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REVIEW ARTICLE

# Effects of a protein-free oat plantlet extract on microinflammation and skin barrier function in atopic dermatitis patients

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**Abstract** Atopic dermatitis (AD) is a common, highly pruritic, chronic inflammatory skin disease. Dysfunction of the epidermal barrier is witnessed by an increased transepidermal water loss in lesional and non-lesional AD skin. The inflammation in lesional AD skin is well characterized. Non-lesional skin of AD patients shows histological signs of a subclinical inflammation and a pro-inflammatory cytokine milieu. This microinflammation is present even in seemingly healed skin and must be taken into account regarding treatment of AD. Emollients provide a safe and effective method of skin barrier improvement, because they provide the skin with a source of exogenous lipids, thus improving its barrier function. The use of emollients is recommended for all AD patients irrespective of overall disease severity. Patients with moderate to severe AD should combine the emollients with a proactive therapy regimen of topical calcineurin inhibitors or topical corticosteroids. Skin areas affected by active eczema in flare should receive daily anti-inflammatory therapy first before introducing emollients, to induce rapid relief of skin lesions and pruritus. The microinflammation persisting in seemingly healed AD lesions should be addressed by a proactive treatment approach, consisting of minimal anti-inflammatory therapy and liberal, daily use of emollients. An emollient containing an extract of Rhealba oat plantlet has shown anti-inflammatory and barrier repairing properties, and was clinically tested in studies targeting the microinflammation in AD. All emollients based on Rhealba oat plantlet extract are free of oat protein, as the Rhealba extract is derived from the aerial parts of the oat plantlet and is unrelated to oatmeal proteins. The Rhealba oat plantlet extract is produced in a specific process, allowing the extraction of high levels of active principles such as flavonoids and saponins, whilst being virtually free of oat proteins to minimize the risk for allergic reactions.
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## Conflicts of interest:

AW has been a consultant for Almirall, Astellas, Beiersdorf, Galderma, Hans Karrer, LEO Pharma, Novartis, Pierre Fabre, Pfizer and Sanofi, has given scientific lectures for Astellas, Beiersdorf, Bioderma, Galderma, GlaxoSmithKline, Hans Karrer, LEO Pharma, L'Oreal, MEDA, Novartis, Pierre Fabre and Sanofi and has performed studies for Astellas, Beiersdorf, Galderma, LEO Pharma, L'Oreal, Novartis, Pierre Fabre and Sanofi. RFH has been a consultant for Johnson&Johnson and L'Oreal, has given lectures for Astellas, Beiersdorf, Neubourg, Pierre Fabre and Novartis and performed studies for Astellas, Beiersdorf, Pierre Fabre, Neubourg and Novartis. MSA is Medical Director of A-DERMA Dermatological Laboratoires and an employee of Pierre Fabre Dermo-Cosmétique. FS is a paid consultant for Pierre Fabre. CV has been a consultant for Leo Pharma, Novartis, Sanofi, Abb-Vie, Pierre Fabre and MSD and given lectures for Novartis, Leo Pharma, Sanofi, Boehringer and Pierre Fabre

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## Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disorder characterized by pruritus and eczematous skin lesions. The disease affects 15–20 per cent of all children in affluent countries and up to 5% of young adults.[1] In more than 60% of these children, the disease started within the first 2 years of life.[2]

The diagnosis of AD is made on clinical grounds, and several diagnostic criteria exist.[3] These include the Hanifin and Rajka criteria from 1980,[4] the UK working party criteria from 2007[5] and the American Academy of Dermatology criteria.[6] All these criteria have pruritus as the primary symptom, but also eczematous skin lesions in typical distribution on the skin, and the fact that it is a chronic or chronically relapsing disease.

The relapsing nature of AD means that it is characterized by flares. There is no globally accepted, uniform definition of flare measurement used in AD trials.[7] However, it is widely accepted that a flare means an acute and clinically significant worsening of signs and symptoms of AD requiring increased therapeutic intervention.[3]

The inflammatory reaction in the skin of AD patients is characterized by an influx of T helper lymphocytes (especially Th2, and also Th22 and Th17 lymphocytes), which are producing IL-4, IL-5, IL-17 and IL-22. Furthermore, keratinocytes of AD patients produce inflammatory cytokines and chemokines, which by their own rights induce or exacerbate the inflammation in the skin. Several studies have shown that the production of inflammatory cytokines and the influx of inflammatory cells are increased in non-lesional, seemingly healthy skin of patients with AD compared to healthy skin.[8] The presence of this microinflammation provides the scientific basis for the proactive treatment regimen for AD, where the frequently relapsing areas of seemingly normal skin are treated twice weekly with topical glucocorticoids (TCS) or topical calcineurin inhibitors (TCI).[9]

Patients with AD also have a disturbed skin barrier function. One of the best described components in the pathogenesis of the decreased skin barrier is the structural protein filaggrin.

Filaggrin cross-links the intermediary keratin filaments in the keratinocytes of the stratum granulosum, and null mutations in the profilaggrin gene will lead to a functionally impaired stratum corneum.[10] This in turn leads to an increased transepidermal water loss (TEWL) and an influx of allergens. As a Th2-dominated inflammation in itself can down regulate filaggrin expression, the microinflammation in non-lesional AD skin may exacerbate and perpetuate the poor skin barrier function of patient with AD.[11,12]

Barrier function and microinflammation may be addressed and improved by regular use of emollients, and various formulations have been investigated to reach this therapeutic goal.[13,14] One of these is emollients containing a protein-free plantlet extract of immature oat plantlets. Saponins and flavonoids have been identified as the active components in plantlet extract in these formulations.[15]

The anti-inflammatory and immunoregulating properties of the active compounds in the Rhealba oat plantlets extract in inflammatory skin diseases such AD, acné, contact dermatitis and irritative dermatitis were proven in studies involving newborns, children and adolescents.[16]

In this study, the impact of microinflammation and skin barrier function on the treatment strategies of AD will be reviewed, with a special focus on the Rhealba protein-free plantlet extract.

## Disease concepts of AD

Atopic dermatitis is a complex disease, and its pathological mechanisms are not completely understood, but both genetic and environmental mechanisms of barrier and immune function are involved. The latter includes an impaired innate and a distorted adaptive immunity, leading to clinical consequences of various IgE-associated immune phenomena and an increased risk for disseminated viral infections.[17] Moreover, cellular and humoral aspects of immunity are involved in AD, raising the need for appropriate allergy tests. Some patients show clinically typical AD but are lacking the characteristic IgE component and are referred to as 'intrinsic' AD patients.[18]

Questionable concepts of '*Outside-in*' and '*inside-out*' hypotheses have raised the hen-and-egg-type question of what would be first in the pathogenesis of AD – a barrier dysfunction or a cutaneous inflammation of the Th2 type.

