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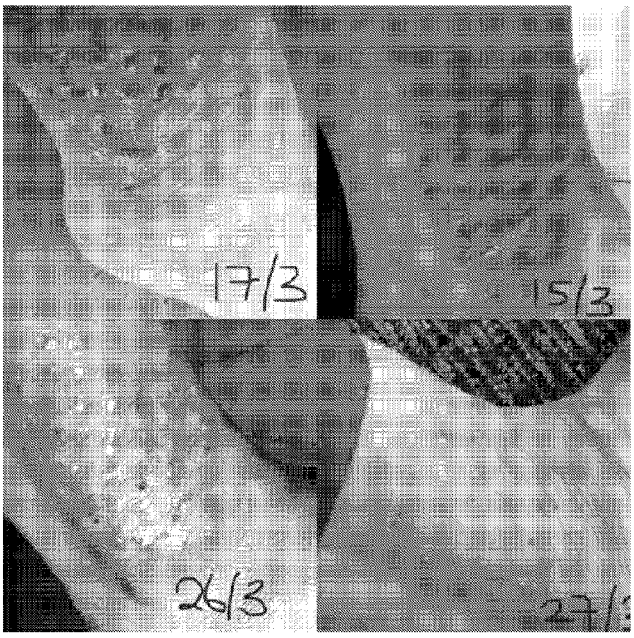

Figure 2

(57) Abstract: The present invention relates generally to a therapeutic composition comprising nanonized actives derived from oil palm and comprising at least one member selected from Group A comprising of Vitamin A and pro-vitamin A; at least one member selected from Group E comprising of Vitamin E and pro-vitamin E; and at least one member selected from a Group C consisting of Vitamin C and pro-vitamin C. The present invention provides the use of the said therapeutic composition to treat or prevent skin with dry or pruritic or inflammatory conditions.

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OIL PALM-DERIVED COMPOSITION FOR SKIN TREATMENT

TECHNICAL FIELD

The present invention relates to compositions comprising nanonized palm-derived Vitamin E and Vitamin A or Vitamin C, which exhibit synergistic effects for use in therapeutic prevention or treatment of common skin disorders.

BACKGROUND ART

One of the most common and chronic skin disorders of the world is eczema or atopic dermatitis (AD). Eczema occurs in individuals of all races and ages. Eczema is an inflammatory skin condition, characterised by ichtyosis (dry skin), erythema (redness), excoriation (interruption of the skin), scratching lesions, lichenification (thickening of the skin), infected lesions (blisters, pus formation) and hypopigmentation in old lesions. Among the various types of eczema, the most prevalent type is atopic eczema or endogenous eczema (also known as atopic dermatitis). AD affects up to 20% of children and up to 3% of adults worldwide; the incidence has increased by 2- to 3-folds during the past decades in industrialized countries and recent data show that its prevalence increasing more rapidly in low-income countries. There is no cure for eczema, but, in most cases, it is manageable and preventable. Up to date, clinical management of eczema involves therapeutic corticosteroids in reducing inflammation of the skin e.g. halcinonide 0.1%, hydrocortisone butyrate 0.1%, hydrocortisone valerate 0.2% and desonide 0.05%. Potent corticosteroids also have anti Staphylococcus aureus properties and have immunosuppressive and vasoconstrictive properties. However, therapeutic corticosteroids have side effects such as skin thinning, skin irritation, skin discoloration, acne, easy bruising, fragile blood vessels and excessive hair growth. Corticosteroids of very high potency must be avoided in children. With the growth of consumer awareness nowadays, the demand for effective nonsteroidal alternatives for eczema managements are all time high.

One known invention (US 8586109 B2) uses a tocopherol (T1) free composition of annatto extract with tocotrienol (T3) and tocotrienol containing extract as therapeutic application to protect against inflammation. However, annatto is not a major industrial

crop plant. The composition of this invention consists of only lipid-soluble compounds. No engineering processes are involved in the production of the said composition.

Another invention (US 4938960) presents a method for the treatment and protection of human and animal skin which contains vitamin E in a high dose and, in addition, may optionally further contain vitamin C, vitamin A, vitamins of the B series, blood circulation-promoting agents and/or vasodilators, phospholipids, unsaturated fatty acids and/or emulsifiers. However, it is not specified of the Vitamin E used, when Vitamin E in the industry commonly refers to tocopherol (T1). The composition also involves the addition of pharmaceutical drugs specifically antihistaminic drugs and Bufexamac, and anti-inflammatory drug.

US 2002/0120001 A1 discloses a formulation of tryptamine, mixed tocotrienols and carotenoids that synergistically inhibits the generation of free radicals and oxidative stress. However, melatonin which is used as the tryptamine of the formulation is a type of hormone that is possible unsafe for children application. Because of its effects on other hormones, melatonin might interfere with development during adolescence. The carotenoids used, specifically astaxanthin, beta-carotene, lutein and lycopene, lack stability (easily oxidized) and are synthetic compounds. The invention does not specify its application for the treatment and prevention of skin disorders.

US 2004/0241254 A1 discloses a cosmeceutical formulation which includes a votated blend of different palm oils to treat a variety of skin conditions or as an effective moisturizer. However, the formula is substantially water free and might not present desirable rheological properties. Similarly, US 2005/0100524 A1 also discloses a combination of oils, majorly from shea butter, mango butter, cocoa butter, jojoba and coconut.

The intervention of nanonization technology to bioactive deliveries are desirable for enhanced and stable bioavailability, resulting in higher therapeutic penetration of bioactives and stability of oil-in-water (O/W) or water-in-oil (W/O) compositions. In addition, as delivery and bioavailability of bioactives increases, dosage of effective bioactive concentration necessary would decrease leading higher cost effectiveness. However, though nanotechnology plays an important role in cosmeceuticals, concerns have been raised regarding the potential dangers that may occur when nanoparticles penetrate the skin.

In the application of nanonized formulations (nanoparticle compositions) for the treatment of inflammation, US 2007/0036831 A1 describes an antimicrobial nanoemulsion composition containing an aqueous phase, an oil phase comprising an oil and an organic solvent, at least one anti-inflammatory agent, and one or more surfactants. However, the composition involves the addition of steroidal drugs or non-steroidal anti-inflammatory drugs (NSAIDS) that possibly causes undesirable side effects. Another embodiment (US 2014/0348938 A1) prepares solid lipid sustained release nanoparticles for delivery of drugs/vitamins, more specifically Vitamin D_3 and retinoic acid (RA) involving microemulsion technique for the treatment of age related macular degeneration, diabetic retinopathy, cancers, hyperpigmentation, acne, and osteoporosis. This invention mixes pure vitamin compounds and does not specify usage for dermatitis.

US 8197851 B2 describes a carotenoids composition in an oil medium with size smaller than 100 nm that can be used in the sunscreen, moisturiser and other skin care products for the treatment of eczema and psoriasis. The composition only uses carotenoids, more specifically from the microalgae *Dunaliella salina*, which is not a major source of carotenoids.

