ZAPAŁA, Magdalena, HUNEK, Adrian, KAZIRÓD, Karolina, CHMIELARZ, Karolina, WIŚNIEWSKA-SKOMRA, Joanna, TYLUTKA, Kinga, HAPON, Anna and DADZIAK, Mikołaj. The use of retinoids in the treatment of skin lesions and prevention of signs of skin aging - a systematic review. Journal of Education, Health and Sport. 2023;27(1):87-107. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2023.27.01.009
https://apcz.umk.pl/JEHS/article/view/44700
https://zenodo.org/record/8173827

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 17.07.2023 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences).
Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 17.07.2023 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159.
Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 24.06.2023. Revised: 20.07.2023. Accepted: 20.07.2023. Published: 25.07.2023.

The use of retinoids in the treatment of skin lesions and prevention of signs of skin aging - a systematic review

Magdalena Zapała[1], Adrian Hunek[1], Karolina Kaziród [2], Karolina Chmielarz[1], Joanna Wiśniewska-Skomra[1], Kinga Tylutka[1], Anna Hapon[1], Mikołaj Dadziak[3]

1. **Uniwersytecki Szpital Kliniczny im. Fryderyka Chopina w Rzeszowie**
2. **Szpital Wojewódzki im. św. Łukasza w Tarnowie**
3. **Medical University of Lublin**

ORCID ID:

Magdalena Alicja Zapała, https://orcid.org/0000-0003-3618-7228, lennyz9612@gmail.com

Adrian Hunek, https://orcid.org/0009-0003-9281-4166, a.k.hunek@gmail.com

Karolina Kaziród, https://orcid.org/0000-0002-6305-6488, kazirodkarolina@gmail.com

Karolina Chmielarz, https://orcid.org/0009-0009-1704-4505, karolina.chmielarz@gmail.com

Joanna Wiśniewska-Skomra, https://orcid.org/0009-0003-7189-4267, joanna.wi.sko@gmail.com

Kinga Tylutka, https://orcid.org/0009-0005-8646-8679, kingatylutka@gmail.com

Anna Hapon, https://orcid.org/0009-0003-6974-4147, ania.hapon@gmail.com

Mikołaj Dadziak, https://orcid.org/0000-0002-6988-5498, mikolaj.dadziak@onet.pl

Correspondence: Magdalena Zapała, lennyz9612@gmail.com

Abstract

Retinoids are a group of substances that include vitamin A and its natural and synthetic derivatives. They are used in the treatment of various skin diseases, such as: rosacea, acne vulgaris, psoriasis. In addition, recently there is a lot of information about the action of preventing photoaging. Oral retinoids have been proven to be the most effective treatment for acne of various severity available today. Through their comprehensive action, affecting the four main factors associated with the pathogenesis of acne, they significantly reduce skin changes. Externally applied retinoids regulate the renewal of epidermal cells, stimulate the production of collagen fibers, increase the production of elastin, and lead to an increase in the number and activity of fibroblasts. Therefore, more and more people are using preparations containing retinoids to prevent skin aging. It has been proven that this procedure leads to shallower wrinkles and slows down the appearance of new ones, and evens out the skin tone. Retinoids are effective substances, but their use is associated with the risk of various side effects, the most common of which are: skin irritation, photosensitisation, headaches, muscle and joint pain, and teratogenicity.

Key words: retinol, skin, acne, aging, bakuchiol

Introduction

Retinol (a derivative of vitamin A) is one of the representatives of retinoids and is increasingly used in "anti-aging" cosmetics and cosmetic procedures [30]. Through metabolic transformations, retinol converts to retinal and then to retinoic acid, which is the most active form of vitamin A. When applied to the skin, it easily penetrates deep layers of the epidermis, accelerating the cell regeneration cycle and stimulating fibroblasts, which are responsible for collagen and elastin production. The most common adverse reaction to topical retinoids is the so-called "retinoid reaction," characterized by itching, burning at the application site, redness, and peeling. Retinol has milder effects and, unlike other retinoids, has fewer side effects and does not cause such strong skin irritation. Another undesirable effect associated with retinoid therapy is photosensitivity, which usually occurs at the beginning of treatment. Patients treated with retinoids are advised to avoid excessive sun exposure and use precautions such as sunscreens for sun protection. However, after several months of therapy, the skin's reaction to UV radiation returns to normal. In some cases, irritating conjunctivitis has also been reported

when retinoids were used near the eye area [54]. Meanwhile, the main adverse effects observed during oral retinoid use include dermatological diseases, psychiatric disorders, headaches, muscle and joint pain, the risk of developing nonspecific intestinal inflammations, teratogenicity (the most dangerous irreversible side effect), increased levels of cholesterol and triglycerides in the blood, increased blood glucose levels, osteopenia, degenerative spinal disease, and corneal opacity [4,22].

