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Innovative approach of nanoformula moisturizer applications in atopic dermatitis: a review

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ABSTRACT

The skin barrier defect is the first step in the development of atopic dermatitis (AD). Various therapeutic guidelines recommend using moisturizers to maintain the skin barrier and the prevention of AD. The use of a moisturizer in the form of barrier cream is considered to improve the skin barrier. However, this dosage form is occlusion and has an oily texture, resulting in patient noncompliance with therapy. Various techniques were developed to improve patient compliance in applying topical preparations, one of which is by developing nanotechnology. Recent studies aim to develop nanoformula preparations because they can help deliver drug molecules to specific targets with minimize side effects. The application of nanoformula moisturizer is promising in the management of AD because of its ability to reduce water loss and prevent irritation and produce formulations with a thinner texture to increase therapeutic compliance in AD patients.

ABSTRAK

Kerusakan sawar kulit merupakan langkah awal perkembangan dermatitis atopik (DA). Berbagai pedoman terapi merekomendasikan pemakaian pelembap untuk pemeliharaan sawar kulit dan pencegahan terjadinya DA. Pemakaian pelembap dalam bentuk *barrier cream* dianggap dapat memperbaiki sawar kulit. Akan tetapi, bentuk sediaan ini bersifat oklusi dan dengan tekstur berminyak, yang berakibat pada ketidakpatuhan pasien terhadap pengobatan. Berbagai teknik dikembangkan untuk meningkatkan kepatuhan pasien dalam mengaplikasikan sediaan topikal, salah satunya dengan pengembangan nanoteknologi. Penelitian terbaru ini lebih ditujukan pada pengembangan sediaan nanoformula karena dapat membantu penghantaran molekul obat ke target spesifik dengan efek samping minimal. Aplikasi pelembap nanoformula bersifat menjanjikan pada tatalaksana DA karena karena kemampuannya untuk meminimalkan kehilangan air dan mencegah iritasi serta menghasilkan formulasi dengan tekstur yang lebih tipis sehingga dapat meningkatkan kepatuhan pengobatan pasien DA.

Keywords:
atopic dermatitis; moisturizer; nanoformula; nanosystem; nanomedicine;

INTRODUCTION

Atopic dermatitis (AD) is an inflammatory disease of the skin characterized by itchy, chronic, and residif. Since 1960, there has been a reported increase of AD prevalence more than tripled. Atopic dermatitis occurs in 20% of children, generally in the first year of life and 1-3% in adults worldwide. Atopic dermatitis can affect patients and their families' quality of life and social and economic problems. Some studies report the incidence of anxiety,

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depression, and other psychological issues in AD patients.

Topical corticosteroids are still the primary treatment of AD.[1-4] The provision of topical therapy in the treatment of skin diseases can reduce the occurrence of side effects due to parenteral and oral therapy administration because it can reduce the metabolism of drugs through the liver.[5] Topical corticosteroids can be used only for a short time and in limited skin lesions because they can cause undesirable side effects.[1–5] Besides, the incidence of topical steroid withdrawal and topical corticosteroid addiction has been widely reported on social media.[6,7] This condition raises fears of the use of topical corticosteroids (corticosteroid phobia), which occurs in about 40% of patients with dermatology and 73% in their parents.[8] Corticosteroid phobia results in reduced adherence and causes therapy failure.[6-8]

Various therapeutic guidelines consistently recommend using moisturizers to maintain the skin barrier and the prevention of AD. The use of a moisturizer is reported to reduce the use of topical steroids.[1] Topical preparations' clinical effectiveness is generally observed in its mechanism of action and its ability to cross the skin's protective barrier.[5] Topical drug application has limitations because of its low drug absorption in the skin barrier, especially in the stratum corneum.[9,10] In this review article, a moisturizing application in the form of a nanoformula in AD will be further examined.

