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The therapeutic potential of polyunsaturated fatty acids in the management of inflammatory skin disorders

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Abstract:

Introduction and purpose: Polyunsaturated fatty acids (PUFAs) are a well-known component of a nutritionally balanced diet. There is a wealth of evidence demonstrating that the ingestion of these substances enhances health, as they are involved in a multitude of metabolic processes that are essential for cellular functionality. However, the contemporary Western diet is distinguished by a reduction in the consumption of omega-3 polyunsaturated fatty acids (PUFAs). The objective of this review is to present the potential therapeutic efficacy of omega-3 PUFA supplementation in the most common inflammatory skin disorders, such as acne vulgaris, atopic dermatitis and psoriasis vulgaris.

State of knowledge: Acne vulgaris, atopic dermatitis and psoriasis vulgaris differ in terms of their pathophysiology. However, they are all characterised by underlying inflammatory processes. Omega-3 fatty acids have been demonstrated to possess anti-inflammatory

properties. They are capable of modulating both the innate and the adaptive immune responses, thereby alleviating the symptoms of the aforementioned skin disorders.

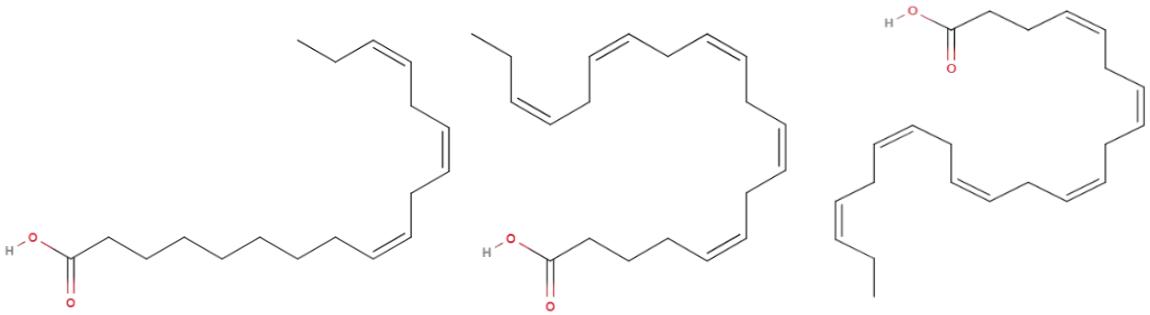
Summary: Given the pluripotent anti-inflammatory qualities of omega-3 polyunsaturated fatty acids, it is reasonable to conclude that they have the potential to become an effective therapeutic tool in the management of inflammatory skin diseases.

Key words: omega-3 fatty acids; acne vulgaris; psoriasis; atopic dermatitis

1. Introduction

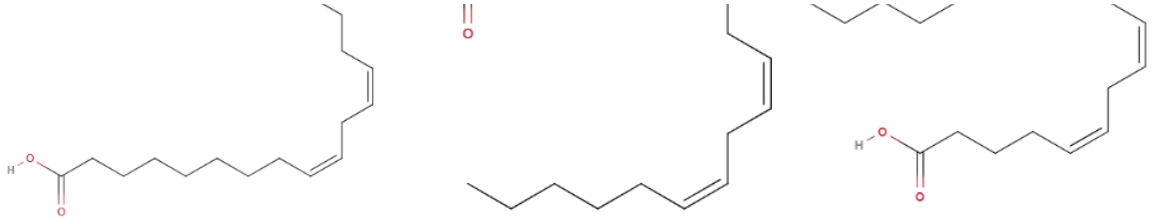
Polyunsaturated fatty acids (PUFAs) are a well-established component of a healthy diet. The consumption of these products has been demonstrated to positively affect health, with the potential to reduce the incidence of certain diseases [1]. As they are involved in a number of metabolic processes in cellular function, these nutrients are of vital importance. Nevertheless, numerous studies have demonstrated that their consumption is inadequate [2–4].

