REVIEW

Fragility of the epidermis, a common pathophysiological mechanism of acne vulgaris, rosacea and reactive skin involving inflammasome activation

Gabriella FABBROCINI[1], Marie-Florence GALLIANO[2], Marie-Françoise ARIES[2], Clémence VAISSIERE[2], Nathalie CASTEX-RIZZI[2], Hélène DUPLAN[2], Christine COUTANCEAU[3], Sandrine BESSOU-TOUYA[2], Florian SCHMITT[3], Markéta SAINT-AROMAN[3]

[1]*Department of Dermatology and venereology, University of Naples Federico II, 80138 Naples, Italy*
[2]*Pierre FABRE DermoCosmétique, R&D, Pharmacologie in vitro, 31035 Toulouse, France*
[3]*Pierre FABRE DermoCosmétique, Direction Médicale A-DERMA, 81506 Lavaur, France*

Correspondence: Markéta SAINT-AROMAN
E-mail: Marketa.saint.aroman@pierre-fabre.com
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Purpose of the study: The goal of this study was to review the recent evidence regarding the pathophysiology of reactive skin, acne vulgaris and rosacea, with a focus on the link between the impaired skin barrier and the inflammasome. In this context, we evaluated the activity of Rhealba® oat plantlet extract on the inflammasome *in vitro*. **Procedures:** Using an *in vitro* inflammatory model of Reconstructed Human Epidermis (RHE), we investigated the biologically active forms of inflammasome products, IL-1β and IL-18 cytokines, in parallel with inflammatory mediators IL-6, IL-8, TNF-α, VEGF-A, MIP-1α/CCL3, sICAM-1. **Results:** We showed that a 2-h pre-treatment with Rhealba® oat plantlet extract with Vitamin E and A-DERMA cream for reactive skin significantly prevented poly I:C-induced up-regulation of inflammatory mediators and inflammasome cytokines, as we observed IL8, IL6, TNFα, VEGF-A, MIP-1α, sICAM-1, IL18 down-regulation, along with a significant reduction of IL1-β. **Conclusions and message of the paper:** We propose that reactive skin, rosacea and acne share skin barrier and innate immunity dysfunctions. Moreover, the results suggest that Rhealba® Oat plantlet extract provides an adequate solution for the management of reactive skin, and probably for the other skin disorders involving inflammasome pathway activation.

Keywords: Acne; Rosacea; reactive skin; inflammasome; innate immunity; interleukin-1 beta; Propionibacterium acnes; skin barrier; toll-like receptor; Trans Epidermal Water Loss

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Introduction

Reactive skin, acne vulgaris and rosacea share a common pathophysiologic origin. These three skin disorders all involve skin barrier dysfunction and inflammasome activation, ranging from the most superficial changes (in reactive skin), to the most profound (in rosacea) [1].

Recent studies at the molecular level suggest that inflammation and an impaired innate immune response play a critical role in their pathogenesis [2, 3]. Indeed, these skin disorders are associated with abnormal activation of Toll-Like Receptor (TLR) and inflammasome in keratinocytes, i.e. involving the organism innate immunity [2-4]. This abnormal TLR activation is patent in the early steps

