EVALUATION OF POLYDATIN EFFECTIVENESS IN ATOPIC DERMATITIS IN ADULTs

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ABSTRACT

Objective: The aim of study is to evaluate the effectiveness of polydatin both for topical use only and in combination with systemic therapy.

Methods: 76 adult patients with facial atopic dermatitis, also with lesions on the trunk and limbs. In 38 of them (average age 29.47 ± 1.48 years - range 18 to 40, 22 males and 16 females) a topical cream and a cleanser, both polydatin based were prescribed, while in 38 others (average age 28.05 ± 1.44 years - range 18 to 38, 24 males and 14 females) an oral supplement containing 40 mg polydatin was added.

Results: The patients showed a reduction of variable degree of lesions and subjective symptoms of atopic dermatitis, such as itching, erythema, xerosis, lichenification of the skin and eczematous lesions.

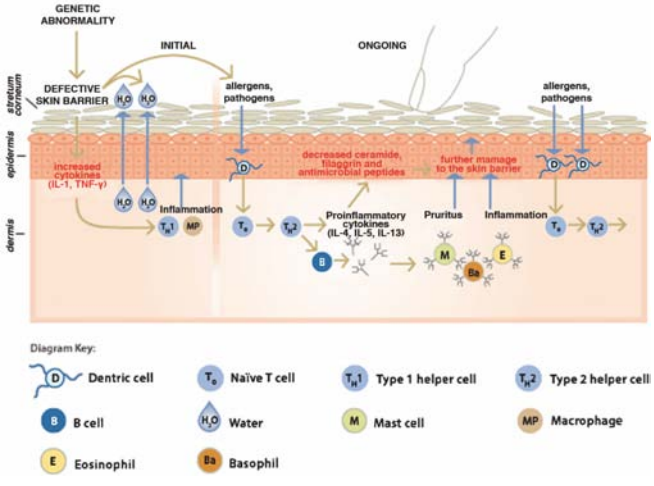
Conclusion: The use of topical cream and detergent associated with oral administration of polydatin tablets restores the function of the skin barrier, counteracts the action of irritants or allergens, reduces the local inflammatory response, and eliminates the itching and scratching, thus blocking the "rash – itch – scratch" vicious cycle.

INTRODUCTION

Atopic dermatitis usually occurs in the first few months of life in subjects with a history of atopy background. It is often localized in various organs with clinical manifestations such as asthma, allergic rhinitis, food allergies, hives, hypersensitivity to many different stimuli (insect bites, contact with jellyfish, taking medication or food, the onset of infection with herpes virus or bacterial or fungal infection), setting conditions that can lead to general situations of extreme severity, such as anaphylactic shock with edema of the glottis and herpetic meningoencephalitis.

In the pathogenesis of atopic dermatitis the following factors are involved (Figure 1); **genetic factors**, such as family history, genetic predisposition, alterations in the barrier function of the skin, and **immunological factors**, such as abnormalities of the Th2 cell response (Th2 response is antibody oriented and is typical of the allergic disease). It is supported by IL-4 that activates B-lymphocytes and the production of IgE by IL-5, which recruit eosinophils in the presence of parasites, interleukin-3 and by IL-10 (which is an anti-inflammatory cytokine that blocks IL-3, IL-5, IL-12, IFN-γ and Th1 response, but is pro-inflammatory with respect to allergic processes) and by the increase of IgE.

FIGURE 1. DIAGRAM OF THE OUTSIDE-INSIDE VIEW OF ATOPIC DERMATITIS



Clinic

Atopic dermatitis is localized preferentially on the face, especially the perioral and periorbital region, neck, ears, and, in general, in the folds and flexures regions.

In its early stages, the dermatosis present exudative lesions very similar to those of acute eczema, and, over time, the skin is thickened and lichenified with frequent hyperkeratosis.

The typical symptom of the disease is itching, which is usually moderate to severe, often unbearable, with the presence of lesions of varying degrees, which result from scratching.

The dermatosis usually regresses around 5-6 years of age, while frequently the symptoms affecting the respiratory system persist or increase and, at times, affect the digestive system.

