Dermatol Ther (Heidelb) (2018) 8:339–347
https://doi.org/10.1007/s13555-018-0239-0

REVIEW

Beneficial Effects of Antioxidant Furfuryl Palmitate in Non-pharmacologic Treatments (Prescription Emollient Devices, PEDs) for Atopic Dermatitis and Related Skin Disorders

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Received: March 20, 2018 / Published online: May 22, 2018

ABSTRACT

Introduction: Atopic dermatitis (AD) is a common chronic inflammatory skin disease; it requires long-term treatments focused on symptomatic relief. Current first-line treatments include moisturizers and topical corticosteroids. Recently, topical antioxidants have been added to moisturizer formulations to alleviate mild-to-moderate AD. The aim of this review was to evaluate the efficacy and tolerability of furfuryl palmitate, a new antioxidant molecule, and furfuryl derivatives.

Methods: A PubMed/Google Scholar search was conducted using the term "furfuryl palmitate" (and its derivatives, including AR-GG27®) combined with "skin," "atopic dermatitis," and "atopic eczema." Existing trials including adult and pediatric patients with AD and related skin disorders were evaluated. The treatment indication(s), number of subjects, treatment protocols, results, and side effects were recorded.

Results: Effective treatments with furfuryl palmitate and furfuryl derivatives have been reported for the following conditions: atopic, seborrheic, irritative, and allergic contact dermatitis, eczema, xerosis, and cutaneous inflammatory pathologies. All the products tested showed a good tolerability profile.

Conclusion: Studies performed up to now showed that furfuryl derivatives can efficaciously contrast signs and symptoms of mild-to-moderate AD, erythema, and widespread diffuse cutaneous pathologies in both adult and pediatric patients, representing a real alternative to steroids and a valid aid in the treatment of skin disorders, with no side effects and without requiring precautions in use.

Funding: Relife S.r.l. - Menarini Group.

Plain Language Summary: Plain language summary available for this article.

Keywords: Antioxidants; Atopic dermatitis; Cutaneous inflammatory pathologies; Dermatitis; Eczema; Furfuryl derivatives; Furfuryl palmitate; Prescription emollient devices; Topical treatments

Enhanced digital features To view enhanced digital features for this article go to https://doi.org/10.6084/m9.figshare.6166121.

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PLAIN LANGUAGE SUMMARY

Atopic dermatitis (AD), also called eczema, is a common skin disease. Its main symptoms are redness and itching of the skin, but symptoms can vary from person to person; it also presents features of asthma and/or hay fever. It tends to flare periodically and clear up for the rest of the

time. It is a disease more common in childhood, but may persist in adolescence and adulthood.

There is no cure for this disease, but it requires long-term treatments to relieve itching and prevent new outbreaks. First-line treatment includes substances called skin moisturizers (that help prevent skin dryness) and corticosteroids (drugs that can lessen redness and itching). Recently, substances called antioxidants have been added to moisturizer formulations to alleviate AD symptoms. Antioxidants can protect the skin from damage caused by harmful molecules called free radicals.

Our research aimed to evaluate the efficacy and safety of using furfuryl palmitate, a new antioxidant, and furfuryl derivatives added to moisturizer formulations. A literature search was conducted, and existing research works including adult and pediatric patients with AD and related skin disorders were evaluated.

What has been seen up to now is that furfuryl palmitate and its derivatives can efficaciously contrast symptoms of mild and moderate AD, erythema, and widespread diffuse cutaneous disturbances in both adult and pediatric patients. Thus, this treatment represents a valid aid in the treatment of skin disorders, with no side effects and without requiring precautions for use.

INTRODUCTION

Atopic dermatitis, also referred as "atopic eczema" or "eczema," is a common, non-contagious, chronically relapsing and inflammatory skin disease [1–4], usually associated with asthma and inhalant allergies [5]. It usually appears in childhood, but with growth most children move to a condition that no longer requires medical care; adults make up only about one-third of all cases. A hereditary component of the disease is known,but a crucial role in disease expression can be attributed to the environment [6–9].

The clinical features leading to a diagnosis of AD are variable, but the hallmark of atopic dermatitis is extremely itchy and dry skin [10–13], resulting in impaired skin barrier function, causing cutaneous inflammation and increased transepidermal water loss (TEWL). Also, the lack of intercellular lipids in the stratum corneum and inadequate ratios among compounds (cholesterol, essential fatty acids, ceramides), typical of AD patients, enhance TEWL, leading to epidermal microfissuring, facilitating easier allergen penetration [14, 15].