SUMMARY OF THE INVENTION

According to the present invention, there is provided a therapeutic composition comprising nanonized palm oil or actives derived from combination of at least one member selected from Group A consisting of Vitamin A and pro-vitamin A; at least one member selected from Group E consisting of Vitamin E and pro-vitamin E; and at least one member selected from a Group C consisting of Vitamin C and pro-vitamin C. The nanonized composition, having average particle sizes below 350 nm, is combined with a topical cosmetic, pharmaceutical, medical or micronized or nanonized base in about 0.1 to 30% (w/w) forming a therapeutic formulation. The therapeutic formulation includes liquid, semi aqueous, cream, serum, gel, oilment, lotion, spray, balm and mist. It is accordingly an object of the present invention to provide the use of a therapeutic composition comprising nanonized palm oil or actives derived from combination of at least one member selected from group consisting of Vitamin A and pro-vitamin A; at least one member selected from group consisting of Vitamin E and pro-vitamin E; and at least one member selected from group consisting of Vitamin C and pro-vitamin C as anti-inflammatory, anti-microbial,

anti-pruritic, wound healing and skin hydration to prevent or treat eczema or psoriasis. The use of the said therapeutic composition topically, in any cosmetic or pharmaceutical base or carrier by liquid, semi aqueous, cream, serum, gel, oilment, lotion, spray, balm and mist, is applied together with a composition comprising oil, solid fat and actives capable of occlusive and humectant moisturizing properties. The use of therapeutic composition is anti-inflammatory, anti-microbial, anti-pruritic, wound healing and skin hydration to prevent or treat eczema or psoriasis. It is another object of the present invention to provide a therapeutically effective cream formulation comprises at least 60% w/w water, between 0.1-5% w/w gelling agent and/or thickener, between 1-5% w/w active ingredient and/or plant extracts, between 1-5% w/w solubilizer, between 1-5% w/w emulsifier, between 1-5% w/w moisturizer, between 1-10% w/w humectant, between 1-15% w/w emollient, between 0.1-2% w/w chelating agent, between 0.1-2% w/w preservatives and emulsion at 1-10% w/w for treatment or prevention of skin with dry or pruritic or inflammatory condition.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a comparison of nanonized formulation with micronized formulation and oil only in penetration of nutrients, average particle size, stability and inhibition of eczema-causing pathogen, *Staphylococcus aureus*.

Figure 2 shows marked improvements of psoriasis condition in a 26 years old female with dry skin and skin interruptions (excoriations) upon 10 days of topical application.

Figure 3 shows improvement of itchiness and dryness conditions upon 7 days of topical application.

Figure 4 shows improvement of all eczema symptoms after 14 days of topical application.

Figure 5 shows improvements of severe eczema in a 48 years old male, localized on both legs (between knee and ankle region) since 2005 that led to severe skin interruption.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

Cosmeceuticals are usually topically applied products that have physiological effects on the skin, simply put: a product that fits the niche between a pharmaceutical drug and cosmetics. As global cosmeceutical market is aggressively expanding, expected to reach US$ 42.4 billion by 2018, consumers all over the world are also expecting more effective, safe and eco-friendly novel cosmeceuticals. Nanobiotechnology is increasingly applied in cosmeceuticals, being the root of numerous innovations, as matter is manipulated at an atomic or molecular level. Manipulation of average particle size of active materials could attributes different functional and application properties for the purposeful design of new cosmeceuticals. Formulations intervened by such manipulations provide new delivery system for cosmeceuticals, as hypothetically, smaller particles can enter and penetrate the skin better for increased active delivery or adsorption. Some examples of particle size manipulations includes micro or nanoformulations in forms of emulsion, capsule, pigment, crystal, multiple-layer particles, solid lipid particles, liposomes, niosomes, cubosomes, tranferosomes, carbon nanotubes, fullerene, dendrimers, graphene and quantum dots.

Nanoemulsion technology, particularly, when used as a cosmetics and topical preparations has a great advantage over the other dosage forms that the formulation can be delivered by various routes including oral, ocular and transdermal. Nanoemulsions consist of fine oil-in-water dispersions, having droplets covering the size range of below 600 nm. The smaller droplet size of emulsions not only suppresses the coalescence or coagulation of emulsion droplets but also suppresses the precipitation of emulsions and also helps to deliver the active agents. Nanoemulsions, usually spherical, are a group of dispersed particles used as delivery vehicles. Depending on the definition of particle sizes, the terms sub-micron emulsion (SME), mini-emulsion and ultra-fine emulsion are used as synonyms. Nanoemulsion is a heterogeneous mixture of lipid and aqueous phase and stability are achieved by using a suitable material known as emulsifying agents. Nanoemulsion is a translucent system compare to ordinary emulsion or microemulsion. Oil in water type (O/W) of nanoemulsion formulation is prepared since long ago while water in oil (W/O) type of nanoemulsion is recently gaining popularity. Both of this type of nanoemulsion have various pro and cons in applications of food, pharmaceuticals and cosmetics. It has been demonstrated that with the help of nanoemulsion as a delivery system retention time of a drug in the body can be increased, so low amount of drug is

required for the therapeutic action. Utilization of nanoemulsion technology is able to enhance bioavailability of lipophilic drug. The basic objectives of the nanoemulsion preparation are to achieve the droplet size range below 600 nm as well as to provide stability to the emulsion formed. Formation of a nanoemulsion system can be achieved either by manipulating mechanical equipment or the chemical potential inherent within the component. Some common methods include phase inversion, sonication and high pressure homogenization. Using the phase inversion method, fine dispersion is obtained by chemical energy resulting of phase transitions taking place through emulsification path. Adequate phase transitions are produced by varying the composition of emulsion at constant temperature or by varying the temperature at constant emulsion composition. Commonly, surfactant becomes lipophilic with increase in temperature due to dehydration of polymer chain. But at low temperature, the surfactant monolayer has a large positive spontaneous curvature forming oil-swollen micellar solution phase. Sonication method is another best way to prepare nanoemulsion. In this method the droplet size of conventional emulsion or even microemulsion are reduced with the help of sonication mechanism. However, this method is not suitable for large batches, only small batches of nanoemulsion can be prepared by this method. High pressure homogenization (HPH) is performed by applying a high pressure over the system having oil phase, aqueous phase and surfactant or co-surfactant. The pressure is applied with the help of a special equipment know as homogenizer. There are some problems which are associated with homogenizer such as poor productivity, component deterioration due to difficult mass production and generation of much heat. Generally with HPH, only oil in water (O/W) liquid nanoemulsion of less than 20% oil phase can be prepared and cream nanoemulsion of high viscosity or hardness with a mean droplet diameter lower than 200 nm cannot be prepared.

Although nanoformulations provide great advantages as a delivery system for bioactives but sometimes the reduced size of droplets are responsible for the limited use of nanoemulsion formulation. One limitation of nanoemulsion is the production cost as the manufacturing of nanoemulsion formulation is an expensive and energy consuming process. Size reduction of droplets is very difficult as it required a special kind of instruments and process methods. For example, homogenizer (instrument required for the nanoemulsion formulation) arrangement is an expensive process. Again microfludization and ultrasonication require high amount of financial support. Also, stability of nanoemulsion mostly requires plenty of study and optimization as

non-stable emulsion creates big problem in the storage of formulation. Ostwald ripening is the main factor associated with unacceptability of nanoemulsion formulations. This is due to the high rate of curvature of small droplet show greater solubility as compared to large drop with a low radius of curvature. Less availability of surfactant and cosurfactant required for the manufacturing of nanoemulsion is another factor which marks as a limitation to nanoemulsion manufacturing.

