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Importance of dermocosmetics in the management of acne

Acne is the major dermatological disease as per the number of patients affected. Adolescents are suffering acne, but also more and more post-adolescent women. Acne is a multifactorial disease involving four main pathogenic pathways: increased and altered sebum production; inflammation; changes in the keratinization process resulting in abnormal keratinization; and follicular colonization by *C. acnes*. Until now, the treatment is mostly based on pharmacological substances, which often present side effects and for this reason offer bad compliance from the patients. Nevertheless, a number of dermocosmetics contain active ingredients, most of them vegetal, capable of focusing all four pathogenic pathways and obtaining satisfactory results. The most relevant sebo regulator substances are butyl avocadate, but also epigallocatechin-3-gallate. In the category of antimicrobial agents, the most commonly used are tea tree oil, decanediol and Quassia amara extract. Among anti-inflammatory substances, we can mention Salix alba and Gingko biloba extracts, but also zinc, panthenol and superoxide dismutase. As per anti-keratolytic agents, alpha-hydroxy acids are commonly used, as well as salicylic acid, a beta-hydroxy acid. Nicotinamide is an ingredient of choice due to its multiple positive effects on the pathogenesis of acne. Early management of acne is crucial, in order to limit its symptoms and severity, but also avoid sequelae as serious as prolonged erythema or acne scars. This early management must be based on a holistic approach of acne, not necessarily including pharmacological treatment, but dermocosmetics, in particular in case of mild acne or as maintenance treatment. In this holistic approach, emphasis must be given on cleansing and moisturizing of the skin, and sun protection,

Key words

Acne, dermocosmetics, cleansing, moisturizing, sun protection.

1. INTRODUCTION

Acne vulgaris is the most common dermatological disorder globally in the world. The prevalence of acne is estimated at 9.4 %, ranking it as the eighth most prevalent disease worldwide [1]. 650 million adolescents and adults are reported to be affected [2]. More than 85 % of individuals worldwide are concerned at some stage of their life [3]. Acne vulgaris, or acne of the adolescent, has a peak incidence in 14- and 17-year-old girls and in 16- and 19-year-old boys [4]. A study concluded that acne persists in 41 % of adult women; half of them reported dyschromia and presence of scars [5].

The exact pathogenesis of acne vulgaris is not yet fully understood, but it is commonly accepted that acne is a multifactorial disease involving four main pathogenic pathways: increased and altered sebum production; inflammation; changes to the keratinization process resulting in abnormal keratinization; and follicular colonization by *Cutibacterium acnes* (*C. acnes*) [4, 5], formerly named *Propionibacterium acnes* [6].

According to international guidelines, the current first-line treatments for acne are conventional

pharmacological therapies such as antibiotics, retinoids, hormonal agents and benzoyl peroxide [7]. Of course, acne treatment recommendations are dependent on the severity of the condition identified by different gradings [8]. Systemic and topical medications recommended by these guidelines are often associated with side effects which can reduce adherence to treatment and thus negatively impact therapeutic outcomes [9]. Patients suffering acne may benefit from specifically designed non-prescription acne treatment, including cleansers and moisturizers that cater to their condition [2]. Further, the side effects related to therapeutic treatments for acne may be improved by such dermocosmetic treatment. Dermocosmetics are also used as adjuncts to pharmacological and light therapies for acne and can be formulated to target the main pathogenic pathways in acne [10]. Adherence to acne therapy has been associated with the use of dermocosmetics, such as moisturizers and cleansers [10]. Dermocosmetics can be used in the maintenance phase of acne management and can impact the pathogenesis of acne, providing beneficial effects [10]. Treating acne taking into account

the complete portfolio of measures available, including skincare, may improve adherence to treatment, reducing skin irritation, and improving patients' outcomes [2].

2. ACTIVE INGREDIENTS USED IN DERMOCOSMETICS FOR ACNE

Obviously, in dermocosmetics designed to be used by acne patients, the active ingredients will address one (or more) pathogenic pathways of acne, i.e. altered sebum production; inflammation; changes to the keratinization process resulting in abnormal keratinization and follicular colonization by *C. acnes*.

