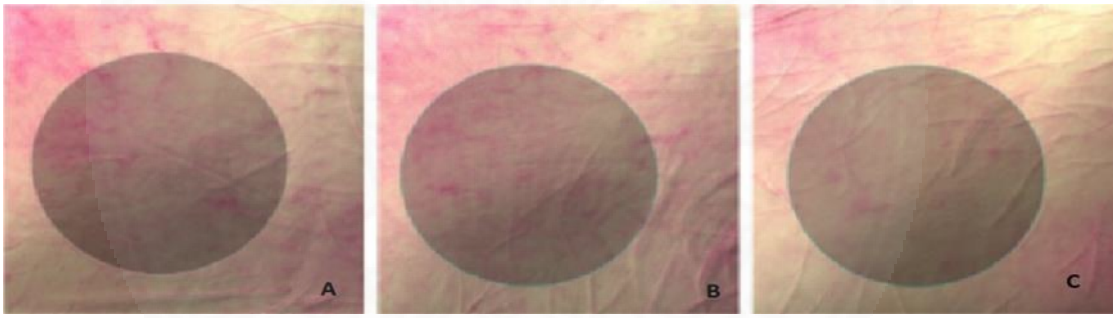


Figure 4.8 The hemoglobin (erythema) image measured by Antera evaluation illustrated the significant improvement of erythema in a patient with xerosis followed by the declined average levels at D0 (1.085) (A), D14 (1.077) (B), D28 (0.953) (C) respectively on MAI treated side.

Turning to the hydrophilic treated side, it showed a statistically significant increase of hemoglobin on both day 14 (p=0.026) and day 28 (p<0.001) compared to baseline presented at 1.19 ± 0.19, 1.24 ± 0.17 and 1.26 ± 0.17 respectively. (Figure 4.9)

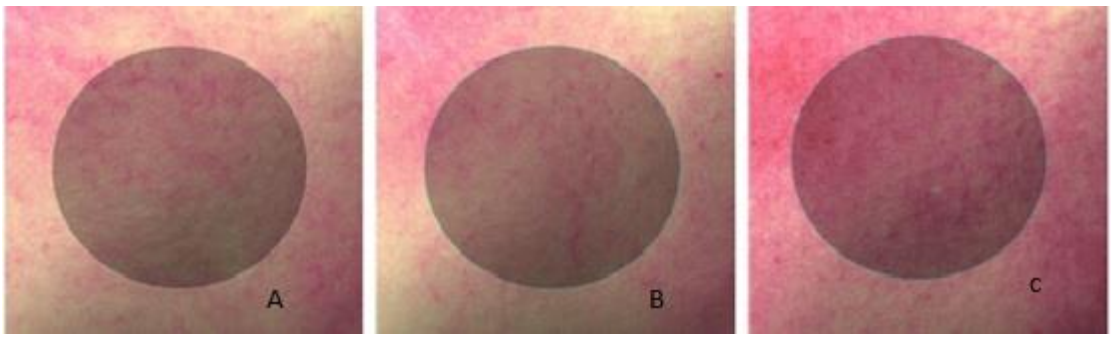


Figure 4.9 The erythema image measured by Antera evaluation on hydrophilic cream treated side expressed the significant increase of hemoglobin in a patient with xerosis followed by the increased average levels at D0 (1.14) (A), D14 (1.14) (B), D28 (1.4) (C)

Table 4.8 Biometric evaluation of hemoglobin index, melanin index, texture and wrinkle on baseline, day 14 and 28 respectively

	MAI	Hydrophilic Cream	p-value
Hemoglobin index			
Baseline	1.2 ± 0.16	1.19 ± 0.19	0.646
Day 14	1.19 ± 0.18	1.24 ± 0.17	0.011*
Day 28	1.15 ± 0.17	1.26 ± 0.17	<0.001*
p-value, day 14	0.492	0.026*	
p-value, day 28	0.039*	<0.001*	
Melanin index			
Baseline	0.57 ± 0.07	0.58 ± 0.07	0.313
Day 14	0.58 ± 0.07	0.59 ± 0.07	0.435
Day 28	0.56 ± 0.07	0.59 ± 0.07	0.005
p-value, day 14	0.158	0.445	
p-value, day 28	0.079	0.452	
Texture (Roughness)			
Baseline	7.67 ± 1.7	7.93 ± 2.61	0.429
Day 14	7.54 ± 2.4	8.52 ± 2.86	0.062
Day 28	5.84 ± 1.47	8.5 ± 1.98	<0.001*
p-value, day 14	0.718	0.014*	
p-value, day 28	<0.001*	0.051	
Wrinkles			
Baseline	7.88 ± 1.52	8.2 ± 2.31	0.263
Day 14	7.8 ± 2.11	8.57 ± 2.34	0.059
Day 28	6.37 ± 1.32	8.62 ± 1.68	<0.001*
p-value, day 14	0.816	0.081	
p-value, day 28	<0.001*	0.136	

Values presented as mean ± SD. P-value corresponds to paired t test.

At baseline, it was seen that the values of hemoglobin were not really different between MAI treated side (1.2 ± 0.16) and hydrophilic treated side (1.19 ± 0.19) with statistical insignificance. However, values of hemoglobin were shown to be statistical significant on day 14 and 28 on MAI treated side compared to hydrophilic treated side presented at (1.19 ± 0.18, 1.15 ± 0.17) and (1.24 ± 0.17, 1.26 ± 0.17) respectively. (Figure 4.10)

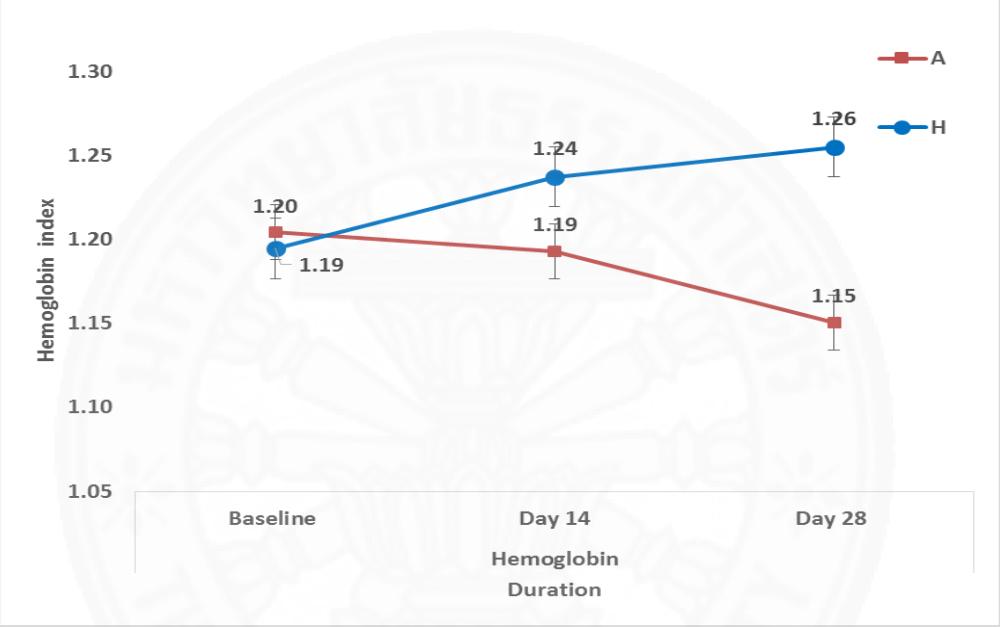


Figure 4.10 Biometric assessment of hemoglobin (erythema) index of MAI and hydrophilic treated side on baseline, day 14 and day 28, respectively. (*p<0.001, A: MAI, H: Hydrophilic cream)

4.5.2 Melanin index

Melanin evaluation on MAI treated side was also proved not to be statistically significant either even though there was a slightly decrease of melanin production on Day28 (0.56 ± 0.07) (p=0.079) compared with day 14 (0.58 ± 0.07) (p=0.158) and the baseline (0.57 ± 0.07). (Figure 4.11)

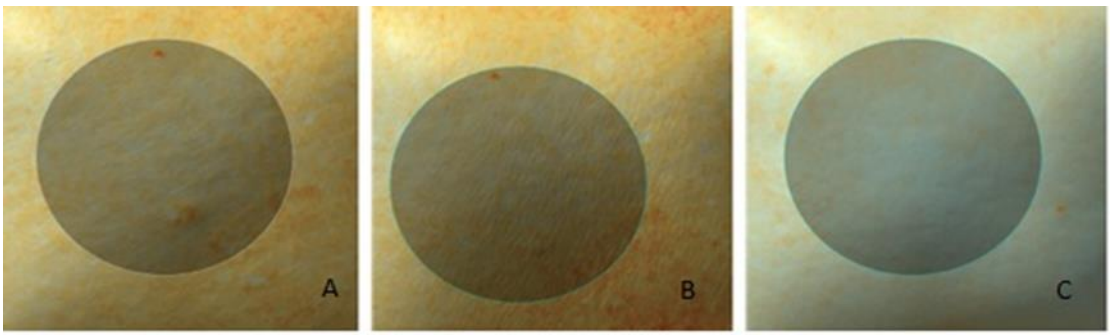


Figure 4.11 The melanin image measured by Antera evaluation exhibited the gradual improvement of hyperpigmentation in a patient with xerosis on MAI treated side followed by the declined average levels at D0 (0.509) (A), (0.523) (B), (0.399) (C)

Melanin evaluation in the hydrophilic side was not determined to have any significant improvement on baseline compared to day 14 (p=0.445) and 28 (p=0.452) on hydrophilic treated side presented at 0.58 ± 0.07, 0.59 ± 0.07 and 0.59 ± 0.07 respectively. (Figure 4.12)