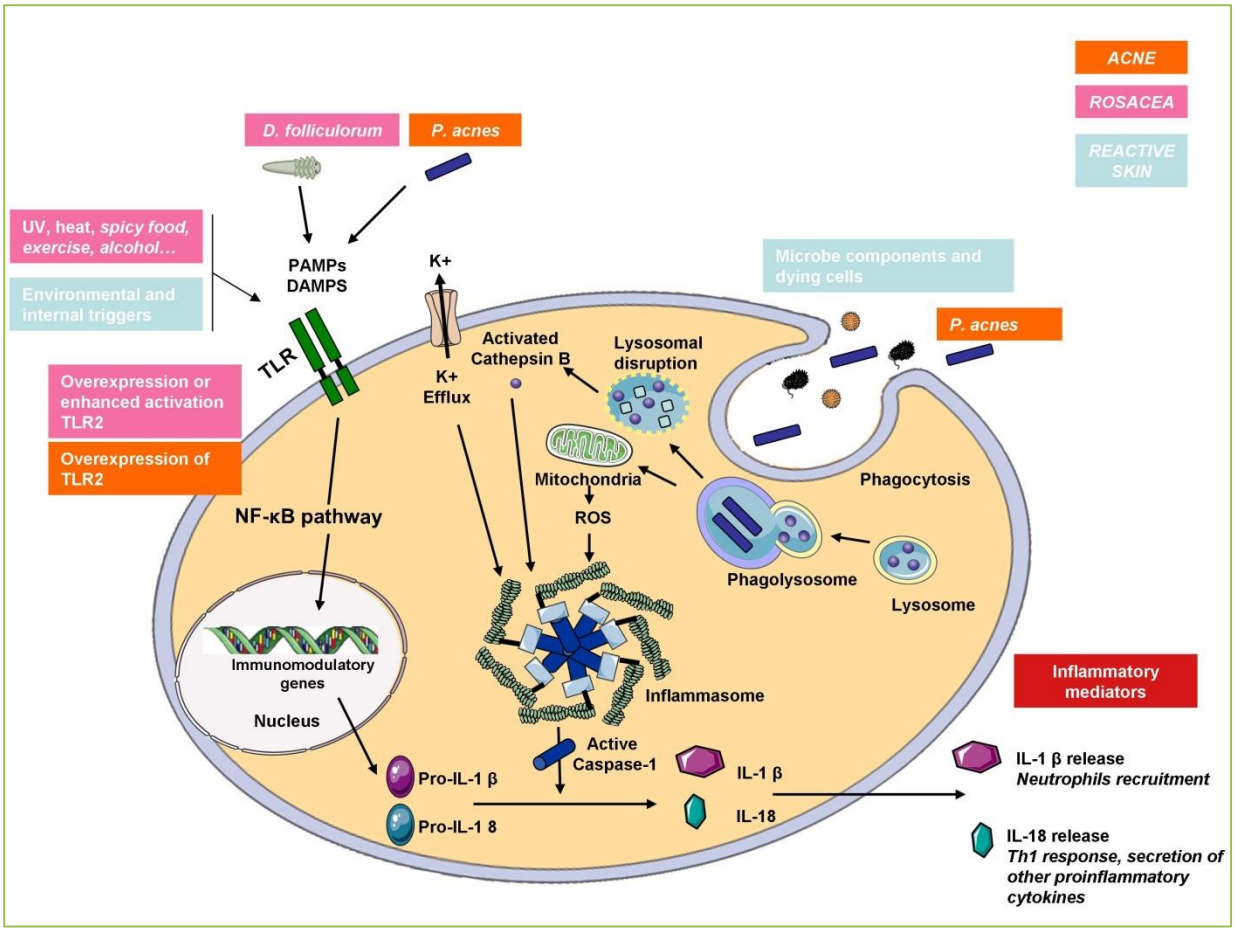

Figure 1. Activation of the inflammasome: a common pathophysiological in reactive skin, acne and rosacea. Maturation and secretion of IL-1β and IL-18 requires 2 signals. The "priming signal" induces the production of pro-IL-1β, pro-IL-18, NLRP3 and other components of the inflammasome. The second signal leads to assembly of the inflammasome, caspase-1 activation, release of the bioactive forms of cytokines IL-1β and IL-18 into the extracellular matrix and triggering of neutrophil-rich local inflammation. **In reactive skin**, both environmental and internal triggers, such as microbe components and dying cells can release endogenous danger signals and activate Toll-like receptors and NLRP3-inflammasome. Patients with **acne** express higher levels of TLR2. Besides, *P. acnes* undergoes phagocytosis, which triggers events involved in inflammasome activation. **In rosacea**, proliferation of organisms such as *Demodex folliculorum* or exposure to UV light or increased ambient heat may serve as a pro-inflammatory trigger which interacts with enhanced TLR2 function to generate an inflammatory response. *DAMP, danger-associated molecular pattern; PAMP, pathogen-associated molecular pattern; dsDNA, double-stranded DNA; ROS, reactive oxygen species; TLR, Toll-like receptor.*

of acne lesion development (macro and microcomedones) as demonstrated by the efficacy of some anti-inflammatory therapeutic approaches (such as photodynamic therapy), as well as during the comedogenic phase [5].

