Fragile Skin: Benefit of Cosmeceuticals based on Rhealba® Oat plantlet in acne vulgaris

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Received: March 19, 2015
Published online: May 07, 2015

Fragile skin is the state of unbalanced skin characterized by lower resistance to aggressions linked with impaired barrier function of skin. Acneic skin becomes fragile due to its own pathophysiological mechanism. Indeed, acneic skin differs from normal skin as it is subject to higher transepidermal water loss and lower stratum corneum hydration. Moreover, acne vulgaris is also characterized by alterations in the lipid content of sebum and an inflammation in the sebaceous gland. These alterations lead to hyperproliferation and to an increased desquamation of keratinocytes within sebaceous follicles. Thus, the accumulation of keratinocytes can block the pilosebaceous unit, preventing sebum drainage. This results in the formation of microcomedones, and further acne lesions. Changes of the pilo-sebaceous environment favour the proliferation of Propionibacterium acnes (P. Acnes). P. acnes exerts several pro-inflammatory activities which trigger the innate immune system by activating toll-like receptor 2 and NLRP3 inflammasome, resulting in IL-1β secretion in human monocytes. Rhealba® Oat Plantlets extract (Pierre Fabre Dermo-Cosmetique) has been reported to restore fragile skin, inhibit bacterial adhesion of P. Acnes, and to be capable of reducing inflammation and irritation in acne. Moreover, cosmeceuticals including Rhealba® Oat Plantlets extract and hydro-compensating actives, which can be associated with anti-comedogenic agents (hydroxyl acids), may be usually used stand-alone or in addition to acne treatments in order to treat acne vulgaris.

Keywords: Fragile skin; Acne vulgaris; Inflammasome; Toll Like Receptor; Rhealba® Oat


Introduction

The most important function of the skin is to provide a protective barrier against external threats such as microorganisms, mechanical impacts, physical insults and chemicals. Fragile skin is the state of unbalanced skin characterized by lower resistance to aggressions linked with impaired barrier function of skin[1]. This impairment is characterized by an excessive water loss and a reduced capacitance. In addition, the ability to fend off potentially invasive microorganisms is also reduced in fragile skin by a disruption of the immune system, including innate immunity and adaptive immunity[1].

Fragile skin can be categorized differently depending on its origin. Four categories were established: Firstly, the physiological fragile skin (age, location). Secondly, fragile skin can be the results of external and internal factors, like climate and stress. This type of fragile skin is therefore classified as circumstantial fragile skin. Then, the fragile skin caused by peeling or isotretinoin is referred to as iatrogenic...
Acne vulgaris is a chronic inflammatory skin disease of the pilosebaceous unit[2, 3]. The acne pathophysiology is multifactorial, with microbiological, immunological and hormonal mechanisms. *Propionibacterium acnes* (*P. acnes*), the predominant organism in the microbiome of facial skin, has been identified in acne lesions and induces inflammatory response and causes keratinocytes damage[4, 5]. These different mechanisms lead to inflammasome activation, and to an alteration of the epidermal barrier, and thus the acneic skin becomes fragile.

**Acne and epidermal barrier**

The epidermal barrier is represented by multiple physiologic activities occurring within the stratum corneum (SC). These activities include maintaining skin water content, protection against microbial organisms, protection from effects of ultraviolet radiations, neutralization of reactive oxygen species (ROS) and an immunologic role against exogenous allergens and haptens[6]. Changes in the epidermal barrier may participate or exacerbate the development of acne[11]. Acneic skin differs from normal skin because of higher transepidermal water loss (TEWL) and lower stratum corneum hydration (decreased conductance), responsible of skin dehydration[7]. The severity of acne appears to be correlated with the increase in transepidermal water loss and the decreased conductance[7, 8]. These impairments of the integrity of the skin barrier can cause an accumulation of corneocytes leading to skin thickening. This build-up of corneocytes may block the release of sebum from the pilosebaceous unit[11]. The hyperkeratosis of the follicular epithelium may result in the formation of comedone[8]. Furthermore, total ceramides (lipid rich matrix) and free sphingosine are significantly reduced. By causing hyperkeratosis, the deficiency of intercellular lipid may also contribute to the comedone formation[8]. Moreover, inflammation in the pilosebaceous unit can lead to the follicular wall rupture with subsequent leakage of sebum, bacteria and keratin into the dermis. This event is characterized by the occurrence of nodulocystic or nodular acne lesions[11].