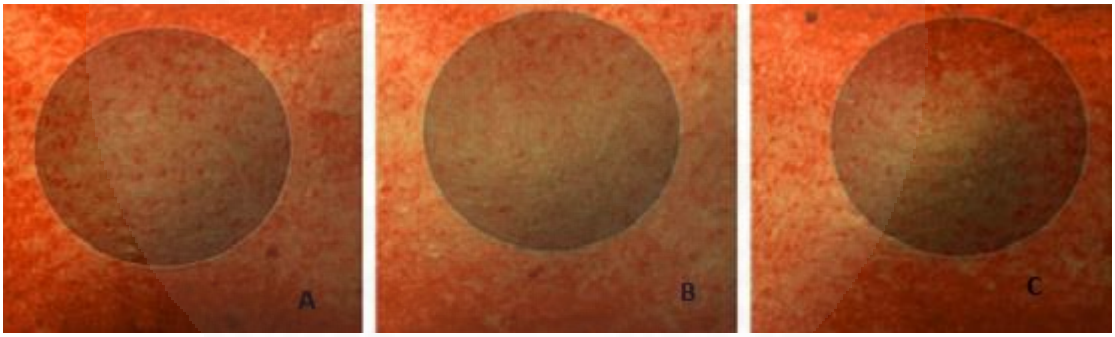
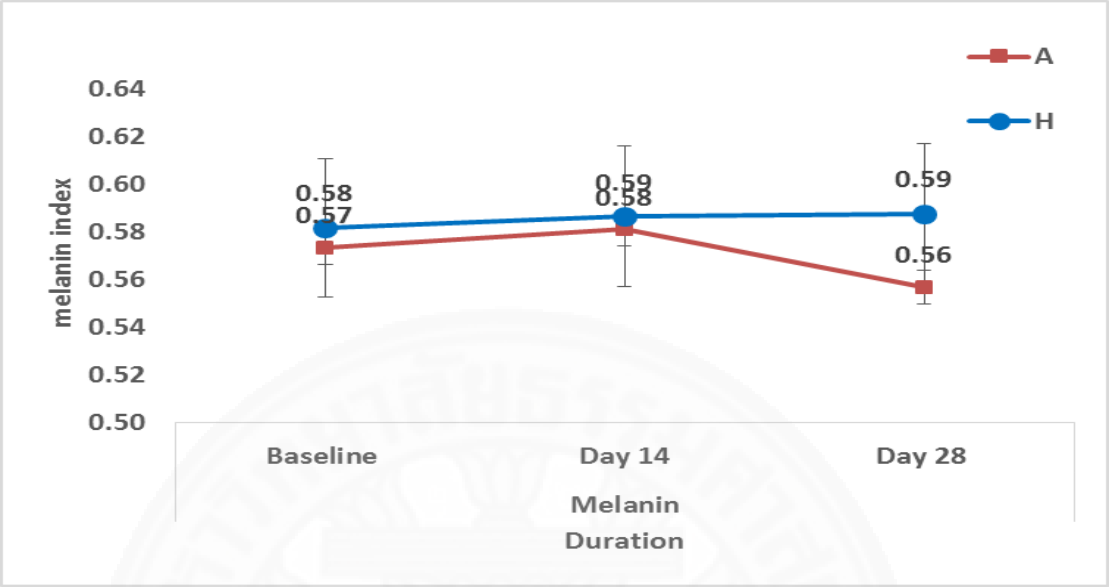


Figure 4.12 The melanin image measured by Antera evaluation exhibited the gradual increase of hyperpigmentation in a patient with xerosis followed by the respective average levels at D0 (1.47) (A), D14 (1.41) (B), D28 (1.51) (C)

Moreover, it did also reveal a statistically significant decrease in melanin on MAI treated side compared to hydrophilic treated side on baseline (0.57, 0.58), day 14 (0.58, 0.59) and day 28 (0.56, 0.59). (p=0.313), (p=0.435), (p=0.005) as shown in the figure 4.13.

Figure 4.13 Biometric assessment of melanin index of MAI and hydrophilic treated side on baseline, day 14 and day 28, respectively. (A: MAI, H: Hydrophilic cream)



4.5.3 Texture (roughness)

Moreover, from the texture (roughness) result on MAI treated side, it showed a statistically significant improvement in roughness from baseline (7.67 ± 1.7), D14 (7.54 ± 2.4) and D28 (5.84 ± 1.47) ($p<0.001$), respectively. Figure 4.14

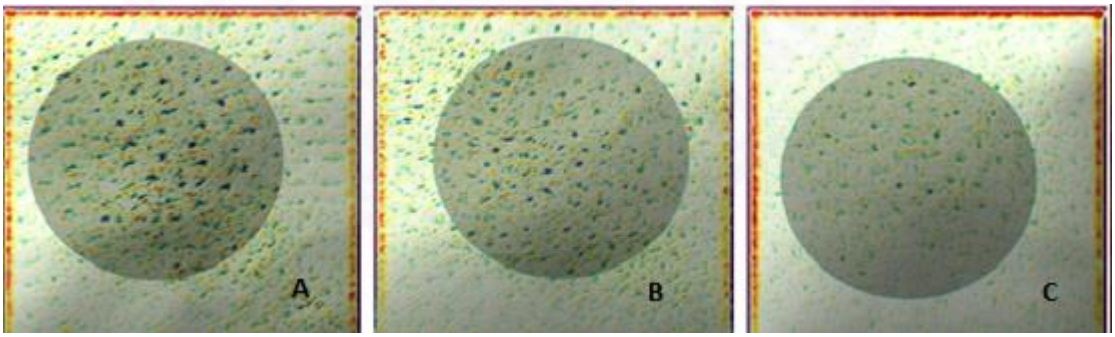


Figure 4.14 The texture image measured by Antera evaluation expressed the dramatic improvement of skin roughness in a patient with xerosis followed by the declined average levels at D0 (11) (A), (9.9) (B), (6.62) (C)

However, there was a statistical significant increase in roughness of the hydrophilic treated side on day 14 (8.52 ± 2.86) ($p=0.014$) compared to baseline (7.93 ± 2.61) and day 28 (8.5 ± 1.98) ($p=0.051$). Figure 4.15

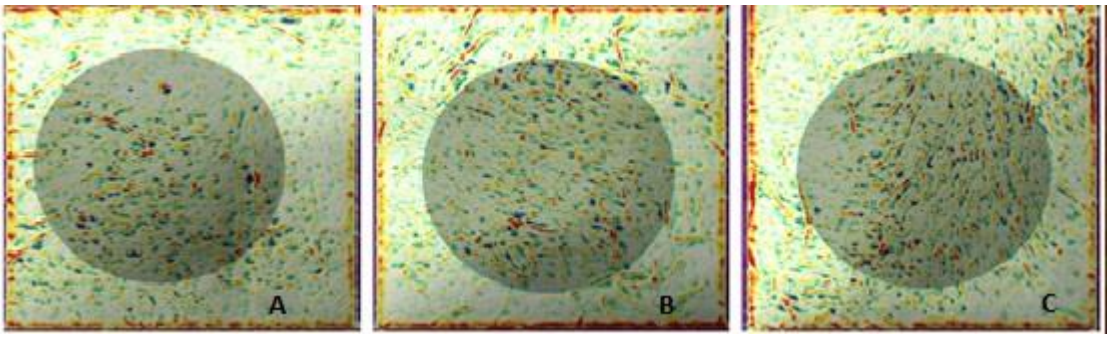


Figure 4.15 The texture image measured by Antera evaluation expressed the gradual increase of skin roughness in a patient with xerosis followed by the increased average levels at D0 (11.4) (A), D14 (12) (B), D28 (12.9) (C)

As a result of the comparison between these two groups, it represented the statistically significant declined values of roughness texture on day 28 on MAI treated side (5.84 ± 1.47) compared to hydrophilic treated side (8.5 ± 1.98) ($p<0.001$) while it didn't prove any statistical significance of roughness value of MAI treated side compared to hydrophilic treated side on day 0 and 14. ($p=0.429$) ($p=0.062$). (Figure 4.16)

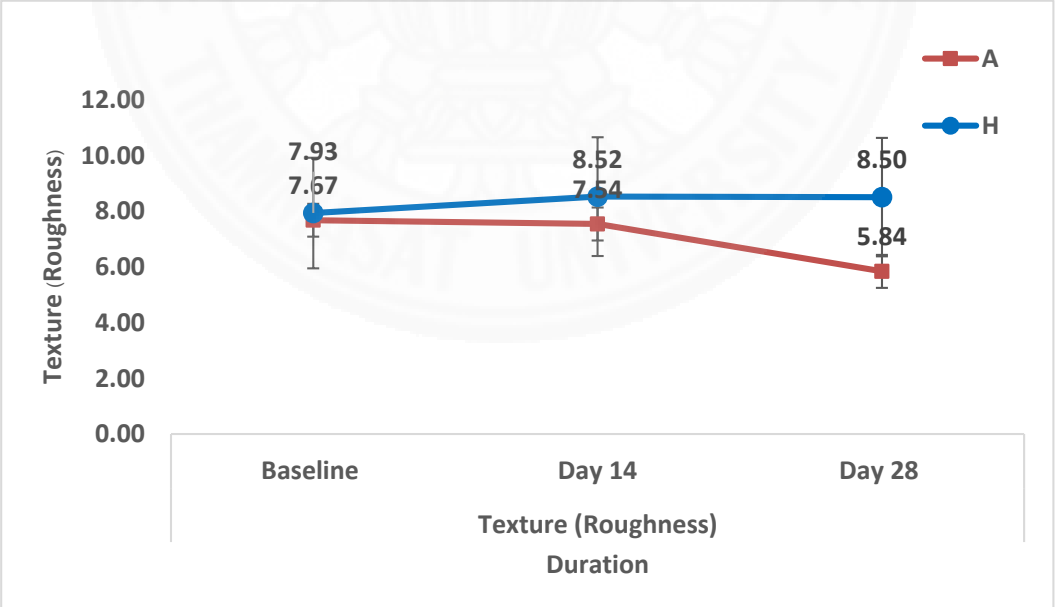


Figure 4.16 Biometric assessment of texture (roughness) index of MAI and hydrophilic treated side on baseline, day 14 and day 28, respectively. (A: MAI, H: Hydrophilic cream)

4.5.4 Wrinkles

Whereas, wrinkles assessment on MAI treated side simultaneously indicated a statistically significant decrease on D28 (6.37 ± 1.32) ($p<0.001$) compared with baseline (7.88 ± 1.52) and D14 (7.8 ± 2.11). Figure 4.17

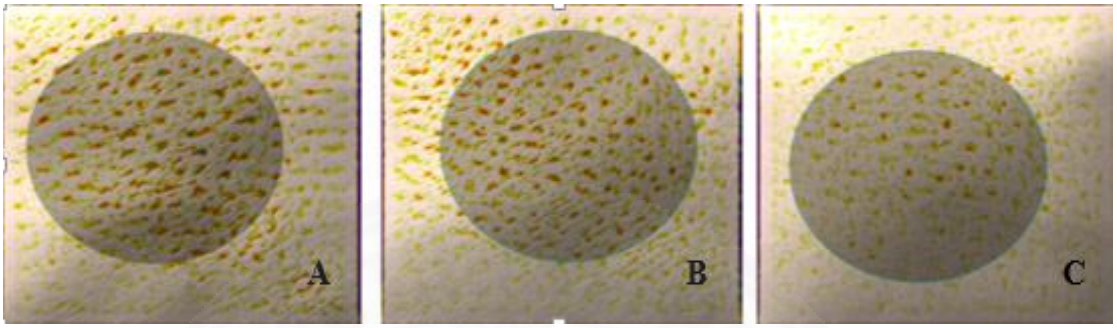


Figure 4.17 The wrinkle image measured by Antera evaluation expressed the significant improvement of wrinkles in a patient with xerosis followed by the declined average levels at D0 (10.9) (A), (9.81) (B), (6.96) (C)

Meanwhile wrinkle assessment on hydrophilic treated side also revealed the slight increase on baseline (8.2 ± 2.31) compared to day 14 (8.57 ± 2.34) ($p=0.081$) and day 28 (8.62 ± 1.68) ($p=0.136$) without any statistical significance.