DISCUSSION

Skin barriers defects in atopic dermatitis

The skin is the largest organ (covering 10% of body weight), which protects against the external environment.[11] The skin consists of layers of the epidermis, dermis, and subcutaneous fat.[12] The epidermis can act as an inside-out barrier that minimizes transepidermal water loss and outside-in barriers that prevent the invasion of infectious agents and toxic substances.[11] The physical barrier function of the skin depends primarily on the integrity of the stratum corneum.[13-15] The skin barrier defect is considered as an initial step in developing AD.[15] Genetic and environmental factors influence the skin barrier defect in AD. Some abnormalities in the epidermal barrier that play a role in the pathophysiology of AD include defects in filaggrin, increased serine protease activity, and decreased levels of ceramides and stratum corneum lipids.[16-18] These factors interact with each other, which can modify the skin barrier.[15]

Filaggrin defects in atopic dermatitis

Filaggrin (filament aggregating protein) is a unique filament related protein that binds to keratin fibers in epithelial cells.[19] Filaggrin is an essential epidermal protein in the formation of corneocytes-intracellular metabolites that contribute to the hydration of the stratum corneum and skin acidity.[20,21] In humans, profilaggrin is encoded by the filaggrin gene in the epidermal differentiation complex (EDC) on chromosome 1q21.[16,19]

In stratum granulosum, filaggrin is produced as profilaggrin and stored in keratohyalin granules. In the transition from stratum granulosum to stratum corneum, filaggrin is converted into filaggrin monomers by proteases such as CAP1/Prss8 and SASPase/ASPRV1.[16,22] Filaggrin monomers bind keratin filaments to form a filament-matrix complex, which is also bound to cornified envelopes (CE).[16] In the upper layers of the stratum corneum, filaggrin is separated from the keratin filaments. Filaggrin monomers are degraded to amino acids (glutamine, arginine, and histidine), which are then converted to urocanic

acid (UCA) and pyrrolidine carboxylic acid (PCA), mediated by protein caspase 14, calpain 1, and bleomycin hydrolase. Urocanic acid plays a vital role as an ultraviolet absorbing chromophore in the stratum corneum and maintaining skin acidity (pH). Pyrrolidine carboxylic acid is a natural moisturizing factor (NMF) element responsible for holding water in the stratum corneum.[22]

A defect in filaggrin can reduce NMF levels, which results in decreased hydration and an increase in skin pH.[23] Filaggrin is essential in maintaining epidermal homeostasis. Impaired filaggrin function is a predisposing factor for AD.[17,24] Filaggrin expression in AD patients is regulated by T helper (Th)-2 cytokines, and filaggrin proteolysis is accelerated after exposure to low humidity or irritant material to the skin.[21]

Serin protease defects in atopic dermatitis

In the stratum corneum of the skin, there are three protease families, including serine specific epidermal kallikrein 5 (stratum corneum tryptic enzyme/SCTE) and kallikrein 7 (stratum corneum chymotryptic enzyme/SCCE); cysteine protease (cathepsin C, L, and V); and aspartate proteases (cathepsin D). Protease is an enzyme that hydrolyzes peptide bonds and plays a role in signaling important molecules in mammals' homeostatic regulation and various pathological conditions.[25] Protease plays a role in the pathogenesis of AD through filaggrin formation, regulation of inflammation, and itching.[18,25]

Protease inhibitors regulate endogenous skin proteases, which are essential in maintaining skin barrier permeability, and homeostasis.[18] Protease inhibitors control the function of exogenous and endogenous proteases.[26] Serine protease inhibitors in the skin function to regulate proteolytic activity to prevent excessive serine protease cascades and maintain skin barrier permeability homeostasis. Lymphoepithelial Kazal-type-related inhibitors (LEKTI)-1 are serine protease inhibitors thought to have a major role in the stratum corneum. It is encoded by the Kazal-type 5 serine protease inhibitor gene (SPINK5), which can inhibit trypsin, plasmin, subtilisin A, cathepsin G, and human neutrophil elastase.[25]

Protease plays a role in the pathogenesis of AD through filaggrin formation, regulation of inflammation, and itching.[18,25] In AD, there is an increase in serine protease activity, which can be caused by changes in skin pH and genetic polymorphisms in the enzyme serine protease or serine protease inhibitors. Serine protease enzymes work optimally at neutral or basic pH so that an increase in skin pH increases serine protease activity.[27] Increases in the enzymes of tryptase and chymotriptase in patients with AD indicate an imbalance between proteases and protease inhibitors, which causes inflammation.[28]

Ceramide defects and stratum corneum lipids in atopic dermatitis

In AD, there is a decrease in total and ceramide lipid levels, changes in the ceramide subfraction, and possible disruption in the activity of enzymes that modulate lipids in skin barrier permeability.[27] Ceramides are the main lipid component in the stratum corneum, consisting of 30-40% of total lipid weight.[29] Ceramides are the main water retaining molecules in the stratum corneum. The reduction of the AD patients' ceramide level was obtained in lesions and skin without skin lesions.[30]