2.1. Active ingredients controlling sebum production

Butyl avocadate, an ester extracted from the oil of *Persea gratissima*, an edible fruit known as avocado, displays anti-seborrheic properties, by inhibiting the activity of 5- α reductase type 1 [11]. The regular application twice a day during 3 weeks of a cream containing 2 % butyl avocadate was shown to reduce by 30 % facial hyperseborrhea [11].

Nicotinamide, an amide form of vitamin B₃, also shows anti-seborrheic activity. A double-blinded, placebo-controlled, randomised trial with 130 patients found that a 2 % nicotinamide moisturiser significantly reduced sebum excretion rates when compared to a placebo moisturiser [12]. Besides, an in vitro study has demonstrated that nicotinamide significantly decreased interleukin-8 secretion in a *C. acnes* keratinocyte model of inflammation, suggesting another possible mechanism of action in the application of nicotinamide for acne [13]. Further, nicotinamide was shown to reduce the levels of most of pro-inflammatory cytokines [14], which makes it a good topical anti-inflammatory. Nicotinamide has also been shown to decrease TEWL, thus improving the skin barrier, which is another potentially beneficial effect for patients with acne, where an impairment of skin barrier function exists [15]. At that time, to the best of our knowledge, four studies used nicotinamide as a single-agent topical product, either at 4 % [16–18] or at 5 % [19]. In three studies, nicotinamide was compared to 1 % clindamycin gel [18, 19] or 2 % clindamycin gel [19]. In all four studies, a significant improvement was noted in acne vulgaris from baseline, whilst in all three studies *vs.* clindamycin, it was stated that nicotinamide and clindamycin resulted in similar reductions in acne lesions. When thinking about prescribing topical antibiotics, we should always consider the alternative offered by topical nicotinamide.

It was found that *Epigallocatechin-3-gallate* (EGCG) reduced sebum by modulating the AMPK-

SREBP-1 signalling pathway. EGCG also reduces inflammation by suppressing the NF- κ B and AP-1 pathways, induces cytotoxicity of SEB-1 sebocytes via apoptosis and decreases the viability of *P. acnes*, thus targeting almost all the pathogenic features of acne. Finally, and most importantly, EGCG was shown to significantly improve acne in an 8-week randomized, split-face, clinical trial, and was well tolerated [20].

2.2. Antimicrobial active ingredients

Tea tree oil is obtained by steam distillation of the leaves of some species of *Melaleuca* genus, in particular *Melaleuca alternifolia*. It was found to be active against *Staphylococcus aureus*, *Staph. epidermidis* and *Propionibacterium acnes* [21]. Topical 5 % tea tree oil was reported as being an effective treatment for mild to moderate acne vulgaris [22]. The results of a study [23] showed that both 5 % tea-tree oil and 5 % benzoyl peroxide had a significant and similar effect in ameliorating the patients' acne by reducing the number of inflamed and non-inflamed lesions (open and closed comedones), although the onset of action in the case of tea-tree oil was slower. Contrarily, fewer side effects were experienced by patients treated with tea-tree oil [23].

Decanediol has also an antibacterial effect against *C. acnes* [24]: its antibacterial action resulted in a significant reduction in pustules and sebum levels during an 8-week treatment period in patients with mild-to-moderately severe acne [24].

The antibacterial activity of **Quassia amara** extract was demonstrated in cultures of *P. acnes* and coagulase-positive *Staphylococci* where the growth of the bacteria was reduced in a significant manner ($p < 0.05$) [25].

2.3. Anti-inflammatory active ingredients

Salix alba (willow bark) extract has been reported to have anti-inflammatory effects such as decreasing tumour necrosis factor (TNF)- α release, cyclooxygenase (COX)-2 expression, nitric oxide release, and interleukin (IL)-1 β and IL-6 release [26].

A combination of **soy isoflavones** reduced the expression of COX-2 and Gadd45 and prevented UVB-induced DNA damage [27].

Nicotinamide, already mentioned, has anti-inflammatory properties, such as reducing production of IL-6, TNF- α and monocyte chemoattractant protein (MCP)-1 [14].

Enoxolone (18 β -glycyrrhetic acid), extracted from licorice root, inhibits inflammation via PI3K/Akt/GSK3 β signalling and glucocorticoid receptor activation [28].