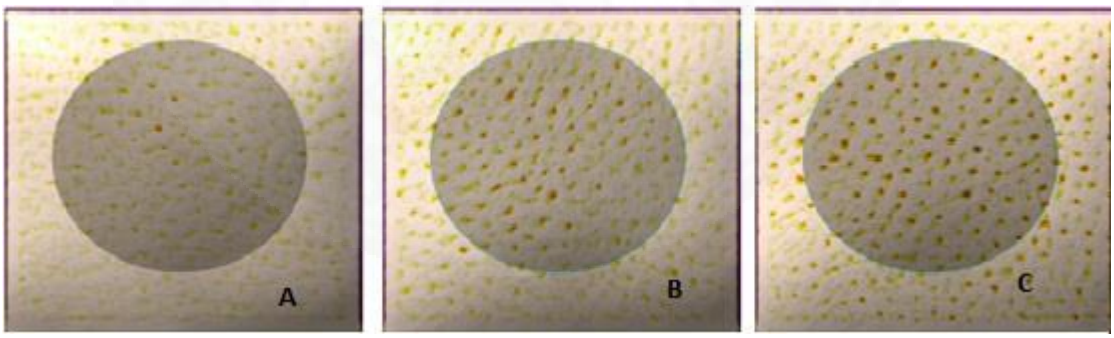


Figure 4.18

Figure 4.18 The wrinkle image measured by Antera evaluation expressed the slight increase of wrinkles in a patient with xerosis followed by the increased average levels at D0 (5.23) (A), D14 (6.76) (B), D28 (6.78) (C)

Simultaneously, there was no any statistically significant improvement in wrinkles on day 0 and 14 either on MAI treated side compared to hydrophilic treated side but the statistically significant improvement in wrinkles have

been surprisingly noticed on MAI treated side compared to hydrophilic treated side on day 28 presented at 6.37 ± 1.32 and 8.62 ± 1.68 ($p<0.001$) respectively. (Figure 4.19)

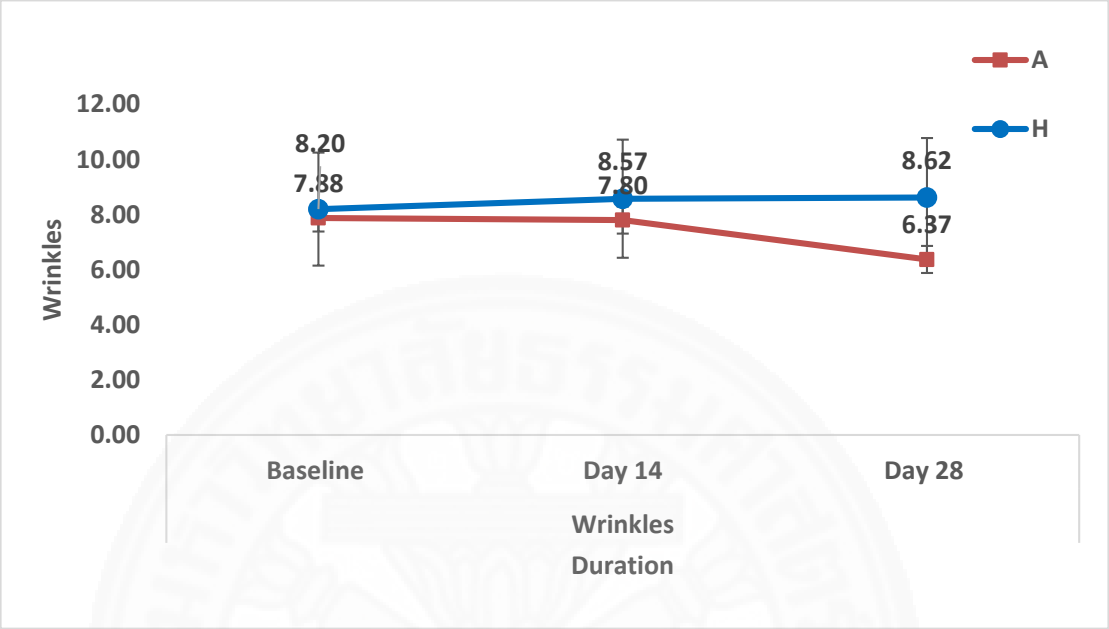


Figure 4.19 Biometric assessment of wrinkle of MAI and hydrophilic treated side on baseline, day 14 and day 28, respectively. (*$p<0.05$, A: MAI, H: Hydrophilic cream)

4.6 Subject global assessment (SGA)

Subject global assessment (SGA) were scored on a 5-point scale: 0 = No improvement, 1 = Slight improvement, 2 = Mild improvement, 3 = Moderate improvement, 4 = Excellent improvement.[49]

4.6.1 Patients' satisfaction

Basing on the table 4.9, it illustrated the satisfactory effects assessed by the subjects including itching, dryness, roughness, moisture, easily absorbed, rapidly improve skin moisture, moisture persist for all day and texture. Meanwhile, it was obviously seen that itching, dryness and roughness on both MAI and Hydrophilic treated side have obtained the same increasing values with the statistical significance on day 14 and day 28 presented at (3.46 ± 0.51, 3.88 ± 0.34), (3.46 ± 0.51, 3.88 ± 0.34) and (3.42 ± 0.5, 3.88 ± 0.34). Since the values increased, it implied that there was no any better improvement in itching, dryness and roughness on both treated sides between day 14 and day 28.

However, focusing on the individual treated side of MAI and hydrophilic cream treated side, it was remarkably noticed that on day 14 and 28, the respective values of moisture (3.46 ± 0.59, 3.88 ± 0.34) (p-value=0.004), rapidly improve skin moisture (3.38 ± 0.58, 3.83 ± 0.38) (p-value=0.005), moisture persist for all day(3.33 ± 0.56, 3.83 ± 0.38) (p-value=0.003) and texture(3.46 ± 0.51, 3.79 ± 0.51) (p-value=0.021) on MAI treated side revealed the statistically significant improvement except easily absorbed (3.38 ± 0.49, 3.67 ± 0.7) (p-value=0.090), while on hydrophilic cream treated side showed a more superior statistically significant improvement on day 14 and 28 of all each mentioned symptoms such as moisture (3.54 ± 0.51, 3.92 ± 0.28) (p-value=0.003), easily absorbed (3.42 ± 0.5, 3.79 ± 0.51) (p-value=0.020), rapidly improve skin moisture (3.38 ± 0.58, 3.88 ± 0.34) (p-value=0.001), moisture persist for all day(3.33 ± 0.56, 3.88 ± 0.34) (p-value=0.002) and texture(3.5 ± 0.51, 3.92 ± 0.28) (p-value=0.002) respectively.

As a result, all the satisfactory effects on MAI treated side proved the statistical insignificance with p-value>0.005 compared to the hydrophilic cream treated side on day 14 and 28.

Table 4.9 Subject global assessment about the satisfactory effects on day 14 and 28, respectively

	MAI			Hydrophilic cream			p-value (b)	
	Day 14	Day 28	p- value	Day 14	Day 28	p-value	Day 14	Day 28
Itching	3.46 ± 0.51	3.88 ± 0.34	0.002*	3.46 ± 0.51	3.88 ± 0.34	0.002*	1	1
Dryness	3.46 ± 0.51	3.88 ± 0.34	0.002*	3.46 ± 0.51	3.88 ± 0.34	0.002*	1	1
Roughness	3.42 ± 0.5	3.88 ± 0.34	0.001*	3.42 ± 0.5	3.88 ± 0.34	0.001*	1	1
Moisture	3.46 ± 0.59	3.88 ± 0.34	0.004*	3.54 ± 0.51	3.92 ± 0.28	0.003*	0.317	0.317
Easily absorbed	3.38 ± 0.49	3.67 ± 0.7	0.090	3.42 ± 0.5	3.79 ± 0.51	0.020*	0.317	0.180
Rapidly improve skin moisture	3.38 ± 0.58	3.83 ± 0.38	0.005*	3.38 ± 0.58	3.88 ± 0.34	0.001*	1	0.317
Moisture persist for all day	3.33 ± 0.56	3.83 ± 0.38	0.003*	3.33 ± 0.56	3.88 ± 0.34	0.002*	1	0.317
Texture	3.46 ± 0.51	3.79 ± 0.51	0.021*	3.5 ± 0.51	3.92 ± 0.28	0.002*	0.317	0.180

Values presented as mean ± SD. P-value corresponds to Wilcoxon signed ranks test

4.6.2 Subject adverse reaction

All subjectively clinical adverse effect assessments were evaluated using a 4-point scale that was ranked as follows: 0 = none, 1 = mild, 2 = moderate and 3 = severe.

There were no any statistically significance (p-value>0.005) of subject adverse reaction on both MAI and hydrophilic cream treated side shown in the table 4.10 such as more itch, more dryness, erythema, burning, pain, edema, eczema, sensitive skin, oozing, hyperpigmentation. However, hyperpigmentation (0.08 ± 0.28) on MAI treated side noticeably showed the better improvement than the hyperpigmentation (0.13 ± 0.34) on hydrophilic cream treated side on day 28 compared to day 14 presented at (0.25 ± 0.44) equally even though the improvements were not statistically significant. (p-value>0.005) (Table 4.10)

Table 4.10 Subject adverse reaction

	MAI			Hydrophilic cream			p-value (b)	
	Day 14	Day 28	p-value	Day 14	Day 28	p-value	Day 14	Day 28
More itch	0 ± 0	0.04 ± 0.2	0.317	0 ± 0	0.04 ± 0.2	0.317	1	1
More dryness	0 ± 0	0 ± 0	1	0 ± 0	0 ± 0	1	1	1
erythema	0.04 ± 0.2	0.04 ± 0.2	1	0.04 ± 0.2	0 ± 0	0.317	1	0.317
Burning	0 ± 0	0 ± 0	1	0 ± 0	0 ± 0	1	1	1
Pain	0 ± 0	0 ± 0	1	0 ± 0	0 ± 0	1	1	1
Edema	0 ± 0	0 ± 0	1	0 ± 0	0 ± 0	1	1	1
Eczema	0.04 ± 0.2	0.08 ± 0.28	0.564	0 ± 0	0.04 ± 0.2	0.317	0.317	0.317
Sensitive skin	0.04 ± 0.2	0 ± 0	0.317	0.04 ± 0.2	0 ± 0	0.317	1	1
Oozing	0 ± 0	0 ± 0	1	0 ± 0	0 ± 0	1	1	1
Hyperpigmentation	0.25 ± 0.44	0.08 ± 0.28	0.157	0.25 ± 0.44	0.13 ± 0.34	0.317	1	0.317

Values presented as mean ± SD. P-value corresponds to Wilcoxon signed ranks test

4.7 Dermatology Life Quality In dex (DLQI) [55]

The Dermatology life Quality Index (DLQI) is a ten-question questionnaire used to measure the impact of skin disease on the quality of life of an affected person. It is designed for people aged 16 years and above consisting of:

1. Over the last week, how itchy, sore, painful or stinging has your skin been?

2. Over the last week, how embarrassed or self-conscious have you been because of your skin?

3. Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?

4. Over the last week, how much has your skin influenced the clothes you wear?

5. Over the last week, how much has your skin affected any social or leisure activities?

6. Over the last week, how much has your skin made it difficult for you to do any sport?

7. Over the last week, has your skin prevented you from working or studying? If "No", over the last week how much has your skin been a problem at work or studying?

8. Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?

9. Over the last week, how much has your skin caused any sexual difficulties?

10. Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?

Owing to the table 4.11, there were a statistically significant improvement Question 1, 2, 3 and 6 with P-value equals 0.002, 0.016, 0.046 and 0.011 respectively. The answer “Not at all” to the question number 1 which was asked that “Over the last week, how itchy, sore, painful or stinging has your skin been?” was significantly changed from 45.8% to 95.8%. Whereas, question number 2 was “Over the last week, how embarrassed or self-conscious have you been because of your skin?” The answer “Not at all” was claimed to be significantly changed from 70.8% to 100%. Meanwhile, question number 3 was “Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?” The answers “not at all” was significantly changed from 83.3% to 10% and “a little” was also significantly changed from 17.7% to 0%. Lastly, the impressive answer “not at all” to the question number 6 which was asked that “Over the last week, how much has your skin made it difficult for you to do any sport?” was significantly changed from 70.8% to 100%. Despite the fact that there were the statistically significant changes for the 4 mentioned questions, the 6 rest questions remained no statistical significant at all.

Table 4.11 DLQI

Baseline	DLQI 1	DLQI 2	DLQI 3	DLQI 4	DLQI 5	DLQI 6	DLQI 7	DLQI 8	DLQI 9	DLQI 10
Not at all	11 (45.8%)	17 (70.8%)	20 (83.3%)	21 (87.5%)	21 (87.5%)	17 (70.8%)	23 (95.8%)	23 (95.8%)	23 (95.8%)	23 95.8%)
A little	5 (20.8%)	2 (8.3%)	4 (16.7%)	1 (4.2%)	3 (12.5%)	6 (25%)	1 (4.2%)	1 (4.2%)	0 (0%)	1 (4.2%)
A lot	7 (29.2%)	4 (16.7%)	0 (0%)	2 (8.3%)	0 (0%)	1 (4.2%)	0 (0%)	0 (0%)	1 (4.2%)	0 (0%)
Very much	1 (4.2%)	1 (4.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Day 28	**DLQI 1**	**DLQI 2**	**DLQI 3**	**DLQI 4**	**DLQI 5**	**DLQI 6**	**DLQI 7**	**DLQI 8**	**DLQI 9**	**DLQI 10**
Not at all	23 (95.8%)	24 (100%)	24 (100%)	24 (100%)	24 (100%)	24 (100%)	24 (100%)	24 (100%)	24 (100%)	24 (100%)
A little	1 (4.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
A lot	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Very much	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
p-value	0.002*	0.016*	0.046*	0.102	0.083	0.011*	0.317	0.317	0.317	0.317

Values presented as number (percent, %). P-value corresponds to Wilcoxon signed ranks test

Furthermore, it was splendidly illustrated that the quality life of the patients have got much better improvement after applying the study moisturizers as well as the statistically significant value (p-value=0.003) of "no effect on patient's life" increased from 54.2% at baseline to 100% on day 28. (Table 4.12)

Table 4.12. DLQI

	Baseline	**Day 28**	**p-value**
Total (score = 30) Mean ± SD.	2.5 ± 3.26	0.04 ± 0.2	0.001*
0-1 = No effect on patient's life	13 (54.2%)	24 (100%)	0.003*
2-5 = Small effect	6 (25%)	0 (0%)	
6-10 = Moderate effect	4 (16.7%)	0 (0%)	
11-20 = Very large effect	1 (4.2%)	0 (0%)	
21-30 = Extremely large effect	0 (0%)	0 (0%)	

Values presented as mean ± SD. and number (percent, %). P-value corresponds to paired t test and Wilcoxon signed ranks test

4.8 Discussion

Many moisturizer formulations have been thoroughly developed to improve the skin texture, provide skin hydration, enhance skin barrier function and effectively treat xerosis. In this study, we found that MAI lotion had a comparable efficacies with hydrophilic cream to successfully improve the clinical symptoms of xerosis as monitored by XSS and SGA except hyperpigmentation after applying MAI lotion considered as a side effect showed the better improvement on day 28 compared to day 14 than hydrophilic cream even though the improvement were not statistically significant. The most interesting view of this study was that according to the results which have been specifically measured by biophysical parameters including Tewameter, corneometer, Antera assessment, it was marvelously noticed that MAI lotion have shown a significant improvement of xerosis condition (hemoglobin, texture and wrinkle), an increase of skin hydration and a decrease of TEWL from baseline compared to hydrophilic cream. MAS062D contains the moisturizer components including humectants, emollients and occlusive ingredients that could significantly improve the skin hydration evaluated by corneometer, skin texture and wrinkle evaluated by Antera camera while the TEWL evaluated by tewameter showed the improving trends at day 14 and day 28 but the improvement were not statistically significant. Moreover, its active anti-inflammatory agents including vitis vinisfera,

telmesteine, HA and GrA, which are not steroid to calmly ameliorate the inflammation in xerosis evaluated by the improvement of hemoglobin from Antera evaluation.[43, 46]

The impressive improvement of xerosis and inflammation after MAI treatment could be from the active ingredients such as vitis vinisfera, telmesteine especially GrA which have their mechanisms individually. The standardized vitis vinifera (grapevine) extract in MAS062D has antioxidant and antiprotease activity, which may help protect against breakdown of the epidermis.[43] Telmesteine also has antiprotease action and inhibits elastase, collagenase, and matrix metalloproteinase, which are expressed at high levels in patients with inflammatory skin disease such as atopic dermatitis.[40, 45] Additionally, according to another journal regarding the anti-inflammatory properties of telmesteine comprehensively claimed that telmesteine topical treatement significantly decreased Tetradecanoylphorbol-13-acetate (TPA) induced skin inflammation as assessed by skin edema and pro-inflammatory cytokines (IL-1b, IL-6, and TNF-a) as well as further analysis results demonstrated that the anti-inflammation properties of telmesteine were obviously able to inhibit an activation of nuclear factor kappa-kB (NF-kB) by blocking phosphoinositide 3-kinase/protein kinase B (PI3K/Akt)/IkB kinase (IKK) activities.[56] Moreover, HA which is another ingredient in MAI lotion was scientifically proved to mediate CD44 interactions through these downstream pathways, such as RhoGTPases (RhoA and Rac1), Rho-kinase, protein kinase-Ng, and phosphoinositide-specific phospholipases in coordinating certain intracellular signaling pathways, for instance calcium mobilization, phosphatidylinositol 3-kinaseeAKT activation, cortactinactin binding, and actin-associated cytoskeleton reorganization; promoting the important keratinocyte activities, such as cell adhesion, proliferation, migration, and differentiation; and performing epidermal functions which basically resulted in improving xerosis conditions basing on these molecular mechanism pathways of HA as mentioned.[57] Finally, GrA is shown as the active metabolite in licorice root extract, shows anti-inflammatory and antipruritic activity and has been shown to block the degradation of endogenous cortisol through inhibition of 11-beta-hydroxysteroid dehydrogenase. Additionally, GrA has been demonstrated to potentiate cutaneous hydrocortisone activity naturally.[41]

However, comparing with other studies, the one conducted by Anne Lynn S. Chang in 2017 [17] showed the significant improvement in visual dryness and corneometry but TEWL were not statistically significant after applying the experimental cream composing of ceramide combined with some fillagrin components. In this aspect, TEWL values which were not significant might be due to the fact that there was no occlusive moisturizer component in the experimental cream to improve TEWL much better. The second one conducted by Teresa M. Weber in 2012 [8] demonstrated that 5%urea with sodium lactate and lactic acid as vehicle plus in a light formulation; and 10% urea with sodium lactate and lactic acid as a vehicle plus in rich formulation obtained a significant improvement in both corneometry and TEWL. The third one conducted by J.H. Shim in 2016 [49] indicated that the improvement in skin hydration and TEWL measured by corneometer and tewameter respectively after applying EGF were as statistically significant as ceramide. (Table 4.13)

In our study, we did not evaluate only the improvement of skin dryness but additionally emphasized the efficacy of anti-inflammatory ingredients containing in the experimental lotion. The active ingredients in MAI such as vitis vinisfera, glycyrrhetinic acid and telmesteine act as the anti-inflammatory ensemble to beneficially help ameliorate skin dryness and inflammation simultaneously without providing any side effects, unlike steroids which are harmful causing many side effects if they are used for long term. Moreover, it also contains HA as an emollient and shea butter as emollient, humectant and occlusive to improve skin surface much better. Due to the effects of these moisturizer components such as emollient, humectant and occlusive especially anti-inflammation that are contained in MAI magnificently contributed to the impressive results of statistical significance in clinical assessment, skin hydration, roughness, wrinkles, erythema even though melanin and TEWL were not significantly shown. Interestingly, one journal scientifically proved that in subsequent tyrosinase assays, GA derivatives 4, 5, and 16 were not active at early time points, but strongly inhibited tyrosinase activity at late time points which implied that GA could be used to improve skin coloration.[58] Reversely, melanin should have been improved if we had prolonged the study duration to let GA inhibit tyrosinase activity. Whereas, the indication of an insignificant improvement in TEWL might be resulted from an inadequate occlusive component in our experimental lotion.

Table 4.13. The comparison between our study and previous studies

Year	Author	Population	Sample size	Study duration	Intervention	Comparison	Outcome	Side effects
2017	Ann Lynn S. Chang et al	Aged 60-73 years	25 subjects	15 days	Ceramide + Fillagrin	No	Significant improvement in visual dryness (94%) and corneometry (71.8%) but not TEWL (15.7%)	No adverse effects were reported
2012	Teresa M. Weber et al	Aged 50-80 years	169 subjects	2 weeks	5% urea + sodium lactate + lactic acid (light formulation)	10% urea + sodium lactate + lactic acid (Rich formulation)	Significant improvement in corneometry L (62%), R (102%) and TEWL L (20%), R (48%)	No adverse effects were reported
2016	J.H. Shim et al	Aged 20-70years	80 subjects	4 weeks	EGF	Ceramide	Significant improvement in corneometry (30%) and TEWL (50%)	No adverse effects were reported
2018	Our study	Aged 50-70years	24 subjects	4 weeks	MAI	Hydrophilic cream	-MAI showed significant improvement in XSS, IGA, dryness (23%) corneometry(87%), TEWL(46%), Antera assessment (wrinkle at day 28, roughness at day 28, erythema at day 14 & 28) compared to hydrophilic cream	No adverse effects were reported

TEWL = Transepidermal water loss, EGF = Epidermal growth factor, MAI = Moisturizer with anti-inflammation, XSS = Xerosis severity score, IGA = Investigator global assessment

According to a comparison between our study and previous study, MAI lotion and ceramide revealed the same significant improvement in visual dryness, corneometry and tewameter but ceramide alone was not proved to subside the inflammation as MAI did. Furthermore, one study also mentioned that ceramides only exist in a very small quantities which cost so expensive leading to the investigation of the pseudoceramide in the dermatological products.[49] Meanwhile, urea and MAI exhibited the significant improvement in skin hydration but urea is not an emollient to smoothen the skin surface as MAI which has emollient to smoothen the skin surface by reducing the wrinkles and roughness.[8] Surprisingly, EGF is one of a popular moisturizer to treat xerosis with significant results of the improvement in skin hydration and TEWL.[49] However, there was a journal claiming that long term use of EGF will trigger a dysregulation of the EGF receptor/ligand system and abnormal activation of EGFR signaling that might be involved in non-melanoma skin cancer and chronic inflammatory disorders. In this case, an excessive activation of EGFR signaling by over expression of EGFR is also found in various types of human tumors.[59, 60] As a result, MAI lotion is an only treatment of choice to treat xerosis effectively to obtain all impressive skin features such as increasing skin hydration, decreasing TEWL, filling skin surface, reducing skin coloration, promoting cell differentiation and especially reducing redness from inflammation without any side effects comparing to EGF.

