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REVIEW

Clinical use of Capilen, a liposomal cream based on fresh plant extracts enriched with omega fatty acids

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Abstract

The skin is the largest organ in the human body; beyond its regulatory and sensory roles, it is meant to protect and act like a barrier against foreign matter. Products intended to restore the skin health should reintegrate the structure of the stratum corneum in which the corneocytes are surrounded by the intercellular lipid lamellae that maintain both corneum integrity and skin permeability barrier. Capilen is a specific liposomal formulation based on a technology through which highly concentrated fresh plant extracts are conveyed into a jelly-like liposomal vehicle and combined with plant-derived omega-3, -6, -7, and -9 fatty acids, phospholipids, and precursors of ceramides. Its components have been widely investigated and produced clinical benefits in atopic dermatitis, bedsores, scars, inflammatory lesions of the skin, and generally whenever signs of xerosis cutis were present. Liposomes contribute to restore the surface lipid layer of the skin and to deliver substances in the activity site. This liposomal cream was proven to limit and delay the occurrence of radiodermatitis in breast cancer patients, and as an add-on provided complete healing of bedsore lesions in geriatric subjects.

Keywords: liposomal cream, liposomes, omega fatty acids, skin disorders.

Citation

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Introduction

The skin, which is the largest organ in the human body, beyond its regulatory and sensory roles is meant to protect and act as a barrier against foreign matter. It is continuously challenged, for instance by extreme climatic factors, the use of aggressive detergents, irritants, friction, allergens, pollution, aging, infections, use of medications, atopic disease, autoimmune disorders, renal, and endocrine diseases. The surface hydrolipidic layer has a major role in the protective activity of the skin and can be damaged by excessively aggressive stimuli; this makes the skin sensitized and prone to atopy and xerosis.[1,2] In addition, loss of stratum corneum intercellular lipids and an inadequate ratio between components (cholesterol, essential fatty acids, ceramides) enhance transepidermal water loss, leading to epidermal microfissuring and worsening of underlying diseases.[3]

Xerosis accompanies several skin disorders, including widespread ones, such as atopic dermatitis (AD) and psoriasis.[3,4] Observational studies showed that xerosis can reach extremely high prevalence in the elderly, ranging between 30% and 75%, and that virtually every individual may experience xerosis at least once in their lifetime.[5–7] Although already common, xerosis is a condition that will become more and more prevalent with aging.[8] Treatment of xerosis not only reduces subjective symptoms but also retards the progression of concomitant skin diseases and facilitates improvement. It was observed that in young children with AD, treating xerosis improves both the quality of life and also lowers the risk of developing percutaneous sensitization.[9] Managing xerosis adequately is important so that epidermal barrier function is restored, and underlying structures are protected from infection and physical damage.[10]

Emollient therapy is effective on xerosis associated with some skin diseases and may have a steroid-sparing effect in AD.[11]

The introduction of topical corticosteroids (TCs) provided an effective and rapid treatment of inflammatory skin diseases. Nevertheless, its extensive use prompted increasing occurrences of abuse and misuse, which led to serious

local, systemic, and psychological side effects. Such misuse occurs more with TCs of a higher potency or when applied on softer areas of the body, such as the face and genitalia.[12] Common side effects of TCs include skin atrophy, permanent stretch marks, bruising and tearing of the skin, telangiectasia, hypertrichosis, local and systemic infections, and adrenal suppression. Systemic side effects are more prone to develop when potent TCs are used in children, who have a low weight/body surface ratio, and a soft skin with high capacity for absorption.[13,14]

Any option that allows to reduce, postpone, or avoid the use of TCs may be beneficial for patients with skin diseases, especially during long-term use.