Other concepts included different mechanisms by defining extrinsic factors such as allergens, soaps and mechanical stress that exert their effect on the skin barrier or the immune response, and intrinsic factors such as promotor region mutations and FLG mutations that lead to AD.[19] This perception of the pathogenesis encompasses both environmental, genetic and the inflammatory process in the skin, offering a collective understanding of the pathogenesis of all different subtypes of AD, yet not a taxonomy to describe all of them.[20]

## Classification of AD subgroups

Atopic dermatitis is considered as a single disease entity; however, it should be approached in a more differentiated way.[21] The disease may be categorized according to its clinical phenotype, its endophenotype or genophenotype. Stratification according to the clinical phenotype can be achieved on the basis of clinical severity, as measured by the EASI or the SCORAD. The overall disease severity should be assessed by a composite score such as the SCORAD and not signs-only score such as the EASI.[22] Clinical severity can be defined as either mild (SCORAD 0–25), moderate (SCORAD 25–50) or severe (SCORAD >50). These categories correspond to specific cut-offs in the severity score. Based on the age of onset, it is possible to distinguish early onset (between 2 and 6 years), childhood onset (between 6 and 12 years), adolescent onset (between 12 and 18 years), adult onset (between 18 and 60 years) and very late onset (>60 years).[23]

In addition to the clinical phenotype, biomarkers are now considered fundamental tools to stratify highly complex diseases into subgroups. A biomarker is defined by the World Health

Organization as 'any substance, structure or process that can be measured in the body or its products and influences or predicts the incidence of outcome of disease or disease'. In a recent study,[24] serum levels of thymic stromal lymphopoietin (TSLP), IL-31 and IL-33 were significantly elevated in AD patients compared with controls. In patients with AD, both IL-31 and IL-33 serum levels were higher in children than in adults. Although none of those biomarkers was an indicator of disease severity, both showed robustness against other atopic diseases. Thijs *et al.*[25] identified four possible AD patient clusters based on their clinical phenotypes such as erythema and lichenification, severity and pruritus, and serological measurements of more than 140 different soluble substances. The identification of these endotypes could enable more tailored prevention and therapeutic strategies for AD in the future.

## Inflammation present in lesional skin of AD

The changes in the inflamed skin of AD are abundant. When describing these inflammatory changes, there are typically two different types of lesions distinguished: acute lesions and chronic lesions. In the beginning, there is an increased influx of lymphocytes mainly of the Th2 type, which produce IL-4, IL-5 and IL-10. However, up to a certain degree, there is also an influx of Th22 cell producing IL-22 and even to a lesser degree Th17 cells producing IL-17.[26–30] Furthermore, there is an increased expression of high-affinity IgE receptors on the Langerhans cells (LC), the inflammatory dendritic epidermal cells (IDEC) and the eosinophils.[31] Lesional skin of patients with AD harbours significant numbers of LC and IDEC expressing the high-affinity receptor for IgE (FcεRI).[31,32] FcεRI-positive IDEC cannot be found in healthy skin, but have been demonstrated in other chronic inflammatory skin diseases such as psoriasis, lichen planus or contact dermatitis.[33] FcεRI+ LC contribute to the acute phase (Th2), while FcεRI+ IDEC contribute to the chronic phase (Th1) of AD. IDEC are detectable as early as 48 h after inducing AD lesions with an atopy patch test procedure in AD patients.[34]

Finally, the expression of antimicrobial peptides on the keratinocytes of the epidermis is decreased.[35–37] When the lesions become more chronic in nature, the Th17 and Th1 lymphocytes are increased in number although the amount of Th2 and Th22 cells is still high. In consequence, an increased expression of IFN-γ and TNF-β can be detected in chronic skin lesions. These changes are not only localized in the skin, but are reflected in the peripheral blood. The increased level of IL-4 increases the production of IgE due to its class switching and stimulating effect on B lymphocytes, whereas IL-5 induces eosinophil activation[24,38,39] (Fig. 1).

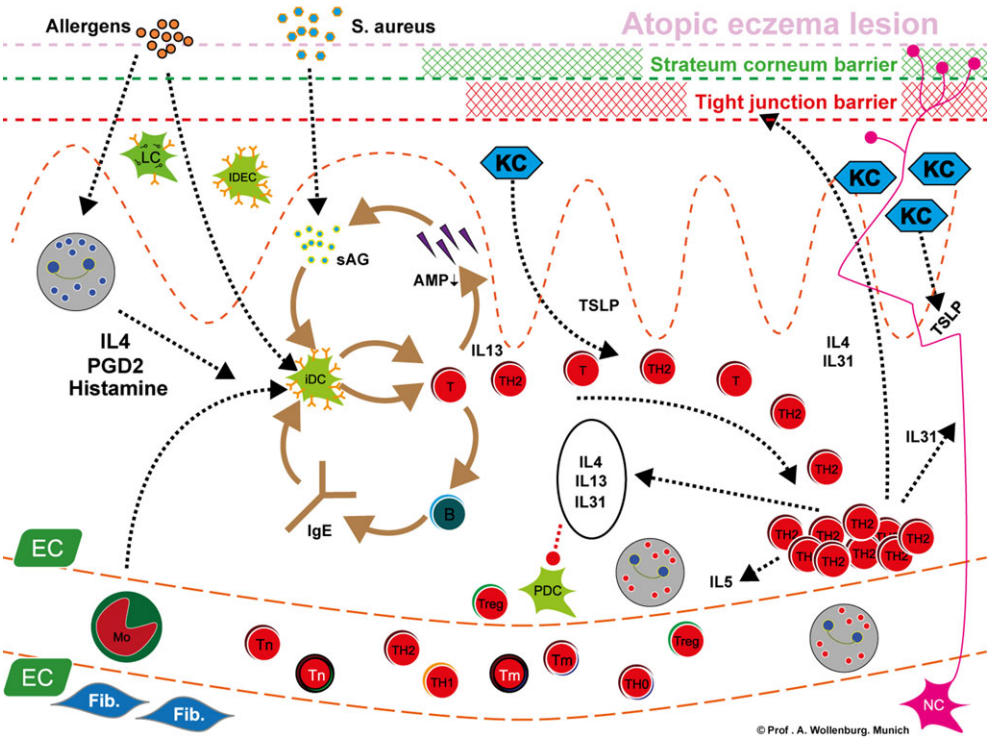


**Figure 1** Pathophysiology of atopic dermatitis.

Another cytokine which has attracted attention in the context of AD is TSLP, which is produced by keratinocytes and induces Th2 polarization in lymphocytes and maturation of LC, as well as maturation and growth of B lymphocytes. TSLP is increased both in the skin and in the peripheral circulation and is a target in one published[40] and many ongoing clinical trials on atopic disease registered on www.clinicaltrials.gov.[41]

## Microinflammation present in non-lesional skin of AD

Several studies have shown that seemingly normal skin and healthy skin of patients with AD are also 'inflamed'. Histological examination of lesional and non-lesional AD skin demonstrated a low-grade lymphocytic infiltrate and venule activation in non-lesional skin of AD.[42] Another early study showed that non-lesional skin of patients with AD harboured significantly more lymphocytes than the skin of healthy controls, although significantly less than in inflamed skin of the AD patients – as determined by stereotaxic counting methods.[43] A more recent study demonstrates similar findings of the number of lymphocytes in lesional and non-lesional skin of AD patients healthy control skin. In this study, significantly increased levels of inflammatory cytokines especially of the Th2 type were seen in non-lesional skin compared to healthy controls.[44] The same difference was demonstrated again in 2012, as the same subtypes of cytokines were detected to be increased in non-lesional AD skin compared to normal skin.[36] Finally, the density of high-affinity IgE receptors on the surface of the epidermal LC, which is an important receptor for the IgE-mediated allergen presentation, is significantly upregulated in non-lesional AD skin.[33] The skin barrier changes present in non-lesional skin, which are also important, will be discussed in a separate chapter below.

Taken together, a low level of inflammatory activity has been demonstrated by various techniques in non-lesional skin of patients with AD. This minimal inflammation is not visible to the naked eye and is also known as subclinical or infra-clinical inflammation or simply as microinflammation. It is clinically important, as it is also the basis for proactive therapy of AD.

## The skin barrier in lesional and non-lesional AD skin

Patients with AD show a skin barrier dysfunction, which is mirrored by an increased TEWL.[45] This facilitates allergen penetration into the skin, with an increased proneness to irritation and subsequent cutaneous inflammation.