Basing on the results which indicated that MAI obviously provide the good efficacy to ameliorate xerosis, there was also other various references claiming that MAI also treats many other inflammatory skin diseases. In this aspect, MAI which is a non-steroidal cream, has been efficacious in several studies in children and adults with atopic dermatitis (AD) and contact dermatitis.[38, 39] As a result from those studies and our study, MAI has beneficially demonstrated its additional potentiality to treat many different kinds of skin diseases such as atopic dermatitis, contact dermatitis and xerosis effectively.

CHAPTER 5
CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

MAI lotion has a more superior efficacy than hydrophilic cream in terms of improving skin hydration, TEWL, skin texture, wrinkles, skin redness and SGA to treat xerosis in elderly without any side effects.

In order to treat xerosis effectively by avoiding the serious side effects from long term use of steroids, MAI lotion could be an alternatively efficacious non-steroidal moisturizer with anti-inflammatory effect to treat the mild to moderate xerosis.

5.2 Recommendations

The limitations of this study are the small sample size and short period of study. In order to ratify the efficacies of this MAI, larger sample size, longer duration and comparison with other moisturizers or steroids should be highly suggested.

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APPENDICES

APPENDIX A

CASE RECORD FORM

แบบบันทึกข้อมูล

แบบสอบถาม		รหัส □□□
โปรดกรอกข้อมูลดังต่อไปนี้ และทำเครื่องหมาย / ในช่อง □ ที่ตรงกับท่าน		
ข้อมูลส่วนตัว เพศ .....1.ชาย .....2. หญิง		
ขณะนี้ท่านอายุเท่าไร	_____ ปี	
อาชีพ	□1) ข้าราชการ □2) รัฐวิสาหกิจ □3) ลูกจ้าง หรือ รับจ้าง □4) ประกอบธุรกิจส่วนตัว □5) อื่นๆ (โปรดระบุ).....	
ข้อมูลด้านสุขภาพ		
ส่วนสูง..... เซนติเมตร น้ำหนัก.....กิโลกรัม		
ท่านเคยได้รับการบอกกล่าวจากเจ้าหน้าที่สาธารณสุข/ แพทย์ ว่าท่านเป็นโรคดังต่อไปนี้ใช่หรือไม่???		
ความดันโลหิตสูง	□ ไม่ใช่ (0)	□ ใช่ (1) โปรดระบุระยะเวลาที่เป็น .....ปี การรักษาที่ได้รับ..... .....
โรคเบาหวาน	□ ไม่ใช่ (0)	□ ใช่ (1) โปรดระบุระยะเวลาที่เป็น .....ปี การรักษาที่ได้รับ..... .....
ระดับไขมันในเลือดผิดปรกติ (ไขมันตัวไดตัวหนึ่ง)	□ ไม่ใช่ (0)	□ ใช่ (1) โปรดระบุระยะเวลาที่เป็น .....ปี การรักษาที่ได้รับ..... .....
โรคหลอดเลือดหัวใจ, กล้ามเนื้อหัวใจตาย	□ ไม่ใช่ (0)	□ ใช่ (1) โปรดระบุระยะเวลาที่เป็น .....ปี การรักษาที่ได้รับ..... .....
อัมพฤกษ์ หรือ อัมพาต (เช่น แขนขาอ่อนแรง)	□ ไม่ใช่ (0)	□ ใช่ (1) โปรดระบุระยะเวลาที่เป็น .....ปี การรักษาที่ได้รับ..... .....
โรคไตเรื้อรัง	□ ไม่ใช่ (0)	□ ใช่ (1) โปรดระบุระยะเวลาที่เป็น .....ปี การรักษาที่ได้รับ..... .....
โรคไทรอยด์	□ ไม่ใช่ (0)	□ ใช่ (1)

		โปรดระบุระยะเวลาที่เป็น .....ปี การรักษาที่ได้รับ..... .....
โรคลับแข็ง	☐ ไม่ใช่ (0)	☐ ใช่ (1) โปรดระบุระยะเวลาที่เป็น .....ปี การรักษาที่ได้รับ..... .....
โรคเอดส์	☐ ไม่ใช่ (0)	☐ ใช่ (1) โปรดระบุระยะเวลาที่เป็น .....ปี การรักษาที่ได้รับ..... .....
โรคมะเร็ง	☐ ไม่ใช่ (0)	☐ ใช่ (1) ท่านเป็นโรคมะเร็งชนิดใด ..... โปรดระบุระยะเวลาที่เป็น .....ปี การรักษาที่ได้รับ..... .....
การสูบบุหรี่	☐ ไม่สูบ	☐ เคยสูบ ระยะเวลาที่เลิกสูบบุหรี่ .....ปี ระยะเวลาที่เคยสูบบุหรี่ ..... ปี จำนวนเฉลี่ย .....มวน/วัน ☐ ปัจจุบันสูบบุหรี่ ระยะเวลานาน ..... ปี จำนวนเฉลี่ย .....มวน/วัน
การดื่มแอลกอฮอล์/สุรา	☐ ไม่เคยดื่ม	☐ดื่มนาน ๆ ครั้ง ☐ดื่มเป็นประจำ ระยะเวลานาน .....ปี เฉลี่ย ...../วัน ประเภทของแอลกอฮอล์/สุรา .....
โรคประจำตัวอื่นๆ	☐ ไม่มี(0)	☐ มี (1) โปรดระบุ .....
ประวัติการแพ้ยา	☐ ไม่มี (0)	☐ มี (1) โปรดระบุ .....
ยาที่ใช้ประจำ	☐ ไม่มี (0)	☐ มี(1) โปรดระบุ ☐1 ยาเบาหวาน ☐2ยาลดความดันโลหิต ☐3ยาลดไขมันในเลือด ☐4ยาขับปัสสาวะ ☐5ยาสำหรับเกล็ดเลือด ☐6ยารักษาโรคกระเพาะ ☐อื่นๆ โปรดระบุ.....

โรคผื่นภูมิแพ้ผิวหนัง	☐ ไม่มี (0)	☐ มี (1) ระยะเวลาที่เป็นโรค.....ปี.....เดือน การรักษาที่เคยได้รับ (ตอบได้มากกว่า 1 ข้อ) oยาทา oยารับประทาน oครีมทาบำรุงผิว oอื่นๆ (โปรดระบุ)..... การรักษาที่ได้รับในปัจจุบัน (ตอบได้มากกว่า 1 ข้อ) oยาทา oยารับประทาน oครีมทาบำรุงผิว อื่นๆ (โปรดระบุ).....
โรคผิวแห้ง	☐ ไม่มี (0)	☐ มี (1) ระยะเวลาที่เป็นโรค.....ปี.....เดือน การรักษาที่เคยได้รับ (ตอบได้มากกว่า 1 ข้อ) oยาทา oยารับประทาน oครีมทาบำรุงผิว oอื่นๆ (โปรดระบุ)..... การรักษาที่ได้รับในปัจจุบัน (ตอบได้มากกว่า 1 ข้อ) oยาทา oยารับประทาน oครีมทาบำรุงผิว อื่นๆ (โปรดระบุ).....
ประวัติครอบครัว เป็นโรคผื่นภูมิแพ้ผิวหนัง	☐ ไม่มี (0)	☐มี โปรดระบุ ...☐ พ่อ (1) ☐ แม่ (2) ☐ พี่สาว (3) ☐ น้องสาว (4) ☐ พี่ชาย (5) ☐ น้องชาย (6) ☐ บุตรชาย (7) ☐ บุตรสาว (8)

		☐ ปู่ (9) ☐ ย่า (10) ☐ ลา (11) ☐ ยาย(12) อื่นๆ โปรดระบุ.....
ประวัติครอบครัว เป็นโรคผิวแห้ง	☐ ไม่มี (0)	☐มี โปรดระบุ ...☐ พ่อ (1) ☐ แม่ (2) ☐ พี่สาว (3) ☐ น้องสาว (4) ☐ พี่ชาย (5) ☐ น้องชาย (6) ☐ บุตรชาย (7) ☐ บุตรสาว (8) ☐ ปู่ (9) ☐ ย่า (10) ☐ ลา (11) ☐ ยาย(12) อื่นๆ โปรดระบุ.....
ท่านมีเส้นเลือดขอดหรือไม่	☐ ไม่มี (0)	☐ มี (1) ระยะเวลาที่เป็นโรค.....ปี.....เดือน การรักษาที่เคยได้รับ (ตอบได้มากกว่า 1 ข้อ) oยาทา oยากิน oอื่นๆ (โปรดระบุ)..... การรักษาที่ได้รับในปัจจุบัน (ตอบได้มากกว่า 1 ข้อ) oยาทา oยากิน อื่นๆ (โปรดระบุ).....
ท่านมีปัจจัยที่ทำให้ผิวแห้งหรือไม่		
1.อาบน้ำนานกว่า 10 นาที	☐ ไม่มี (0)	☐มี
2. อาบน้ำมากกว่า 2 ครั้งต่อวัน	☐ ไม่มี (0)	☐มี
3. อาบน้ำอุ่น	☐ ไม่มี (0)	☐มี
4. อยู่ในห้องที่เปิดเครื่องปรับอากาศมากกว่าหรือเท่ากับ 6 ชั่วโมงต่อวัน	☐ ไม่มี (0)	☐มี
5. อื่นๆ	☐ ไม่มี (0)	☐มี โปรดระบุ .....
ท่านทาครีมบำรุงผิวหรือไม่	☐ ไม่ใช้ (0)	☐ใช้โปรดระบุ ชื่อผลิตภัณฑ์ ..... ความถี่ในการทาครีม.....ครั้งต่อวัน

		.....วันต่อสัปดาห์
ท่านใช้สบู่อาบน้ำหรือไม่	☐ ไม่ใช้ (0)	☐ใช้โปรดระบุ ☐สบู่ก้อน ระบุยี่ห้อ ..... ☐สบู่เหลวระบุยี่ห้อ .....
ท่านใช้แป้งทาตัวหรือไม่	☐ ไม่ใช้ (0)	☐ใช้โปรดระบุ ชื่อผลิตภัณฑ์ ..... ความถี่ในการทาแป้ง .....ครั้งต่อวัน .....วันต่อสัปดาห์
ท่านมีอาการเหล่านี้ที่ผิวหนังหรือไม่		
รู้สึกผิวแห้ง	☐ ไม่มี(0)	☐ มี (1)
คัน	☐ ไม่มี(0)	☐ มี (1)
ผิวลอก	☐ ไม่มี(0)	☐ มี (1)
ผิวเป็นสะเก็ด	☐ ไม่มี(0)	☐ มี (1)
ผิวแดง	☐ ไม่มี(0)	☐ มี (1)
แสบร้อนผิว	☐ ไม่มี(0)	☐ มี (1)
ปวด	☐ ไม่มี(0)	☐ มี (1)
อาการคันผิวรบกวนชีวิตประจำวัน	☐ ไม่มี(0)	☐ มี (1)
อาการคันผิวทำให้นอนไม่หลับ	☐ ไม่มี(0)	☐ มี (1)