Moreover, all these three skin disorders (reactive skin, vulgaris acne, rosacea) are characterised by an impaired skin barrier function, and are classified as fragile skin. Fragile skin is the state of unbalanced skin characterised by lower resistance to aggressions linked with impaired skin barrier function (mechanical and immunological one) [4].

Our manuscript presents an update of the literature on the epidemiology and pathophysiology of these three skin conditions, focusing on the link between the epidermal barrier impairment and the inflammasome. We also report an *in vitro* study, showing the effects of Rhealba® Oat Plantlet extract on the regulation of the inflammasome.

REACTIVE SKIN

1) Clinical Signs and Epidemiology

Reactive skin (or sensitive skin) is defined as cutaneous hyperreactivity to environmental factors (heat, cold, UV rays), cosmetics, and emotional (stress, etc.) or hormonal triggers. It manifests as tingling and tightness, stinging, burning, generally perceived on the face, in absence of any skin disease [4]. An epidemiological survey carried out in 2007 in a cohort of 994 subjects (495 men, 499 women)

showed that 44.6% of North American population declares to have reactive skin [6]. A European epidemiological study performed in 8 European countries found a prevalence of 37.6% in 4506 respondents to the survey [7]. Furthermore, women self-perception is considerably higher compared with men [8].

2) Pathophysiology

Recent findings suggest that the higher sensitivity characterizing reactive skin could result from different mechanisms. Firstly, an impaired skin barrier function, with a thinner stratum corneum (SC), leading to an excessive transepidermal water loss (TEWL), may promote contact with irritants and transcutaneous penetration of water-soluble chemicals [9]. Besides, the abnormal sensations and vasodilation would reflect the involvement of the cutaneous nervous system, in particular, alterations in vanilloid receptors and in synaptic transmission [10]. Finally, enhanced immune responsiveness could also play a role [11]. Indeed, reactive skin results from intricate relationships between external and internal factors including inadequate hygiene and care, pollution, fatigue and stress, which can induce danger signals at the cellular level. These endogenous danger signals released from dying cells and microbe parts are recognized by pattern recognition receptors (PRRs), which include Toll-like receptors (TLRs), and can trigger innate immune and inflammatory responses, and activate the inflammasome pathway. Inflammasome is an intracellular multi-protein complex, containing mainly caspase-1, which is involved in the maturation of interleukin-1beta (IL-1β) and interleukin-18 (IL-18), playing major roles in inflammatory skin and potentially in reactive skin [12] (*Figure 1).*

ACNE VULGARIS

1) Clinical Signs and Epidemiology

Acne is a frequent inflammatory cutaneous disease, characterised by comedones, papules, pustules and nodules, localized on the face, trunk and back. With 9.4% of the population affected by acne, it is the eighth most frequent disorder worldwide [13]. It is observed in 88–95% of adolescents, 64% of adults in their twenties and 43% in their thirties [14]. First-degree relatives of acne patients have 80% chance of being affected [14]. Randomized controlled trials evaluating dietary influence demonstrated close relationships between acne and sugar intake [3].

Although acne is more frequent among teenaged males, it usually disappears by the age of 25, whereas females may continue to experience acne sometimes beyond the age of 40. A large number of adult females are thus affected by post-adolescent acne, up to 17% of women between 25 and 40 years [15], which may be associated with a significant negative impact on their psychological, social and emotional well-being [16]. Whereas adolescent acne (male and female) is characterised by numerous comedonal and inflammatory lesions in the T-zone (forehead, nose and ears), adult female acne mostly presents with inflammatory lesions affecting the U-zone (chin, jawline, and neck).

2) Pathophysiology

According to a meta-analysis of the literature published over the last 10 years [3], four distinct factors mostly contribute to the formation of acne lesions. Firstly, there is an increase of sebum production. Secondly, the hyperkeratinisation of the pilosebaceous unit leads to obstruction and comedones formation. Then, the follicular colonisation by *Propionibacterium acnes* (*P. acnes*) finally generates an inflammatory response [3]. These factors would be more intertwined than previously thought. Other factors susceptible to be involved in acne pathophysiology are T helper (Th) 17 cell, inflammasome, *P. acnes* sequence type and nutrition. In order to draw a synthetic view of acne pathogenesis, two main system defects can be described: skin barrier impairment and the inflammasome-mediated inflammatory response.