In the early 1980s, the opportunity of natural options as a possible alternative treatment for skin diseases was well received when growing concerns reached phobic proportions regarding the use of TCs for atopic dermatitis.[15]

Products intended to restore the skin barrier function should respect the structure of the stratum corneum. The stratum corneum may be described as a brick wall, in which the corneocytes or 'bricks' are surrounded by the intercellular lipid lamellae, which maintain both corneum integrity and the skin permeability barrier. Thus, emollients should nourish the skin and act as 'fillers' by integrating the 'building blocks' beyond providing a mere 'sensory feeling' (Figure 1).[11,16,17] In addition, topical preparations should enable actives to cross the stratum corneum and reach the site of action.

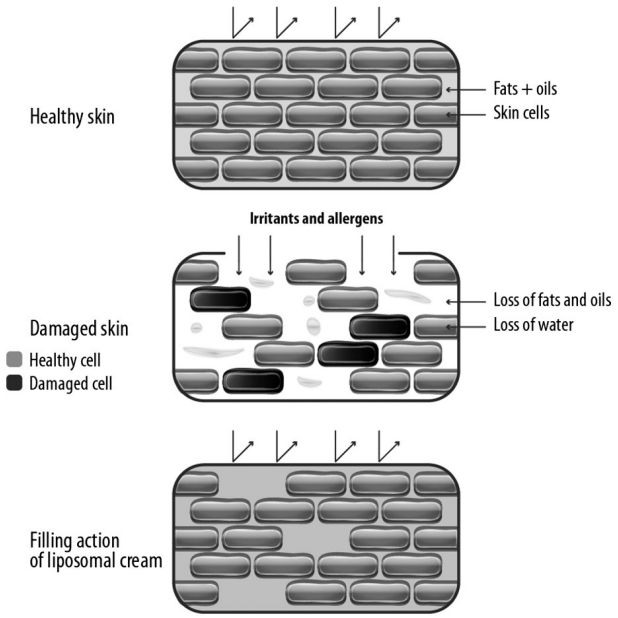
Restoration of the lipid composition of both the surface layer and of the stratum corneum may rebalance water loss control, and reconstitute a barrier against physical, chemical, and microbiological external agents. Recent studies have shown the benefits of topical products based on linoleic acids, phospholipids, fatty acids, and precursors of ceramides in subjects affected by AD and other skin diseases; such products topically deliver natural substances that may integrate into the skin structure.[11,13,18]

This article presents the characteristics of a liposomal cream (Capilen, Dermilen®, Capietal Italia srl, Bergamo, Italy; which will be referred to as CLC throughout the text) produced using a proprietary technology (high concentration frozen phospholipo [HCFP], in the patenting phase) through which highly concentrated fresh plant extracts, were conveyed into a jelly-like liposomal vehicle together with plant-derived omega-3, -6, -7, and -9 fatty acids, phospholipids, and precursors of ceramides.[19] The rationale that led to the development of CLC is expressed by the Latin *similia similibus* concept; in short, the more a substance has similarity with the skin structure the more this substance can be absorbed and integrated.

Methods

A search was performed in PubMed, up to April 2019, with the following keywords: linoleic acid, linolenic acid, sea buckthorn oil, phospholipids, atopic dermatitis, xerosis, liposome/liposomal, Echinacea, Calendula, radiodermatitis, omega-6, omega-3, omega-7, palmitoleic acid, Hypericum, rice oil, and antioxidants. Only full-text articles were retrieved. The authors selected papers from this search as the basis for this review.

Figure 1. 'Filler' effect of CLC.