Everyone suffers dry skin at some point during their life regardless of gender. It is characterized by parched, dull looking, flaky skin, that is prone to dry patches or itching. The elderly and those in ill-health or on medication are more likely to experience skin dryness as the skin has reduced or abnormal levels of natural oils. Body changes such as pregnancy or menopause, changes in climate, reactions to irritants and chronic diseases e.g. cancer, diabetes and asthma may all cause dry skin. Certain jobs or hobbies can trigger dry skin, particularly those which require regular hand-washing such as nursing or catering, or activities that involve regular exposure to chemicals, such as hair-dressing. While dry skin is very common amongst the society nowadays, it is commonly accompanied by itchiness. Itchy, dry skin is irritating and can be painful if it cracks or gets infected. Extreme dryness can cause the skin to crack, which can then become infected causing inflammation and itching. This is particularly common on areas of the body that may have reduced blood circulation such as the heels of the feet and stretch marks. One such skin condition of extreme dryness is eczema where the very dry skin are followed by cracked, inflamed, itchy, pus-seeping, blistery skin with a burning desire to be scratched. The key clinical manifestation of eczema and psoriasis is inflammation. Although the pathophysiology pathway underlying the inflammation is intricate and is not completely resolved, it has been known to be correlated with the activation of nuclear factor κB transcription factor. Activation of nuclear factor κB transcription factor promotes the production of proteinases such as collagenase, leading to skin destruction. In addition, activation of nuclear factor κB transcription factor also causes the production of inflammatory mediators including tumor necrosis factor-alpha, cytokines, chemokines and cell adhesion molecules. During inflammation, arachidonic acid is also released and oxidised via cyclooxygenase or lipoxygenase pathway to form hydroxyeicosatetraeenoic acid, prostaglandins and leukotrienes, leading to free radical production and causing erythema and oedema to the skin. Production of free radical further provokes inflammation. Histamine a substance that involved in the inflammatory response is also released to fight the pathogens, but it

triggers pruritic. The described skin disorders intended to include in the present invention are eczema or psoriasis of all stages. In an embodiment, the types of eczema including atopic dermatitis, contact dermatitis, nummular dermatitis, seborrheic dermatitis, stasis dermatitis, neurodermatitis, hand eczema, dyshidrotic dermatitis, dermatitis herpetiforms or asteototic eczema. In an embodiment, the types of psoriasis including plaque psoriasis, pustular psoriasis, guttate psoriasis, erthrodermic psoriasis, arthropathic psoriasis, inverse psoriasis, psoriatic arthritis or nail psoriasis.

The present invention provides a formulation which when administered topically, is able to work synergistically for the prevention or treatment of skin disorders. In the present invention, the therapeutic composition comprises nanonized phytonutrients of oil palm origin and vitamin C. The oil palm based phytonutrients within the scope of this invention includes preferably oil rich in tocotrienols, tocopherols, carotenoids or their mixtures thereof, including crude palm oil, red palm oil or red palm olein. Preferably, the tocotrienol species includes alpha-, beta-, gamma-, and delta-tocotrienol and mixtures thereof. While the tocopherol species includes alpha-, beta-, gamma-, and delta-tocopherol and mixtures thereof. The carotenoid species preferably includes beta-carotene, alpha-carotene, *cis*-alpha-carotene, *cis*-beta-carotene, lycopene, phytoene, beta-zeacarotenes, phytofluene, delta-carotene, gamma-carotene and mixtures thereof. Most preferably, the carotenoid species includes beta-carotene, alpha-carotene and mixture thereof. The composition of topical composition for prevention or treatment of eczema and psoriasis includes at least 0.1% w/w of tocotrienols, at least 0.1% w/w of tocopherols and at least 0.1% w/w of carotenoids, which are derived from red palm olein, and at least 0.05% w/w of vitamin C, in nanonized formulation.

Vitamin E incorporates 8 different compounds. These include 4 tocopherols (alpha, beta, gamma and delta) and 4 tocotrienols (alpha, beta, gamma and delta). Vitamin E is an antioxidant and anti-inflammatory which is most abundant in human skin with alpha-tocopherol being the most predominant form. Naturally, bioaccumulation of vitamin E following oral administration in the epidermis could be achieved when sebaceous glands secrete vitamin E onto the skin and followed by skin penetration and accumulation. It was previously reported that, in order to alter the concentration of vitamin E in the skin through oral administration, it took at least seven days (Free Radic Biol Med 2004: 36(4):456-463). In the market, Vitamin E labelled in many

products usually refers to tocopherol or its analogues, unless specified otherwise. Tocopherol molecules have a long tail with no double bonds. This inhibits the functional effects of the vitamin within the body. Hence, it has a much lower anti-oxidative capacity than its counterpart. Tocotrienol molecules have a short tail with 3 double bonds. This unique structure enables the vitamin to perform various functions, especially antioxidative, with greater efficacy. Among tocopherols and tocotrienols, it was found that tocotrienols were found to be able to penetrate into the skin more efficiently and rapidly as compared to tocopherols. An animal study demonstrated that tocotrienol was able to suppress cycloocygenase-2 expression in the skin after induction of UV radiation (J Agric Food Chem 2010: 58(11):7013-7020). It has also been revealed that tocotrienol significantly reduced histamine release and improved dermal thickening, scratching behaviour in mice with allergic dermatitis (J Oleo Sci 2013: 62(10):825-834). Although taken together, vitamin E seems to be useful in relieving the symptoms of skin disorders, a study involving application onto fifteen patients who had undergone skin cancer removal surgery showed otherwise. Baumann and Spencer (The effects of topical vitamin E on the cosmetic appearance of scars. Dermatologic Surgery 25.4 (1999): 311-315) showed that there is no benefit to the cosmetic outcome of scars by applying vitamin E after skin surgery and that the application of topical vitamin E may actually be detrimental to the cosmetic appearance of a scar. In 90% of the cases in this study, topical vitamin E either had no effect on, or actually worsened, the cosmetic appearance of scars. Of the patients studied, 33% developed a contact dermatitis to the vitamin E. Therefore, they concluded that use of topical vitamin E on wounds should be discouraged. The use of tocopherol and tocotrienol in oil mixtures or emulsions have not been reported in cosmeceutical and topical applications yet.

Carotenoids are potent antioxidant that plays an essential role in the antioxidative protective system of human skin. It is well known with its ability to quench free radical species, serves to suppress inflammation. Among various types of carotenoids, non-polar carotenes and lycopene seem to be the predominant forms. Beta-carotene is one of the non-polar carotenes with provitamin A activity is found abundantly in red palm olein. Earlier study indicates that foods high in beta-carotene reduced the risk of developing psoriasis (Brit J Dermatol 1996: 134(1):101-106). Beta-carotene regulated inflammation by functioning as an inhibitor for redox-based nuclear factor κB transcription factor activation. In an animal study, it has been suggested that beta-

carotene in combination with other carotenoids are effective in promoting wound healing (J Nutr 1982: 112(8):1555-1564).

Research indicates that topical application is an ideal way to increase vitamin C concentration in the skin as absorption of vitamin C following oral administration is limited by active transport mechanisms nutrient absorption (Proc Natl Acad Sci U S A 2001: 98(17):9842-9846). Vitamin C is a potent anti-inflammatory agent that mediates inflammation by inhibiting tumor necrosis factor alpha, which promotes nuclear factor κB transcription factor activation. Suppression of nuclear factor κB transcription factor activation reduces the proinflammatory cytokine production, suggesting that vitamin C is an appropriate agent for preventing and treating wide inflammatory conditions including skin inflammation, erythema and UV radiation damages. Based on the antioxidant network theory, administration of vitamin C in combination with vitamin E may work synergistically to improve the anti-inflammatory activity. Hence, it is worth noted that vitamin C in combination with vitamin E in a stabilised emulsion provided superior effect in improving the symptoms of skin disorder in comparison with single vitamin administration.