In the forms that persist beyond childhood or in those that occur in adults, the most common manifestation is dry, extremely itchy, thickened and lichenified skin.

Staphylococcal super infections and allergic contact dermatitis are frequent.

Polydatin

The stilbenes are a vegetable substances of the family of fitoalexine, capable of interacting with biological structures by activating repair processes and defense mechanisms.

Polydatin is the glucoside of resveratrol, which is known for its powerful action against free radicals [1].

Compared to resveratrol, polydatin has many advantages:

- Anti-oxidant - increased resistance to enzymatic oxidation
- Transport - it penetrates the cell via an active carrier mechanism using glucose carriers
- High degree of solubility in water - due to its water solubility, polydatin is totally absorbed in the intestine

Consequently the bioavailability of polydatin is 4 - 5 times greater than that of resveratrol, with a total absence of side effects in the intestine (diarrhea) caused by high amounts of resveratrol [1,2,3,4].

A proportion of polydatin, once inside the cell, is transformed into resveratrol by the presence of glycosidase, with diffusion in various organs and systems [5].

TABLE 1. CHANGE IN SYMPTOMS IN THE TWO GROUPS DURING THE STUDY

		GROUP A				GROUP B							
ITCHING		T.0	T.1m	T.2m	T.6m	T.0	T.1m	T.2m	T.6m		global	control times	group
	Score 2	38	1	1	1	38	0	0	0	Chi-square:	63,60	58,70	4,90
	Score 1	0	20	12	11	0	10	8	6	degrees of freedom:	7	6	1
	Score 0	0	17	25	26	0	28	30	32	*p*-value:	P<0.001	P<0.001	P<0.05
	average	**2,00**	**0,58**	**0,37**	**0,34**	**2,00**	**0,26**	**0,21**	**0,16**				
Mann Whitney U test: A vs. B		*n.s.*	*P=0,008*	*n.s.*	*n.s.*								
ERYTHEMA		T.0	T.1m	T.2m	T.6m	T.0	T.1m	T.2m	T.6m		global	control times	group
	Score 2	38	1	1	1	38	0	0	0	Chi-square:	85,12	80,10	5,01
	Score 1	0	16	12	4	0	8	4	2	degrees of freedom:	7	6	1
	Score 0	0	21	25	33	0	30	34	36	*p*-value:	P<0.001	P<0.001	P<0.05
	average	**2,00**	**0,47**	**0,37**	**0,16**	**2,00**	**0,21**	**0,11**	**0,05**				
Mann Whitney U test: A vs. B		*n.s.*	*P=0,022*	*P=0,011*	*n.s.*								
XEROSIS OF THE SKIN		T.0	T.1m	T.2m	T.6m	T.0	T.1m	T.2m	T.6m		global	control times	group
	Score 2	38	1	0	0	38	0	0	0	Chi-square:	74,59	69,67	4,91
	Score 1	0	30	18	5	0	18	9	6	degrees of freedom:	7	6	1
	Score 0	0	7	20	33	0	20	29	32	*p*-value:	P<0.001	P<0.001	P<0.05
	average	**2,00**	**0,84**	**0,47**	**0,13**	**2,00**	**0,47**	**0,24**	**0,16**				
Mann Whitney U test: A vs. B		*n.s.*	*P=0,001*	*P=0,031*	*n.s.*								
SKIN LICHENIFICATION		T.0	T.1m	T.2m	T.6m	T.0	T.1m	T.2m	T.6m		global	control times	group
	Score 2	38	1	0	0	38	0	0	0	Chi-square:	75,07	71,42	3,66
	Score 1	0	35	16	9	0	25	9	7	degrees of freedom:	7	6	1
	Score 0	0	2	22	29	0	13	29	31	*p*-value:	P<0.001	P<0.001	n.s.
	average	**2,00**	**0,97**	**0,42**	**0,24**	**2,00**	**0,66**	**0,24**	**0,18**				
Mann Whitney U test: A vs. B		n.s.	P=0,001	n.s.	n.s.								
ECZEMATOUS LESIONS		T.0	T.1m	T.2m	T.6m	T.0	T.1m	T.2m	T.6m		global	control times	group
	Score 2	38	1	1	1	38	0	0	0	Chi-square:	61,86	48,89	12,97
	Score 1	0	37	30	21	0	27	13	11	degrees of freedom:	7	6	1
	Score 0	0	0	7	16	0	10	24	26	*p*-value:	P<0.001	P<0.001	P<0.001
	average	**2,00**	**1,03**	**0,84**	**0,61**	**2,00**	**0,72**	**0,36**	**0,30**				
Mann Whitney U test: A vs. B		*n.s.*	*P=0,001*	*P=0,001*	*0,008*								
SUM OF SYMPTOMS		T.0	T.1m	T.2m	T.6m	T.0	T.1m	T.2m	T.6m		global	control times	group
	Score 2	190	5	3	3	190	0	0	0	Chi-square:	593,88	554,99	38,89
	Score 1	0	138	88	50	0	88	43	32	degrees of freedom:	7	6	1
	Score 0	0	47	99	137	0	101	146	157	*p*-value:	P<0.001	P<0.001	P<0.001
	average	**10,00**	**3,89**	**2,47**	**1,47**	**10,00**	**2,32**	**1,13**	**0,84**				
Mann Whitney U test: A vs. B		*n.s.*	*P=0,001*	*P=0,001*	*n.s.*								