PUFAs are fatty acids, characterised by multiple double bonds in their chemical structure. Among the various types of PUFAs omega-3 and omega-6 fatty acids are of particular importance. Omega-3 PUFAs encompass, among others, alpha-linolenic acid (ALA; C18:3n-3), eicosapentaenoic acid (EPA; C20:5n-3) and docosahexaenoic acid (DHA; C22:6n-3). The chemical formulae of these compounds are presented in Figure 1. The main acids belonging to the omega-6 PUFAs are linoleic acid (LA; C18:2n-6), gamma-linolenic acid (GLA; C18:3n-6) and arachidonic acid (AA; C20:4n-6), whose chemical structures are illustrated in Figure 2. ALA and LA fatty acids are regarded as essential fatty acids due to the inability of the human body, as well as other mammals, to synthesise them internally. Consequently, these fatty acids must be obtained from dietary sources such as marine animals and plants. Among the most efficacious dietary sources are fish oils, flaxseeds, and walnuts [5].



ALA EPA DHA

Figure 1. Chemical structures of omega-3 polyunsaturated fatty acids. Abbreviations: alpha-linolenic acid ALA; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid. The chemical structures were generated using the MolView tool (molview.org).



LA GLA AA

Figure 2. Chemical structures of omega-6 polyunsaturated fatty acids. Abbreviations: LA, linoleic acid; GLA, gamma-linolenic acid; AA, arachidonic acid. The chemical structures were generated using the MolView tool (molview.org).

Omega-3 PUFAs are an integral part of the composition of phospholipids and cholesterol esters, which are crucial for the formation of membrane structures in cells, particularly in the brain and retina [6]. Moreover, they are also precursors of the intracellular synthesis of eicosanoids, which are bioactive lipid mediators that play critical roles in inflammation, immunity, and as signalling molecules in various physiological processes [7,8].

A number of studies have demonstrated that omega-3 PUFAs may play a protective role in reducing the incidence of cardiovascular disease [9]. Furthermore, omega-3 PUFAs are of significant importance for brain health, as they support cognitive function and may potentially reduce the risk of neurodegenerative diseases such as Alzheimer's disease [10,11]. Additionally, they have the potential to improve mental disorders [12]. Omega-3 PUFAs have been shown to have significant anti-inflammatory properties, which may help in the management of chronic inflammatory diseases, such as rheumatoid arthritis. Furthermore,

research indicates that omega-3 PUFAs may contribute to the reduction of the risk and progression of certain digestive system cancers [13].

Building on their anti-inflammatory and immunomodulatory properties [14], as well as potential anti-cancer effects [15], omega-3 PUFAs are also being investigated for their impact on dermatological conditions [16,17]. This review aims to explore the influence of omega-3 PUFAs on various dermatological conditions, with a particular focus on their therapeutic potential in managing skin inflammation.

2. Acne vulgaris

Acne vulgaris is a prevalent inflammatory skin disease, with an estimated global incidence of over 630 million cases [18]. It is estimated that approximately 80% of the population experiences acne to some extent at least once during their lives [19].

2.1. The pathogenesis

The pathophysiology of acne is multifactorial, with various compounds playing a role on a molecular and cellular level. Nevertheless, an analysis of the pathogenesis reveals that it can be broken down into four key factors, namely: increased sebum secretion, hyperproliferation of commensal bacteria, mainly *Cutibacterium acnes*, epithelial hyperkeratinisation within the pilosebaceous follicles, and inflammatory mechanisms [19–22]. From a molecular perspective, it appears that insulin-like growth factor-1 (IGF-1) functions as a binding agent between the four determinants. A positive correlation between the quantity of acne lesions and serum concentration of IGF-1 has been observed [20]. Developing sebocytes, along with suprabasal cells of sebaceous ducts, exhibit the most pronounced expression of IGF-1, a factor that stimulates lipogenesis within these cells [23]. Together with androgen hormones, IGF-1 is responsible for the promotion of excessive sebum production. However, concurrently, insulin-like growth factor 1 increases androgen levels itself. Consecutively, androgens lead to an increase in IGF-1 plasma concentration, creating a positive feedback loop. The final result is hyperseborrhea which remains one of the key factors of acne [22].

2.2. Acne vulgaris and fatty acids

Omega-3 PUFAs have been observed to decrease IGF-1 levels, which has a multifaceted effect on acne-affected skin [20,22,24]. A decline in IGF-1 serum concentration enables the inhibition of mTORC1 signalling, which in turn downregulates the transcription of SREBP-1, consecutively leading to decreased sebum secretion and sebocyte proliferation

[22,25–27] . Furthermore, the inhibition of the mTORC1 pathway results in a reduction in androgen synthesis, which contributes to the decline in both sebum and IGF-1 production [21].