Atopic dermatitis, being a complex and multifactorial disease, can be treated by different physicians according to different therapies and approaches. However, all clinical modifications have to be considered as one condition and, requiring AD lifelong or long-term perspective treatments, special attention must be given to safety aspects.

Several guidelines have been published [16] to suggest a proper clinical approach to manage AD, but the goal of any treatment is to gain a state in which no or only minor symptoms occur and drug treatments are not much needed, with the disease rarely showing acute or intense exacerbations. No treatments can heal the disease, but treatments basically focus on symptom relief.

All the management guidelines review topical therapy for AD [17–20]; current first-line treatment includes moisturizers and topical corticosteroids. According to the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology [11], the regular use of moisturizers represents the mainstay of the general management of AD and of maintenance of remission from flares [10]. They relieve the severe dryness of the atopic skin and the accompanying symptoms, such as intense pruritus and inflammation, improving the barrier function and decreasing the TEWL [21]. Their constant use could be sufficient to control mild eczema and should also form part of the treatment regimen for more severe forms, being also able to decrease the use of topical steroids [22–25].

Moisturizers ideally perform all the following functions: improve skin barrier functions by delivering lipids and water to the stratum corneum [26] (restoring barrier function and thus also ameliorating antimicrobial defense); maintain skin integrity and appearance; reduce TEWL; facilitate barrier repair by encouraging

the natural restorative process [27, 28]. They can be formulated in a variety of delivery systems and have different compositions and properties to enhance efficacy; the most efficacious moisturizers contain both occlusive and humectant ingredients [18, 21, 26, 29].

Moisturizers are considered very safe, but adverse skin reactions are not uncommon, also considering that atopics are particularly at risk for adverse skin reactions because of their impaired barrier function, whereas systemic side effects are extremely rare [30, 31].

Recently, new antiinflammatory agents have been added into the moisturizer formulations to alleviate mild to moderate AD. The term *PED* (prescription emollient devices) has been introduced to identify this new class of topical agents designed to target the specific defects in skin barrier function observed in AD, and they contain several components including antiinflammatory agents, emollients or humectants. PEDs are also knows as prescription barrier repair creams (BRCs) [18, 28, 32, 33]. They are approved as 510(k) medical devices based on the assertion that they serve a structural role in skin barrier function and do not exert their effects by any chemical actions. The moisturizers qualify as devices because they can change the water content of the skin, demonstrated by measuring the TEWL. According to this approval route, safety, not efficacy, is of primary concern.

These compounds represent the answer to the awareness of the primary role of the stratum corneum in the pathogenesis of AD and of the need not only to treat the inflammation but also to restore the barrier, delivering stratum corneum-specific lipids to help correct the epidermal barrier dysfunction [34].

PEDs may provide additional barrier repair and control xerosis without topical corticosteroid treatment and include preparations having distinct ratios of lipids that mimic endogenous compositions.

PEDs may contain an antioxidant agent, such as furfuryl palmitate or furfuryl derivatives. Oxidative stress and altered antioxidant defenses are involved in the pathophysiology of acute exacerbation of AD, and AD patients are more prone to report damages caused by reactive oxygen species (ROS) or oxidants. Thus, it is possible that antioxidants may be beneficial in the treatment of AD, i.e., that suppressing the oxidative stress may be a potentially useful strategy for the treatment of AD [1, 35–39].

Furfuryl palmitate is an ester obtained when furfuryl alcohol reacts with palmitic acid, and it has remarkable singlet oxygen-quenching properties, $^1O_2$. This is a radical with no ionic charge and relatively low reactivity, which facilitates its spread through the dermis and into the cells, where it can damage cytoplasmic structures and nuclear material. Besides being one of the prime causes of skin aging, $^1O_2$ plays a role in the genesis of symptomatic topical disorders such as irritant and allergic contact dermatitis, seborrheic dermatitis, inflammation, psoriasis and sun erythema [30, 40].

$^1O_2$ is formed from atmospheric O_2 by photochemical activation, and the process has intensified in recent years following the thinning of the ozone layer and the reduction in its protection against UV radiation. Production of $^1O_2$ from O_2 is effectively inhibited by the presence of furfuryl alcohol, as widely demonstrated by experimental data [41]. Thanks to the presence of a conjugated diene, furfuryl alcohol and its derivatives can interact with PO_2 by either conversion to oxygen in the ground state (triplet state) or sequestering the radical through a Dies Alder type diene dienophile addition reaction. Esterification of the furyl ring with palmitate enhances molecule penetration into the membranes, thus facilitating skin absorption [42].