Polydatin for its anti-free radical activity inhibits lipid peroxidation leading to the destruction of membrane lipids and determines the formation of modified LDL (fundamental in the genesis of the atheroma), reducing the atherogenic index, with a cardioprotective action [6].
The anti-inflammatory activity is important as well: it modulates cytokines and nitric acid production, which have regulatory and pro-inflammatory properties [7,8,9,10].
Polydatin is also capable of increasing beta defensin, which normalizes the inflammatory process and boosts the immune system of the skin [11,12,13,14,15,16,17].
At the end, the antimutagenic and anticarcinogenic action goes through molecular mechanisms involving components of the cell cycle and the molecules that regulate apoptosis, both of which regulate angiogenesis and metastasis progression [18,19].

METHODS

On the basis of what emerged from the studies of researchers, we tested the efficacy of a treatment with polydatin on 76 patients with atopic dermatitis, ranging in age between 18 to 40 years, 36 males and 30 females, divided into two groups:

- **Group A** was treated with only a cream with 1.5% polydatin, in a particular formulation suitable for individuals who do not tolerate allergens (two applications per day for two months), accompanied by a detergent containing the molecule with a concentration of 0.2%.
- **Group B** was treated with the same topical preparation together with tablets of polydatin 40 mg (three per day for two months and 1 per day for four months).

In the first visit (T.0) was evaluated, along with a thorough medical history, clinical subjective and objective of atopic dermatitis, with particular reference to itching, erythema, xerosis, lichenification of the skin and eczematous lesions.
Symptoms were assessed with a semi-quantitative rating scale (0 - absent, 1 - medium grade; 2 - high grade). Both the patient and the doctor expressed the assessment of treatment efficacy (0 - totally ineffective, up to 10 - excellent efficacy).

The following laboratory tests were also prescribed, repeated before each visit and at the end of treatment:

- Blood Sugar
- BUN
- Creatinine
- Blood count with white cell
- Total and HDL cholesterol
- Triglycerides
- Fibrinogen

After one, two and six months (T.1m, T.2m, T.6m, respectively), the patients were reviewed, the clinical situation evaluated, the laboratory parameters examined, and the polydatin-based products given.