Ginkgo biloba extract also has anti-inflammatory properties, through suppression of nuclear factor

kappa B (NF- κ B), TNF- α and downregulation of COX-2 expression [29].

Zinc permits inflammatory regulation by inhibition of IL-6 and TNF- α production but also inhibition of inflammatory mediator production, such as nitric oxide (owing to its presence in Zn-Cu prosthetic groups in superoxide dismutase) [30]. Clinically, zinc reduces the number of acne lesions and reduces sebum production with good tolerability [30].

Panthenol also has anti-inflammatory properties and has previously been investigated as a topical treatment in acne [6].

Quassia amara extract is a potent anti-inflammatory, significantly reducing the protein levels of inducible NO synthase (iNOS) and the cyclooxygenase-2 (COX-2) and also significantly inhibiting (by 50 %) TNF- α , IL-1 β and IL-12 secretions [31].

Superoxide Dismutase (SOD) deserves special attention at this stage. It was demonstrated that SOD3 suppressed toll-like receptor-2 (TLR-2) expression in *P. acnes*- or PGN-treated keratinocytes and sebocytes [32]. Moreover, it was found that SOD3 suppressed the expressions of phosphorylated nuclear factor- κ B (NF- κ B) and p38 in *P. acnes*- or PGN-treated cells. SOD3 also exhibited an anti-inflammatory role by reducing the expression of inflammasome related proteins (NLRP3, ASC, caspase-1) and inhibiting the expression of pro-inflammatory cytokines, including tumour necrosis factor- α , interleukin-1 β , interleukin-6, and interleukin-8. In addition, SOD3 reduced lipid accumulation and expression of lipogenic regulators in *P. acnes*-treated sebocytes [32]. Recombinant SOD3-treated wild-type mice and SOD3 transgenic mice, which were subcutaneously infected with *P. acnes*, showed tolerance to inflammation through reducing inflammatory cell infiltration in skin, ear thickness, and expression of inflammatory mediators [32].

Probiotics may also be useful components in dermocosmetic formulations. When compared with tea tree oil, lactobacillus fermented *Chamaecyparis obtusa* resulted in a greater reduction in inflammatory lesions (65.3 vs. 38.2 %), decreased the size of sebaceous glands and reduced the amount of sebum excreted [33]. Similarly, *Lactobacillus plantarum* has demonstrated anti-inflammatory and antimicrobial properties by reducing skin erythema, repairing the skin barrier and modulating skin microflora, resulting in the reduction of acne lesion size [34].

2.4. Keratolytic active ingredients

There are a number of agents that have been shown to be effective against hyperkeratinization, so-called keratolytic agents [6].

Alpha hydroxy acids increase epidermal thickness and collagen synthesis within the dermis, in addition to thinning the stratum corneum [10].

Salicylic acid (SA) is a beta-hydroxy acid extracted from natural botanical sources and can also be artificially synthesized [35]. Variation of SA concentration from 0.5 to 30 %, even 50 % [36], changes its activity from cleaning and anti-inflammation to chemical peeling [37]. The safety and tolerance of SA have been demonstrated, thus it is widely used in dermatology [36]. SA can soften the stratum corneum and rapidly dissolve desmosomes, leading to decreased adhesion of corneocytes and exfoliation of corneocyte sheets [38]. As a result, SA has comedolytic properties and promotes cell turnover. Due to its lipotropism, SA permeates to the sebaceous gland easily and antagonizes hyperseborrhea, for an added curative effect [36]. It was also postulated that therapeutic activities of SA in acne vulgaris treatment could be associated with the regulation of SREBP-1 pathway and NF- κ B pathway in human SEB-1 sebocytes [39].

Lipohydroxy acid is a derivative of salicylic acid that can penetrate further into the sebaceous gland, providing efficacy in the treatment of acne [40]. Lipohydroxy acid can reduce the number of acne lesions [40, 41], and linoleic acid interrupts cornification thereby reducing the size of microcomedones [42]. Additionally, the slow penetration of lipohydroxy acid results in exfoliation at a cellular level and can induce dermal thickening through the stimulation of collagen and elastin production [40].