The function of the stratum corneum depends on a proper differentiation of keratinocytes, pH of the skin, lipid composition and production, as well as enzyme constituents[19] and composition of the skin microbiome.[46]

A key structural protein in the skin barrier function is filaggrin, a protein encoded by the FLG-gene, which is located on chromosome 1 in epidermal maturation complex. Filaggrin is produced as prefilaggrin, a preprotein with 8–12 repeats of filaggrin. Once activated by proteolytic cleavage, filaggrin binds to the intracellular keratin intermediate filaments, thus providing a tight network of intracellular keratin, a vital part of the stratum corneum.[47] The clinical role of filaggrin in AD was demonstrated in 2006,[48] in which a significant over-representation of patients heterozygous for mutations in FLG was found in an Irish and Danish birth cohort. These findings have been confirmed in many studies all around the world, and the number of clinically significant null mutations described is now well over 40. However, only 20–40% of all patients with AD have an FLG mutation, whereas all patients with AD have a decreased skin barrier function. Inflammation decreases the expression of the filaggrin protein either through suppression of filaggrin expression itself[49] or through inhibition of the maturation pathway of filaggrin, e.g. by inhibition of caspase 14 expression.[50] Thus, both the acute and chronic inflamed skin lesions inhibit the skin barrier function through inhibition of filaggrin, but the microinflammation in non-lesional AD skin may affect the skin barrier function in a detrimental way.[51] A lack of important intercellular stratum corneum lipids and an inadequate ratio between these lipid compounds (cholesterol, essential fatty acids and ceramides) as well as FLG defects enhance TEWL leading to epidermal microfissuring, which may also cause direct exposure of LC dendrites as well as nerve endings to the environment.[3]

In conclusion, poor epidermal barrier function is not only dependent on FLG mutations. Most patients with AD do not have any FLG mutation, and up to 60% of mutation carriers will not develop AD, which means that FLG mutations are neither necessary nor sufficient to cause AD. Other genetics factors might impair various aspects of barrier function, as well as environmental exposures such as soaps, detergents, exogenous proteases and repetitive scratching. It is commonly accepted that skin barrier defects have a major role in allergic sensitization.[52]

## Reactive and proactive treatment of AD

Management strategies of AD are complex, which is due to the chronic and relapsing nature of this disease, must consider the clinical and pathogenic variability of the disease and target flare prevention. Different therapies are suggested according to the degree of severity and many other considerations, especially if systemic therapy is considered (Fig. 2). A major distinction must be made between 'reactive treatment' and 'proactive treatment' approach.[9]

The reactive treatment is well established since decades and is performed using symptomatic anti-inflammatory therapy consisting of TCS or TCI for visible lesions on an 'as needed' basis, together with a daily application of emollients with or without antibacterial ingredients.[13,14] This reactive approach must be tailored to every patient.

The proactive approach targets the subclinical inflammation. It starts with an intensive topical anti-inflammatory therapy

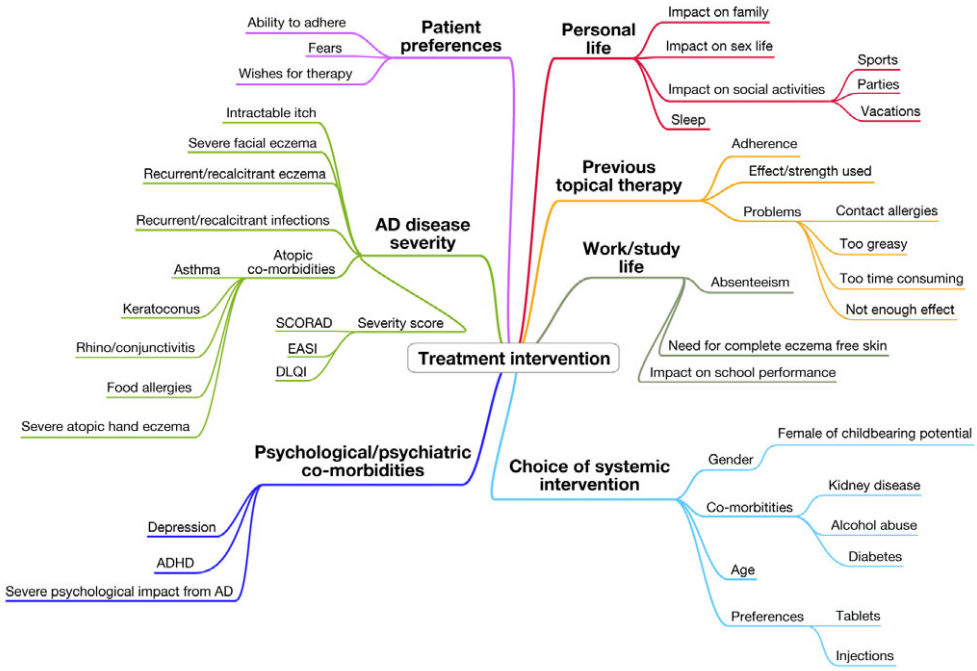


**Figure 2** Mind Map of considerations before choosing a therapeutic regimen in atopic dermatitis.

until all lesions have mostly cleared, followed by a long-term, low-dose intermittent application of anti-inflammatory therapy to the previously affected skin together with daily application of emollients to unaffected areas.[9] Data from different trials with TCI and TCS have confirmed a significant improvement of skin lesions, a significant reduction in flares and improved quality of life for the patients. From a patient perspective, the disease no longer controls the patient's actions, but the patient himself is actively controlling the disease.[53] Another important aspect is the scheduling of the control visits: in proactive therapy, these are planned beforehand and time contingent, whereas control visits in a reactive treatment concept are taking place symptom contingent following acute relapses.[53]

The general concept of an immunobiologically based, time contingent, low-dose anti-inflammatory therapy with behavioural therapeutic background was presented by Wollenberg *et al.*[53] in 2007 at the biannual meeting of the German Dermatological Society (DDG) in Dresden and has been published in detail as 'proactive treatment' concept in 2009. The term 'proactive treatment' had been deliberately chosen by the authors in accordance with the writings of Viktor Emil Frankl[54] and the existing nomenclature of a physician-initiated scheduling of patient contacts in the behavioural therapeutic context.[53]

A number of randomized, controlled clinical trials with a proactive trial design have been performed with fluticasone propionate and methylprednisolone aceponate for up to 20 weeks, as well as with tacrolimus ointment for up to 52 weeks duration. These trial data have been extensively reviewed in 2012.[8]

## Emollients in the treatment and prevention of AD

As AD is associated with skin barrier anomalies which cause an increased proneness to irritation and subsequent cutaneous inflammation, barrier improving topical agents are an important treatment and prevention option. The maintenance of the patient's skin barrier may be achieved in a variety of ways, such as the use of emollients and moisturisers and more appropriate bathing habits—namely using tepid versus hot water and mild versus strong soaps.[13,14,55]

Emollients are responsible for improvement of xerosis and pruritus, improvement of skin hydration, reduction in skin permeability (TEWL), reduction in frequency and intensity of flare-ups and reduction in corticosteroid use.[56–58]

A randomized clinical study[58] in which neonates in high risk of developing AD were randomized to either full body emollient therapy at once per day starting from 3 weeks of age, or no emollient therapy, showed a statistically significant protective effect with the use of daily emollient on the cumulative incidence of AD with a relative risk reduction in 50%. Another randomized clinical trial[59] showed that daily application of moisturizer during the first 32 weeks of life reduced the relative risk of AD/eczema by 32% in treated infants compared to controls. Longer trials are currently

 

performed to investigate the value of prolonged treatment and later efficacy endpoints.