Statistical analysis

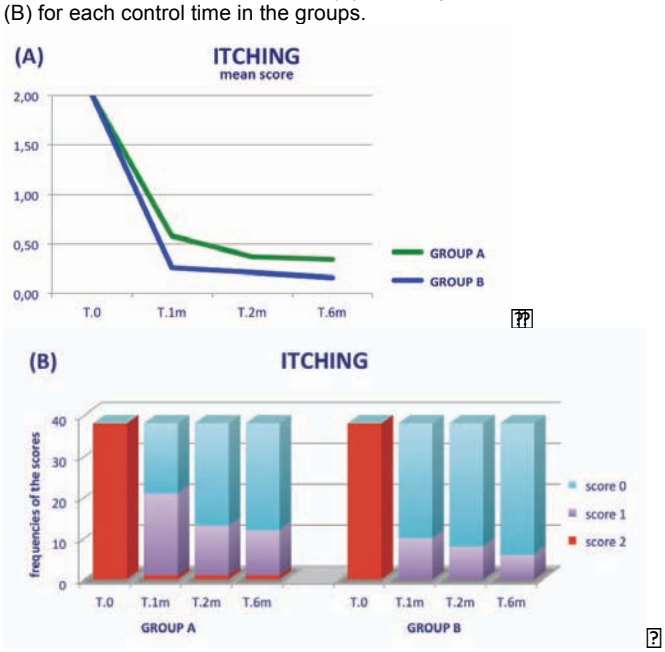
In the Table 1 for each symptom and control time, the frequencies of the scores and the mean score are reported. The significance of the difference between the control and each experimental test condition was analyzed by Mann Whitney U test and chi-square Test. P values of 0.05 were considered statistically significant.

RESULTS

The patients in the study showed a reduction of variable degree of lesions and subjective symptoms, as shown in the Table 1.

In particular:

FIGURE 2. ITCHING: mean score (A) and frequencies of the scores (B) for each control time in the groups.

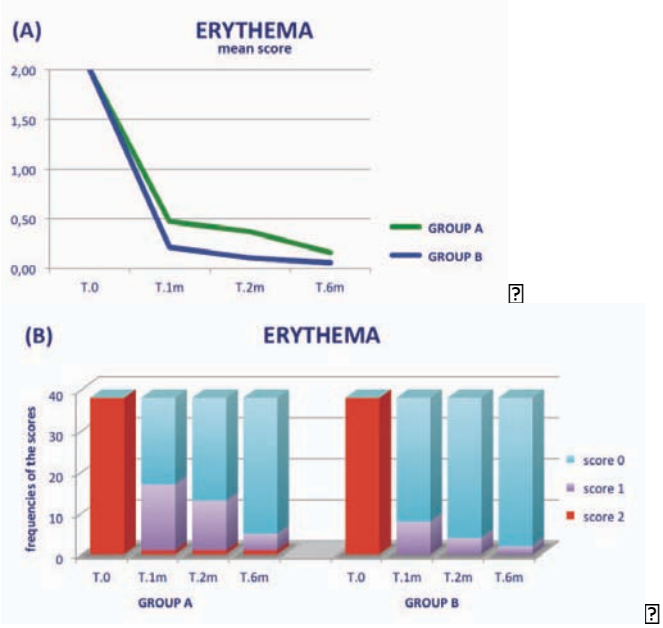


In the group of patients who only used the topical product (group A), the itching decreased after the first ten days of treatment. Only one patient continued to complain of an annoying itch for all six months of the study (Figure 2).

The efficacy of the combination therapy with topical and systemic polydatin is demonstrated by the sharp reduction of the itching in group B, the most troublesome subjective symptom of atopic dermatitis, which originates or worsens the clinical lesions typical of dermatitis.

The statistical comparison between the two groups indicates a significant difference at the 1st month (P=0.008).

FIGURE 3. ERYTHEMA: mean score (A) and frequencies of the scores (B) for each control time in the groups.