Immunological mechanisms of skin barrier defect in atopic dermatitis

Defects in the skin barrier cause an increase in trans-epidermal water loss (TEWL), which facilitates allergens' entry so that allergic initiation and sensitization or exacerbation of inflammation in AD can occur.[17,24] An increase in TEWL causes an increase in pH that can activate serine proteases.[24] The biological activity of proteases is mediated by the activation of protease-activated receptors (PAR).[18,25]

Increased serine protease activity will activate PAR2 in stratum granulosum keratinocyte cells, causing a decrease in lamellar body secretions that are important in maintaining skin barrier permeability homeostasis overcome skin barrier recovery.[25,26,31] Activation of PAR2 can act as a positive regulator of skin barrier permeability improvement, namely by accelerating cornification, which then induces corneocyte cell formation.[25]

The stimulation of PAR2 in keratinocyte cells will increase the secretion of interleukin (IL)-6 and granulocyte macrophage-colony stimulating factor (GM-CSF). Activation of PAR2 in keratinocytes increases IL-8/CXCL8 secretion, which will cause the release of granulocytes and T cells.[25] Activation of PAR2 in keratinocytes will also induce thymic stromal lymphopoietin (TSLP) release and contribute to allergic inflammation.[24,32,33]

Increased expression of TSLP is a vital pathogenesis factor in AD development. Thymic stromal lymphopoietin causes migration of Langerhans cells, maturation, activation, and polarization of dendritic cells, which trigger Th-2 cell responses to AD skin lesions.[34] Thymic stromal lymphopoietin activates mature dendritic cells and Langerhans cells by increasing the expression of CD83, CD86, OX40 ligand (OX40L), and major class II histocompatibility complex (MHC), which will cause expansion and differentiation of T cells. Dendritic TSLP cells induce naive T cells to become pro-allergic T cells with increased IL-4, IL-5, IL-13, and tumor necrosis factor (TNF) –α and decreased IL-10.[35]

Disorders of the skin barrier also cause an increase in IL-1 from keratinocytes, which activate vascular endothelium to induce adhesion molecules' expression and cause skin inflammation.[17] Dysregulation of skin homeostasis causes direct or indirect stimulation of sensory nerve endings that induces itching.[24] Schema of the relationship between the skin barrier defect with the immune response to AD can be seen in FIGURE 1.

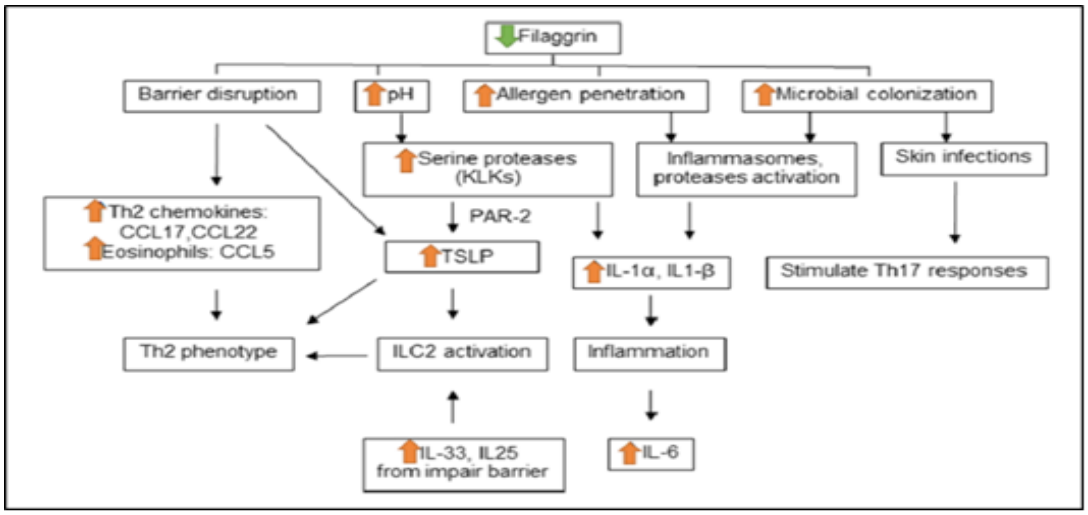

FIGURE 1. Relationship between skin barrier defects and immune response in DA. It was modified from reference.[36]