In 2008, furfuryl derivatives and their use in the treatment of dermatologic disorders, especially when caused by free radicals, were the objects of a US patent [43].

The first in vitro experiments for sorbityl furfural palmitate (ARGG27®) demonstrated its antioxidant and lenitive actions [44, 45], supporting the hypothesis of a positive effect of the ARGG27® molecule on the control of AD and other inflammatory skin diseases.

METHODS

A search using PubMed and Google Scholar was conducted up to September 2017 using the term "furfuryl palmitate" (and its derivatives

including AR-GG27®) combined with "skin," "atopic dermatitis," "atopic eczema," "dermatitis" and "eczema." The search results were reviewed for clinical trials, case reports and case series examining the usage and efficacy of furfuryl palmitate to treat dermatologic conditions. The following information was recorded from these publications: the dermatologic condition being studied, test agents, number of subjects, treatment protocol, results and safety profile.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

Six papers on furfuryl palmitate and its derivative therapies (meeting the following criteria: being a clinical study; having furfuryl palmitate and its derivatives as one of the experimental agents; describing a dermatologic application for furfuryl palmitate and its derivatives) were obtained and reviewed, including adult and pediatric patients with AD and related skin disorders.

The studies are outlined in Table 1 [37, 42, 46–49].

In the clinical study by Tripodi et al. [49], the efficacy and tolerability of furfuryl palmitate were evaluated, and the main results are shown in Table 1.

The quality and scientific validity of the study have been challenged, based on the following issues.

Concerning the study product, the percentage of furfuryl palmitate was not specified, thus potentially invalidating the study and in any case confounding the outcome, and a proper placebo or a pure emollient alone (as control) was missing. Concerning the study methodology, it seemed that only a comparison within groups was presented, whereas a comparison between groups was missing; furthermore, the statistical power calculation was at minimum − 80%, invalidating the reliability of conclusions. No superiority or non-inferiority design was clarified, and only results for the per protocol populations were reported (this could also be the reason for the discrepancy between the table and figure reporting mean SCORAD index scores). The sample size (relatively small) was not based on differences from baseline, and a possible bias in statistics could also be attributed to the difference in food allergy in the groups (respectively 28% and 39% in group A and B). Concerning patient selection, eligibility criteria were not completely clarified, no minimal/maximal severity of disease score was mentioned for inclusion, and the SCORAD index was not homogeneous between groups, being 25.6 (mean score, corresponding to "mild," up to 25) in the basic emollient cream group, group A, and 28.1 (mean score, corresponding to "moderate," between 25 and 50) in the furfuryl palmitate cream group, group B. The analysis seemed not to have considered this difference, and the standard deviation was high (respectively 10.1 and 10.6 in group A and B), increasing the doubts regarding patient selection.

CONCLUSIONS

Moisturizers traditionally have a key role in improving and maintaining the skin barrier function and reducing skin susceptibility to irritants; they represent the standard care for AD therapy, useful for both prevention and maintenance therapy, and it has been shown that their regular use has a short- and long-term steroid-sparing effect in mild-to-moderate AD.

Over time, the traditional therapy based on moisturizers has been enriched and improved by topical agents for physiologic lipid base barrier repair. They focus on physiologic lipid replacement therapy, particularly ceramides, being able to restore the normal balance of the epidermal barrier.

Several studies demonstrated that these agents are safe and effective in treating AD, as either monotherapy or adjuvant treatment, showing comparable efficacy, in terms of improving symptoms and timing to resolution compared with traditional agents [28, 50].

Today, considering the new research performed on the role of oxidative stress in AD,

Table 1 Clinical studies

Disease	Test agent	Comparison agent	*N*	Study design	Treatment protocol	Results	Safety	Year	References
Atopic dermatitis and pityriasis alba	ARGG27®	Placebo	60 pediatric patients	RCT BL DB	BID × 30 days	Itching and severity significantly reduced in the AR GG27® group compared with placebo group after 15 and 30 days of treatment	No SAEs reported No AEs reported in ARGG27® group 6 AEs reported in placebo group (2 possibly correlated)	2012	[37]
Atopic dermatitis (33), irritant and allergic contact dermatitis (17), miscellaneous pathologies with an inflammatory cutaneous component and symptomatic manifestations such as eczema or xerosis (10, including 3 seborrheic dermatitis and 2 psoriasis)	Superoxidodismutase (SOD), 18 beta glycyrrethic acid, vitamin E, alpha bisabolol and furfuryl palmitate	None	60 pediatric patients	CT UL	BID × 2 weeks	Significant improvement of the inflammatory skin conditions, with evident and fast inflammation and eczema reduction in all the investigated pathologies	The product did not show any relevant side effect	2002	[42]
Atopic dermatitis (40), seborrheic dermatitis (30), allergic contact dermatitis (13), irritative and irritative contact dermatitis (25)	Superoxidodismutase (SOD), 18 beta glycyrrethic acid, vitamin E, alpha bisabolol and furfuryl palmitate	None	64 adult and 44 pediatric patients	CT UL	BID × 2 weeks	Efficacy assessed as good or excellent in most of the cases treated; a significant reduction in erythema, itching and the presence of blisters is obtained just 48 h after starting to apply the product	No relevant side effects or intolerances were observed	2002	[46]