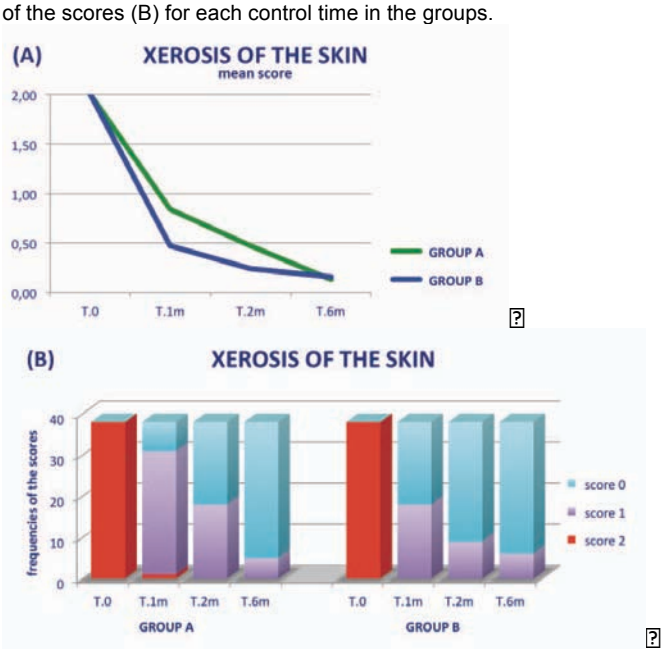


Even erythema decreased in all patients treated topically with POLIDAL cream and detergent, except that previously reported (Figure 3).

To confirm what was reported for itching, in the group B erythema declined rapidly in an extremely relevant manner.

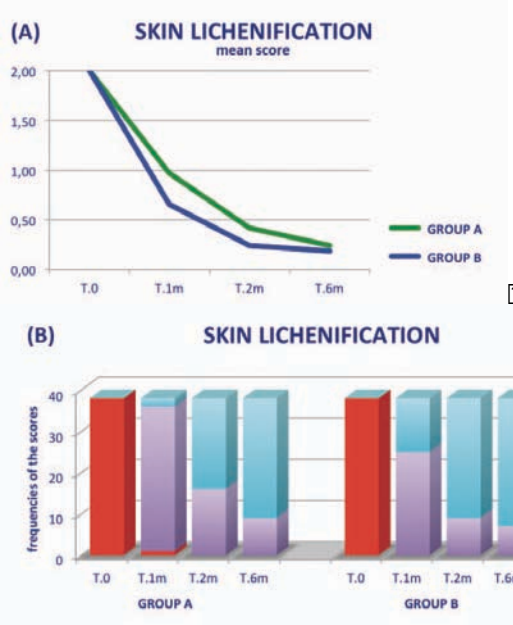
The statistical comparison between the two therapeutic models (topical POLIDAL and association of topical POLIDAL with POLIDAL tablets) indicates a significant difference at the 1st month (P=0.022) and the 2nd month (P=0.011).

FIGURE 4. XEROSIS OF THE SKIN: mean score (A) and frequencies of the scores (B) for each control time in the groups.



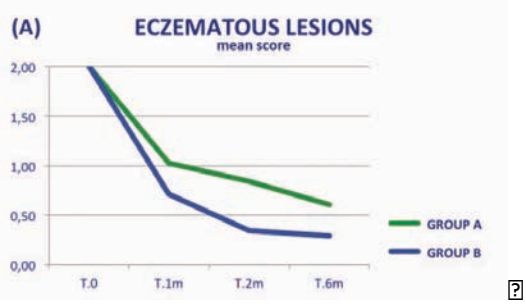
The xerosis of the skin was more or less rapidly reduced, until it almost completely disappeared in all patients who used only the topical product (Figure 4).
In group B, xerosis of the skin underwent a drastic reduction in intensity, rapidly reaching almost normal levels.
The statistical comparison between the two groups (topical POLIDAL and association of topical POLIDAL with POLIDAL tablets) indicates significant differences at the 1st month (P=0.001) and at the 2nd month (P=0.031).

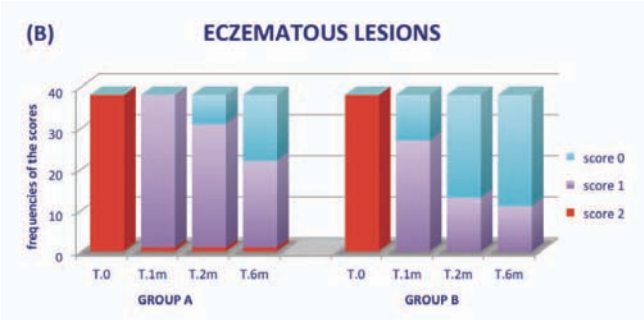
FIGURE 5. SKIN LICHENIFICATION: mean score (A) and frequencies of the scores (B) for each control time in the groups.