## Atopic dermatitis in infancy

Atopic dermatitis is the most common chronic inflammatory skin disease in infancy, as up to 20% of the Western population is affected. The disease may manifest itself during the first 6 months of life and is associated with a significant impairment of the quality of life of the patient and the whole family.[60] Age-specific aspects of AD in infants have been reviewed.[60]

### Barrier function and structure in children

Infants show an impaired epidermal barrier structure and function due to different factors: the epidermis is thinner, and there are less natural moisturizing factor (NMF) and surface lipids present.[61] In contrast, the pH and proliferation rate are higher, and there is more desquamation. The higher ratio of body surface to bodyweight puts children at risk for systemic drug effects. All of these factors should be considered in managing AD in this age group regarding systemic effects of topically applied drugs.[62]

### Clinical aspects of infantile AD

Clinically there are also differences in AD in infants compared with older children and adults with regard (Figs 3 and 4). These are also the reasons for considering other differential diagnoses in this special age group (Figs 5 and 6).

The predilection sites of infant AD are the head and the face, which are firstly affected followed by the extensor of the extremities.[60] It is striking that the diaper area is usually spared, which is related to the high hydration under the occlusive condition of the diaper. This is an excellent clinical finding to differentiate the infantile AD from other diagnoses such as psoriasis and seborrhoeic eczema. Many infants show very exudative lesions (erythema, papules, pustules, crusts and oozing). In this early age, the nummular form of AD, affecting the extremities and the trunk, is common, while the typical lichenification is missing.

Infantile AD may present as an erythroderma, which requires a detailed investigation of possible differential diagnoses. In addition to other eczema disorders, immunodeficiency syndromes should be considered, especially if the infants show an increased tendency to infection and failure to thrive.[63–65] Diverse differential diagnoses and missing standardized diagnostic criteria for this age group explain the difficulties to make the definite diagnosis of AD in infancy. The UK working party criteria, as well as the criteria of Hanifin & Rajka, are not appropriate in infants.[65,66] Therefore, age-specific criteria have been suggested recently by Taieb & Boralevi, which have been partly adapted from the UK working party criteria.[67,68]

### Role of allergens in infantile AD

Most infants with mild and moderate AD are intrinsic, and not associated with respiratory allergic disease, show normal serum

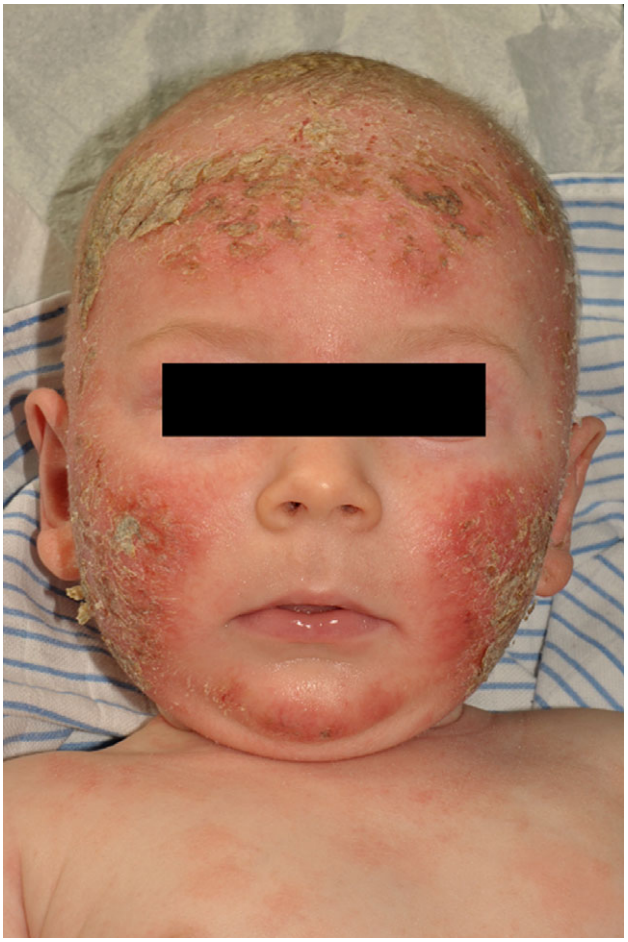

**Figure 3** Infantile atopic dermatitis. Redness and haemorrhagic crusts of the scalp and cheeks, sparing the nose and the perioral region.

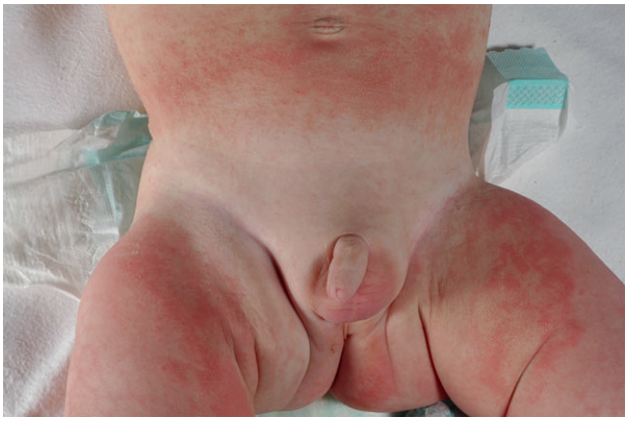

**Figure 4** Infantile atopic dermatitis. The eczematous lesions are sparing the diaper area.

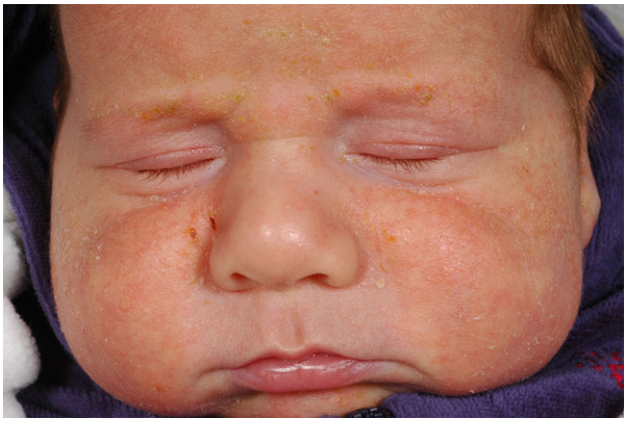

**Figure 5** Differential diagnosis of atopic dermatitis: seborrhoeic dermatitis, with yellow scales at the face including the eyebrows.

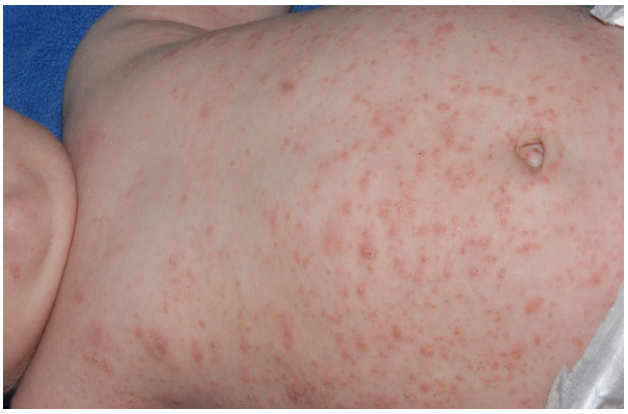

**Figure 6** Differential diagnosis of atopic dermatitis: generalized scabies, showing an eczematous rash with numerous red papules and pustules.