3) Acne and epidermal barrier impairment

Epidermal barrier dysfunctions have been reported in acne. These alterations affect the surface epidermis, including the stratum corneum, but also the follicular barrier, directly involved in comedogenesis and inflammation steps, in particular with follicular rupture [17].

Compared with normal skin of acne-free people, the facial skin of individuals with acne shows an increased sebum production and larger size of sebaceous glands [17]. Moreover, increased TransEpidermal Water Loss (TEWL) and reduced SC hydration (conductance) have also been observed, of greater intensity in patients with moderately severe acne compared with those with mild acne [18]. Furthermore, significantly decreased free sphingosine and total ceramides levels were reported in the stratum corneum of acne-prone individuals, evidencing a deficiency of the intercellular lipid membrane, which correlated with SC permeability barrier impairment [18].

As regards the follicular epidermis, the proliferation of *P. acnes* in the follicle triggers inflammatory cascades. If inflammation progresses further, the follicular wall weakens and can break, leading to sebum, keratin and bacteria leakage into the dermis [4]. The presence of foreign substances in the

dermis in turn increases inflammation, and can induce nodular or nodulocystic acne lesions [17].

As a central protein involved in the differentiation of the epidermis, filaggrin contributes to the structure and function of the SC [4]. Changes in filaggrin levels have been observed within acne lesions in keratinocytes coating the follicle wall. Moreover, in cultured keratinocytes and explants of human skin, *P. acnes* was shown to increase filaggrin expression [17]. However, it is not clear whether these modifications in filaggrin levels occur as primary or secondary events [17]. Because of those barrier alterations, acne is classified as pathological fragile skin.

Finally, in addition to the barrier defects associated to acne, some topical agents, systemic drugs and physical procedures used in the treatment of acne can induce an impaired SC permeability barrier function, as evidenced by increased TEWL and sometimes xerosis [17]. This iatrogenic alteration of cutaneous barrier in acne patients is classified as iatrogenic fragile skin.

4) Acne and inflammasome

Several research groups have reported that innate immunity involvement is important in acne pathogenetic mechanisms, especially through inflammasome activation [3]. This pathogenetic step could be one of the first steps conducting to acne lesions. *P. acnes* would activate the NLRP3-inflammasome, triggering IL-1β and IL-18 production.

Among its various functions, IL-1β recruits neutrophils and inflammatory cells. It also induces its own expression and the expression of genes coding for other cytokines (TNF-α or IL-6), triggering a real inflammatory cascade [19]. IL-18 induces a Th1 response and activates the secretion of other pro-inflammatory cytokines [19].

According to the recent review by Suh *et al.*, *P. acnes* was initially thought to induce inflammatory cytokines and metalloproteases via activation of the TLR-2 signalling pathway [20]. A recent study demonstrated that circulating monocytes in acne patients expressed increased levels of TLR2 [21]. Moreover, *P. acnes* indeed markedly activates the inflammasome in peripheral neutrophils [22]. Acne is thus characterised by altered innate immune signalling triggered by *P. acnes (Figure 1).*

ROSACEA

1) Clinical Signs and Epidemiology

Rosacea is a common, chronic and incurable cutaneous disorder, affecting parts of the face. This disorder is characterised by bouts of exacerbation and remission periods of variable length. Rosacea is localized on the central third of the face, and particularly observed among adult in middle age with blond hair, light skin and blue eyes. Despite being long mostly associated with fair skin types (I-II), affecting up to 10% of Northern European or Celtic heritage individuals, rosacea has also been described in about 4% of subjects with darker skin types, such as African Americans, Hispanics/Latinos, and Asians [23]. Rosacea is more frequent in women, especially during menopause, than in men. A hereditary factor of rosacea is suspected, since it often affects several family members, however, the genetic basis remains unclear [24].

Clinical signs or symptoms of rosacea include diffuse transient to persistent erythema of the face, telangiectasias, papules, pustules, oedema or a combination of these, and can be associated to intense burning, stinging and itching sensations [25]. Rosacea can be triggered by several environmental stimuli, including ultraviolet radiation, temperature change, spicy foods, alcohol, stress and exercise [24]. Moreover, infestation by Demodex mites plays a role in certain subtypes of rosacea, in particular in papulopustular lesions [24].