The supplementation of omega-3 PUFAs has been demonstrated to be an effective means of counteracting the inflammatory processes associated with acne. A study conducted by Jung et al. [28] found that daily supplementation of 2000 mg of EPA and DHA over the course of 10 weeks led to a significant reduction in inflammatory acne lesions [29]. IL-1, IL-6, IL-8 and TNF-α are pro-inflammatory cytokines that play a pivotal role in the pathophysiology of acne [30]. Omega-3 PUFAs have been shown to suppress their secretion, as well as their expression in sebocytes [24,25,28,31]. Furthermore, in their study, Jung et al. concluded that a 10-week long daily supplementation of 400 mg of γ-linolenic acid had a similar inhibitory effect on the aforementioned cytokines by means of prostaglandin E1 (PGE1) production [28] . Finally, it has been suggested that omega-3 and omega-6 PUFAs hinder the synthesis of leukotriene B4, thereby reducing inflammation [20,22,24,27,28].

3. Atopic dermatitis

Atopic dermatitis, also known as atopic eczema, is one of the most common chronic inflammatory skin conditions, affecting up to 20% of individuals over their lifetime [32][33]. This disease typically begins in infancy and manifests as dry skin with scaly, itchy, erythematous lesions and lichenification [34] . The lesions are typically located in characteristic areas such as elbow and knee flexures [35].

3.1. The pathogenesis

The pathogenesis of atopic eczema is complicated and multicausal, including a defective skin barrier, an imbalance in cell-mediated immune responses, immunoglobulin E mediated hypersensitivity, and environmental factors [36] . However, epidermal barrier dysfunction and immune dysregulation seem to be crucial. The theory of immune imbalance assumes that atopic dermatitis is caused by an imbalance in T cells - the imbalance between T helper (Th)2 vs. Th1/Th17 cells is observed during the early phase of atopic dermatitis, while a mixed Th1/Th2 pattern of inflammation is typically present during the chronic stage. The predominance of Th2 results in an elevated synthesis of interleukins, mainly IL-4, IL-5, and IL-13. This, in turn, leads to elevated levels of IgE, while the differentiation of Th1 is correspondingly inhibited [37][38]. The concept of skin barrier dysfunction as a pathogenesis of atopic dermatitis is based on the finding that mutations in the filaggrin gene might cause inflammation and infiltration of T cells, resulting in the development of atopic dermatitis [35] [32] . Moreover, not having enough filaggrin can cause severe atopic dermatitis by

potentially increasing the trans-epidermal loss of water, altering skin pH, and causing dehydration [36]. The loss of barrier integrity is believed to allow allergens, pollutants, and microorganisms to penetrate, triggering an inflammatory immune response that leads to sensitization and the development of a proinflammatory atopic state. Overall, both defective epidermal barrier and type 2 (T2) inflammation are strongly associated with the development of eczema lesions [39].

3.2. Atopic dermatitis and fatty acids

Recent studies suggest that a deficiency in fatty acids may be associated with the development of atopic dermatitis [40]. The changes in stratum corneum lipid composition indicate the significance of ceramides and free fatty acids for skin barrier dysfunction in atopic dermatitis [41]. J.A.W. van Gool et al. conducted a study to examine whether supplementing 118 infants at risk with gamma-linolenic acid (GLA) can potentially prevent the development of atopic dermatitis. During the first six months of life, the participants received a borage oil supplement containing 100 mg of GLA or a placebo of sunflower oil daily. When they were 1 year old, the researchers assessed the severity of atopic dermatitis and the total serum IgE levels. The intervention did not have an impact on total serum IgE. However, it did tend to reduce the severity of atopic dermatitis throughout later infancy in these children [42]. Meta-analysis by Anandan et al. revealed that supplementation with omega-3 and omega-6 oils did not have a protective effect on atopic dermatitis development [43]. Another study aimed to investigate if omega-3 PUFAs supplementation during pregnancy can reduce the risk of eczema among children of different ages. Jia et al. conducted a meta-analysis including 7 studies and 1,646 mother-infant pairs. They found that the intervention cannot reduce the risk of eczema or IgE-associated atopic dermatitis in children [44]. Researchers also conducted studies on the impact of dietary supplementation with PUFAs on the symptoms of atopic dermatitis. The study by Eriksenim revealed that administration of antioxidants combined with PUFAs improved symptoms of eczema in 14 of 17 patients by more than 50% after 8 weeks and 16 weeks of treatment. However, the sample size was very small [45]. Nevertheless, a study with a larger sample size found that there were no significant differences in atopic dermatitis symptoms between the group treated with fish oil and the placebo group [46]. According to other study omega-3 FA-based lipid infusions are beneficial in hospitalized patients with moderate-to-severe atopic dermatitis [47].