APPENDIX B

DERMATOLOGY QUALITY OF LIFE INDEX (DQLI)

DLQI Thai version

แบบสอบถามวัดคุณภาพชีวิตของผู้ป่วยโรคผิวหนัง

(ข้อมูลของท่านจะเป็นความลับ ไม่ถูกนำไปเปิดเผยเป็นรายบุคคลต่อผู้ใดทั้งสิ้น)

ชื่อ _____ H.N. ____/_____ DLQI Score: _____

เพศ ☐ ชาย ☐ หญิง อายุ _____ปี อาชีพ_____

Study No. _____วันที่ ___ / _____ / _____ Diagnosis_____

จุดประสงค์ของแบบสอบถามนี้ เพื่อประเมินว่า ผื่นผิวหนังทำให้เกิดปัญหากับคุณมากน้อยเพียงใดในช่วงหนึ่งสัปดาห์ที่ผ่านมา? กรุณาตอบคำถามโดยทำเครื่องหมาย ✓ ลงในช่องทางขวามือ (ขอความกรุณาตอบคำถามทุกข้อ)		
1. ช่วงสัปดาห์ที่ผ่านมา คุณมีอาการคัน, เจ็บ, ปวด, หรือปวดเสียว ที่ผิวหนังมากน้อยเพียงใด	มาก ☐ ปานกลาง ☐ เล็กน้อย ☐ ไม่มีเลย ☐	
2. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังทำให้คุณรู้สึกอับอาย, ขาดความมั่นใจ มากน้อยเพียงใด	มาก ☐ ปานกลาง ☐ เล็กน้อย ☐ ไม่มีเลย ☐	
3. ในช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังทำให้คุณมีปัญหาในการออกจากบ้านไปจับจ่ายซื้อสินค้า, ดูแลบ้าน หรือดูแลสวน มากน้อยเพียงใด	มาก ☐ ปานกลาง ☐ เล็กน้อย ☐ ไม่มีเลย ☐	ไม่มีความเกี่ยวข้อง ☐
4. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังของคุณ มีผลกระทบต่อการเลือกเสื้อผ้าที่จะสวมใส่ มากน้อยเพียงใด	มาก ☐ ปานกลาง ☐ เล็กน้อย ☐ ไม่มีเลย ☐	ไม่มีความเกี่ยวข้อง ☐
5. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังของคุณ มีผลกระทบต่อการเข้าสังคม หรือต่อกิจกรรมใดยามว่าง มากน้อยเพียงใด	มาก ☐ ปานกลาง ☐ เล็กน้อย ☐ ไม่มีเลย ☐	ไม่มีความเกี่ยวข้อง ☐
6. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังมีผลกระทบต่อการเล่นกีฬา การออกกำลังกายของคุณ มากน้อยเพียงใด	มาก ☐ ปานกลาง ☐ เล็กน้อย ☐ ไม่มีเลย ☐	ไม่มีความเกี่ยวข้อง ☐
7. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังมีผลทำให้คุณขาดงานหรือขาดเรียนหรือไม่	มี ☐ ไม่มี ☐	ไม่มีความเกี่ยวข้อง ☐
ถ้า "ไม่มี" ในช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังทำให้มีคุณมีปัญหาในการทำงาน หรือ การเรียน มากน้อยเพียงใด	ปานกลาง ☐ เล็กน้อย ☐ ไม่มีเลย ☐	
8. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังของคุณ ได้สร้างปัญหาให้กับคู่ครอง หรือญาติหรือเพื่อนสนิท มากน้อยเพียงใด	มาก ☐ ปานกลาง ☐ เล็กน้อย ☐ ไม่มีเลย ☐	ไม่มีความเกี่ยวข้อง ☐
9. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังทำให้คุณมีปัญหาในการมีเพศสัมพันธ์ มากน้อยเพียงใด	มาก ☐ ปานกลาง ☐ เล็กน้อย ☐ ไม่มีเลย ☐	ไม่มีความเกี่ยวข้อง ☐
10. ช่วงสัปดาห์ที่ผ่านมา การรักษาผื่นผิวหนังก่อให้เกิดปัญหาแก่คุณ มากน้อยเพียงใด เช่น ทำให้มีการเปลี่ยนเปื้อนในบ้าน, การรักษาทำให้เสียเวลา เป็นต้น	มาก ☐ ปานกลาง ☐ เล็กน้อย ☐ ไม่มีเลย ☐	ไม่มีความเกี่ยวข้อง ☐

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APPENDIX C
CONSENT FORM

แบบฉลากที่ MF 10_2

หนังสือแสดงเจตนายินยอมเข้าร่วมการวิจัย

(Consent Form)

โครงการวิจัยเรื่อง การศึกษาเปรียบเทียบประสิทธิภาพและความปลอดภัยของโลชั่นทาเบาเฉมเอเอสสูนย์หกสองดี กับคลิมโบโลฟิลิล ในการเพิ่มความชุ่มชื้นและความแข็งแรงของเกราะป้องกันผิวหนังในผู้สูงอายุที่มีผิวแห้ง

วันที่ให้คำยินยอม วันที่ .....เดือน .....พ.ศ.....

ก่อนที่จะลงนามในใบยินยอมให้ทำการวิจัยนี้ ข้าพเจ้าได้รับการอธิบายจากผู้วิจัยถึงวัตถุประสงค์ของการวิจัย วิธีการวิจัย อันตรายหรือจากการที่อาจเกิดขึ้นจากการวิจัยหรือจากยาที่ใช้ รวมทั้งประโยชน์ที่จะเกิดขึ้นจากการวิจัยอย่างละเอียด และมีความเข้าใจดีแล้ว ซึ่งผู้วิจัยได้ตอบคำถามต่างๆ ที่ข้าพเจ้าสงสัยด้วยความเต็มใจ ไม่ปิดบัง ซ่อนเร้น จนข้าพเจ้าพอใจ และเข้าร่วมโครงการนี้โดยสมัครใจ

ข้าพเจ้ามีสิทธิ์ที่จะบอกเลิกการเข้าร่วมการวิจัยนี้เมื่อใดก็ได้ ถ้าข้าพเจ้าปรารถนาโดยไม่เสียสิทธิในการรักษาพยาบาลที่จะเกิดขึ้นตามมาในโอกาสต่อไป

ผู้วิจัยรับรองว่าจะเก็บข้อมูล เฉพาะเกี่ยวกับตัวข้าพเจ้าเป็นความลับและจะเปิดเผยได้เฉพาะในรูปแบบที่เป็นสรุปของการวิจัย

การเปิดเผยข้อมูลเกี่ยวกับตัวข้าพเจ้าต่อหน่วยงานต่างๆ ที่เกี่ยวข้องกระทำได้เฉพาะกรณีจำเป็นด้วยเหตุอหารวิชาการเท่านั้นและจะต้องได้รับคำยินยอมจากข้าพเจ้าเป็นลายลักษณ์อักษร

ในการวิจัยครั้งนี้ จะมีการถ่ายรูปก่อนและหลังการรักษา ตอนแบบส่วนลาย และเข้าร่วมการวิจัยโดยการทาโลชั่น 2 ชนิดที่หน้าแข้ง โดยแบ่งเป็นหน้าแข้งทาโลชั่นชนิดที่ 1 และ หน้าแข้ง ด้านขวาทาโลชั่นชนิดที่ 2 และทาเช้าเย็น เป็นระยะเวลา 28 วัน โดยทาปริมาณครั้งละ ครึ่งช้อนชา ต่อข้าง โดยมีการตรวจติดตามทั้งสิ้น 3 ครั้ง (วันแรก, 2 และ 4 สัปดาห์หลังเข้าร่วมการวิจัย)

การทาโลชั่นอาจสามารถมีอาจจะมีอาการคันหรือแสบ หรือแห้งร่วมประกอบในโลชั่นได้แต่พบได้น้อยมาก หากอาการเป็นมาก อาสาสมัครจะได้รับการหยุดการใช้โลชั่นดังกล่าวและได้รับการรักษาได้ทันที โดยอาสาสมัครไม่มีภาระใดๆค่าใช้จ่ายใด ๆ ท่านจะได้รับการดูแลจากแพทย์ที่ดีไปให้เกิดภาวะแทรกซ้อน

ผู้วิจัยรับรองว่าหากเกิดภาวะแทรกซ้อนใดๆ ที่มีสาเหตุจากการวิจัยดังกล่าว ข้าพเจ้าจะได้รับการรักษาพยาบาลโดยไม่คิดค่าใช้จ่าย และหรือจะมีการชดเชยค่าตอบแทน ตลอดจนเงินทดแทนความพิการที่อาจเกิดขึ้นตามความเหมาะสม

ข้าพเจ้ายินยอมให้ผู้กำกับดูแลการวิจัย ผู้ตรวจสอบ คณะกรรมการจริยธรรมการวิจัยในคน และคณะกรรมการที่เกี่ยวข้องกับการควบคุมยา สามารถเข้าไปตรวจสอบข้อมูลทางการแพทย์ของข้าพเจ้า เพื่อเป็นการยืนยันขั้นตอนโครงการวิจัยทางคลินิก โดยไม่ถือเป็นเหตุละเมิดสิทธิ์ ในการเปิดเผยข้อมูลของการสมัครสมาชิกรวมทั้งอนุญาตให้คัดลอกเอกสารบางส่วนได้

แบบฟอร์มที่ MF 10_2

ข้าพเจ้าได้อ่านข้อความข้างต้นแล้ว และมีความเข้าใจดีทุกประการ และได้ลงนามในใบยินยอมนี้ด้วยความเต็มใจ

ในกรณีที่ข้าพเจ้าไม่สามารถอ่านหนังสือได้ ผู้วิจัยได้อ่านข้อความในใบยินยอมนี้ให้ข้าพเจ้าฟังจนเข้าใจดีแล้ว ข้าพเจ้าจึงลงนามในใบยินยอมนี้ด้วยความเต็มใจ

ข้าพเจ้าสามารถติดต่อผู้วิจัยได้ที่ หน่วยจริยธรรม วิทยาลัยแพทยศาสตร์นานาชาติจุฬาภรณ์ มหาวิทยาลัยวลัยลักษณ์ ถ.วิภาวดี ปทุมธานี 10120 โดยบุคคลที่รับผิดชอบเรื่องนี้ คือ อาจารย์ นายแพทย์ เสาวธิ เสื่องจรุล โทรศัพท์ 0624625142, 02-986-9213

ข้าพเจ้าขับทราบว่า ข้าพเจ้าสามารถขอรับคำปรึกษาแจ้งเรื่องร้องเรียน ได้ที่สำนักงานคณะกรรมการจริยธรรมการวิจัยในคน มธ.ชุดที่ 1 อาคารจามจุรี ชั้น 4 คณะแพทยศาสตร์ โทรศัพท์ 02-926-9704

ลงนาม.....ผู้ยินยอม

(.....)