Four major subtypes of rosacea have been defined [26]. The two most common types are erythematotelangiectatic rosacea (ETR) and papulopustular rosacea (PPR). ETR is characterised by permanent redness (erythema) in addition to telangiectasias, i.e. apparent widened small blood vessels on the face[27]. PPR is characterised by some degree of permanent redness associated with inflammatory lesions in the form of papules and/or pustules. ETR patients and some patients with PPR present signs of skin sensitivity (stinging, burning, scaling, flaking) [28, 29].

Then, the phymatous rosacea (PhR) is characterised by an enlargement of the nose called rhinophyma. PhR can also involve the cheeks, the chin (gnatophyma), the forehead (metophyma) and ears (otophyma)[26]. In PhR, some telangiectasias may be present.

The fourth subtype is the ocular rosacea. In this subtype, the eyes and eyelids are affected and may appear red due to the telangiectasias. Ocular rosacea is associated with an inflammatory state leading to dry skin, irritated skin, sensitivity to light and common symptoms (itching, burning, stinging) [30]. It is not clear whether these four subtypes occur individually or may represent progressive steps of a same disease [28].

2) Pathophysiology

The pathophysiology of rosacea is multifactorial, involving lipid-rich matrix alterations, immunological and inflammatory mechanisms, neurosensory impairment and vascular biology alterations. The interplay between those various elements has not yet been fully elucidated, as they are intertwined.

In presence of a primary vascular anomaly, external factors, such as climate and cutaneous flora changes, ultraviolet exposure, etc., can induce the formation of abnormal superficial blood vessels, with a high permeability. The resulting oedema favours the colonization and proliferation of *Demodex folliculorum*. This parasite can generate inflammation, both directly and indirectly, as observed in the papules, pustules and granulomas [31]. However, as shown by recent body of evidence, the presence of *D. folliculorum* is not an absolute prerequisite in the pathogenesis of rosacea, but could just represent a pro-inflammatory trigger, especially in patients presenting with PPR [28]. Indeed, a hyper-responsive innate immune system has been reported to play a role early in the development of rosacea lesions and in the two most common subtypes of rosacea as well as in phymatous rosacea [28].

3) Rosacea and inflammasome

Recent studies suggest that patients with rosacea express higher amounts of Toll-like receptor 2 (TLR2) than rosacea-free individuals [2]. This abnormal function of innate immune PRRs could explain why rosacea sufferers present an enhanced sensitivity. In normal skin, upon activation by a triggering agent (i.e. bacteria, virus), the cathelicidin (antimicrobial peptide) is converted and degraded by a SC serine protease called kallikrein-5 (KLK5), resulting in the formation of pro-inflammatory peptides. The major cathelicidin-derived peptide in skin is LL-37, which exhibits anti-microbial properties and in turn promotes vasodilation, angiogenesis, and inflammation locally at the affected cutaneous site [28]. In 2011, Yamasaki *et al*. [2] demonstrated that the abnormal activation or overexpression of TLR2 in keratinocytes result in a calcium-dependent release of KLK5 from keratinocytes. Abnormal TLR2 function associated with increased levels of the precursor of cathelicidin [32] may thus contribute to enhanced inflammatory responses to external stimuli and could play a pivotal role in the pathogenesis of rosacea. Moreover, in rosacea, KLK5 activation is also induced by an upregulation of several matrix metalloproteinase enzymes (MMPs), responsible for vascular effects and the inflammatory response [29].

The pathogenesis of rosacea is also associated with *Demodex folliculorum* colonisation [33]. More than 100 species of *Demodex* mites have been described, and various kinds of *Demodex* mites may infest the skin, but all are highly specific for various areas of the skin of the host [34]. However, mite infestation is generally asymptomatic [35]. In rosacea, recent study has demonstrated that increases in *D. folliculorum* could act as a triggering factor [36]. Indeed, *D. folliculorum* was detected more often in rosacea sufferers than healthy subjects, and was 5.7 times more present in rosacea patients. Moreover, this study showed that rosacea patients present an overexpression of inflammasome-related genes (NALP-3 and CASP-1) indicating the innate immune system activation [36]. In fact, *D. folliculorum* activates the NLRP3-inflammasome, which activates caspase-1, eventually leading to the release of the proinflammatory cytokines IL-1β and IL-18 [37]. In addition, *D. folliculorum* stimulates Toll-like receptor-2, which activates the calcium-dependent production of KLK5, and thus induces an inflammatory response [38] *(Figure 1)*. By destroying epithelial cells, *D. folliculorum* is often responsible for the epithelial barrier impairment.