Retinoids will not be discussed in this paper, as they are part of the pharmacological treatment of acne.

3. SKIN CLEANSING: A MAJOR CONCERN IN THE MANAGEMENT OF ACNE

This is a common misconception among the patients that they suffer acne because they have a poor cleansing of their skin. Many people still believe that acne is a result of poor hygiene and cleanliness. In a study focused on the beliefs and perceptions of acne patients [43], poor skin hygiene was implicated as a causative factor for acne by 29 % of responders, whilst 62 % believed that dirt was an aggravating factor. Despite the dearth of sound scientific evaluation, most popular treatment regimens continue to recommend routinely washing the face twice a day with a mild cleanser. To clarify the effect of frequency of face washing on acne vulgaris, a clinical trial was conducted on males with mild to moderate acne vulgaris [44]. Subjects washed their faces twice daily for 2 weeks with a standard mild cleanser before being randomized to one of three

study arms, in which face washing was to be done once, twice, or four times a day for 6 weeks. Significant improvements in both open comedones and total noninflammatory lesions were observed in the group washing twice a day. Worsening of acne condition was observed in the study group washing once a day, with significant increases in erythema, papules, and total inflammatory lesions [44]. Careful face washing improves the lesions and prevents acne development by removing excess sebum and preventing hair follicular obstruction. The myth associated with acne is that vigorous scrubbing of the skin with soap and water several times a day will reduce the oiliness; however, it only leads to an aggravation of acne and sometimes even may cause acne detergentans [45]. On another hand, harsh cleaners or overwashing the skin to remove excess sebum might remove these lipids from the stratum corneum surface, resulting in excessive skin drying [46]. Hypothesizing that skin care combining mild skin cleansing and intensive moisturizing («combination skin care») might be effective in the care of acne in subjects with dry skin and/or sensitive skin, Isoda et al. [47] developed a combination skin care with a weakly acidic foaming facial skin cleanser based on a mild detergent, an aqueous lotion with eucalyptus extract and a moisturizing gel containing pseudo-ceramide and eucalyptus extract. They performed a 4-week clinical trial with 29 post-adolescent Japanese women with mild acne with dry and sensitive skin. The acne significantly decreased after this trial accompanied by the improvement of dry skin, and a significantly increased endogenous ceramide level in the stratum corneum [47]. In general, a nonionic, fragrance-free dermatologic bar or liquid cleanser with good rinsability is the preferred cleanser in acne [45].

4. IMPORTANCE OF SKIN MOISTURIZING IN A GLOBAL APPROACH OF ACNE

In the treatment and management of acne, moisturizers can prevent skin dryness, reduce skin irritation caused by some topical acne therapies, and soothe the skin by slowing the evaporation of water (i.e. TEWL) [48]. Ceramide-containing moisturizers should be considered for dermocosmetics for acne [49]. There is a reduction in skin surface ceramides when the skin barrier function is impaired resulting in increased TEWL, and therefore application of moisturizers containing ceramides may lead to improvements in skin dryness and irritation [49]. Furthermore, moisturizers containing ceramides will likely improve adherence to existing treatment regimens (especially those with retinoids) by counteracting the symptoms and side

effects (skin dryness and irritation) that commonly result in nonadherence [49]. However, greasy creams, such as W/O emulsions, must be avoided, because of the risk of comedogenicity.

5. SUN PROTECTION IN ACNE

Use of sunscreen is an important recommendation for patients with acne, especially in those using topical therapy and in those treated with oral antibiotics associated with increased risk of photosensitivity [50].

Both the moisturizer and sunscreen components can assist in prevention of residual hyperpigmentation, which can result from skin irritation and inflammation, especially in individuals with darker skin (post-inflammatory hyperpigmentation (PIH)) [50]. The sunscreen component may also protect against photosensitivity induced by UV radiation in patients using certain Rx medications for acne [51]. It is important to highlight in this case the use of a sunscreen protecting not only against UVA/UVB but also from visible light. When recommending a sunscreen to acne patients, it is better avoiding greasy formulas, and mineral sunscreens, as their microparticles tend to be comedogenic. Gel textures are usually better accepted than emulsions. SPF formulations have to be shown not to be acnegenic or comedogenic and do not exacerbate or worsen acne with continued use, including in subjects using a variety of Rx products [52].