Topicals including cream, cold cream, ointment, gel, paste, semi-powder, liniment or lotion are semisolid dosage forms containing one or more actives or drug substances dissolved or dispersed in a suitable base. A topical base is utmost important for the preparation of any cosmeceutical or cosmetic compositions, especially skin and body care as it determines the skin feel, smell, sometimes taste, and stability of the topical. A good topical base also complements or synergizes the function of the actives that would be added into it for the production of a final product. Commonly, a topical aqueous cream comprises of extracts, emollient, humectant, moisturizer, surfactant, emulsifier, diluent and preservative.

In an embodiment, the topical aqueous cream composition comprises emollient, which are biocompatible with the current invented composition and suitable for topical application. As used herein, the term emollient is substance with an occlusive property that is able to trap the natural moisture into the skin and prevent transepidermal moisture loss. They act by mimicking the role played by sebum. This skin hydrating effect helps to reduce scaling, fissuring, inflammation as well as pruritus, making the affected areas feel more comfortable. They also improve skin texture and preventing skin cracks. The emollient useful in the topical composition

includes isononyl isononanoate, dimethicone, dimethiconol, dimethicone crosspolymer, phenyl trimethicone, cetearyl alcohol, stearyl alcohol, lanolin, C12-15 alkyl benzoate or cyclopentasiloxane.

In an embodiment, the topical aqueous cream composition comprises humectants, which are biocompatible with the current invented composition and suitable for topical application. As used herein, the term humectant is a compound which attracts water by mimicking the role of natural moisturising factor that present within the upper epidermis of the skin in nature, such as pyrrolidone carboxylic acid. This helps to rehydrate the affected skin areas, which is important in maintaining intact skin surface and normal skin barrier function. The humectant useful in the topical composition includes butylenes glycol, propylene glycol, glycerin or sodium hyaluronate.

In an embodiment, the topical aqueous cream composition comprises moisturisers, which are biocompatible with the current invented composition and suitable for topical application. As used herein, the term moisturiser is a substance which could increase the level of moisture in the skin by filling in spaces between corneocytes of skin. The moisturiser useful in the topical composition includes sodium salt of pyroglutamic acid, sodium lactate, allantoin or urea.

In an embodiment, the topical aqueous cream composition comprises a base of aloe vera extract. Aloe vera has long been used owing to its skin moisturising effect. Research suggests that aloe vera has wound healing attribute. Topical and oral administration of aloe vera is effective in enhancing wound healing by regulating glycosaminoglcans synthesis and promoting collagen synthesis. Aloe vera is known to have anti-inflammatory and antibacterial properties too. With respect to its biological activity, aloe vera has been used in treating eczema and psoriasis, to alleviate pruritic and xerosis symptoms.

In an embodiment, the topical aqueous cream composition comprises a base of emulsifier or surfactant. The emulsifier useful in the topical composition includes ceteareth-25 and ceteareth-6. In an embodiment, the topical aqueous cream composition comprises surfactant. The surfactant useful in the topical composition includes Polysorbate 20, Polysorbate 40 and Polysorbate 80. In addition to the above mentioned ingredients, the compositions of current invention may also contain

additional auxiliary ingredients such as diluents. Such additional auxiliary ingredients can be used to modify the rate of dissolution, viscosity, stability, osmolarity and rate of dissolution.

In another embodiment, the composition of active ingredients within the scope of invention are stable in the topical preparation and as well as on skin. It is bioavailable to the skin. This type of formulation is an effective carrier for both fat- and water-soluble compounds.

In another particular embodiment, it was discovered that, when the topical compositions were administered over the inflamed skin, similar or superior improvement on the inflammatory status was noticed as compared to topical corticosteroids. Additionally, the topical compositions according to the present invention are also effective in relieving symptoms of eczema and psoriasis, such as erythema, pruritus, bumpiness, swelling, scratches, scaly and xerosis of skin. The topical compositions according to the present invention are also found to be essential effective in promoting wound healing and preventing wound formation caused by eczema or psoriasis. In accordance with the previous filed patent (PI2014703657), Vitamin E and carotenoids derived from red palm olein has been proven to exhibit antimicrobial activity. In the present invention, the formulated compositions are effective in preventing the complication of eczema or psoriasis caused by microbial infection from, including, but not limited to, staphylococcal, streptococcal or *Malassezia* yeasts.

The topical compositions described herein exhibit anti-inflammatory, anti-microbial, anti-pruritic, wound healing and skin hydration attributes. Preferred embodiments of the invention are illustrated in the following examples. Example 1 showed the advantages of nanonization compared to conventional preparations. Compared to micronized formulation and non-processed formulation (raw oil), nanonized formulation showed superior oil-water combination stability that could last non-separated for approximately 24 months, stored at or below room temperature. As nanonized formulation has markedly reduced average particle size compared to micronized formulation and non-processed formulation (raw oil), nanonized formulation showed better penetration (in volume and time taken) into collagen (denatured). Nanonized formulation also inhibits growth of *S. aureus*, a bacteria long associated with atopic dermatitis and eczema, better compared to micronized

formulation and non-processed formulation (raw oil). Example 2 to 4 regarding the therapeutic effect of formulated compositions which work synergistically in alleviating symptoms of eczema and psoriasis.

Example 1

Advantages of nanonized formulation as compared to conventional formulations.

Composition	**Nanonized formulation**	**Micronized formulation**	**Oil only**
Penetrability	High	Slight	Not observed
Average particle size (nm)	<350	>600	>1000
Stability (presence of separation)	No separation observed	Separation observed	N/A
Inhibition of *Staphylococcus aureus* (mm diameter)	35	18	11

Example 2

Male, 48 years old, was diagnosed with atopic dermatitis in both legs (between knee and ankle region) since 2005. He was treated with steroid cream for 1 year and the treatment was effective. However, in 2009 he was diagnosed with psoriasis in the same leg area, and was given steroid cream treatment. The affected areas were really itchy and unconscious scratching at nights often led to bleeding (stained bedsheet). The disfiguring (reddish skin and scales) in both legs regions was uncomfortable. The skin in the affected areas actually looked darker like he was wearing *Roman leg armour*. The more he scratched, the scales became more prominent (big, dry and flaking). The steroid treatment was a temporary relief [effective for months but not lasting]. Finally he gave up using the steroid cream for 2 years until current treatment, which started on 28 January 2016.

During the 1st week, he applied the cream daily at every 6-hour intervals. A generous amount was used to apply and massage gently (5-10 minutes) on both legs (between knee and ankle regions). The effect was quite impressive i.e. itchiness reduced

significantly (90%)….a great relief to him. Inflammation (redness due to occasional scratching) in the affected areas was greatly reduced.

Due to his busy schedule at work, the application of the cream from the 2nd weeks onwards was limited to twice daily i.e. after early morning bath before going to work and after work [applied after the evening bath]. Similar generous amount of cream was applied with the same routine of 5-10 minutes massage on both legs. So far, he used 100ml of the cream per week. The overall results so far are slight thinning of the scales and reduction of itchiness (95% gone).

Example 3

Female 33 year old, diagnosed with eczema since the age of 4. This condition affected uncertain small areas on the legs and hands. The affected areas look like small raised bumps that envelop some fluids. Areas around the bumps are usually slightly swollen and are often itchy. Sometimes it's also painful especially when the lumps of fluid are broken. The itchiness occurs mostly at night. (She wonders if it's because she is free to scratch at night). The frequency of occurrence is also uncertain.

As a remedy she was recommended hydrocortisone creams which initially did dry up the sore areas but it did not cure it. She was also introduced steroidal products but knowing the negative effects she was persistent to not ever touch it.