4) Rosacea and epidermal barrier impairment

Another potential pathophysiological factor is SC permeability barrier alterations. Rosacea sufferers often have intolerant skin, suggesting an impaired barrier function. A recent study showed that the facial skin of rosacea patients is more intolerant to irritants as a result of impaired barrier function. Moreover, this impairment would be limited to the face, by contrast with dermatitis atopic where the skin barrier dysfunction is generalised [39]. Indeed, the skin of rosacea patients shows increased transepidermal water loss compared with normal skin and reduced stratum corneum hydration (decreased conductance) in central facial skin [39]. This defect would also interact with the innate immune response, through the increased expression and secretion of anti-microbial peptides (i.e. cathelicidin) [29]. SC permeability is thus a potential pathophysiological factor. As the barrier is impaired, rosacea can be classified as pathological fragile skin.

Finally, neurovascular dysregulation and altered immune response represent integral components of vasodilatory reactivity and “neurogenic” symptoms such as stinging and burning [29]. The fact that rosacea essentially affects facial skin could result from the dense presence of sebaceous glands in this area (cheeks, nose, chin, and forehead), and a specific innervation and vascular composition. However, this is still a matter of debate [24]. As regards rhinophyma, its etiology remains poorly understood: the vascular abnormalities induce production of transforming growth

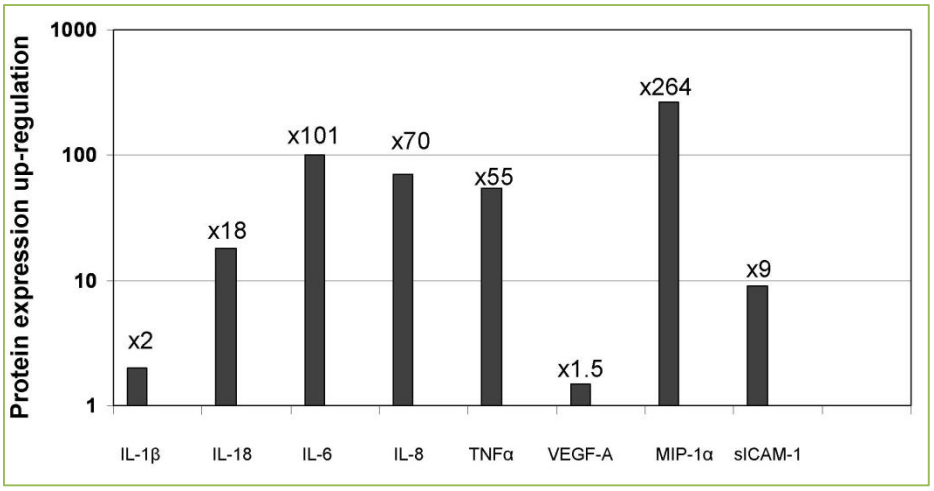

Figure 2. *In vitro* inflammatory model of Reconstructed Human Epidermis (RHE). The up-regulation of the protein expression in the extracellular compartment of the Reconstructed Human Epidermis (RHE) model was observed by Luminex™ technology analysis after a 48h stimulation by 5µg/ml poly I:C Toll Like Receptor-3 (TLR-3) ligand.

factor β1 (TGF-β1) locally, which can lead to fibrosis and cutaneous thickening [6, 31].

Rhealba® Oat plantlet extract: inflammasome pathway modulation

In traditional medicine, oat grain has been described as early as in 400 BC as an emollient, anti-inflammatory and wound-healing active, used in cases of pruritus, erythema, ulcers and burns [40, 4]. In 2003, the FDA approved the colloidal oatmeal as a « safe and effective » ingredient in the Final Monograph for Skin Protectant Drugs for Human Use [41].