In all patients of group A, the texture of the skin improved, appearing much less thickened and lichenified (Figure 5).
As a result of the effectiveness of therapy on the above parameters, the skin lichenification also became normal in the group of cases treated with the association of topical POLIDAL with POLIDAL tablets.
The statistical comparison between the two therapeutic models (topical POLIDAL and the association of topical POLIDAL with POLIDAL tablets) indicates a significant difference at the 1st month (P=0.001).

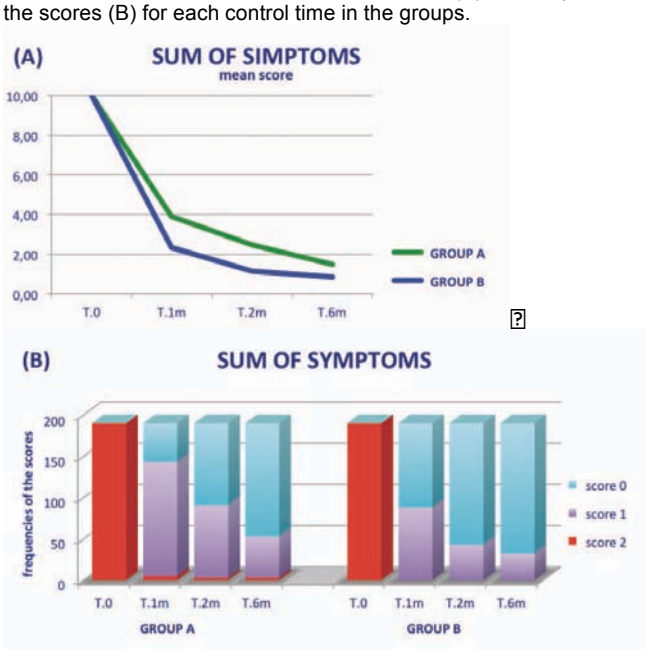
FIGURE 6. ECZEMATOUS LESION: mean score (A) and frequencies of the scores (B) for each control time in the groups.





The eczematous lesions typical of atopic dermatitis of the face in patients who have used only the topical product are generally improved (Figure 6). No obvious changes in the non-responder patient that we talked about earlier have occurred.
In group B the size of the eczematous lesions of atopic dermatitis has remarkably and readily decreased.
The statistical comparison between the two groups (topical POLIDAL and the association of topical POLIDAL with POLIDAL tablets) indicates significant differences in both 1st and 2nd month (P=0.001) and at 6th month (P=0.011).

FIGURE 7. SUM OF SYMPTOMS: mean score (A) and frequencies of the scores (B) for each control time in the groups.



All the symptoms of atopic dermatitis were more or less rapidly reduced, almost virtually disappearing in all patients who used only the topical product (Figure 7).
In group B, the sum of the symptoms suffered a drastic reduction in the intensity, normalizing very quickly.
The statistical comparison between the two groups (POLIDAL topical and the associations POLIDAL topical with POLIDAL tablets) indicates significant differences between the 1st and 2nd month (P = 0.001).

Global evaluation
Both investigators and patients have expressed in the topical POLIDAL group an agreed about the effectiveness equivalent to 7-8 in the belief that the topical polydatin is efficient for the treatment of atopic

facial dermatitis in adults, but that the integration with the same molecule systemically is necessary to optimize and extend over time the result obtained.
Investigators have expressed an overall opinion on the combined therapy with topical and general polydatin equal to 9, and are convinced of the efficacy of combining together the two modes of administration.
All patients in group B, who underwent the association of topical POLIDAL with POLIDAL tablets, have shared the opinion of the physician, rating the therapy a 9, which they were subjected to.
All patients treated with polydatin showed no alteration of laboratory parameters, which were monitored periodically during the trial period, or side effects.