Current treatments for xerosis

Xerosis is a highly prevalent skin manifestation, frequently associated with a history of atopy, especially atopic dermatitis, psoriasis, and aging. Other factors that may predispose to xerosis are external aggressions, climate, medications, malignant diseases, endocrine disorders, infections, and renal failure in dialyzed patients.[6]

Skincare products for xerotic conditions should ideally share some features: they should re-establish skin hydration and lipids, decrease inflammation, enhance the barrier activity, and exert a soothing effect without an unwanted seal-off effect, which could block the skin's natural ability to breathe and absorb nutrients and lock in residue and bacteria. The skin must retain its natural ability to breath, while absorbing nutrients, while bacteria and residues should not be locked in. Independently of concurrent skin disease, topical preparations are usually used to soothe and hydrate the skin. The most used components are petrolatum/paraffin liquid/mineral oil, lanolin, urea, and colloidal oatmeal.[3] Although these substances are usually useful, some shortcomings were reported. Contact allergy was associated with lanolin, mainly in children younger than 2 years; urea proved to be locally irritant and to have systemic adverse effects on the kidney of infants (and of toddlers if high concentrations were used).[3] Paraffinum liquidum (also known as mineral oil) consists of a complex combination of hydrocarbons obtained from intensive

treatment of a petroleum fraction. Paraffinum may provide soothing and filming effects; however, it does not integrate skin constituents, such as lipids and ceramides, and effects are sensorial and superficial. Paraffinum was often found to contain impurities, mainly hydrocarbons, which may be dangerous for the health.[20]

Liposomal formula: beyond improved absorption

Liposomes are small vesicles prepared with phospholipids as the main substance. Their structure is similar to the cellular membrane and, therefore, may help promote the interaction with cell membranes.[21] Liposomes for skin topical use can play the role as both vehicles of cosmeceutical materials and active agents themselves.

Regarding the vehicle function, it has been observed that liposomal formula, compared to classical emulsions, uniformly penetrates the horny layer. The concentrations of active substances, when a liposomal formulation is used, were found to be 4–8 times higher in the epidermis and 9–14 times higher in the dermis in comparison to conventional emulsions.[22] Liposomes have been intensively investigated as carriers of bioactive molecules for different applications in dermatology. In addition, it has been demonstrated that some specific types of liposomal vesicles diffuse through the different layers of the skin allowing successful treatment of different pathologies and restricting the systemic exposure to drugs.[23–25] The lipid formulation offers gradual delivery of active compounds, optimized absorption, higher efficacy, and improved tolerability over conventional topical treatments.[22] When liposomes are used as carriers for delivery of active molecules, they may enhance their penetration, solubility, or stability and increase longevity – this assists the targeting of molecules to the desired site of action, reducing toxicity, increasing control over pharmacokinetics and pharmacodynamics, and makes the product cost-effective.[26]

In CLC, liposomes are built starting from high-grade lecithin, particularly rich in phospholipids and omega-6 linoleic acid.

Beyond their role as a delivery system, liposomes can be considered as active agents thanks to their richness in phospholipids and omega fatty acids for the treatment of dry, scaly, and flaky skin. As the structure and composition of liposomes closely resemble the stratum corneum, cutaneous administration causes the lipid components to be deposited in the skin.[27] When skin is affected by eczema or is damaged due to a lack of moisture, phospholipids are delivered into the surrounding tissue by liposomes and integrate into the skin structures, so that they may function as substitutes of the lost lipid component of a damaged corneum.[26] Liposomes deliver lipids, among which omega-6 linoleic acid, a precursor of ceramide 1, that has an important role in skin barrier function and has been found to be deficient in AD skin.[26] The majority of liposomes that are used topically onto the skin will accumulate as a reservoir providing a prolonged effect in the upper layers of the stratum corneum.[27]

Skin health benefits of plant-derived omega

CLC contains sea buckthorn-seaberry oil and rice bran oil that are rich in omega-7, -9, -6, and -3 fatty acids. In addition, bioactive substances such as flavonoids, carotenoids (A, C-carotene, lycopene), vitamins (C, E, and K), tannins, triterpenes, and Y-orizanol are present.[28]

Rice bran oil functions in cosmetics as a conditioning agent and is well known for its high content in fatty acids, omega-9 and -6, and antioxidants (CoQ10, γ-orizanol, tocopherols). It is especially indicated in delicate skin (e.g. children), and it has skin-regenerating properties.[29]