The results of the studies are not coherent. It seems unlikely that FAs provide protection against the development of atopic dermatitis. The efficacy of dietary supplementation with PUFAs in alleviating symptoms of eczema remains inconclusive. The majority of the studies had a small sample size. Thus, additional prospective randomized clinical trials with a larger sample size are needed to reach final conclusions.

4. Psoriasis

Psoriasis is a chronic, non-infectious inflammatory skin condition with global prevalence rates that vary from approximately 1% to 3% [48] . Despite the existence of distinct clinical phenotypes, plaque type or psoriasis vulgaris remains the most common [49,50]. The lesions are typically well-defined erythematous plaques covered with waxy white scales. The scalp, the hair margin, the trunk and the extensor surfaces of the knees and elbows are the most characteristic locations for psoriatic lesions to occur [49–51].

4.1.The pathogenesis

Despite the continued inability to identify a singular cause of psoriasis, it is evident that autoimmune mechanisms, in conjunction with a genetic predisposition and environmental factors, play a role in its development [49]. The formation of lesions is a consequence of the reduction in the turnover time, which is accompanied by an increase in the proliferation rate of epidermal cells. As psoriatic lesions have been found to consist of both keratinocytes and leukocytes, it seems as if the main underlying cause of the disease is a disruption between the innate and adaptive immune responses. Various environmental triggers may lead to the activation of dendritic cells, which in turn prompts them to synthesize IL-23, IL-12 and TNF-α. IL-23 and IL-12 are involved in the differentiation of T helper (Th)17 and Th1 cells. Consequently, Th17 secrete interleukins, namely IL-17 and IL-22. This process results in the uncontrolled proliferation of keratinocytes, which ultimately leads to the formation of psoriatic plaques [50,51] . Furthermore, IL-17 induces the expression of CCL20, which functions as an attractant for Th17 cells, thus creating a positive feedback loop [49] . Activation of T cells creates a pro-inflammatory environment by means of arachidonic acid. Several pro-inflammatory compounds are derived from it, including prostaglandins, thromboxanes and leukotrienes [51]. Prostaglandin E2 (PGE2) has been shown to promote the production of IL-23 by dendritic cells, facilitating the differentiation of Th17, which in turn

secrete IL-17 [52] . In conclusion, the IL-23/Th17 axis is the most important factor in the pathophysiology of psoriasis vulgaris.

4.2. Psoriasis and fatty acids

Recently, there has been a growing interest in the anti-inflammatory and pluripotential qualities of omega-3 FAs in the context of psoriasis. In a study by Qin et al. [53], the impact of endogenous omega-3 PUFAs on the development of psoriasis-like lesions in a fat-1 transgenic mouse model subjected to IMQ induction was investigated. Transgenic mice expressing the fat-1 gene are capable of endogenously converting omega-6 PUFAs to omega-3 PUFAs, which act as anti-inflammatory agents. The study concluded that omega-3 PUFAs target the hallmark of psoriatic lesions, namely the IL-23/Th17 axis. A reduction in the number of Th17 cells has been observed, accompanied by a reduction in the levels of pro-inflammatory interleukins, including IL-17, IL-22, and IL-23. Consequently, the process of uncontrolled proliferation of keratinocytes is significantly inhibited, resulting in a reduction in plaque formation. In addition, omega-3 PUFAs have been demonstrated to stimulate the secretion of anti-inflammatory agents, such as Foxp3, by regulatory T cells (Treg cells), thereby suppressing inflammation within the skin [53,54]. Resolvin E1 (RvE1) is a derivative of EPA, which acts as a lipid mediator. The compound's mechanism of action involves the inhibition of the stimulation of dendritic cells, which in turn results in the failure to secrete IL-23. By blocking the signalling of LTB4, RvE1 additionally suppresses the migration of Th17 [52] , thereby decreasing the overall pro-inflammatory environment. Omega-3 PUFA supplementation has been demonstrated to significantly reduce PASI score, scaling and erythema in psoriatic patients [29,51,55,56] . Nevertheless, Clark et al. [51] observed more pronounced improvements with dosages above 1800 mg/day and durations of less than 8 weeks. Despite the promising effects in terms of the aforementioned factors, research remains inconclusive with respect to the reduction of itching, desquamation, percentage of total body surface area affected (%TBSA) and infiltration [51,56] . Consequently, further research is required to address these remaining uncertainties.