Studies show that topically applied retinol at a concentration of 0.4% exhibits anti-aging effects by improving the homeostasis of the epidermis and dermis, stimulating keratinocyte and endothelial cell proliferation, and activating skin fibroblasts. It is a promising and safe treatment method for naturally aging human skin [52].

Objective

A literature review on the impact of using preparations containing retinoids on the treatment of skin diseases, skin condition, and aging processes.

Materials and Methods

A review of literature available in PubMed and Google Scholar. Abstracts, comments, and articles in languages other than English and Polish were excluded.

ARTICLE CONTENT

Differences between oral preparations of vitamin A derivatives and topical application of retinol in the form of creams and peels

The regenerative and therapeutic effects of vitamin A on the skin have been utilized in dermatology and cosmetology. Its derivatives are known and available in the form of topical and oral preparations. They are effective in treating acne, psoriasis, reducing wrinkles, and inhibiting skin aging processes [54]. Due to their lipophilic properties, they penetrate the stratum corneum and reach the dermis, which is why many preparations are used topically on the skin. In such forms, retinols are present, such as tretinoin (all-trans retinoic acid) - 0.025% to 0.1% in cream, gel, or gel with microspheres, isotretinoin (13-cis retinoic acid), as well as synthetic third-generation polyaromatic derivatives: adapalene (0.1%, 0.3% in cream and 0.1% in balm), and tazarotene (0.05%, 0.1% cream, gel, foam) [3,59]. These preparations treat adolescent and common acne, reduce the number of blackheads, and sebum secretion. Tazarotene is also used in the treatment of psoriasis.

Retinoids are the primary drugs for the topical treatment of acne, as they remove microcomedones and have anti-inflammatory effects. According to the recommendations of the American Academy of Dermatology from 2016, topical retinoids are used as the first-line treatment for acne of mild, moderate, and severe intensity, either as monotherapy or in combination with benzoyl peroxide and antibiotics. Among the oral derivatives of vitamin A, isotretinoin (Accutane) is the best known. It has been approved for the treatment of severe nodular acne, moderate acne, and acne that is resistant to treatment. It is also effective in treating acne scars and rapidly recurring pimples after antibiotic therapy. The commonly used doses range from 0.1 mg/kg/day to 1 mg/kg/day. In the case of severe acne, higher doses are associated with a lower frequency of acne relapses. On the other hand, lower doses ranging from 0.25-0.4 mg/kg/day in the treatment of moderate acne are equally effective as the standard recommended doses (0.5 and 1.0 mg/kg/day), which additionally reduces the risk of side effects [3].

Topical preparations with vitamin A derivatives are equally effective as oral preparations. In one clinical study, the efficacy of topically applied isotretinoin (0.05%) and tretinoin (0.05%) was compared. After 12 weeks of use, both preparations equally reduced the number of papules and nodules on the face [18]. Both preparations were topical. In another study, the effectiveness of an oral dose of isotretinoin 10 mg/day was compared with tretinoin 0.025% cream applied topically in the treatment of resistant or severe rosacea. The oral medication resulted in faster improvement in reducing redness, the number of papules and nodules, but the final effect was the same. Both medications provide desired benefits to the same extent and are well-tolerated. However, the combined use of oral and topical therapy did not show greater benefits [20].

The anti-aging effects of retinol, such as slowing down skin aging, reducing wrinkles, and discolorations, are also well-known. Recently, the influence of the form of the drug in a specific concentration on the anti-aging effect has been studied. In a randomized controlled trial involving forty-five women aged 35-65 years, some of them used gradually increasing doses of retinol serum (0.25%, 0.5%, 1%), while others used tretinoin cream (0.025%, 0.05%, 0.1%). Over the 12-week study period, photodamage visible on the skin was assessed. It was observed that retinol serum and tretinoin cream were equally effective in reducing the effects of skin aging. Histological skin biopsies of individuals using retinol serum showed newly formed collagen and thickening of the epidermis, resulting in reduced facial roughness and skin smoothing, which was not observed in individuals using the cream [17]. Currently, oral isotretinoin is not approved for anti-aging therapy due to the side effects of retinoids, while

the use of topical preparations provides a beneficial alternative to oral therapy due to its effectiveness [26]. Another form is tretinoin peels, which reduce skin discolorations, photoaging, and precancerous skin lesions [57].

It is worth mentioning the preparation called adapalene. This drug has keratolytic and proliferative effects on the epidermis. It is effective and safe in the treatment of adolescent acne and excessive keratinization. Tazarotene has similar effects and is also used in the treatment of psoriasis, discolorations, and wrinkles [66].

Improving the derivatives of retinol applied to the skin leads to an increase in their effectiveness. They become competitive with the popular Isotretinoin, which, regardless of the dosage, is a potent medication that exposes the body to side effects. The most common side effects include dry skin and mucous membranes, as well as conjunctivitis. Other, rarer side effects include inflammatory bowel diseases, anxiety, depression, increased cardiovascular risk, and teratogenicity [3]. Therefore, topical preparations contribute to improving the patient's well-being and increasing treatment comfort, and their effectiveness is only slightly lower than that of oral isotretinoin.