Plant oils have been used for cosmetic and medical purposes on the skin for a long time because they have many positive physiological benefits. For example, plant oil application may act as a protective barrier to the skin, which allows the skin to retain moisture, and results in decreased transepidermal water loss (TEWL) values.[16] The importance of essential fatty acids for skin structure and function is well established and is clearly exemplified by the cutaneous abnormalities occurring in essential fatty acid deficiency. This includes faulty desquamation and a severely impaired barrier.[30] Omega-6 linoleic acid (the most abundant fatty acid in the epidermis) and its derivatives have an essential role in the structure and function of the stratum corneum permeability barrier, and their deficiency is most prominent in AD. Moreover, a recent clinical trial has shown that omega-6 linoleic acid, administered as an emulsion in adult patients with AD, reduced transepidermal water loss, erythema, and echo density of dermis, with increased stratum corneum hydration, compared with baseline.[11,31] In skincare products, linoleic acid inhibits barrier and cornification disorders. In addition, it lowers transepidermal water loss and also increases skin moistness. Linoleic acid is part of the ceramide 1, which is the most important barrier substance in the horny layer.[11,32]

In addition, omega-9 oleic acid and omega-3 α-linolenic acids contribute to reduce transdermal water loss.[31,33]

Plant oils may contain several omega fatty acids, and topical administration can restore the corneum lipid composition in skin conditions.[16] One of the main features of CLC is the presence of omega-7, which is found in sea buckthorn oil. To obtain a pure oil without contaminants and to preserve the full actives, the oil from organic sea buckthorn berries and seeds are extracted via supercritical fluid extraction in carbon dioxide (supercritical CO_2 extraction) in aseptic condition; hence, the oil has no solvent residues, no inorganic salts, and no heavy metals that could contaminate the final product. The genus name *Hippophae* comes from two Greek words,

hippo, which means horse, and *phaos*, which means to shine. In ancient times, the leaves of this plant were used as horse fodder, which gave the horses a shiny coat. The plant has a large number of bioactive substances (estimated between 100 and 200 different substances), the properties of which are successfully used in the cosmetic industry.[34] A study by Burnett and colleagues has shown that out of 120 plant-derived fatty acid oils, sea buckthorn had, by far, the most abundant content of omega-7.[35] In addition to omega fatty acids, sea buckthorn contains flavonoids, carotenoids (A, C-carotene and lycopene), vitamins (C, E, and K) and tannins, among others.[28] Valuable substances contained in sea buckthorn oil play an important role in the proper functioning of the human body.[35]

Applied to the skin, sea buckthorn oil has the ability to activate physiological functions stimulating wound healing, minimizing scars formation and inducing skin repair. In a burn wound model, it improved the healing process. Indeed, it increased wound contraction, hydroxyproline, hexosamine, DNA, and total protein contents compared with control treated with silver sulfadiazine ointment. Sea buckthorn seed oil treatment upregulated the expression of matrix metalloproteinases-2 and -9, collagen type III, and vascular endothelial growth factor (VEGF) in granulation tissue. It also possessed antioxidant properties that is a factor that mediates wound healing activity as evidenced by a significant increase in reduced glutathione levels (a major endogenous thiol antioxidant) and reduced production of reactive oxygen species (ROS) in wound granulation tissue.[36] The proposed mechanisms of action are the stimulation of epidermis regeneration and collagen synthesis.[18,37] Omega-7 palmitoleic acid – a rare fatty acid – has a major role in stimulating regenerative processes in the epidermis and promoting wound healing. In addition, unsaturated omega-3 and -6 fatty acids, carotenoids, and tocopherols that are present stimulate fibroblast proliferation, collagen biosynthesis, and expression of specific matrix metalloproteinases that induce tissue reparation and angiogenesis.[18]