5. Discussion

The referenced studies underscore the potential therapeutic benefits of omega-3 PUFAs for various skin diseases. However, there is a paucity of evidence-based guidelines regarding omega-3 PUFAs supplementation specifically for dermatological conditions. It is

also important to note that the available studies have certain limitations, including methodological, small research sample sizes and sample bias. In addition, different doses and sources of omega-3 PUFAs can lead to different biological effects.

In general, the literature indicates that the requirement for PUFAs varies according to age, physiological condition and health status. It is therefore recommended that the daily diet provides an appropriate amount of PUFAs from both the omega-3 and omega-6 families. The Adequate Intake (AI) for an adult, as defined by the Nutrition Standards for the Polish population and their application, is as follows: omega-3 ALA 0.5% of dietary energy (%E), DHA + EPA two portions of fish per week, including one portion of oily fish or 250 mg/day and omega-6 LA 4% E [57] . The Food and Nutrition Board of the National Academy of Medicine has developed intake recommendations for ALA, which state that adult men should consume 1.6 grams per day and adult women should consume 1.1 grams per day. However, specific daily recommended amounts for EPA and DHA have not been established. The American Heart Association (AHA) recommends consuming two servings of fish, particularly fatty fish, per week. Omega-6 fatty acids, like LA, have an AI of about 14-17 grams per day for men and 11-12 grams per day for women [58,59].

In addition, research has shown that an important element of PUFA supplementation is the ratio of omega-6 to omega-3. This disproportionate intake can contribute to inflammation and the development of various health problems, including cardiovascular disease, cancer and autoimmune disorders. However, the Western diet is marked by higher consumption of omega-6 PUFAs, and trans fats, alongside a general reduction in omega-3 PUFAs intake. Therefore, to mitigate the risks associated with excessive consumption of omega-6 PUFAs, it is recommended to aim for an optimal omega-6 to omega-3 ratio of 4-5:1 [60,61]. Moreover, according to Choudhury et al. a ratio of 1:1 or close to that is beneficial for healthy living and avoiding various health complications [62].

Recent studies have focused on the post-translational role of soluble epoxide hydrolase (sEH) in skin physiology. sEH metabolises epoxyeicosatrienoic acids (EETs) derived from PUFAs. EETs promote keratinocyte proliferation and possess anti-inflammatory properties. However, by converting EETs into less active dihydroxyeicosatrienoic acids (DHETs), sEH reduces these beneficial effects. Inhibiting sEH increases EET levels, enhancing keratinocyte proliferation and potentially improving wound healing and inflammatory skin conditions [63]. A further study indicates that a lipidomics-based approach which employs modern analytical techniques, can provide more accurate identification of various lipid types and elucidate the

role of each one. The authors of the study emphasise the advantages of lipidomics analysis and the necessity for further research integrating the medical fields of genomics, proteomics, microbiomes, and exosomes [64].

6. Conclusions

Omega-3 PUFAs, due to their anti-inflammatory and immunomodulatory properties, show promising therapeutic potential in the management of various skin conditions, including acne vulgaris, atopic dermatitis and psoriasis vulgaris. Nevertheless, further research is required to better understand the mechanisms of action of omega-3 PUFAs and to determine their recommended doses, efficacy and safety in the treatment of skin diseases.

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