Moisturizer in atopic dermatitis

Various therapeutic guidelines consistently recommend using moisturizers to maintain the skin barrier and prevent AD.[1] Atopic dermatitis patients are characterized by decreased skin barrier function and dry skin (xerosis), facilitating the entry of pathogens, irritants, and allergens.[2,37] Some studies show that moisturizer application can reduce the use of topical corticosteroids. Moisturizers are reported can improve AD complaints and are well tolerated in children as young as six months.[1] The use of a moisturizer is recommended as monotherapy in mild AD cases, should be applied twice a day on the whole body both in the condition of disease and no disease. Long-term use of a moisturizer in AD patients aged 2-6 years decreased xerosis and AD scores better than the control group without significant side effects.[38]

The use of a moisturizer in the form of a barrier cream that is a form of water-in-oil (W/O) emulsion and oil-in-water (O/W) emulsion is considered to improve the skin barrier function in inflammatory conditions by causing occlusion and change allergens and other irritant molecules. However, patients' adherence to these preparations is influenced by their cosmetic properties, where the preparations are very occlusive tend to have a glossy or partially blurry appearance and oily texture. To increase cosmetics' attractiveness, more elegant textures, and obtain additional benefits, nanomaterial use in barrier cream formulations has been developed.[39]

Dermatopharmacokinetics

Dermatopharmacokinetics describes the pharmacokinetics of topical drugs on the stratum corneum with their pharmacodynamic effects.[9] Drug absorption in the skin depends on drug interactions with intracellular lipid bilayers, drug interactions with keratinocytes, and drug interactions with permeation enhancers, which cause a reversible dissolution of the skin barrier so that the drug can penetrate the skin.[10]

One limitation of topical drug application is the low absorption of the drug on the skin barrier, especially on the stratum corneum.[9,10] Strategies to increase the absorption of drugs to the skin are choosing a vehicle system, adding substances that enhance absorption (permeation enhancers), choosing a new drug delivery system (drug carrier systems), and transdermal patches.[10] Recent studies have focused more on the selection of nanoparticle drug dosage forms.[40]

Nanoparticles are particulate dispersions or solid particles with sizes in the range of 10 to 1000 nm. The drug is dissolved, encapsulated, or attached to a nanoparticle matrix. The primary purpose of nanoparticles as a drug delivery system is to control particle size, drug surface, the release of active pharmaceutical ingredients to reach the specific site of action of the drug, and improve drug stability.[41] Properties are affecting the penetration of nanoparticles through the stratum corneum, as well as the potential for deposition in the skin, appendage, and deeper layers of the skin, including size, shape, charge properties, surface properties such as coatings or functional groups, aggregation status on surface properties.[42]

Topical drug delivery with nanosystem

At present, nanosystems have been developed to help deliver drug molecules to specific drug targets and minimize side effects.[43] The forms of nanosystems include microemulsions (MEs), nanoemulsions (NEs), nanoparticles with various compositions including solid lipid nanoparticles (SNLs), nanostructured lipid carriers (NLCs), liposomes, and vesicles.[42,44,45] Nanosystems can provide

significant advantages in hydrophobic molecular formulations, increasing their solubility and bioavailability of drugs.[45]

Several factors influence nanosystem drugs' release, namely particle size, lipid matrix, surfactants, drug loading, and medication type.[46] The size and shape of drug particles affect drug release, physical stability, and cellular absorption of drug nanoparticles. In contrast, the attachment of nanoparticles to cell membranes is affected by the surface particle charge. Nanoparticles show high affinity in cell membranes, mainly due to their electrostatic interactions. Formulations of nanoparticles with different surface properties can influence cellular uptake and intracellular distribution. It is possible to localize nanoparticles to specific intracellular targets (lysosomes, mitochondria, and cytoplasm) by modifying their surface charges.[9] Vehicle components such as oil, surfactants, and alcohol interact with the stratum corneum, which affects the distribution and performance of nanoparticle drugs on the skin.[47] The topical drug absorption nanosystem scheme is listed in FIGURE 2.