Sea buckthorn oil has been used in the treatment of different skin diseases, such as eczema, dermatoses, ulceration, psoriasis, and atopic dermatitis. It may also reduce bedsores, spots, acne, scars, discoloration, and allergic and inflammatory lesions of the skin when applied topically.[18] Moreover, sea buckthorn oil improves AD-like skin lesions via inhibition of NF-κB and STAT1 activation.[35]

Proprietary technology: fresh plant extracts delivered through liposomes

Natural remedies, formerly part of the traditional 'herbalism', are nowadays gaining attention in the scientific community, their efficacy being supported by mounting evidence and new knowledge of the mechanism of action. Well-prepared and standardized plant-based preparations can have a major role in skincare, limiting the need for TCs.[38,39] In particular, a number of studies has shown that natural remedies based on *Calendula officinalis*, St John's wort (*Hypericum perforatum*), *Achillea millefolium* (Yarrow), *Echinacea purpurea*, and *Viola tricolor*, thanks to their content in tannins, carotenoids, flavonoids, polysaccharides, terpenes, and mucilage, may help to decrease local inflammation shielding tissue from irritants, exerting antioxidant effect and also facilitating tissue hydration.[40]

Recent clinical studies on the use of *Echinacea purpurea* extract in atopic dermatitis and pruritus have shown a novel mechanism of action of the plant. The activation of the endocannabinoid system via the cannabinoid (CB)-2 receptors is responsible for anti-inflammatory effects alleviating symptoms of eczema.[41,42]

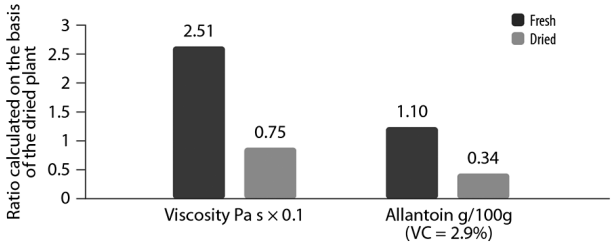
Similarly, a study on the use of *Hypericum perforatum* in AD has confirmed its efficacy in skin problems beyond the well-known effects on mood disorders.[43,44]

Several studies investigated the risk of contact dermatitis to plant derivatives, which is a recurrent fear in patients and health personnel, showing that the incidence of this adverse event is lower than usually believed. For instance, the incidence of dermatitis due to contact with calendula is lower than 0.2%.[40]

Fresh plant preparations were observed to exert a superior effect as compared with those made from dried plants. When the plant is dried, an appreciable amount of the active substances is lost. As an example, the allantoin content and the viscosity are about three times as high in fresh plant products from *Symphyti officinalis* in comparison with dried products (Figure 2).[45]

The quality of an extract depends also on other factors, such as solvents and techniques employed for the extraction. In CLC, only extracts from mother tinctures, produced according to the German Pharmacopeia, have been used.[46] This procedure guarantees the extraction of the full phytocomplex from each plant and exploits the synergic effect of the actives. CLC is thought to exert an antioxidant activity due to the properties of some components: gamma-oryzanol, flavonoids, carotenoids, and ingredients of phytocomplex. In addition, it may exert skin conditioning, soothing, protecting, and

Figure 2. Comparison between fresh and dried plant characteristics for *Symphyti officinalis*. Adapted from Tobler et al.[45]



emollient effects. Such activities are thought to be due to blended plant extracts complemented by the nourishing effect of the liposomes, sea buckthorn, and rice bran oils.