In early March 16' she was introduced to our non-steroidal eczema cream. After knowing that all the ingredients are natural she tried it. The first comment after a week was "The cream does not have much effect other than a cooling feeling which she perceive prevented the affected part from feeling itchy".

Though skeptical she continued to use the cream daily. After nearly 4 weeks, her affected area does not even feel itchy even when she forgets to apply the cream. It has not totally recover yet but the bag of fluid seems to be gone.

Example 4

Female, 26 years old, was diagnosed with eczema or atopic dermatitis on her ankle. This skin condition has long affecting the subject since three years ago. The skin around her ankle areas appear red, inflamed, peeling, cracked, dry together with intense itchiness especially after wake up in the morning. The dryness associated with eczema also caused skin cracked even from general movement and some scratching also caused the skin to ooze pus. Crusty and scabbed patches were found on her ankle.

During the past 3 years, she tried on different methods including steroid treatment as suggested by the specialist doctor. However, none of above methods is effective; including steroid treatment (only a temporary relief). Under the advice of doctor, the patient dares not to use the steroid treatment with big dosage in a consecutive period of time (more than 2 months). Finally, she gave up all the possible treatment and leave the skin condition with ignorance. With the daily bad habit and carelessness, the eczema spread to the face area. The subject was forced to turn back to the topical steroid treatment to keep the condition under control. Unfortunately, the repeatedly use of topical steroids thin her skin and make the part of skin start developing some 'stretch marks'.

The condition worries the subject a lot and when she encountered the current treatment (tocotrienol cream); she decided to give it a try. During the first 3 times of treatment, the itchiness reduced by 50% and the subject did not rub her face that frequent. After she used the cream for a week (2 times in a day), the itchiness on face has totally gone. The redness and peeling has diminished together with the itchiness.

For the ankle part, she starts using the cream after the face condition has fully recovered. After a week of applying the cream, the redness and dryness on the skin was found to be significantly reduced (50%). When the dryness reduced, the skin becomes less itchy and the subject able to retrain herself from scratching the wound. Now (after 2 weeks of treatment), the color of the infected skin has recovering and slowly back to its normal tone.

Preferred embodiments of the invention are illustrated in the following figures. Figure 1 illustrtated obvious penetration of nutrient into gelatin (hydrolysed collagen) in nanoformulation (observed as the dark reddish color of Vitamin E and carotenoids). No reddish color is observed in the gelatin layers treated with micronized formulation and palm oil only. Meanwhile, synergistic activity is observed in anti-*Staphylococcus aureus* activity by nanonized formulation where higher inhibition activity were exhibited in formulation with nano-size (<350 nm) compounds compared with that with micro-size (>600 nm) and palm oil only. Figure 2 showed marked improvements upon application of topical cream containing nanonized bioactives for 10 days. Figure 3-4 showed improvement in relieve of itchiness and dryness upon application of the topical cream containing nanonized bioactives in 7-14 days. Figure 5 exemplified significant relief of itchiness and inflammation (redness) on a 48 years old male in the 1st week of application with prolonged conditions of severe scratching lesions, lichenification (thickening of the skin), infected lesions (blisters, pus formation) and hyperpigmentation in old lesions.. Continuous application (twice daily) resulted in thinning of lichenification, hyperpigmentation and reduction of itchiness after 4 months.

While particular example of the present invention has been shown and described, it is apparent that changes and modification may be made therein without departing from the invention in its broadest aspects. The aim of the appended claims, thereof, is to cover all such changes and modifications as fall within the scope of the invention.

CLAIMS

1. A therapeutic composition having nanonized actives, comprising:

one or more compound member selected from Group A comprising of Vitamin A and pro-vitamin A;

one or more compound member selected from Group E comprising of Vitamin E and pro-vitamin E; and

one or more compound member selected from Group C comprising of Vitamin C and pro-vitamin C,

wherein the one or more compound member of Group A and Group E are derived from oil palm.

2. The therapeutic composition of claim 1, wherein the therapeutic composition is a nanonized composition.

3. The therapeutic composition of claim 2, wherein the nanonized composition has average particle sizes below 350 nm.

4. The therapeutic composition of claim 2, wherein the nanonized composition is nanoemulsion, nanocapsule, nanopigment, nanocrystal, solid lipid nanoparticles, liposomes, niosomes, cubosomes, tranferosomes, carbon nanotubes, fullerene, dendrimers or any combinations thereof.

5. The therapeutic composition of claim 1, wherein the said Group A further comprises retinol, retinal, retinoic acid, retinyl palmitate, carotenes xanthophylls or any combinations thereof.

6. The therapeutic composition of claim 1, wherein the said Group E further comprises tocotrienol, tocopherol, tocopherol acetate, tocopheryl acetate, tocopheryl succinate, singly or in combinations, preferably with at least two types of isomers from α-, β-, δ-and γ-tocopherol or at least two types of isomers from α-, β-, δ-and γ-tocotrienol,

7. The therapeutic composition of claim 1, wherein the said Group A and the said Group E are collectively obtainable from crude palm oil, palm oil

distillates, red palm oil, red palm olein, palm stearin, super palm olein, singly or in combinations.

8. The therapeutic composition of claim 1, wherein the said Group C including ascorbic acid, sodium ascorbate, calcium ascorbate, potassium ascorbate, sodium ascorbyl phosphate, ascorbyl palmitate, ascorbyl tetraisopalmitate or ascorbyl stearate, singly or in combinations.

9. The therapeutic composition of claim 1, wherein the therapeutic composition is nanonized in combination with oil and oil soluble actives including palm oil, olive oil, coconut oil, theobroma oil, shea oil, corn oil, seed oil, plant essential oil, vegetable fats, polyunsaturated fatty acids, medium chain triacylgycerides or any combinations thereof in an amount less than 70% v/v of the total nanonized composition.

10. The therapeutic composition of claim 1, wherein the therapeutic composition is blended with phenolic compound, flavonoid or combinations in amount less than 50% v/v of the total nanonized composition.

11. The therapeutic composition of claim 1, wherein the therapeutic composition is blended with preservatives including plant extracts, marine extracts, organic acids, alcohols, mineral salts or any combinations thereof.

12. The therapeutic composition of claim 1, wherein the therapeutic composition is combined with a topical cosmetic base forming a cosmetic formulation, said topical cosmetic base including plant extract, solubiliser, emulsifier, emollient, humectant, thickener, moisturizer, colorant, neutralizer, vitamins or chelating agent.

13. The therapeutic composition of claim 1, wherein the therapeutic composition is combined with a topical pharmaceutical base forming a pharmaceutical formulation, said topical pharmaceutical base including plant extract, solubiliser, emulsifier, emollient, humectant, thickener, moisturizer, colorant, neutralizer, vitamins or chelating agent.

14. The therapeutic composition of claim 1, wherein the therapeutic composition is combined with a topical medical or clinical base forming a medical formulation, said topical medical or clinical base including plant extract, solubiliser, emulsifier, emollient, humectant, thickener, moisturizer, colorant, neutralizer, vitamins or chelating agent.

15. The therapeutic composition of claim 1, wherein the therapeutic composition is combined with a micronized or nanonized base forming a micronized or nanonized formulation, said micronized or nanonized base including plant extract, solubiliser, emulsifier, emollient, humectant, thickener, moisturizer, colorant, neutralizer, vitamins or chelating agent.

16. The therapeutic composition of claims 12 to 15, wherein the therapeutic composition is present from 0.1 to 30% w/w of the overall therapeutic formulation.