ลงนาม.....พยาน

(.....)

ลงนาม.....พยาน

(.....)

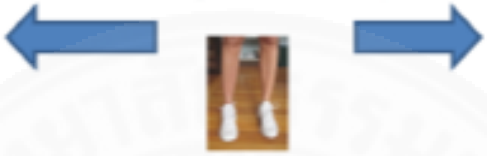
APPENDIX D

SIDE EFFECTS FORM

Code……Date ……. OD14 OD28

แบบสอบถามอาการข้างเคียงต่อโลชั่นที่ทา

โปรดทำเครื่องหมาย / ในช่องที่ตรงกับความรู้สึกของท่านมากที่สุด



	ขาขวา						ขาซ้าย				
	ไม่มี	มีเล็กน้อย	มีปานกลาง	มีมาก	มีมากที่สุด		ไม่มี	มีเล็กน้อย	มีปานกลาง	มีมาก	มีมากที่สุด
คันมากขึ้น											
ผิวแห้งมากขึ้น											
แดง											
แสบ											
ปวด											
บวม											
เกิดผื่นคัน											
ผิวหนังไวต่อสิ่งกระตุ้น											
น้ำเหลือง											
สิผิวเข้มขึ้น											

อาการผิดปกติอื่นๆ (โปรดระบุ)

……

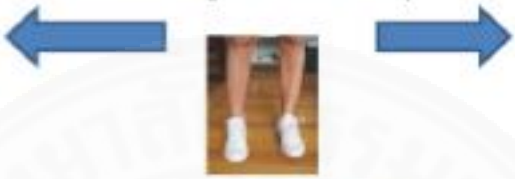
APPENDIX E

SATISFACTORY EFFECTS FORM

Code……Date …….. OD14 OD20

แบบสอบถามความพึงพอใจต่อโลชั่นที่ทา

โปรดทำเครื่องหมาย / ในช่องที่ตรงกับความรู้สึกของท่านมากที่สุด



	ขาขวา					ขาซ้าย			
	ไม่เห็นด้วยอย่างยิ่ง	ไม่เห็นด้วย	เห็นด้วย	เห็นด้วยอย่างยิ่ง		ไม่เห็นด้วยอย่างยิ่ง	ไม่เห็นด้วย	เห็นด้วย	เห็นด้วยอย่างยิ่ง
ทำให้อาการคันลดลง									
ผิวแห้งลดลง									
ผิวหยาบขรุขระลดลง									
โลชั่นทำให้ผิวนุ่มชื้น									
โลชั่นดูดซึมได้อย่างรวดเร็ว									
รู้สึกชุ่มชื้นผิวทันทีหลังทาโลชั่น									
รู้สึกชุ่มชื้นผิวหลังทาโลชั่นทั้งวัน									
ชอบเนื้อโลชั่น									

ข้อเสนอแนะอื่นๆ (ถ้ามี).....

APPENDIX F

THE ASSESSMENT FORM OF XSS, IGA, TEWL AND CORNEOMETER

แบบบันทึกและประเมินสำหรับผู้วิจัย									
			รหัส						
Fitzpatrick skin type	0 1 0 2 0 3 0 4 0 5 0 6								
		D0		D7		D 14		D 28	
		ขวา	ซ้าย	ขวา	ซ้าย	ขวา	ซ้าย	ขวา	ซ้าย
วัน/เดือน/ปี									
กรอกแบบสอบถาม									
ถ่ายรูปจากกล้องดิจิทัล	ตำแหน่ง		cm						
ถ่ายรูปจาก Dermoscopy	ตำแหน่ง		cm						
		ขวา	ซ้าย	ขวา	ซ้าย	ขวา	ซ้าย	ขวา	ซ้าย
ระดับผิวแห้งXerosis severity scale (XSS)									
		ขวา	ซ้าย	ขวา	ซ้าย	ขวา	ซ้าย	ขวา	ซ้าย
Site measurement : distance from medial tubercle		cm	cm						
อุณหภูมิห้อง									
ความชื้นห้อง									
ค่า TEWL (g/h/m)									
		ขวา	ซ้าย	ขวา	ซ้าย	ขวา	ซ้าย	ขวา	ซ้าย

ค่าความชุ่มชื้นของผิวหนัง corneometer (AU)									
		D0		D7		D 14		D 28	
		ขวา	ซ้าย	ขวา	ซ้าย	ขวา	ซ้าย	ขวา	ซ้าย
ตรวจร่างกาย grade* (0-4+)									
Redness									
Thickness									
Scratching									
Lichenification									
Hyperpigmentation									
Edema									
Dermatitis									
Others									

Severity (0=none: no; 1= minimal: 2= 1–25%; mild: 3= 26–50%; moderate: 4=51–75%; and severe: 76–100%)

Table 1 Xerosis Severity Scale presented by Rogers *et al.*[17]

Mild	0	Normal skin
	1	Dusty appearance, occasional minute skin flakes
	2	Generalized dusty appearance, many minute skin flakes
Moderate	3	Defined scaling with flat borders
	4	Well-defined heavy scaling with raised borders, shallow fissures
Severe	5	Large scale plates, fissures
	6	Large scale plates, deep erythematous fissures

APPENDIX G

ACCEPTANCE LETTER FOR PROCEEDING

Thai Journal of Pharmaceutical Sciences (TJPS)
34th International Annual Meeting in Pharmaceutical Sciences
and 2nd CU FPhS - RIKEN CDB Symposium
(IAMPS34 and 2nd CU FPhS - RIKEN CDB)

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Date: April 2, 2018

Proceeding manuscript: Efficacy and safety of MAS062D moisturizer lotion in treatment of xerosis in the elderly: a prospective therapeutic clinical trial

Authors:
Bith Soktepy, Suparuj Lueangarun

Dear Khun. Bith Soktepy,

We are pleased to inform you that your proceeding manuscript has been accepted for presentation in the 34th International Annual Meeting in Pharmaceutical Sciences and 2nd CU FPhS - RIKEN CDB Symposium (IAMPS34 and 2nd CU FPhS - RIKEN CDB), which is held on March 8-9, 2018 at Arnoma Grand Hotel Bangkok, Bangkok, Thailand. Your proceeding manuscript will be published in The Thai Journal of Pharmaceutical Sciences (TJPS), 2018, Vol.42 (Supplement Issue), page 154-157

Yours truly,

Pornchai R.

Assoc. Prof. Pornchai Rojsitthisak, Ph.D.

Chair of Scientific Program Committee

APPENDIX H

FULL MANUSCRIPT FOR PROCEEDING

TJPS Vol.42 (Supplement Issue) 2018

Thai Journal of Pharmaceutical Sciences (TJPS)

34th International Annual Meeting in Pharmaceutical Sciences and
2nd CU FPhS - RIKEN CDB Symposium
(IAMPS34 and 2nd CU FPhS - RIKEN CDB)

Efficacy and safety of MAS062D moisturizer lotion in treatment of xerosis in the elderly: a prospective therapeutic clinical trial

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Keywords: Xerosis, Moisturizer, Anti-inflammation, Moisturizer with anti-inflammatory ingredient, Treatment, Elderly

Introduction

Xerosis is a very common skin disease in elderly, characterized by an itchy, dry, rough, fissured and scaling skin.[1] Elderly are noticeably vulnerable to skin barrier impairment due to a decrease or dysfunction of stratum corneum lipid. Moreover, inflammation and pruritus are also signs of xerosis commonly occurring in elderly which result from an increased permeability due to perturbation of the defensive functions of the stratum corneum.[1,2] Treatment of xerosis principally consists of moisturizer application.[3] Despite moisturizers could partially help improve the symptoms of dry skin, patients with severe pruritus and inflammation cannot be treated by only moisturizers alone. In this circumstance, topical corticosteroids, antihistamines or phototherapy is used to additionally treat inflammation and prevent pruritus.[4] Since steroid was medically known to provide many side effects to elderly patients especially skin atrophy and further perturbation of skin integrity.[5]

The objectives of this study are to evaluate the efficacy and safety of MAS062D lotion, the moisturizer with anti-inflammatory ingredients (MAI) in the treatment of xerosis in elderly to provide efficaciously alternative therapy and also avoid side effects from steroid.

Methods

Subjects: All patients aged more than 50 years old diagnosed with mild to moderate xerosis defined by the xerosis severity scale (XSS)[6] were enrolled into the study. Subjects were known sensitivity to test ingredients, current history of any dermatologic diseases requiring treatment (such as psoriasis, atopic dermatitis and eczema), a condition that could interfere with the study's conduct, use of oral/topical corticosteroids or oral isotretinoin or immunosuppressant or light therapy within 4 weeks prior to the study were absolutely excluded from the study. The written informed consents must be signed respectively for their participation.

Study Design: This prospective clinical therapeutic study was conducted during March and June 2017. MAS062D is a MAI which contains vitis vinifera, vitamins C and E, telmesteine, hyaluronic acid (sodium hyaluronate), glycyrrhetinic acid (GrA) and Butyrospermum parkii (shea butter) as key ingredients. The product (oil in water emulsion) contained emollient, humectant and occlusive components. The test agent was prepared in a 50ml bottle.

Study evaluation: All clinical assessments and non-invasive objective measurements were performed at baseline, day 14 and 28, respectively by a blind dermatologist. The xerosis severity was evaluated using XSS. Redness, thickness, pruritus, lichenification, hyperpigmentation, edema, dermatitis were scored on a 4-point scale.[6] The Investigator global assessment (IGA) and Subject global assessment (SGA) were scored on a 6-point scale.[7] All of the non-invasive objective evaluations were performed after subjects were allowed to acclimate to standard atmospheric conditions for at least 30 min by one blinded researcher through the whole study. During the measurements, the relative humidity was controlled at 40-60% and the room temperature was maintained at 21-23 °C. Every measurement was made at the same spot on the shin. Three measurements were taken and the mean result was reported. Participants were advised not to use their lotions on the day of the visit and then they were instructed to resume normal use of their personal lotions after their study visit. The participants were informed to regularly apply MAS062D agent on the shins twice daily for 4 weeks. The participants were instructed to refrain from using any other topical treatment or moisturizers on their shins.

Electrical capacitance was measured using a Corneometer CM 825 (Courage & Khazaka Electronic GmbH, Germany) in order to assess the skin's hydration status.[8] Transepidermal water loss (TEWL) was measured using a Tewameter TM 210 (Courage & Khazaka Electronic GmbH).[9] Meanwhile, the biometric assessment using Antera 3D™ analysis camera (Miravex limited, Dublin, Ireland) was obtained in a bid to evaluate the following parameters; hemoglobin (erythema), wrinkles, melanin, and skin texture of the shins to compare the parameters before and after the treatment with the test study agent.