Part of the quality of an extract is due to its toxicological profile. It is important that plants are not contaminated by heavy metals nor grow in polluted areas.[45] In CLC, the extracts come from plants grown and harvested according to strict and rigorous standards in the Italian side of the Alps. Fields are located in a special 'oasis', away from urban traffic where no synthetic pesticides and fertilizers are used. Harvesting occurs only in the optimal balsamic period to guarantee the highest content of actives, and the extraction is carried out immediately after the harvest of the plants. Both lipophilic and hydrophilic compounds are extracted, exposure to heat sources is very low to maintain thermolabile and easily degradable substances.[45–47]

CLC has a pH of 5.5–6 on the skin, and the toxicological evaluation based on the margin of safety and systemic exposure dosage calculations according to International Cosmetic regulations has shown that CLC can be used also in infants and children.[48]

Clinical evidence on the use of CLC

Clinical experience on the use of CLC is wide because it has been marketed in several countries for over 10 years, although randomized clinical trials are still missing. Some patient cohort studies and clinical case series have been published.[49]

Stefanelli and colleagues showed the ability of CLC to limit acute radiodermatitis occurrence and also delay the use of corticosteroids in patients with breast cancer.[50] From January 2012 to August 2012, 30 consecutive patients undergoing adjuvant radiotherapy were invited to use CLC two times daily for 2 weeks before and during radiotherapy. A historical group of 30 patients was used as an external control; the patients were treated with TCs at the first sign of skin alteration (e.g. erythema). Acute skin toxicity was scored weekly according to Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer criteria. The endpoint was measured as the time of occurrence of acute skin toxicity. The compliance was good. Overall, the rate of acute radiation dermatitis was 46.7% in the experimental arm compared with 63.3% in the historical control group. Furthermore, only 3.3% of CLC-treated patients had a grade 3 acute radiation dermatitis compared with 10% of the control group (Figure 3). There was a delay in the onset of radiation dermatitis in patients treated with CLC (p=0.04) (Figure 4). These findings suggest that CLC may play a role in reducing and delaying acute radiation dermatitis in patients with breast cancer who are treated with adjuvant radiotherapy.[50] CLC was shown to be an important therapeutic option, as radiodermatitis dramatically reduces the compliance of patients to treatment. Radiodermatitis occurs in up to 95% of the patients undergoing radiotherapy, often very early and patients may not be able to complete the cycle of therapies with a consequent lower efficacy.[51] It is difficult to manage and there is the need to limit TCs, petroleum derivatives, zinc, and aluminum-based products.

CLC was beneficial on ulcerous lesions and bedsores in geriatric patients, in a pilot clinical study.[52] Five patients (aged 80–101 years) were enrolled, presenting sacral decubitus and dystrophic ulcers stage 3–4. CLC was applied in a thin layer once a day in the perilesional area of ulcerous-dystrophic lesions and three times/day in the perilesional area of lesions of the sacral area. Conventional cleaning of the wound was conducted. Patients with infected ulcers were treated with proper antibiotic therapy. The same investigator evaluated patients by the Norton-Exton Smith scale and took pictures and measured the dimensions of the lesions on a weekly basis. The complete healing of the lesions occurred in 80% of the patients, in a time between 7 days and 25 days. Even if the level of evidence of this study is low, its encouraging results might suggest that CLC

Figure 3. Incidence of overall toxicity (Panel A) and G3 toxicity (Panel B) in breast cancer patients treated with CLC and in a historical control group. Adapted from Stefanelli.[50]