6. NEW TRENDS AND UNMET NEEDS IN THE DERMOCOSMETIC APPROACH OF ACNE

6.1. Insulin-like growth factor pathway and insulin-sensitizing agents

This is probably an innovative approach for the treatment of acne.

IGF-1 is a hormone in the IGF-1 signalling pathway, which is induced by insulin and may affect the production of androgens and sebaceous lipogenesis [53] as well as the formation of comedones [54]. *Metformin* is an insulin-sensitizing agent approved for the treatment of type 2 diabetes, which has also been used as an off-label treatment for acne [55]. *Metformin* 500 mg twice daily combined with a low glycaemic diet (1500–2000 kcal and low in carbohydrates) for 6 months was reported in a randomized study of 20 male patients as showing improvement in acne and insulin sensitivity [56].

Obviously, *Metformin* is a pharmacological treatment and cannot be used in dermocosmetics. In the nature there is a substitute of *metformin* as per its activity: *berberine*. *Berberine* is an isoquinoline alkaloid present in several plants, including

Berberis sp. (barberry). During 2009–2015, more than 110 clinical trials and animal studies have evaluated and demonstrated antidiabetic effect of berberine [57]. This is due to its property of increasing insulin sensitivity. It also shows an antiproliferative effect on keratinocytes, which may also attenuate acne lesion development [58]. Additionally, in hamsters, berberine appeared to decrease lipogenesis by sebaceous glands, which may translate to human sebaceous glands [59]. Berberine also showed strong activity against clinical isolates of *Propionibacterium acnes* isolated from acne patients [59]. In a study, Gong Lao Qu Huo herbal supplements comprised of Mahonia fruits, a natural source of berberine, was used to treat 92 patients with acne vulgaris. Ninety eight percent of the treatment group on berberine improved compared to 91 % of the control group taking minocycline. Statistical analysis suggested there was no difference between the berberine and minocycline groups [60].

6.2. A holistic approach to acne

Moving towards a patient-centred holistic approach is the future for optimizing acne treatment [55]. Patients often have misconceptions about acne, and it is of utmost importance that the dermatologist brings them an accurate information. Emphasis must be given on external factors susceptible of influencing acne, such as lifestyle, diet, smoking or exposure to pollution. Besides the traditional pharmacological treatments, one must insist on the importance of accurate cosmetic care. A psychological support is also often needed by the patient, as acne has a negative impact on his well-being and quality of life.

6.3. Recent trends in the management of acne

Recently, an international panel including specialists of acne of various European countries met and

brought updated recommendations about the management of this disease [2]. Its general conclusion was that prevention, early treatment (not necessarily with pharmacological agents), and maintenance approaches were needed. The panel also agreed that although data is lacking, adult female acne is an increasing issue [2]. Special needs of this population, because of their aging skin and social environment different from those of adolescents must be considered [2]. It is suggested that an acne treatment regimen such as dermocosmetics may offer a suitable option for adult females with acne either as a monotherapy for the milder acne or in combination with prescription treatments [2]. Finally, and this is not the least, panel members agreed that guidelines for non-prescription acne treatment, prevention and maintenance would fill an important unmet need [2].

7. CONCLUSION

Acne is currently the most common dermatologic disease, and for this reason deserves special attention. Early management of acne is necessary, as it can avoid aggravations and sequelae such as persistent erythema or acne scars. This early management does not necessarily require systematic pharmacological treatment as we use to do it, but may be successfully achieved with dermocosmetics, which reduces the risks of side effect and hence permits a better compliance from the patients. Even in such case, we have to make sure that we are addressing the four pathogenic pathways of acne, i.e. altered sebum production; inflammation; changes to the keratinization process resulting in abnormal keratinization; and follicular colonization by *C. acnes* for a better success of treatment. Finally, a holistic approach of acne must be preferred to an «all-pharmacological» one.