Filaggrin is a fundamental protein in the differentiation of the epidermis and is involved in the functional and structural integrity of the stratum corneum[9]. Filaggrin support cytoskeletal aggregation and formation of the cornified cell envelope, providing additional strength and structure to epidermal barrier. Some skin diseases, and especially atopic dermatitis, are associated with the alteration of filaggrin expression, responsible for skin barrier impairment. However, in cultured keratinocytes and human skin explants, *P. acnes* causes an increase of filaggrin expression. Thereby, in acne lesions, the expression of filaggrins in keratinocytes lining the follicle wall is increased[10, 11]. Moreover, inflammatory cytokines have been reported to contribute to the overexpression of filaggrin in sebaceous gland explants[12]. These findings suggest that filaggrin expression would play a significant role in acne lesions formation. Another study on the filaggrin mutation in patients with xerosis comes consolidate these findings[13]. This study suggested that some patients may be protected against acne vulgaris whether they present one copy of a null mutation in the filaggrin gene. Nevertheless, a larger study specifically examining the presence of filaggrin null mutations in acne sufferers did not confirm these conclusions[14]. Actually, the filaggrin expression is linked with the differentiation of keratinocytes and alterations in the stratum corneum associated with acne lesion.

Although in acne filaggrin expression seems to be augmented, in acne affected skin we curiously find different parameters typically associated with filaggrin function impairment: Yamamoto *et al.* observed that patients with acne vulgaris exhibited markedly greater TEWL and lower skin hydration with an evident permeability barrier impairment. The decrease of skin hydration and increase of TEWL were higher in patients with acne vulgaris of moderate severity as compared to those with mild acne severity and as compared to normal control subjects. This suggests that the degree of the impairment of stratum corneum permeability barrier is correlated directly with the acne vulgaris severity. Another consideration: if filaggrin, that is a protein with an important activity against bacterial colonization, is augmented in acne, why do we observe in acne affected skin an abnormal bacterial colonization? All this apparent contradictions can be probably explained by considering not only quantitative, but also qualitative representation of filaggrin. It’s probable, in fact, that in acne lesions augmented levels of filaggrin coexist with a functional impairment of this protein, that could be unable or less able to complete its natural maturation from profilaggrine, trough filaggrin, to natural moisturizing factors (NMFs), the final filaggrin products, essential to maintain skin hydration, normal TEWL and skin permeability, and to contrast bacterial colonization. For these reasons, the use of topical products containing functional filaggrin could be an effective and innovative therapeutic option. It is also important to consider that some medications, usually used in the acne treatment, can be responsible for additional alterations of the skin function and its integrity. The origin of these additional alterations may be the active substance or the vehicle, or both, but in any case specific skin care recommendations are very important in the management of
Figure 1. Pathophysiology of acne vulgaris. Keratinocyte hyperproliferation, increased desquamation, sebum accumulation, altered sebum lipid composition and *P. acnes* growth into the pilo-sebaceous unit, lead to fragile skin, involving barrier impairment and dehydration, and follicular rupture. TEWL, TransEpidermal Water Loss.

Acne vulgaris in order to potentiate the efficacy of drugs in the reduction of acne lesions[7].

Indeed, systemic medications, topical medications, and surgical and physical procedures used to treat acne and acne scarring can cause impairment in stratum corneum barrier function. Benzoyl peroxide and retinoids are particularly responsible for fragile skin, as characterized by irritated skin (burning and stinging), erythema, scaling, and xerosis[6]. The mechanism of action of retinoids involves the increase of epithelial cells turnover and the shedding of corneocytes[15]. Moreover, topical retinoids cause hypergranulosis, acanthosis, desquamation, and a decrease in stratum corneum thickness. “Retinoid dermatitis” is usually transitory, arising after 2-4 weeks and vanishing afterwards. As for the mechanism of action of benzoyl peroxide, reactive oxygen species are produced and the cohesion of keratinocytes are disrupted in the stratum corneum (keratolysis)[16].

**Pathology of acne: inflammatory role of *P. acnes***

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit. Acne is a common condition, with a lifetime prevalence of 80% but it occurs more frequently during the adolescence between 15 and 17 years old[17]. Features of acne include hyperseborrhoea (excessive sebum production), non-inflammatory lesions (comedones), inflammatory lesions characterized by papules, and pustules associated with diverse degrees of scarring, and in the most severe cases, nodules and cysts. Acne lesions are distributed essentially on face, chest, and back.