IgE levels and lack a sensitization to environmental allergens.[69] Early onset of AD predisposes to the extrinsic form of AD. A recent microarray study performed in children with AD found the highest total number of allergen-specific sensitizations in children with severe AD and not mild or moderate disease.[70] Early AD has other relevant trigger factors than AD seen in later childhood and adulthood. They are more common in early childhood and refer to other allergens than in later life. While pollen-associated food allergens are of relevance in later childhood and adulthood, cow's milk and eggs are most important in early childhood.[65] Because food allergy in early childhood is often of transient nature, it is important to check the clinical relevance again later in life. Low levels of milk-specific IgE, low skin prick test weal size and mild forms of AD predict the resolution of food allergy.[71] Half of the infants with milk allergy may resolve after 3 years.[71]

### Therapy of infantile AD

Off-label drug use in children is a general practice, mainly in infancy. Different dose and frequency of the drug than recommended, other disease indications than intended, age groups which are not licensed for use and different routes of administration are only a few examples for the off-label use in this age group.[60,72]

Topical treatment for infants with AD must consider the high ratio of body surface to bodyweight, which determines the absorption of drugs and substances of emollients. The usual anti-inflammatory topical drugs, i.e. corticosteroids and calcineurin inhibitors, are safe and well tolerated even in infancy, if application guidelines are followed. Both reactive and proactive therapy are safe, effective and suitable, but the proactive approach will reduce the need of anti-inflammatory drugs, lead to fewer relapses and less fear of side-effects.[3,73] These considerations are also part of the education programmes for patients and parents of affected children,[74] as they are in adults.[75]

Some children with severe AD are refractory to conventional therapy. At present, there is no consistent approach to systemic therapy in these cases. The European treatment of severe atopic eczema in children taskforce (TREAT) found that ciclosporin (43%), corticosteroids (30.7%) and azathioprine (21.7%) are most frequently used for severe infantile AD at present.[76]

## Rhealba oat plantlet extract – History and introduction

Oat plantlet extract is derived from aerial parts of oat and has nothing to do with oatmeal or oat growing proteins. The Rhealba oat plantlets variety has been selected from hundreds of different varieties and is grown in strictly controlled, Good Agricultural Practice (GAP) quasi-pharmaceutical conditions following the principles of organic agriculture in the south-west of France. The extract is obtained using a specific process, allowing the extraction of high levels of active principles, such as flavonoids and saponins, to be finally free of its proteins to minimize the risk of allergic sensitization or reaction.

The isolation and purification of the active fractions of the Rhealba plantlet extract, which contained flavonoids and saponins, and demonstration of the lack of sensitizing proteins have been achieved in 2009 by Pierre Fabre Dermo-Cosmetics, Dermatological Laboratoire A-DERMA (Pierre Fabre Dermo-Cosmétique, Les Cauquillous, 81100 Lavaur, France). The invention to produce an extract of the aerial part of Rhealba oat (excluding grains), and the description of the method how to obtain a protein-free oat plantlet extract, is protected by three international patents (WO2010/054879A2, WO2010/054878 and FR2938439).

The aerial, extracted part of the Rhealba preparation contains flavonoids (polyphenols) and saponins (polar molecules).[77] It has been shown that Rhealba extract has a repairing effect on the disrupted epidermal barrier. This barrier repairing efficacy is

mediated by stimulating keratinocyte differentiation and increasing filaggrin expression, as well as by activating the synthesis and secretion of the epidermal lipids (ceramides, cholesterol and fatty acids).[77]

Flavonoids have an anti-inflammatory efficacy.[78] They inhibit a large variety of enzymes involved in the cellular activation process,[77] such as phospholipase A2 (PLA2) and cyclooxygenase-2 (COX-2), which are involved in the metabolism of arachidonic acid and the cellular inflammatory response (Fig. 7).

Furthermore, saponins exert an immunomodulating efficacy by reducing the release of prostaglandin I2 (PGI-2) and IL-2 in activated T lymphocytes and by reducing the expression of MHC-II and the production of the TH2 cytokines IL-13 and IL-4 in peripheral blood mononuclear cells (PBMC).[15]

In 2017, the anti-inflammatory action of the Rhealba extract-based emollient in AD was improved by addition of BioVect, a naturally sourced enhancer to the active compounds made up of glycolipids and a combination of three biomimetic molecules: glycerol (a humectant), capric/caprylic triglycerides (a natural oily emollient) and cetearyl glucoside (a natural emulsifier; INCI International Nomenclature of Cosmetic Ingredients registered formulation). Thanks to its glycolipid properties, BioVect has a very strong bio-affinity for the hydrophilic molecules of the Rhealba extract, as well as for the hydrophobic molecules of the epidermal lipid layer.

The anti-inflammatory efficacy of the Rhealba extract-based emollient with BioVect technology on reduction in prostaglandin PGI2 (PG6K) is about 30% more powerful *in vitro* compared to the previous formulation (Pierre Fabre study WO 2015/014949A2, data on file).

## Biochemical characterization of the protein-free Rhealba oat plantlet extract

Current understanding of the risk factors for cutaneous sensitization has led to a call for emollients and topical leave-on cosmetics for patients with AD to be essentially free of potentially sensitizing protein allergens.[3] Therefore, a series of experiments were performed to formally prove that the Rhealba extract is indeed protein-free, thanks to its specific extraction process.

The protein content of the Rhealba extract during the different purification steps has been visualized by SDS-PAGE electrophoresis (Fig. 8) and confirmed the absence of a Coomassie Blue band at the Rhealba extract after the purification process. The protein-detection limit of the SDS-PAGE assay was determined at 10 ppm in the Rhealba oat plantlet extract.

In daily routine, this method of electrophoresis is used to verify that each industrial batch of Rhealba extract produced is

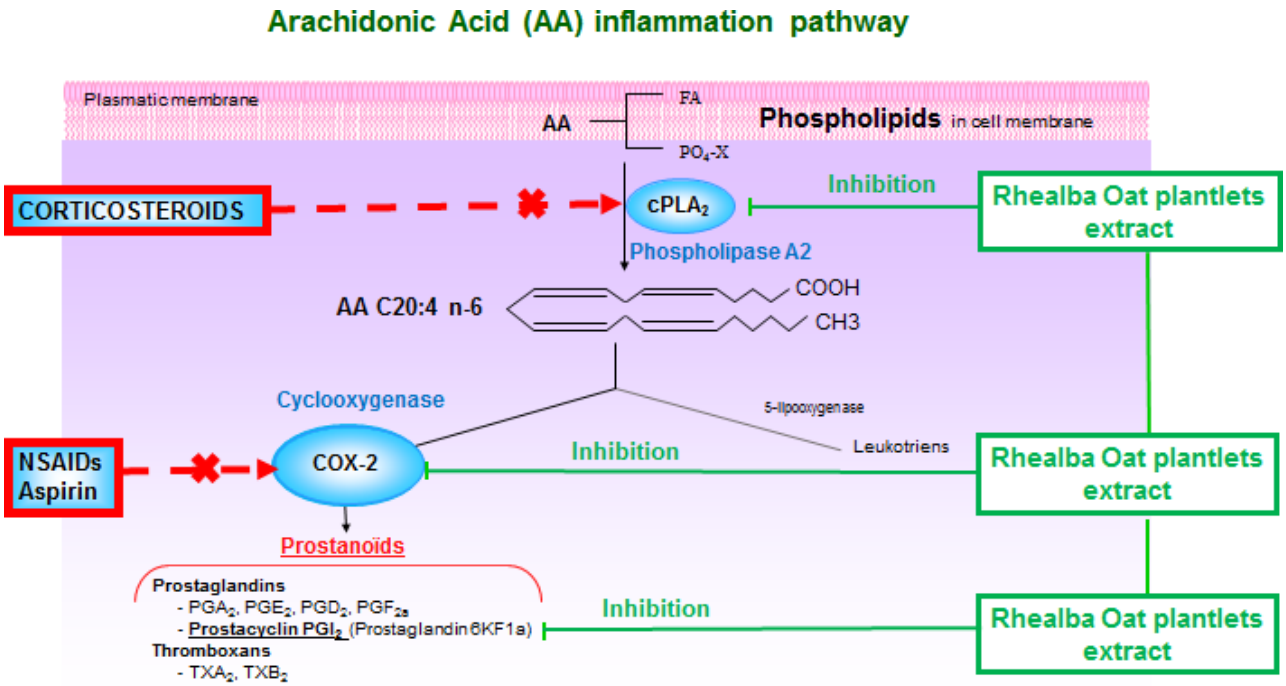


**Figure 7** Arachidonic acid inflammation pathway. Inhibition of target enzymes by corticosteroids, NSAIDs, aspirin and Rhealba oat plantlets extract.