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Важливість дермокосметики в лікуванні акне

Акне є основним дерматологічним захворюванням за кількістю пацієнтів з цим ураженням шкіри. На акне страждають не лише підлітки. Захворювання діагностують також у все більшій кількості жінок більш старшого віку. Акне — це багатофакторне захворювання, в розвитку якого виділяють чотири основних патогенетичних механізми: підвищення і зміна продукції шкірного сала; запалення; порушення процесу кератинізації, що призводять до аномального ороговіння; колонізація *S. acnes* у фолікулах. Досі терапія акне ґрунтується в основному на застосуванні фармакологічних засобів, які часто мають побічні ефекти, внаслідок чого пацієнти не дотримуються режиму лікування. Проте низка дермокосметичних засобів містить активні інгредієнти, більшість із яких є рослинними, здатними впливати на всі чотири патогенетичних механізми та отримувати задовільні результати лікування. Найбільш актуальними себорегулювальними речовинами є бутиловий авокадат, а також епігаллокатехін-3-галлат. Як протимікробні засоби найчастіше використовують олію чайного дерева, декандіол і екстракт *Quassia amara*. Серед проти-запальних речовин можна згадати екстракти *Salix alba* і *Ginkgo biloba*, а також цинк, пантенол і супероксиддисульфу. З групи антикератолітичних агентів зазвичай використовують альфа-гідрокси кислоти, а також саліцилову і бета-гідрокси кислоту. Нікотинамід є переважним інгредієнтом завдяки його множинній позитивній дії на патогенез акне. Ранній початок лікування має вирішальне значення, оскільки дає змогу зменшити вираженість симптомів і тяжкість акне, а також уникнути таких серйозних наслідків, як тривала еритема або рубці від вугрів. Раннє лікування має ґрунтуватись на цілісному підході до вугрового висипу і не завжди включати проведення фармакологічної терапії. При легкій формі акне або як підтримувальне лікування можна застосовувати дермокосметичні засоби. За такого цілісного підходу акцент має бути зроблено на очищенні і зволоженні шкіри, а також на захисті від сонця.

Ключові слова: акне, дермокосметика, очищення, зволоження, захист від сонця.

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Значення дермокосметики в лікуванні акне

Акне является основным дерматологическим заболеванием по количеству пациентов с данным поражением кожи. Акне страдают не только подростки, заболевание диагностируют также у все большего количества женщин более старшего возраста. Акне — это многофакторное заболевание, в развитии которого выделяют четыре основных патогенетических механизма: повышение и изменение продукции кожного сала; воспаление; нарушения процесса кератинизации, приводящие к аномальному ороговению; колонизация в фолликулах *S. acnes*. До сих пор терапия акне основывалась в основном на использовании лекарственных средств, которые часто имеют побочные эффекты, вследствие чего пациенты не соблюдают режим лечения. Тем не менее ряд дермокосметических средств содержит активные ингредиенты, большинство из которых являются растительными, способными воздействовать на все четыре патогенетических механизма и получать удовлетворительные результаты лечения. Наиболее актуальными себорегулирующими веществами являются бутиловый авокадат, а также эпигаллокатехин-3-галлат. В качестве противомикробных средств наиболее часто используют масло чайного дерева, декандиол и экстракт *Quassia amara*. Среди противовоспалительных веществ можно упомянуть экстракты *Salix alba* и *Ginkgo biloba*, а также цинк,

пантенол и супероксиддисмутазу. Из группы антикератолитических агентов обычно используют альфа-гидроксикислоты, а также салициловую и бета-гидроксикислоту. Никотинамид является предпочтительным препаратом для терапии благодаря его множественному положительному воздействию на патогенез акне. Раннее начало лечения имеет решающее значение, поскольку позволяет уменьшить выраженность симптомов и тяжесть акне, а также избежать таких серьезных последствий, как длительная эритема или рубцы от угрей. Раннее лечение должно быть основано на целостном подходе к угревой сыпи и не всегда включать проведение фармакологической терапии. При легкой форме акне или в качестве поддерживающего лечения можно использовать дермокосметические средства. При таком целостном подходе акцент должен быть сделан на очищении и увлажнении кожи, а также на защите от солнца.

Ключевые слова: акне, дермокосметика, очищение, увлажнение, защита от солнца.

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