17. The therapeutic composition of claims 12 to 16, wherein the therapeutic composition includes liquid, semi aqueous, cream, serum, gel, oilment, lotion, spray, balm and mist.

18. Use of a therapeutic composition as described in claim 1for the treatment or prevention of skin with dry or pruritic or inflammatory condition.

19. The use of claim 18 includes topical administration, in any cosmetic or pharmaceutical base or carrier.

20. The use of claim 18 includes topical administration by liquid, semi aqueous, cream, serum, gel, ointment, lotion, spray balm and mist.

21. The use of claim 18, wherein the said therapeutic composition is used with a composition comprising oil, solid fat and oil-soluble actives including palm oil, olive oil, coconut oil, theobroma oil, shea oil, corn oil, seed oil, plant essential oil, vegetable fats, polyunsaturated fatty acids, medium chain triacylgycerides or any combinations thereof.

22. The use of claim 18, wherein the said therapeutic composition is used with a composition comprising starch, petroleum jelly, wax, collagen, gelatin, peptides, amino-lipids, disaccharides or monosaccharides derivatives capable of occlusive and humectant moisturizing properties.

23. The use of claim 18, wherein the said therapeutic composition is anti-inflammatory, anti-microbial, anti-pruritic, wound healing and skin hydration to prevent or treat eczema or psoriasis.

24. The use of claim 18, wherein the said skin with dry or pruritic or inflammatory condition includes itchiness, ichtyosis, erythema, psoriasis, dermatitis, eczema, mild to severe skin inflammation, lichenification, infected lesions and boils.

25. A therapeutically effective cream formulation comprises at least 60% w/w water, between 0.1-5% w/w gelling agent and/or thickener, between 0.5-10% w/w oil palm-derived active ingredient and/or plant extracts, between 1-5% w/w solubilizer, between 1-5% w/w emulsifier, between 1-5% w/w moisturizer, between 1-10% w/w humectant, between 1-15% w/w emollient, between 0.1-2% w/w chelating agent, between 0.1-2% w/w preservatives and emulsion at 1-10% w/w for treatment or prevention of skin with dry or pruritic or inflammatory condition.

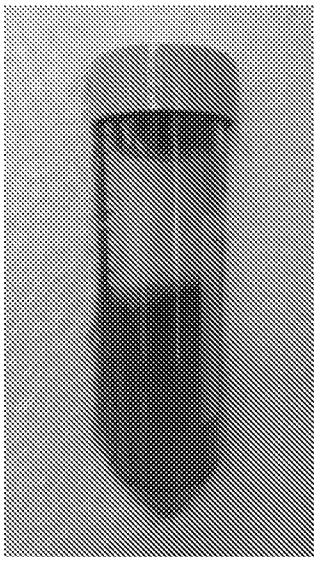
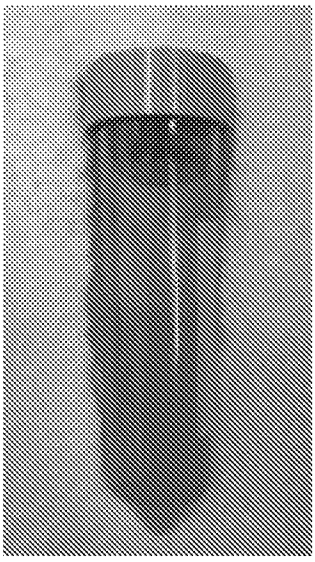
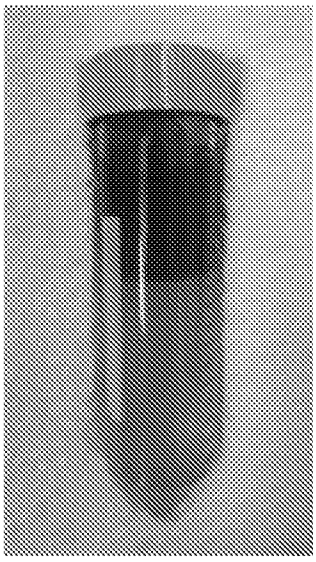
Composition	Nanonized formulation	Micronized formulation	Oil only
Penetrability			
Average particle size (nm)	<350	>600	>1000
Stability (presence of separation)	No separation observed	Separation observed	N/A
Inhibition of *S. aureus* (mm diameter)	35	18	11