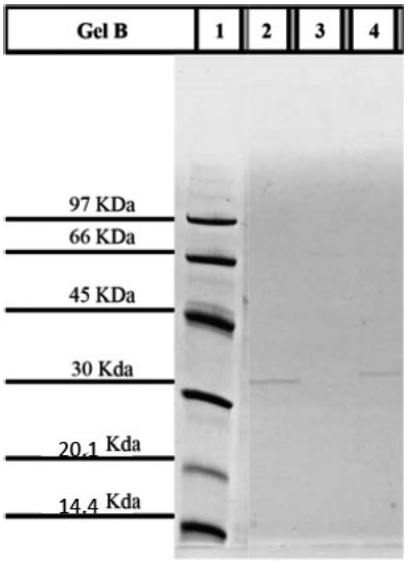


**Figure 8** Coomassie-stained SDS-PAGE electrophoresis and demonstration of the lack of proteins in Rhealba oat plantlets extract. SDS-PAGE showed the absence of a Coomassie Blue band for the Rhealba oat plantlets extract (lane 3). Description of lanes: lane 1: molecular weight marker; protein sizes are indicated on the left of the gels, lane 2: standard protein (carbonic anhydrase, 30 ng) – positive control, lane 3: Rhealba oat plantlet extract alone, free of proteins and lane 4: protein-enriched control (carbonic anhydrase, 30 ng) plus Rhealba oat plantlets extract.

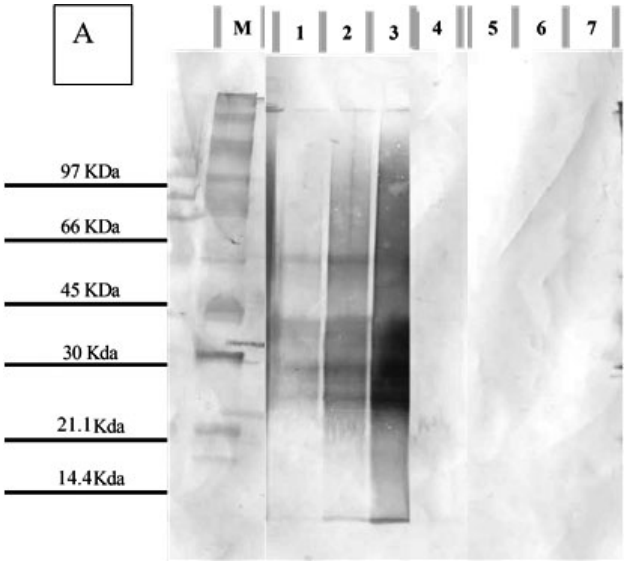


**Figure 9** Western Blot analysis of Rhealba oat plantlet extract, seed proteins (SP) and plantlets proteins (PP) with anti-SP antibodies (A). No immunological cross-reaction was detected between SP and plantlet proteins. M: molecular weight marker, protein sizes are indicated on the left of the gel. Lanes 1–3: SP (respectively 0.07, 0.27 and 1.35 μg protein equivalent). Lane 4: Rhealba oat plantlet extract (500 μg). Lanes 5–7: PP (respectively 0.04, 0.19 and 0.93 μg protein equivalent).

without detectable proteins at a detection threshold of 10 ppm. In commercialized products, the detection threshold corresponds to less than 0.05 ppm (0.05 μg/g) in hygiene products such as foaming gel for bath and less than 0.025 ppm (0.025 μg/g) for topical dermatological products such as lotion, cream or balm. Considering either the normal or the maximal daily dose of a cream, the dose applied is far below the sensitization threshold described for the most allergenic foods such as peanut proteins. In other words, the sensitization threshold for groundnut proteins applied by oral route is 60 times higher than the amount present in products containing Rhealba extract.

Moreover, Western blotting and ELISA would fail to detect oat seed-specific proteins in the Rhealba plantlet extract (Fig. 9). Using specific anti-seed protein antibodies, there was no immunological cross-reaction detected between seed proteins (SP) and plantlet proteins (PP). In addition, no PP were detected in the Rhealba oat plantlet extract using Western blot (Fig. 9). Glutelin and gliadin proteins found in some cereals and better known as 'gluten' were also not detected in the Rhealba extract using an ELISA with omega wheat and Mendez R5 antigliadin antibodies.

In summary, these results confirmed the absence of a cross-reaction between gluten proteins, oat SP and the plantlet extract proteins and furthermore demonstrated that the Rhealba extract does not contain proteins detectable by ELISA and Western blot methods. Thus, there is no molecular basis for an immunological cross-reaction with other types of cereals.

## *In vitro* studies demonstrating the efficacy of Rhealba oat plantlet extract

The inhibitory action of the Rhealba extract on pro-inflammatory cytokines has been investigated by a number of *in vitro* studies, all demonstrating an anti-inflammatory effect of the compound.[15,77] The activity of the Rhealba extract on the production of IL-2 and other pro-inflammatory cytokines during the acute phase was evaluated *in vitro*. Calcium ionophore-stimulated human PBMC were pre-incubated with Rhealba extract at 3, 10 and 30 μg/mL or with purified active compounds at 1, 3 and 10 μg/mL for 2 h. The secreted cytokines, namely IL-4, IL-5 and IL-13, were measured using a cytometric bead array (CBA). The rate of IL-2 producing T cells was measured using four colour flow cytometry and quadruple marking with anti-CD4, anti-IL-2, anti-CD3 and anti-CD69 antibodies. The Rhealba extract induced a dose-dependent inhibition of Th1 and Th2 pro-inflammatory cytokine secretion, with a more significant effect on IL-2 and IL-13 production. At a concentration of 3 μg/mL, the Rhealba extract exerted a strong inhibitory effect on the IL-4

and IL-13 production, as well as a significant, dose-dependent immunomodulating action on IL-2 expressing CD4+ T cells.[15]

A second series of experiments demonstrated a significant inhibitory effect of a Rhealba extract-based emollient on TSLP production by stimulated human keratinocytes of reconstructed human epidermis. Once stimulated, there was a robust TSLP production by keratinocytes. This inhibition of TSLP was statistically significant ($P < 0.05$) compared to a *vitreoscilla filiformis*-based emollient.[16] The Rhealba extract-based emollient inhibited the TSLP release from keratinocytes *in vitro* by 44%, compared to a hydrocortisone-induced inhibition of 68% ($P < 0.05$; Study WO 2015/014949A2, Pierre Fabre, data on file; Fig. 10).