Generally, the first lesions appear around 12 years old. In fact, acne is often linked with puberty and less prevalent in adulthood. Nevertheless, juvenile acne can still be found in people between the ages of 20 and 30. It happens to 64% of individuals for the former, and to 43% for the latter and lead to a considerable psychological and social impact[3]. Although this skin disorder is most frequently not severe, people with acne are often subject to anxiety in social situations, and embarrassed with their appearance leading to reduce their quality of life[17]. Formation of acne lesions is well known to be associated with genetic and environmental factors, and especially emotional stress[2, 3].

*P. acnes* has been identified as a contributing factor in acne lesions by playing an important role in the pathogenesis because of colonization of the pilosebaceous unit and inflammation caused[3, 12, 18]. Acne lesions first develop in the pilosebaceous unit as subclinical microcomedones and may evolve into inflammatory (papules, pustules) and non-inflammatory lesions[2, 19]. The overproduction of sebum and increased follicular hyperkeratosis were thought to be first events leading to establish an environment favourable for the proliferation of *P. acnes*, and therefore responsible for the appearance of the initial eruptions (microcomedones). However, most recent evidence points that the inflammation begins before the primary eruptions[18]. Indeed, inflammation
and the infiltration of perivascular lymphoid can precede lymphoproliferation. Under normal circumstances, the keratinocytes differentiate into corneocytes, which will then desquamate and lost from the stratum corneum surface.[20] In acne vulgaris, changes in the lipid content of sebum associated with the inflammation in and around the sebaceous gland result in keratinocytes hyperproliferation and increased desquamation within sebaceous follicles[18, 9]. Inflammation of the pilosebaceous unit and the build-up of keratinocytes prevent sebum drainage, and thus microcomedones formation[6]. (figure 1)

*P. acnes* is responsible for several pro-inflammatory activities. This microorganism triggers the innate immune system by activating toll-like receptor 2 (TLR2) and the inflammasome pathway[21, 22]. The Toll Like Receptors (TLRs) are transmembrane proteins activated by pathogen-associated molecular patterns. The activation of TLRs by exposure to microbial agents leads to the activation of the NF-κB pathway which modulate expression of many immune response genes[23, 24]. *P. acnes* induces the production of monocyte cytokines, via a TLR2-dependent pathway. Indeed, TLR2 activation leads to stimulate the release of pro-inflammatory cytokines by the monocytes, such as IL-12 and IL-8. It allows to recruit neutrophils to the active lesion site. Through the release of lysosomal enzymes, these neutrophils cause the rupture of follicular epithelium triggering the inflammation[23]. TLR2 expression in acne suggests that the activation of TLR2 by *P. acnes* can be involved in the inflammatory lesion development[26]. Furthermore, *P. acnes* can also be phagocyted by myeloid cells resulting in IL-1β release, responsible for the inflammatory response by the neutrophils[22]. Indeed, in human monocytes, *P. acnes* activates NLRP3-inflammasome leading to maturation of pro-IL-1β to active IL-1β by means of caspase 1[27]. The inflammasome is an intracellular and molecular complex that has the function of initiate inflammation. The danger- and pathogen-associated molecular patterns (DAMPs/PAMPs) activate the inflammasome which will regulate the release of several caspase-1 activation-dependent cytokines, and especially IL-1β[28]. Overall, NLRP3-inflammasome activation requires the phagocytosis of *P. acnes*, the release of cathepsin B by the lysosomal rupture, K⁺ efflux and formation of reactive oxygen species (ROS)[29]. (figure 2)

**Rhealba® Oat plantlet extract**
The healing properties of oat have been known for thousands of years. Since 400 BC, traditional medicine has been using oat in the form of flour or gruel, for its emollient and anti-inflammatory benefits. The healing virtues of oat are frequently employed for several skin disorders, such as pruritus, burns, ulcers as well as erythema. Today, Rhealba® Oat plantlet extract (Pierre Fabre DermoCosmetique) is usually used for treating fragile skin due to its varied biochemical properties. Indeed, the non-dietary aerial parts of Rhealba® Oat contain essentially flavonoids and saponins, two molecular species which would have interesting anti-inflammatory and immunomodulatory activities. The active components of Rhealba® Oat Plantlets extract were separated by reverse phase liquid chromatography followed by semi-preparative reverse phase HPLC. Two C-glycosylated flavonoids were isolated, one of the apigenin type, isoorientin-2′′-O-arabinoside, and the other of the luteolin type, isovitexin-2′′-O-arabinoside. (figure 3)

The immunomodulatory and anti-inflammatory activity of Rhealba® Oat Plantlets extract and its purified active substances were therefore studied in vitro in several cell models mimicking the different pathways of activation of inflammation. The results suggest that Rhealba® Oat Plantlets extract exerts interesting immunomodulatory activity. In fact, Plantlets extract causes dose-dependent inhibition in the secretion of pro-inflammatory Th1 and Th2 cytokines and particularly on IL-13 and IL-2 production, cytokines that play a central role in controlling the immune response. Moreover, Rhealba® Oat Plantlets extract has an inhibitory effect on the capacity of dendritic cells to stimulate T lymphocyte proliferation. This reduced efficacy of dendritic cells might be due to the weaker expression of the MHC I and II costimulatory molecules on their surface, negatively regulated by the extract.