Statistical analysis

The sample size of subjects was calculated based on the equivalence randomized trial. All of the measured values were expressed as means SDs and were summarized using a descriptive statistical technique. ANOVA test was used to measure changes in the XSS, electrical capacitance, TEWL and Antera assessment between treatment subjects at baseline, 2 and 4 weeks. Wilcoxon signed ranks test was also used to measure differences in the SGA, IGA and pruritus grade at 2 and 4 weeks. In all cases, statistical significance was defined as $p < 0.05$.

Results

Demographic Data: A total of 20 subjects with xerosis were included and successfully completed the study. The majority of the subjects (87.5%) were female, with a mean age of 58.04 ± 6.93 years and mean XSS of 4.83 ± 0.7.

Clinical Assessment: The improvement of XSS was distinctively observed. The mean XSS of MAI treatment decreased significantly for 4.83 ± 0.7, 3.33 ± 0.82 and 1.83 ± 0.82 at baseline, day 14 and 28, respectively ($p<0.001$). The improvement of clinical presentation was also remarkably noticed with a significant improvement of dryness from day 14 (1.25 ± 0.44) compared with day 28 (0.96 ± 0.46) ($P=0.005$). While smoothness showed the significantly better results on day28 (3.58 ± 0.58) compared with day14 (3.04 ± 0.36) ($p<0.001$). Simultaneously, it also indicates the statistically noticeable improvement of moist on day 28 (3.75 ± 0.44) compared with day14 (2.65 ± 0.65) ($p<0.001$) as shown in Figure 1.

Figure 1. The 3D image from Antera camera assessment showed the clinical improvement in the treatment of xerosis with MAI at a baseline (A), day 14 (B) and day 28 (C) respectively.

Biophysical skin parameters Tewameter: From the Tewameter measurement, there were a decline from 8.87 ± 10.11, 5.4 ± 3.18 and 4.83 ± 1.84 g/m2h at the baseline, d14 and d28 respectively, however the result was not statistically significant (D14 $p=0.111$, D28 $p=0.056$). (Figure 2)

Corneometer: The corneometer measurement significantly illustrated a statistically significant increase of skin hydration from 26.86 ± 7.94 to 41.24 ± 6.92 and 50.49 ± 8.2 at baseline, day 14 and 28, respectively ($p<0.001$). (Figure 3)

Biometric evaluations: The Antera measurement showed a decrease of hemoglobin that, reflecting the erythema from inflammation of the skin for 1.2 ± 0.16, 1.19 ± 0.18 and 1.15 ± 0.17 at baseline, day14 and 28, respectively and the result appeared to be statistically significant ($p=0.039$). (Figure 4) Melanin evaluation was also proved not to be statistically significant either even though there was a slightly decrease of melanin production on Day28 (0.56 ± 0.07) ($p=0.079$) compared with day 14 (0.58 ± 0.07) ($p=0.158$) and the baseline (0.57 ± 0.07).

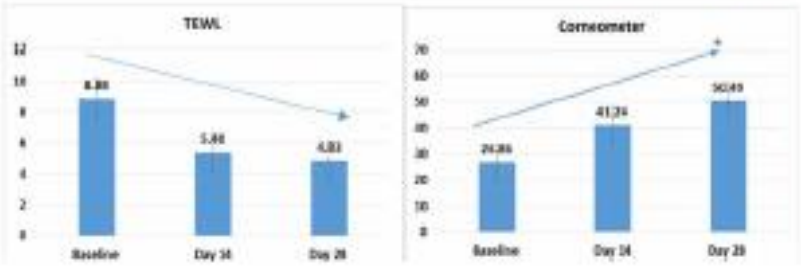

Figure 2 MAS062D provided a decrease in the transepidermal water loss (TEWL, g/m2 h) between baseline, week 2 and week 4 respectively without statistical significance. ANOVA Test, p>0.05

Figure 3 Skin hydration measured by corneometer was proved to obtain a statistically significant improvement after the treatment with MAS062D from baseline to day14 and 28, respectively. *ANOVA Test *p<0.001

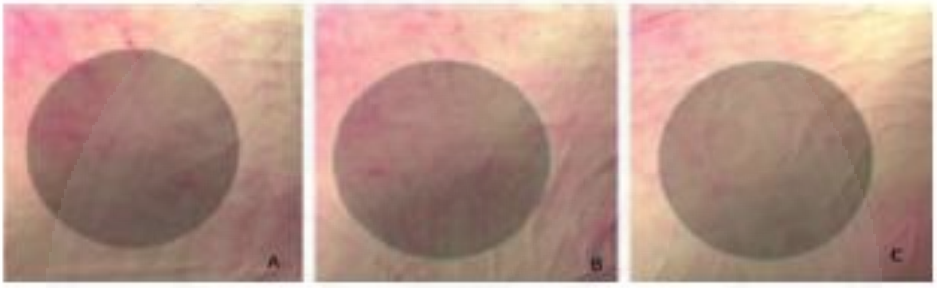

Figure 4 The erythema image measured by Antera evaluation illustrated the significant improvement of erythema in a patient with xerosis followed by the declined average levels at D0 (1.085) (A), D14 (1.077) (B), D28 (0.953) (C) respectively.

Moreover, from the texture result, it shows a statistically significant improvement in roughness from baseline (7.67 ± 1.7), D14 (7.54 ± 2.4) and D28 (5.84 ± 1.47) (p<0.001), respectively. Whereas, wrinkles assessment simultaneously indicates a statistically significant decrease in D28 (6.37 ± 1.32) (p<0.001) compared with baseline (7.88 ± 1.52) and D14 (7.8 ± 2.11).

Adverse effect: The subjects were tolerated to the test agent very well. No serious adverse effects were detected or reported over the course of the study.

Discussion

Many moisturizer formulations have been thoroughly developed to improve the skin texture, provide skin hydration, enhance skin barrier function and effectively treat xerosis. In this study, we found that MAS062D lotion has successfully improved the clinical symptoms of xerosis as monitored by XSS, pruritus grade, IGA and SGA. We noticed that according to the results which have been specifically measured by biophysical parameters including Tewameter, corneometer, Antera assessment have shown a significant improvement of xerosis condition (hemoglobin, texture and wrinkle) from baseline after use of MAS062D. MAS062D contains the moisturizer components including humectants, emollients and occlusive ingredients that could improve the skin hydration evaluated from corneometer, skin texture and wrinkle evaluated from Antera camera. Moreover, its active anti-inflammatory agents including vitis vinisfera, telmesteine, GrA, which are not steroid to calmly ameliorate the inflammation in xerosis evaluated by the improvement of hemoglobin from Antera evaluation.[10,11] The impressive improvement of xerosis and inflammation after MAI treatment could be from the active ingredients such as vitis vinisfera, telmesteine especially GrA which have their mechanisms individually. The standardized vitis vinifera (grapevine) extract in MAS062D has antioxidant and antiprotease activity, which may help protect against breakdown of the epidermis.[10] Telmesteine also has antiprotease action and inhibits elastase, collagenase, and matrix metalloproteinase, which are expressed at high levels in patients with inflammatory skin disease such as atopic dermatitis.[12,13] Finally, GrA is shown as the active metabolite in licorice root extract, shows anti-inflammatory and antipruritic activity and has been shown to block the degradation of endogenous cortisol through inhibition of 11-beta-hydroxysteroid dehydrogenase. Additionally, GrA has been demonstrated to potentiate cutaneous hydrocortisone activity naturally.[14]

Basing on the results which indicated that MAI obviously provide the good efficacy to ameliorate xerosis, there was also other various references claiming that MAI also treats many other inflammatory skin

diseases. In this aspect, MAI which is a non-steroidal cream, has been efficacious in several studies in children and adults with atopic dermatitis (AD) and contact dermatitis,[15,16] As a result from those studies and our study, MAI has beneficially demonstrated its additional potentiality to treat many different kinds of skin diseases such as atopic dermatitis, contact dermatitis and xerosis effectively.

The limitations of this study are the small sample size and short period of study. In order to ratify the efficacies of this MAI, larger sample size, longer duration and comparison with other moisturizers or steroids should be highly suggested.

Conclusion

In order to treat xerosis effectively by avoiding the serious side effects from long term use of steroids, MAS062D lotion could be an alternatively efficacious non-steroidal moisturizer with anti-inflammatory effect to treat the mild to moderate xerosis.

Conflict of Interest: All authors have none to declare

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APPENDIX I

ETHICAL APPROVAL

บันทึกข้อความ

ส่วนราชการ สำนักงานคณะอนุกรรมการจริยธรรมการวิจัยในคน มธ. ชุดที่ ๑ คณะแพทยศาสตร์

โทร. ๐๒-๙๒๖-๙๗๐๔, ๐๒-๕๖๔-๔๔๔๔ ต่อ ๗๕๓๕

ที่ ๒๗๔ /๒๕๖๐ วันที่ ๗ ธันวาคม ๒๕๖๐

เรื่อง ขอแจ้งผลการพิจารณารายงานความก้าวหน้าโครงการวิจัย รหัสโครงการ MTU-EC-OO-2-087/59

เรียน อ.นพ.เศารยะ เลื่องอรุณ

ตามที่ท่านได้ส่งรายงานความก้าวหน้าของโครงการวิจัย เรื่อง "การศึกษาเปรียบเทียบประสิทธิภาพและความปลอดภัยของโลชั่นทาผิวเอ็มเอสศูนย์หกสองดี (MAS062D) กับครีมไฮโดรฟิลิค ในการเพิ่มความชุ่มชื้นและความแข็งแรงของเกราะป้องกันผิวหนังในผู้สูงอายุที่มีผิวแห้ง" รหัสโครงการ MTU-EC-OO-2-087/59 เพื่อเข้ารับการพิจารณาจากคณะอนุกรรมการ ฯ นั้น

บัดนี้ คณะอนุกรรมการจริยธรรมฯ ได้พิจารณาเอกสารดังกล่าว ในที่ประชุมครั้งที่ ๒๒/๒๕๖๐ วันที่ ๓๐ พฤศจิกายน ๒๕๖๐ ระเบียบวาระที่ ๕.๒.๓ (๗) ห้องประชุมงานบริหารการวิจัย ชั้น ๔ อาคารราชสุดา ที่ประชุมมีมติ ดังนี้

๑. รับทราบรายงานความก้าวหน้า

๒. ขอให้ผู้วิจัยรายงานความก้าวหน้าทุก ๖ เดือน โดยทั้งนี้ขอให้ผู้วิจัยส่งรายงานความก้าวหน้าตามกำหนดอย่างเคร่งครัดโครงการวิจัยของท่านจะครบกำหนดรายงานความก้าวหน้าครั้งต่อไปในวันที่ ๒ กุมภาพันธ์ ๒๕๖๑

๓. หากผู้วิจัยรวบรวมผลการศึกษาเสร็จสมบูรณ์แล้ว ขอให้ผู้วิจัยรายงานสรุปผลการวิจัย

จึงเรียนมาเพื่อโปรดทราบและดำเนินการ

(ผู้ช่วยศาสตราจารย์ ดร.สุมาลี คอนโด)
อนุกรรมการและผู้ช่วยเลขานุการ

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