A third series of experiments demonstrated an inhibitory action of the Rhealba extract on PLA2 and COX-2 enzymes *in vitro* by measuring the PGE2 production with an ELISA (Fig. 11).[77] A transcriptomic study was performed in a small number of adult patients to further elucidate the efficacy and mode of action of the Rhealba extract-based emollient in patients with AD treated half-sided once daily. The primary objective of the study was to evaluate the inflammatory signature of the dry or lichenized chronic AD lesion by transcriptomic analysis at D1 and D30. Each patient treated the lesion on one forearm only, whereas one contralateral forearm lesion was not treated. Non-lesional skin of the buttock served as control. The heat map of gene expression analysis showed a shift of the molecular profile of the lesional skin towards the non-lesional signature during treatment with the Rhealba extract-based emollient. Expression of cell proliferation genes (CDK1), stress response genes (IL-8 and CXCL1) and genes involved in antigen presentation were shifted towards a non-lesional signature (Fig. 12). The gene expression of PLA2 (Fig. 13) and S100As (S100A2 and S100A7) was down-regulated in lesional skin treated by Rhealba oat plantlets extract-based emollient (Pierre Fabre data on file. No ID RCB: 2015-A01255-44).

## Clinical studies investigating the efficacy of a Rhealba extract-based emollient in AD patients

The clinical efficacy of a Rhealba extract-based emollient has been investigated in all age groups from newborns with a risk for development of AD up to adult AD patients.

### Clinical study data on neonates

Fifty-three healthy full-term neonates at risk for AD were included in a clinical study for AD prevention with a Rhealba extract-based emollient. As the value of emollient use from birth for prevention of AD manifestation has already been shown in two different studies,[58,59] the objective of the study

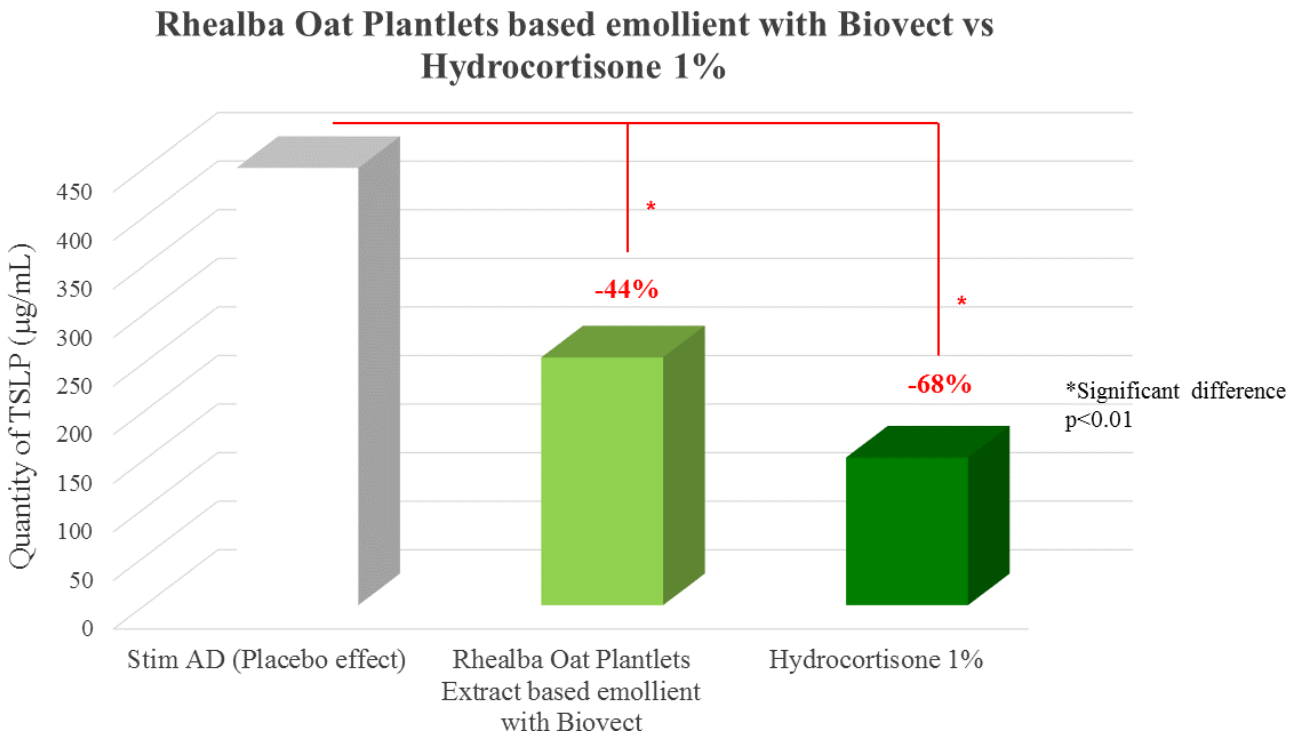


**Figure 10** Anti-inflammatory efficacy of Rhealba oat plantlets extract-based emollient with Biovect vs hydrocortisone 1%. *In vitro* study in cutaneous model which mimics the inflammation in Atopic dermatitis flare. Evaluation in three donors, after one application Rhealba oat plantlets extract-based emollient with Biovect vs hydrocortisone 1%. *$P < 0.01$.

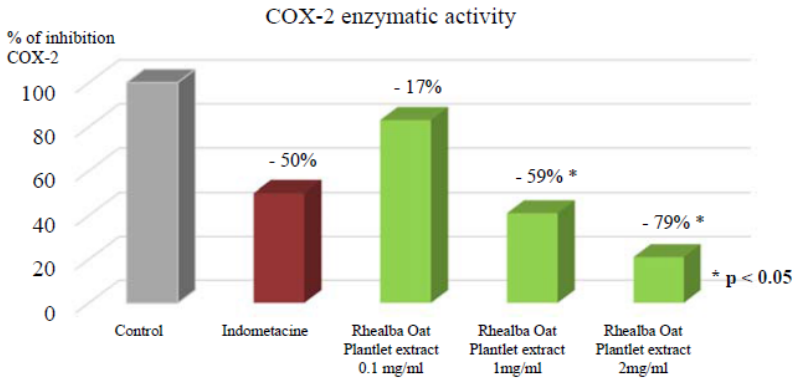


**Figure 11** *In vitro* study showing inhibition of cyclooxygenase 2 (ICOX-2) enzyme by NSAID (indometacin) and Rhealba oat plantlets extract. Each bar indicates the mean ± SD of three experiments. Evaluations of various dosages of Rhealba oat plantlets extract and unique dosage of indometacin. *$P < 0.05$.

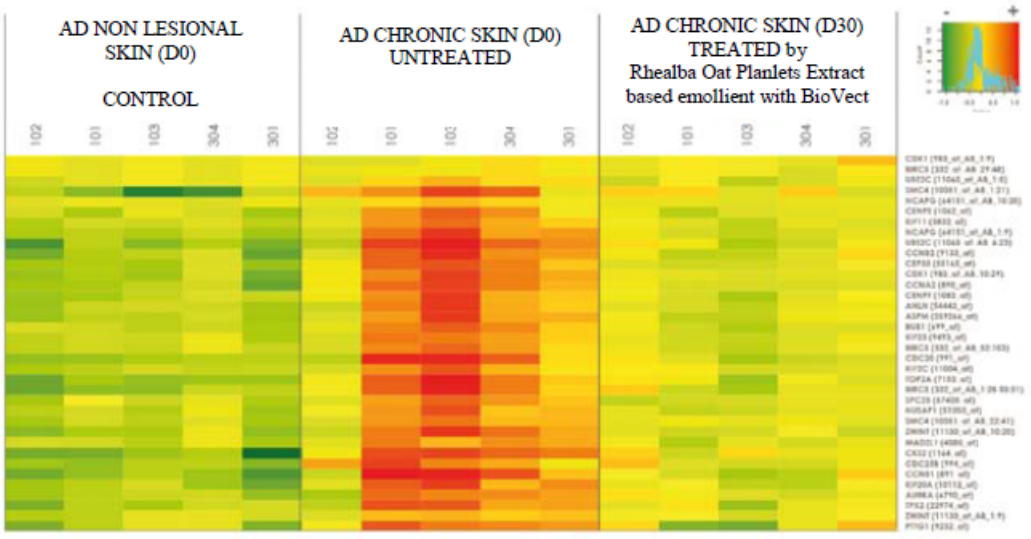


**Figure 12** Transcriptomic analysis of five adult atopic dermatitis (AD) patients. Evaluation at D0 and D30. The heat map describes the expression of genes in patients with AD at D0 in non-lesional AD skin and in chronic AD skin and at D30 after treatment with Rhealba oat plantlets extract-based emollient with Biovect.