In addition, Rhealba® Oat Plantlets extract presents an anti-inflammatory activity. Indeed, the extract inhibits significantly the production of the prostacycline PG6KF1α, a prostaglandin which is a major metabolite of arachidonic acid resulting from the cyclo-oxygenase pathway in keratinocytes. This effect appears to be exerted by directly inhibiting the activity of the COX-2 enzyme and not by reducing quantity of arachidonic acid.

Rhealba® Oat Plantlets extract has also been identified to inhibit bacterial adhesion, especially Staphylococcus aureus, enhance the production of ceramides, cerebrosides and free acide both involved in cutaneous barrier homeostasis. Moreover, the extract stimulates the proliferation of keratinocytes and enhances the production of collagen IV, hyaluronic acid, and sphingomyelin. All of these findings suggest that Rhealba® Oat Plantlets extract is capable of reducing inflammation and irritation in acne.

Cosmeceuticals based on Rhealba® Oat plantlet extract

FDA identified colloidal oatmeal in 1989 as a skin protectant drug available over the counter and offered to classify it as a category I ingredient which means safe and effective, while waiting for the standardization of its formula.

Rhealba® Oat plantlet extract (Pierre Fabre Dermo-Cosmetique) is an oat plantlet extract without protein used to heal fragile skin and is an exclusive ingredient of A-DERMA. This extract is also part of the Phys-AC range, the product line of A-DERMA to treat acne. A-DERMA products contain also hydro-compensating actives to restore fragile skin and reduce irritation and inflammation. Indeed, acne is often associated with irritation and dry skin and the symptoms can be aggravated by anti-acne treatment such as topical tretinoin or isotretinoin.

The Phys-AC range encompasses four products. The first, Phys-AC Global, is employed as a stand-alone cream which associates Rhealba® Oat plantlet extract, anti-comedogenic agents and hydro-compensating actives. In Phys-AC Global, the anti-comedogenic agents are represented by the hydroxy acids. The main hydroxy acid used, is the glycolic acid, a natural product from sugar cane, known to reduce the cohesion of corneocytes, and favor desquamation.

Lactic acid, another hydroxyl acid, is used to inhibit the growth of P. acnes and promote keratinocyte desquamation. The last anti-comedogenic agent is the salicylic acid which has keratolytic activity. Another product of Phys-AC is the Hydra cream, which is composed of Rhealba® Oat plantlet extract and hydro-compensating actives. This cream is to be used in addition to anti-acneic...
treatments in order to lessen the irritation and restore fragile skin. The last two Phys-AC products are the purifying foaming gel and the purifying micellar water. They also contain Rhealba® Oat plantlet extract as well as hydro-compensating actives and can be used as daily cleansers.

Conclusions

In acne, fragile skin has two origins; the impairment of the skin barrier and the inflammatory nature of this skin disease. These events are mainly attributed to the proliferation of P. acnes. Thanks to its anti-inflammatory, immunomodulatory and barrier restoration properties, Rhealba® Oat plantlet extract is able to reduce inflammation, inhibit adhesion of P. acnes, and thus, restore the fragile skin. Therefore, cosmeceuticals based on Rhealba® Oat plantlet extract associated with anti-comedogenic agents (hydroxyl acids), may be usually used stand-alone or in addition to anti-acneic treatment for acne vulgaris treatment.

Conflict of interest

GF declares no conflicts of interest. MSA is an employee of Pierre Fabre and FS is a trainee of Medical Direction of A-DERMA

Abbreviations

COX: Cyclooxygenase; IL: Interleukin; NMF: Natural Moisturizing Factors; MHC: Major Histocompatibility Complex; P. acnes: Propionibacterium acnes; PG6KF1α: ProstaGlandin 6KF1α; ROS: Reactive Oxygen Species; SC: stratum corneum; TEWL: TransEpidermal Water Loss; Th: Lymphocyte T helper; TLR: Toll Like Receptor.

References