Figure 1

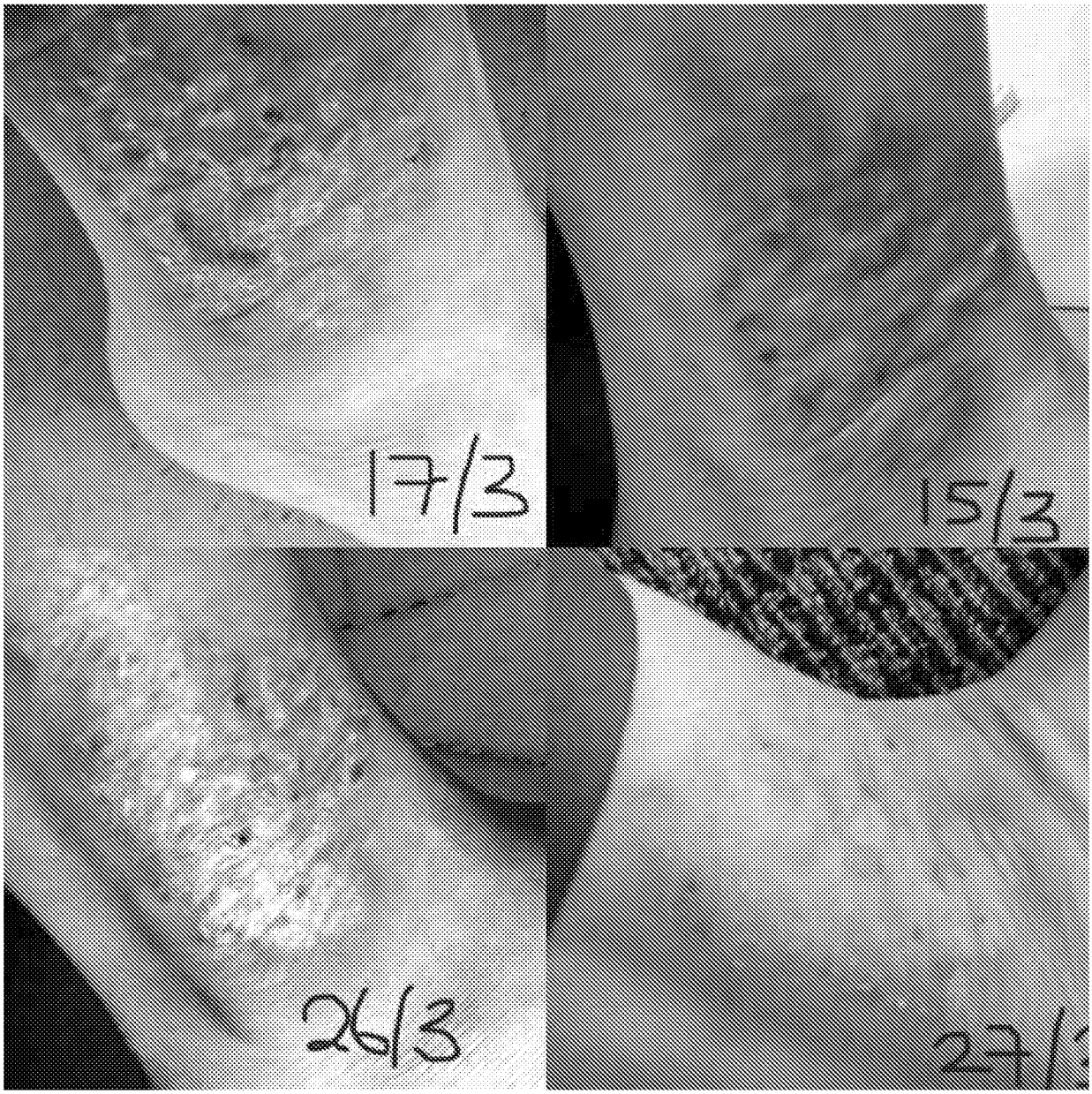


Figure 2

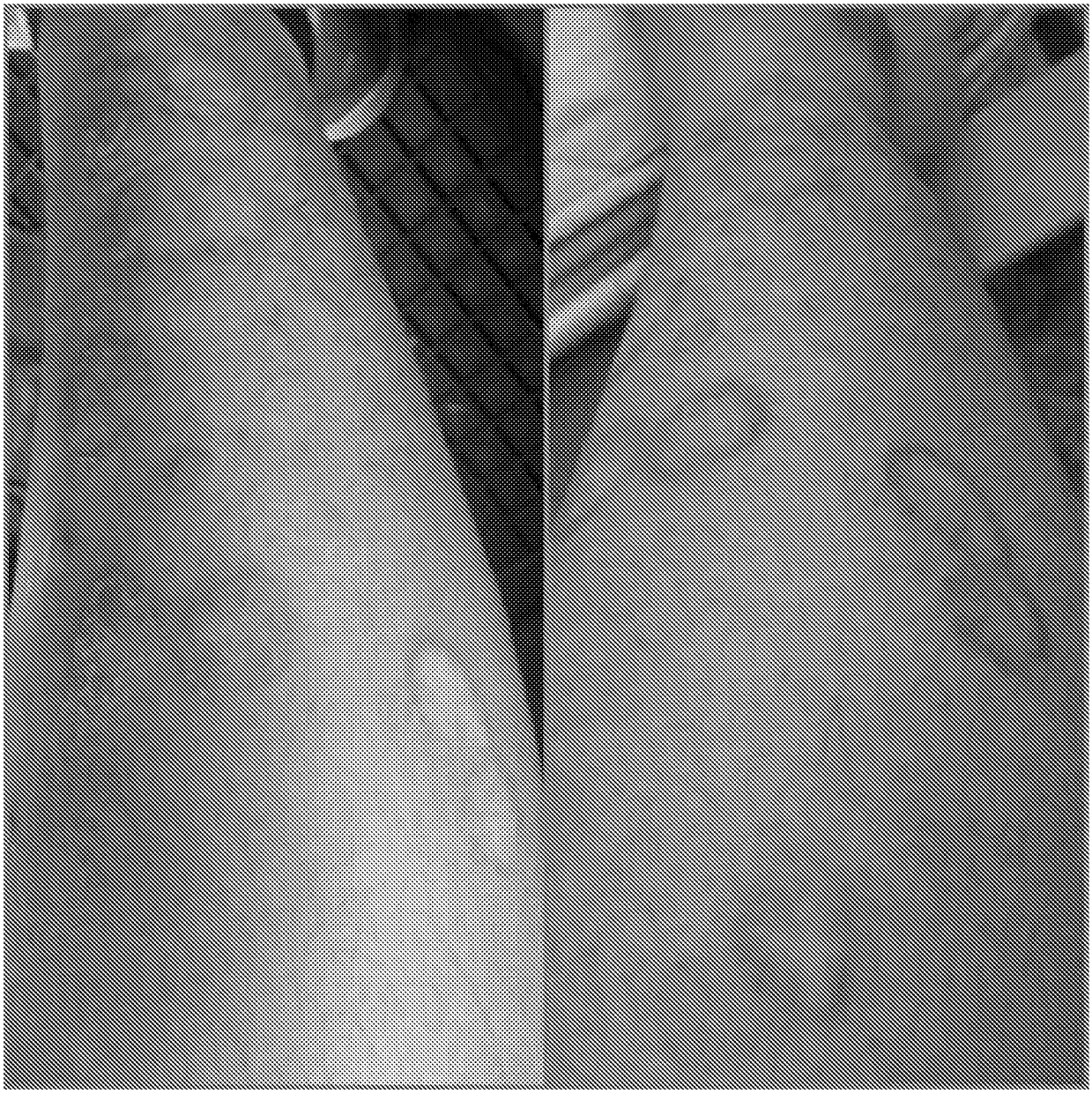


Figure 3

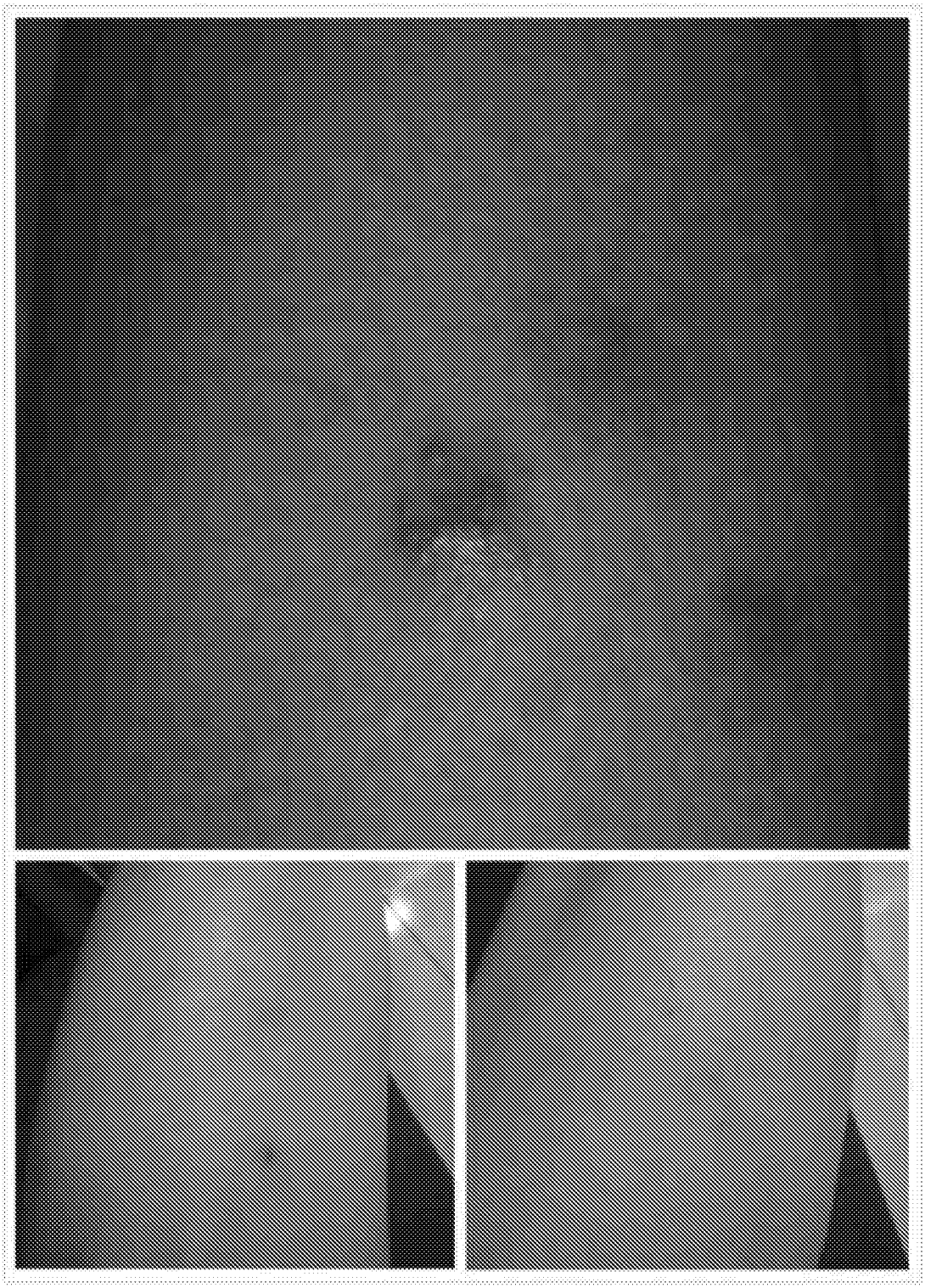


Figure 4

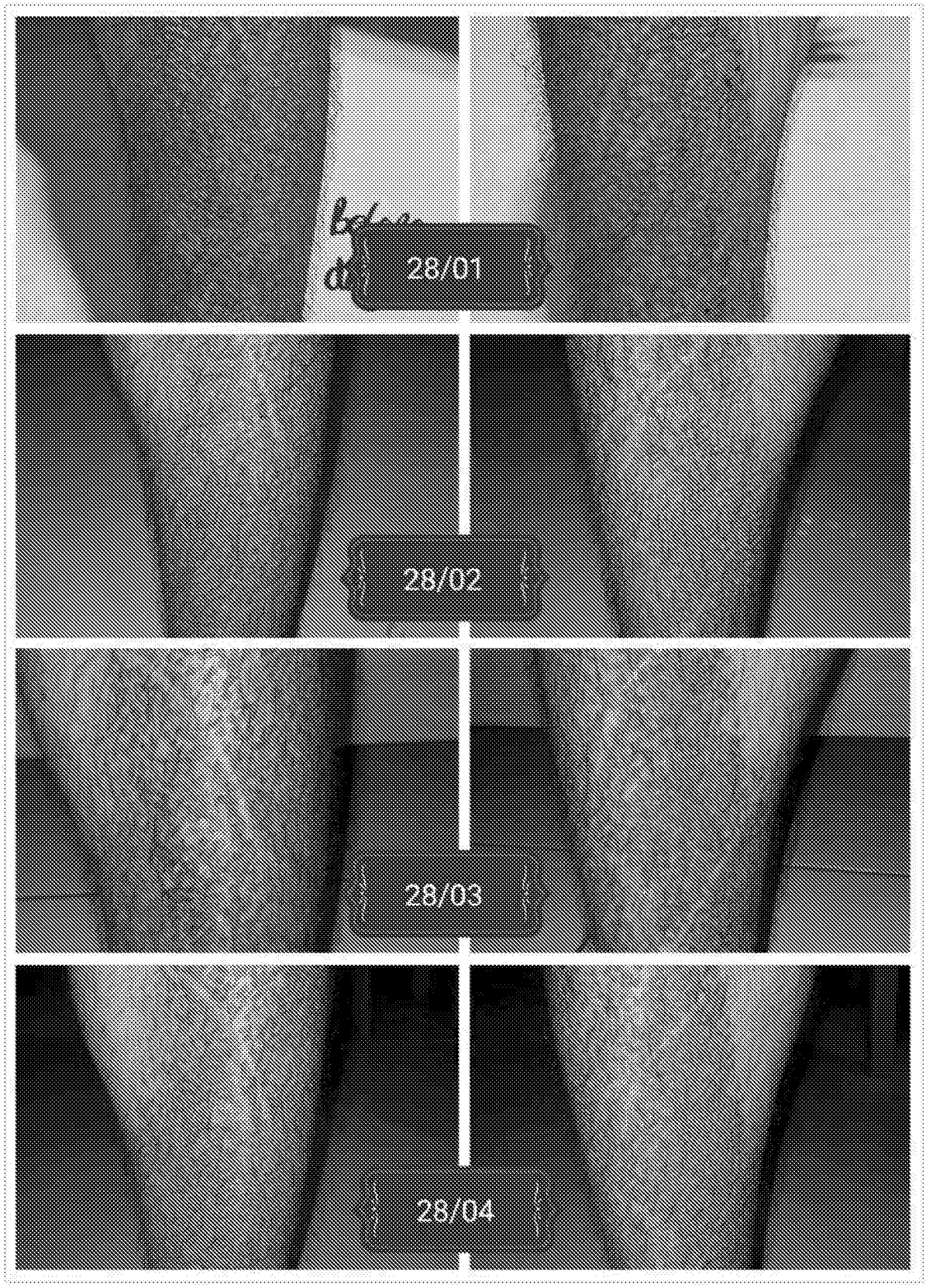


Figure 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/MY2018/050037

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/07(2006.01)i, A61K 31/355(2006.01)i, A61K 31/375(2006.01)i, A61K 36/889(2006.01)i, A61P 17/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 31/07; A61K 31/355; A61K 8/37; A61K 8/49; A61K 8/55; A61K 9/14; A61P 35/00; A61Q 19/08; C07C 7/10; C07J 9/00; A61K 31/375; A61K 36/889; A61P 17/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: vitamin A, vitamin E, vitamin C, oil palm, nano, cream, skin, pruritic, immflammatory

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2010-0055187 A1 (AHN, D. J.) 04 March 2010 See paragraphs [0005], [0017]; and claims 4, 5, 20, 23.	1-15,18-24
A		25
Y	US 2005-0250953 A1 (MAY, C. Y. et al.) 10 November 2005 See abstract; and claim 1.	1-15,18-24
Y	US 2010-0197780 A1 (P. MANICKAM, K. S. et al.) 05 August 2010 See claims 1, 2.	10
X	WO 2016-026527 A1 (AMANTIN EXPERTS) 25 February 2016 See page 2, lines 12-15; page 12, lines 1-11; page 14, lines 16-20; page 16, line 22; and claims 2, 6, 12, 18, 20, 21.	25