Rhealba® Oat plantlet extract (Pierre Fabre Dermo-Cosmetics) is a protein-free extract from oat plantlets used in A-DERMA products to restore fragile skin. Indeed, active components of Rhealba® Oat plantlet extract, especially flavonoids and saponins, have shown anti-inflammatory and immunomodulatory properties [42]. Moreover, Rhealba® Oat plantlet extract is frequently used in the treatment of several skin disorders such as atopic dermatitis, reactive skin, acne and rosacea to restore and protect the epidermal barrier.

The inflammasome is the common base for reactive skin, rosacea and acne. The inflammasome can rapidly initiate inflammation by regulating the secretion of caspase-1 activation-dependent cytokines, mainly including IL-1β [43]. The aim of the study was to evaluate the activity of Rhealba® Oat plantlet extract on the inflammation caused by inflammasome pathway activation. The study focused on reactive skin; therefore the A-DERMA product dedicated for reactive skin, including Rhealba® Oat plantlet extract and Vitamin E, was used. In order to assess the activity of the association Rhealba® Oat plantlet extract with Vitamin E, the expressions of the biologically active mature forms of inflammasome products, IL-1β and IL-18 cytokines, in parallel with inflammatory mediators (IL-6, IL-8, TNF-α, VEGF-A, MIP-1α/CCL3, sICAM-1) were explored in an *in vitro* inflammatory model of Reconstructed Human Epidermis.

The *in vitro* Reconstructed Human Epidermis (RHE) is a culture of normal human keratinocytes, histologically similar to human epidermis. The inflammatory model of RHE is based on the up-regulated expression of inflammatory mediators in the extracellular compartment. This overexpression of inflammatory proteins is mediated by the activation of Toll Like Receptor-3 (TLR3) with a poly I:C ligand at a concentration of 5 µg/ml. Protein expression was observed by Luminex™ technology analysis after 48 hours of TLR3 stimulation. The up-regulation of mature IL-1β and IL-18 inflammasome products suggest that the inflammasome pathway is properly activated *(figure 2)*.

In a second step, the model of RHE has been pretreated with Rhealba® Oat plantlet extract, either "systemically" with Rhealba® Oat plantlet extract (0.32 mg/ml) and Vit. E 0.32mg/ml) added in the culture medium or "topically" with the A-DERMA cream for reactive skin directly applied on the RHE (5 mg/cm²), for two hours before up-regulating the inflammasome cytokines and inflammatory mediators with the poly I:C ligand (5 µg/ml). After a 48-hour stimulation by 5µg/ml poly I:C TLR-3 ligand, the release of IL-1β *(Figure 3A)* and of the other inflammatory mediators *(Figures B,C)* was observed by Luminex™ technology. The Rhealba® Oat plantlet extract with Vitamin E prevented the release of