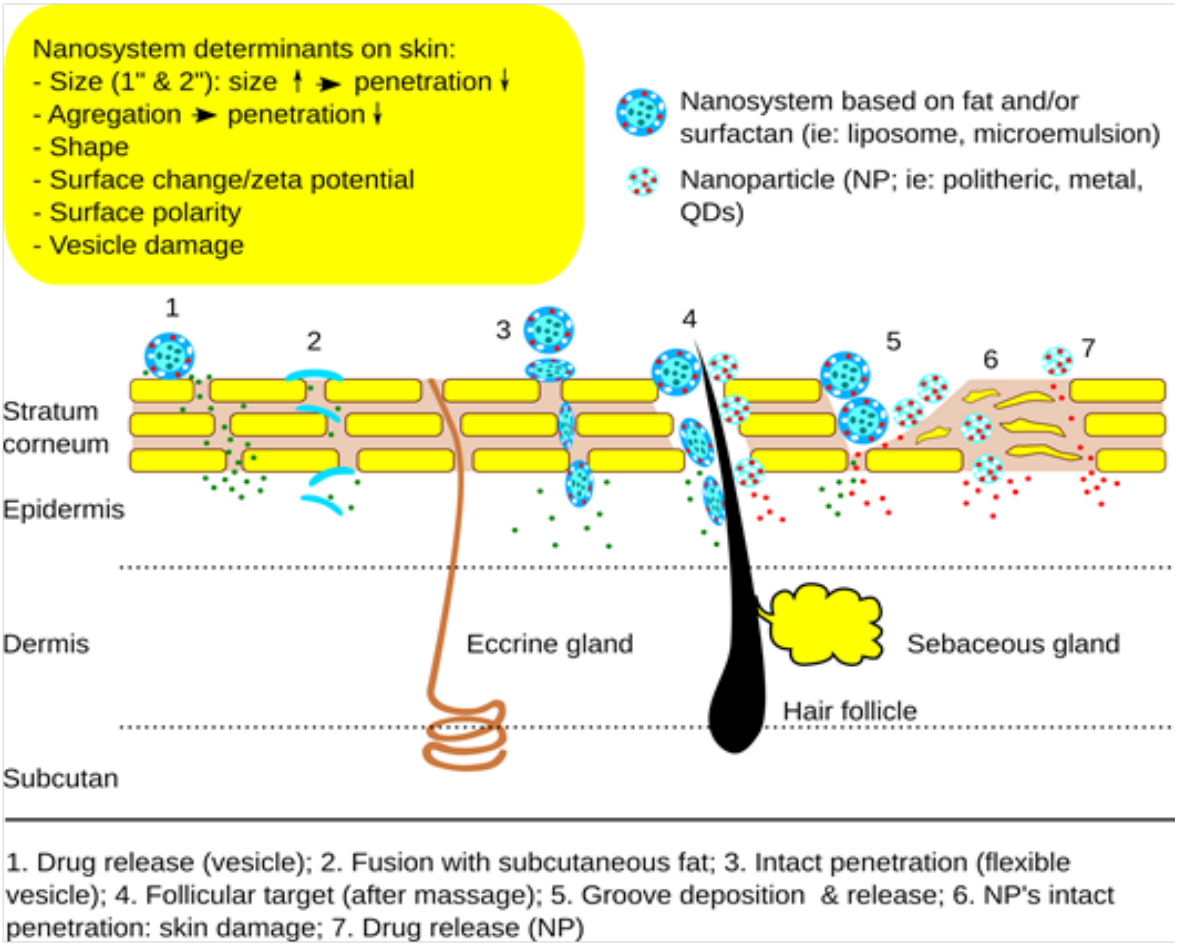

FIGURE 2. The nanosystem scheme determines the absorption of topical drugs and potential penetration routes. It was modified from reference.[42]

Nanoemulsion

Nanoemulsion is a water and oil phase dispersion that is stabilized by surfactants.[42] Nanoemulsion is an ultrafine emulsion because of the formation of droplets in the submicron range. Nanoemulsion droplet sizes generally range between 200-300 nm, smaller than macroemulsion droplet sizes ranging from 1-100 μm. Small droplet size causes NE to be stable, not experience creaming, sedimentation, flocculation, and coalescence allows effective transportation of material to the skin.[42,48]

Nanoemulsion application to the skin has several advantages, including the small size of the droplets allowing it to be stored evenly on the skin, suitable for delivering active ingredients through the skin.[42] The small size of the droplets causes the product to be transparent so that the NE appearance does not change by adding the oil phase.[49] Nanoemulsion is mainly used in drugs with low absorption by increasing drug absorption through the skin, better drug retention time in the target area, which leads to fewer side effects.[50]

Nanoemulsion can increase drug penetration in the skin through several mechanisms. First, nanoemulsion provides a high dissolving capacity for lipophilic and hydrophilic compounds, increasing the loading capacity and dosage formulation application. Second, nanoemulsion has a large surface area and good skin contact, coupled with occlusive properties that allow good surface contact with the surface of the stratum corneum. Third, The oil and surfactant components in NE directly increase the permeation effect on the stratum corneum lipids structure.[42]