Y		11-15,18-24
A	EP 2859882 A1 (AULIVE NV) 15 April 2015 See claims 4, 6, 7.	1-15,18-25

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
04 October 2018 (04.10.2018)	**05 October 2018 (05.10.2018)**

Name and mailing address of the ISA/KR
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/MY2018/050037

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 16,17
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/MY2018/050037

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2010-0055187 A1	04/03/2010	None	
US 2005-0250953 A1	10/11/2005	AT 322474 T	15/04/2006
		CN 1477147 A	25/02/2004
		DE 60304407 T2	12/04/2007
		EP 1394144 A1	03/03/2004
		EP 1394144 B1	05/04/2006
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		JP 4424939 B2	03/03/2010
		MY 142319 A	15/11/2010
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US 2010-0197780 A1	05/08/2010	BR PI0811416 A2	16/06/2015
		CN 101808654 A	18/08/2010
		CN 101808654 B	14/11/2012
		CO 6241128 A2	20/01/2011
		DK 2148690 T3	17/08/2015
		EP 2148690 A1	03/02/2010
		EP 2148690 B1	05/08/2015
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		WO 2008-130216 A1	30/10/2008
WO 2016-026527 A1	25/02/2016	EP 3182955 A1	28/06/2017
		US 2017-0246090 A1	31/08/2017
EP 2859882 A1	15/04/2015	None	