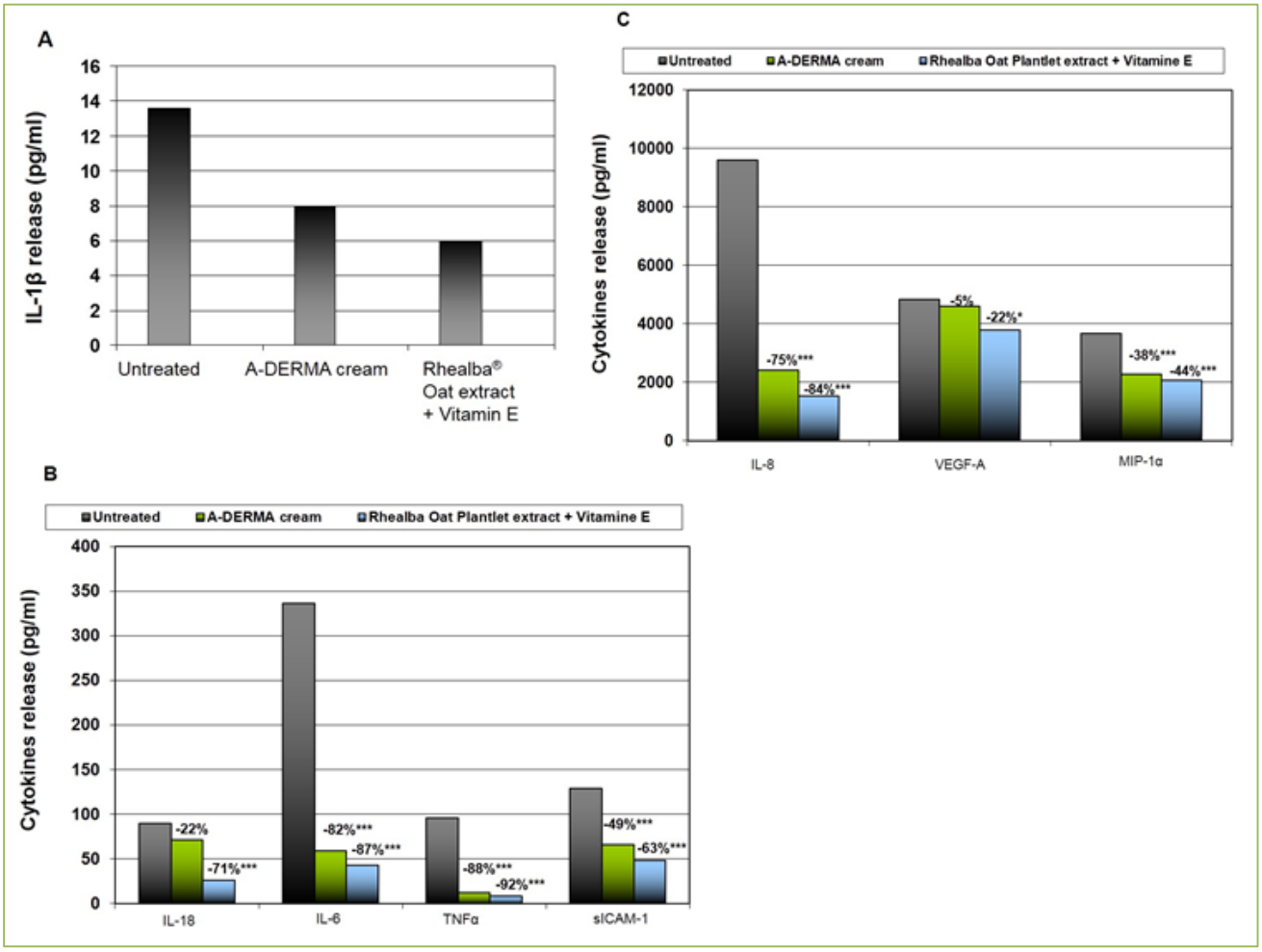

Figure 3. (A, B, C) Inflammasome pathway modulation by the association Rhealba® Oat Plantlet extract with Vitamine E. The Reconstructed Human Epidermis (RHE) was left untreated or was pretreated for 2 hours: (1) either "topically" by direct application of A-DERMA cream for reactive skin on the RHE. (2) or systemically, by addition of Rhealba® Oat extract + Vitamin E into the culture medium. Then, the release of IL-1β **(A)** and the other cytokines **(B, C)** was observed by Luminex™ technology analysis after a 48h stimulation by 5µg/ml poly I:C TLR-3 ligand. **** p<0.001*

inflammatory mediators and inflammasome products, with a significant reduction of IL-1β, the main inflammasome product. These results suggest that the addition of Rhealba® Oat plantlet extract in a dermo-cosmetic product may prove adequate in the management of reactive skin.

Conclusions

Reactive skin, acne, and rosacea are classified as fragile skin because of skin barrier impairment and innate immunity dysfunction. Rhealba® Oat plantlet extract already demonstrated its anti-inflammatory and immunomodulatory activities, and its properties to restore and protect the epidermal barrier. In this study, Rhealba® Oat plantlet extract effectively inhibited the inflammasome pathway, and thus inhibited the release of proinflammatory mediators, such as IL-1β. This could explain why cosmeceuticals based on Rhealba® Oat plantlet extract, actually provide an adequate solution for the management of reactive skin. Considering that the common point of these skin disorders is the activation of NLRP3-inflammasome pathway, Rhealba® Oat plantlet extract could be probably used for the treatment of the other disorders involving inflammasome pathway activation.

Conflict of interest

MFG, MFA, CV, NCR, HD, CC, SBT, MSA and FS are employed by Pierre Fabre Laboratory. GF declares no conflict of interest.

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