Table 1 continued

Disease	Test agent	Comparison agent	*N*	Study design	Treatment protocol	Results	Safety	Year	References
Mild-to-moderate atopic dermatitis	Furpalmate	Vehicle	40 adult patients	RCT BL DB	BID × 21 days	The study product was shown to efficaciously contrast signs and symptoms of mild-to-moderate atopic dermatitis in adult patients, resulting in a more effective vehicle	One patient requested rescue therapy with corticosteroids for a flare up of inflammation in the furpalmate group compared with six in the control group ($p < 0.01$). No SAE	2011	[47]
Atopic dermatitis of hands	Furpalmate	Topical corticosteroid	40 adult patients	RCT BL investigator blinded	BID × 14 days	Both groups significantly improved in signs and symptoms on either the physician's or patient's evaluation scores with respect to baseline ($p < 0.001$) with no significant difference between the two groups	–	2011	[48]
Atopic dermatitis	Emollient cream enriched with furfuryl palmitate	Emollient cream	117 pediatric patients	RCT	BID × 14 days	While the emollient cream containing furfuryl palmitate was efficacious to a certain extent, the results were less clinically relevant than those observed for the same cream not containing the active ingredient	No statistical differences were found for the tolerability of the two products, even if the enriched cream was reported to be less well tolerated, with complaints of itching and burning sensation after application	2009	[49]

CT clinical trial, *RCT* randomized clinical trial, *DB* double blind, BID bis in die/twice daily, *UL* unilateral comparison, *BL* bilateral comparison (test versus control)

products enriched in antioxidants, such as furfuryl derivatives, can represent a valid aid in the treatment of a range of skin disorders, such as atopic and seborrheic dermatitis, with no side effects or requirement of precautions in use.

Even if the preliminary data shown should be confirmed in larger trials considering both pediatric and adult patients, studies performed up to now have shown that furfuryl derivatives are able to efficaciously contrast the signs and symptoms of mild-to-moderate AD and erythema and also widespread diffuse cutaneous pathologies, such as irritative, seborrheic and allergic contact dermatitis, in both adult and pediatric patients [37, 42, 46–48]. The only paper published up to now not agreeing with what is outlined here is biased by several issues, as discussed above, whereas all other clinical investigations carried out not only did not highlight any negative aspects, but instead confirmed several positive outcomes, showing a clear superiority of *verum* with respect to placebo.

The products containing these compounds can constitute a valuable alternative to topical corticosteroids in mild-medium severity skin disorders, especially when preferring to avoid a pharmacologic agent, such as in pediatric patients, intolerant subjects or atopic patients. In addition, they can also act in synergy with other topical or systemic treatments, as well as pharmacologic, to promote faster recovery of the normal skin condition, reducing inflammation and restoring the skin barrier.

Thus, in patients with mild or moderate AD, these products represent a real alternative to steroids, which instead constitute an important health risk.

All the products tested showed, in addition, a good tolerability profile, thus promoting compliance by both the patient and caregiver. This is of main importance, because the choice of therapy can be primarily considered as dependent on the patient's preferences and also the ideal moisturizing agent should be safe, effective, inexpensive.

Despite the positive results outlined above in the confirmatory studies, research with bigger sample sizes is advisable to confirm and emphasize the results already achieved.

ACKNOWLEDGEMENTS

Funding. This research was sponsored and funded by Relife S.r.l. Menarini Group. Article processing charges were funded by Relife S.r.l. Menarini Group.

Medical Writing and/or Editorial Assistance. Medical writing and editorial assistance in the preparation of this manuscript were provided by Dr. Federica Sbrocca, MSc (SPRIM ALS GCP, Milan, Italy). Support for this assistance was funded by Relife S.r.l. Menarini Group. The authors are fully responsible for all content and editorial decisions related to the development of this manuscript.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

Disclosures. Paolo Pigatto and Marco Diani have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. The manuscript has no associated data.

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