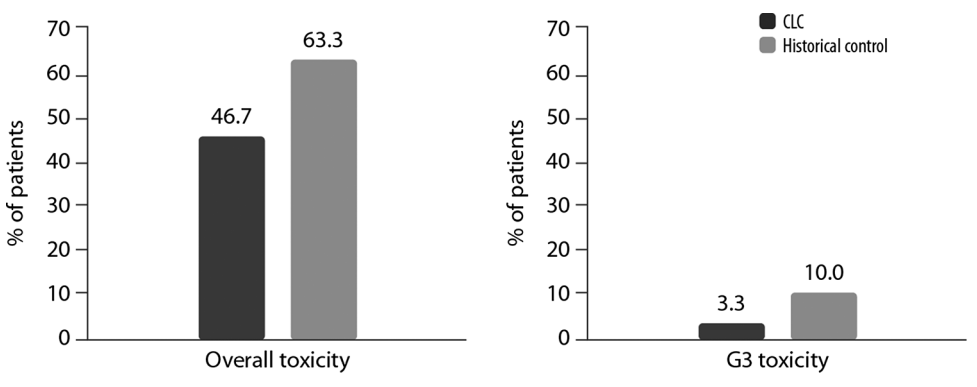
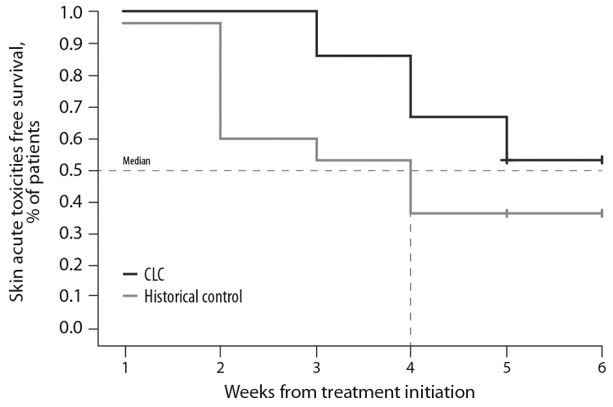


Figure 4. Time to occurrence of radiodermatitis in breast cancer patients treated with CLC and in a historical control group. Adapted from Stefanelli.[50]



can be added to the therapeutic armamentarium to support the epithelialization of decubitus lesions and dystrophic ulcers. These findings have great relevance for clinical practice because pressure ulcers in hospitalized patients can involve up to 30% of the patients, with a marked burden of illness, and costs for the health system.

Conclusion

CLC is a concentrated functional cosmetic, which is based on an innovative proprietary technology (HCFP, patent-pending) that allows the delivery of fresh plant extracts in liposomal forms in combination with plant-derived omegas for deep and prolonged hydration and restoration. Although TCs have an important role in the treatment of skin inflammatory diseases, based on the literature data and pharmacological properties, it could be hypothesized that the product described here could complement TC therapy by facilitating recovery or, in certain cases, having a TC-sparing effect. CLC may improve the skin barrier activity, promote regeneration of the epidermis, have a soothing effect, and represent an effective treatment alone or as an add-on for skin conditions where stratum corneum disruption is prevalent. The liposomal component is thought to actively contribute to skin repair and to stratum corneum barrier function restoration, by delivering phospholipids, fatty acids, and precursors of ceramides and by facilitating the effects of actives. In addition, it is thought to restore the hydrolipidic layer and control the water loss from the stratum corneum without an occlusive effect. CLC contains sea buckthorn-seaberry oil, rice bran oil, and liposomes that are rich in omega-3, -6, -7, and -9 fatty acids. In addition, bioactive substances such as flavonoids, carotenoids, mucilage, vitamins, tannins, and triterpenes are present.[28] These components have been investigated and observed to produce clinical benefits in AD, bedsores, and inflammatory lesions of the skin.[13,20] CLC potentially could limit and delay the occurrence of radiodermatitis in breast cancer patients, and as an add-on, it can be suggested to promote complete healing of bedsore lesions in geriatric subjects.[50,52] Finally, many conditions may benefit from the application of a soothing and emollient cream. The authors acknowledge that further clinical research is needed to demonstrate the cream efficacy in skin conditions, where clinical experience has already suggested good results. Further studies are needed to understand the mode of action, not only of single components but also of the cream as a whole.

CLC may be used as an add-on to standard medical treatment in patients with a number of skin conditions, such as psoriasis, atopic dermatitis, and in wound care with the aim of a TC sparing effect, delay of progression, and early resolution of the underlying skin condition. Effective treatment of xerosis could be obtained with regular administration of CLC alone, preventing progression toward a dermatitis occurrence, and improving subjective symptoms such as pruritus and discomfort.

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