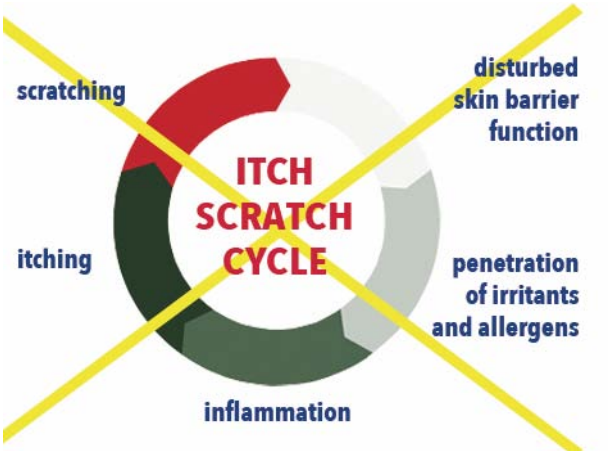
DISCUSSION

Keratinocytes are not only primary indicators of stressful conditions but also major players of the extremely complex response in the skin conducting an orchestrated recruitment and functions of the immune cells, fibroblasts, and vascular cells involved in the inflammatory responses and wound healing. Epidermal growth factor receptor (EGFR) located on the cellular membrane of keratinocytes is widely recognized as a key regulator of numerous essential processes underlying skin development, homeostasis, and repair. EGFR belongs to a group of membrane bound receptor tyrosine kinases with extracellular ligand-binding domain and cytoplasmic domain possessing intrinsic protein kinase activity.
EGFR is expressed through all layers of human epidermis with the strongest presence in the basal layer of epidermal keratinocytes.
Polydatin is able to normalize the EGFR system in human keratinocytes [15]. The cytoprotective action of polydatin on stressed keratinocytes in vitro is not only documented through the reduction of the inflammatory response, but especially through the production by keratinocytes themselves of β -defensins, which are proteins active against bacteria, fungi and viruses [17]. The study shows that the defensins continue to be produced by stressed keratinocytes when treated with polydatin, while under stress keratinocytes are not capable of producing defensins.
The main symptom of atopic dermatitis is itching. The itching can be severe and persistent, especially at night. Scratching the affected area of skin usually causes a rash. The rash is red and patchy and may be long lasting (chronic) or come and go (recurring).
The rash may:

- develop fluid-filled sores that can ooze fluid or crust over. This can happen when the skin is rubbed or scratched or if a skin infection is present. This is known as an acute (sudden or of short duration), oozing rash.
- be scaly and dry, red, and itchy. This is known as a sub acute (longer duration) rash.
- become tough and thick from constant scratching (lichenification).

Our study clinically confirmed the already *in vitro* documented effects of polydatin.
The use of POLIDAL cream and detergent associated with oral administration of POLIDAL tablets restores the function of the skin barrier, counteracts the action of irritants or allergens, reduces the local inflammatory response, and eliminates the itching and scratching, thus blocking the “rash - itch - scratch” vicious cycle (Figure 8).

FIGURE 8. ITCH-SCRATCH CYCLE



On the basis of this open study, we can say that the polydatin, with the dual topical and systemic administration, is a safe and effective support for patients who are suffering from atopic dermatitis, even in its most severe forms, being able to usefully accompany with the other types of treatment, topical and systemic, normally used in the therapy of dermatitis.
We can thus consider the polydatin as a very interesting molecule that can be usefully employed in dermatology, in cases of psoriasis, as well as in the treatment and prevention of photo aging.
We do think though that other clinical trials are mandatory to fully assess the possible uses of the molecule.

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POLIDAL is marketed by Ghimas S.p.A. (Casalecchio di Reno - BO, Italy) under exclusive license GLURES - Spin-off of Ca’ Foscari University of Venice (Italy) and is the result of Italian research, with the contribution of the MIUR (RIC 1009 Decree: 16/07/2007 Legislative Decree No. 297/1999). Polydatin, natural glycoside of resveratrol, is extracted with a patented method in Europe (EP2087894A1) and Italy (0001388133 MISE).
The opinions expressed in the current article are whose of the author. The author is fully responsible for all content, editorial decision and opinions expressed in this article. The author received no honoraria or other form of financial support related to the development of this manuscript.

DISCLOSURES

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