The nanoemulsion system consists of oil, water, one or more surfactant materials, O/W or W/O. The aqueous phase can contain pharmaceutically active ingredients, cosmetics, or preservatives, which are hydrophilic. In contrast, the oil phase contains mineral oils, silicone oils, plant oils, fatty acid esters, and lipophilic active ingredients. The addition of surfactants such as disodium stearoyl glutamate, sucrose alkyl ester, sorbitan alkyl ester, and dimethicone copolyol form stable dispersion formations that guarantee storage time. The use of NE in cosmetics is generally in the form of O/W containing 10-20% oil and stabilized with an emulsion material of 0.5-2%.[44] The limitation of NE application to the skin is discomfort when used because NE has a low viscosity and spreadability. To overcome this problem, the NE is combining with a gel system known as nanoemulgel.[50]

Nanoemulgel

Nanoemulgel acts as a drug reservoir that controls the release of drugs to the skin. The ability of nanoemulgel to seep into the skin and release therapeutic agents is influenced by the drug's affinity to diffuse out of the vehicle and penetrate the skin barrier. The addition of emulsifiers and thickening agents results in better drug stability, absorption, and viscosity, suitable for topical drug delivery. Nanoemulgel on intact skin will release oil droplets that act as lipophilic drug carriers. Nanoemulgel has excellent adhesion properties on the skin, high dissolving capacity, thus causing a more significant concentration gradient towards the skin, which will affect further drug penetration in the skin. The nanoemulgel dosage form also improves patient compliance because it is not sticky and is easier to apply than other topical preparations on the skin.[50]

Nanoformula moisturizer in atopic dermatitis

Nanocarriers like liposomes, NEs, SLNs, and niosomes are extensively

added to the moisturizers as they form a thin film of humectants and retain the moisture for a prolonged span.[51] In cosmetics formulation, NEs provide rapid penetration and active transport of active ingredients and hydration to the skin.[52] The nanoformula moisturizers are superior to conventional creams to minimize water loss, prevent irritation, and produce a thinner texture.[39]

Clinical trials in humans have found that combined SLN on O/W emulsions can significantly increase hydration than conventional moisturizers.[39,53] After four weeks of application periods, there were significant changes in skin hydration for both formulations. The SLN-enriched cream was significantly more effective than the conventional cream (+24% for the cream vs. +31% for the SLN cream).[53] The addition of nanomaterials to moisturizing preparations provides cosmetic benefits. Kato *et al.*[39] stated that fullerene nano preparation dissolved in squalene minimizes water loss and significantly improves wrinkles' appearance. A study by Berardesca *et al.*[54] showed that eight weeks of application of topical skin lipid mixture containing ceramide-3 and nanoparticles alone, or combined with topical corticosteroids, will improve the skin physiology, barrier properties, and clinical symptoms. in AD patients.[54,55] This study indicated that the nanoparticles' optimized lipid mixture could improve skin barrier repair and improve various skin diseases with the damaged skin barrier.[54]

Bernadi *et al.*[56] concluded that rice bran oil nanoemulsion could serve as an alternative treatment for AD and psoriasis because it showed a stable formulation, low potential irritation, improved skin moisturizer, and maintained normal skin pH value. The rice bran oil application significantly increases the skin hydration with moisturizing variance by about 38% in normal skin volunteers and 30% in AD volunteers. This study showed a satisfactory result because a high-quality commercial moisturizer only increased skin hydration 20% after 14 days of application.[56]

Nasrollahi *et al.*[57] have compared the efficacy and safety of a w/o emulsions containing 1.5% linoleic acid and w/o emulsion containing 5% urea in AD patients. Both formulations significantly improved the epidermal barrier function and alleviate AD symptoms. Based on previous studies, it can be concluded that the application of nanoformula moisturizer is promising in the management of AD because of its ability to minimize water loss and prevent irritation and product formulations with a thinner texture to increase therapeutic compliance in AD patients.

CONCLUSION

There are recommendations for using moisturizers to maintenance skin barrier and prevention of AD. The use of a moisturizer in the form of a barrier cream, a form of water emulsion in oil or oil emulsion in water, is considered to improve the skin barrier function in inflammatory conditions by causing occlusion and changing allergens and other irritant molecules. Barrier cream is occlusive, with an oily texture, which results in patient noncompliance with therapy. The application of nanoformula moisturizer is promising in the management of AD because of its ability to minimize water loss and prevent irritation and produce formulations with a thinner texture to increase therapeutic compliance in AD patients.

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