with neonates was to evaluate the global and local tolerance of three different textures (balm, cream and lotion) after 21 days of single daily application in this age group. No adverse event related to the products was reported during the study. The tolerability of the three different Rhealba extract-based emollients with BioVect in newborns was judged as very good by investigators (Pierre Fabre data on file. Clinical Study RV3424I201650).

### Clinical study data on infants

A Rhealba extract-based emollient was administrated in an open-label study involving 108 children aged 6 months to 6 years, who were diagnosed with moderate AD.[77] After an initial treatment phase with corticosteroids for 2 weeks, a Rhealba extract-based emollient was administrated once daily to all children for 3 months. During this 'maintenance period', the duration and number of flares were reduced significantly

 

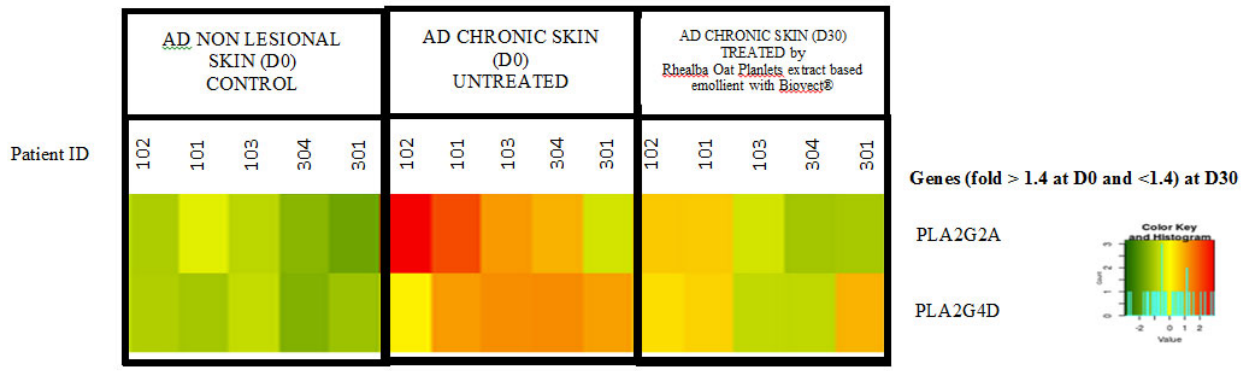


**Figure 13** Transcriptomic analysis of five adult atopic dermatitis (AD) patients, showing inhibition of phospholipase 2 (PLA2) gene by Rhealba oat plantlets extract-based emollient with Biovect. Evaluation at D0 and D30. The heat map describes the expression of the PLA2 gene in patients with AD at D0 in non-lesional AD skin and in chronic AD skin and at D30 after treatment with Rhealba oat plantlets extract-based emollient with Biovect.

($P < 0.0001$). The corticosteroid use was reduced by half ($P < 0.0001$), and the overall severity of disease evaluated by SCORAD and PO-SCORAD improved significantly ($P < 0.0001$).[79] The tolerability of the Rhealba extract-based emollient was very good.[77]

### Clinical study data on children and adults

An open-label clinical study was conducted in 97 AD mild patients with a SCORAD index at inclusion of 10–25, stratified by age into three groups of 32 infants 3–23 months old, 33 children 2–11 years old and 32 adults 18–45 years old. After 21 days of treatment with a Rhealba extract-based emollient containing BioVect, the disease severity decreased from mild disease with a mean SCORAD of 20 to almost cleared with a mean SCORAD of 4 ($P < 0.05$; Pierre Fabre data on file. Study Code: RV4660B 2015 247).

## Clinical studies investigating the efficacy of a Rhealba extract-based emollients in other skin diseases

A topical acne cream based on the Rhealba oat plantlet extract was clinically tested in 2014 in mild to moderate acne vulgaris patients and was effective in reduction in the inflammatory lesions such as papules and pustules (−24% at 3 weeks, $P < 0.05$), as well as the retentional lesions such as comedons (−54% at 2 weeks, $P < 0.0001$). This acne cream is well tolerated, which seems due to the hydro-compensating active compounds in the biolamellar emulsion with prolonged release. The cream reduces skin dryness, irritation and improves epidermal barrier function in the follicular stratum corneum, as we as the skin surface.[80] As the first lesions of acne may start as early as 9 years of age, a 3 months clinical trial was performed in 84 children with acne aged 9–12 years. A significant reduction ($P < 0.05$) of inflammatory lesions was seen in the treated group at week 4 and 12 compared to baseline, whereas a non-significant decrease ($P < 0.05$) of inflammatory lesions was seen in the untreated group.[16] The efficacy of the Rhealba oat plantlet extract on wound healing was evaluated in a comparative study involving 21 healthy volunteers. Re-epithelialization after Erbium-Yag-laser ablation occurred faster in a Rhealba extract-based cream-treated group compared to control.[81]

The effect of the Rhealba oat plantlets extract on chronic pruritus, defined as itch persisting for more than 6 weeks, was evaluated in a randomized crossover study in elderly patients aged 60 years and above. The Rhealba oat plantlet extract-based emollient provided better relief of pruritus, as measured by VAS ($P < 0.0001$) and the 5-D itch scale ($P = 0.0042$). Sleep and xerosis ($P < 0.001$) were also improved in this study.[82]

## Conclusion

Atopic dermatitis is the most common skin disease encountered in daily practice by dermatologists and paediatricians. It is a clinically defined disease, characterized by complex disease mechanisms both from a clinical and a pathophysiologic point of view. This complexity of the disease is reflected by different clinical phenotypes, diagnostic criteria and possible treatments.

Dysfunction of the skin barrier is witnessed by an increased TEWL in lesional and non-lesional AD skin. This facilitates allergen penetration into the skin, with an increased proneness to irritation and subsequent cutaneous inflammation.

The inflammatory reaction of lesional AD skin is relatively well characterized. However, non-lesional skin of patients with AD shows histological signs of a subclinical inflammation and a pro-inflammatory cytokine milieu. This microinflammation is

present even when the disease is seemingly healed and in remission and must be taken into account regarding treatment of AD. Emollients provide a safe and effective method of skin barrier improvement, because they provide the skin with a source of exogenous lipids, thus improving its barrier function. The use of emollients is recommended for all patients with AD irrespective of overall disease severity, which may be assessed by a composite score such as the SCORAD.[83] Patients with moderate to severe AD should combine the emollients with a proactive therapy regimen of TCI or TCS. Skin areas affected by intense, active eczema in flare should receive daily anti-inflammatory therapy first before introducing emollients, because some irritation can occur, and a rapid relief of skin lesions and pruritus is most desirable.[3,16] The microinflammation persisting in seemingly healed AD lesions should be addressed by a proactive treatment approach, consisting of minimal anti-inflammatory therapy and liberal, daily use of emollients.

## Acknowledgements

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