The anti-acne effects of topical retinoids

Acne vulgaris is one of the most common skin diseases affecting all age groups. The peak incidence of acne occurs at ages 14-17 in females and 16-19 in males [46]. The symptoms include sebum production, microcomedones transforming into closed or open comedones, as well as papules and pustules. In more severe cases, inflammatory infiltrates, pustular lesions, and even systemic symptoms such as fever and joint pain may occur. The lesions are mainly localized on the face, sometimes also on the back and chest. The pathogenesis is complex, involving disorders in follicular keratinization, excessive sebum production, and the presence of Propionibacterium acnes bacteria in the sebaceous glands [44,47]. Several substances are used in acne therapy, including retinoids, both topically and orally. They can be used as monotherapy or in combination with other topical and systemic medications. Retinoids belonging to the first and third generation are used in the treatment of acne. The first-generation includes tretinoin (all-trans retinoic acid), isotretinoin (13-cis retinoic acid), and retinaldehyde. Adapalene and tazarotene belong to the third generation [46]. Retinoids interact with tissue processes through nuclear receptors: retinoic acid receptors (RAR) and retinoid X receptors (RXR) [44,47]. Topical retinoids have a minor suppressive effect on sebaceous gland function but normalize keratinization. By exerting a keratolytic effect, they promote the emptying of follicular units of horny sebum plugs and prevent the formation of

microcomedones. Through the elimination of the barrier in the pilosebaceous unit's outflow tract, they facilitate sebum evacuation. Additionally, they indirectly reduce the intensity of the inflammatory response by creating an unfavorable microenvironment for P. acnes development [46]. Topical retinoids have been used in acne therapy for several decades. Tretinoin and isotretinoin are considered first-line agents and are used in long-term treatment [6]. Tretinoin is applied topically at concentrations ranging from 0.001% to 0.4% in the form of gel, cream, or ointment [67]. Topical retinoids should be applied once daily, usually in the evening, to the entire area of affected skin, several minutes after washing, to allow complete drying. The introduction of retinoids should be gradual, starting with application every 3 days in the first week, every 2 days in the second week, and daily in the third week. In maintenance therapy, which can last for several years, retinoids are applied 2-3 times a week. Moisturizers should be used during topical retinoid therapy to prevent skin irritation and dryness [46]. The use of photoprotective cosmetics is also necessary [14]. Numerous studies confirm the effectiveness of topical retinoid therapy in acne treatment. In a study by Lavker et al., a 0.1% tretinoin cream was applied, resulting in a 50% reduction in the number of microcomedones by the 6th week and an 80% reduction by the 12th week of treatment. Biopsy samples showed a transformation of microcomedones from well-developed keratin plugs containing numerous bacteria to only a few layers of keratin sparsely populated by Propionibacterium acnes [34]. Tretinoin has been found to be effective in combination with other anti-acne substances. In a study by Mills et al., the twice-daily application of a 2% erythromycin base solution in an alcohol-water mixture, accompanied by once-daily application of a 0.05% tretinoin solution, was significantly more effective than monotherapy in the treatment of moderate inflammatory acne [41]. In another multicenter study involving 1337 patients, the high efficacy and tolerability of a fixed gel formulation containing 0.025% tretinoin and 4% erythromycin were confirmed [31]. In a study by Gupta et al., comparing combination therapy with tretinoin plus erythromycin and benzoyl peroxide, a 3% erythromycin/5% benzoyl peroxide combination provided greater reduction in acne symptoms, as assessed by both physicians and patients, and better tolerability than 0.025% tretinoin/4% erythromycin after two weeks of treatment [24]. Isotretinoin, which is the 13-cis isomer of tretinoin, can also be an effective therapy for acne. A study by Dominguez et al. showed that a 0.05% isotretinoin gel was equally effective as a 0.05% tretinoin cream [16]. A meta-analysis of five well-controlled studies involving over 900 patients demonstrated comparable efficacy between 0.1% adapalene and 0.025% tretinoin, with a mean reduction in total acne lesion count of 57% in patients receiving adapalene for 12 weeks and 53% in those receiving tretinoin, but with a faster onset of action with adapalene

[13]. Topical tretinoin and adapalene are classified as FDA pregnancy category C, which means that the risk cannot be ruled out due to the lack of human data and either positive animal studies or no available data. They may be prescribed when the benefits outweigh the risks, although their use during pregnancy is difficult to justify as there are alternative acne treatments available. During lactation, their use is not recommended since their penetration into breast milk has not been studied, and adverse effects on breastfed infants cannot be excluded [58].

The anti-acne action of oral retinoids

Isotretinoin (13-cis-retinoic acid) belongs to the first generation of cyclic retinoids and is administered orally. Currently, it is the only substance that, when used as monotherapy, can affect all four major factors related to the pathogenesis of acne. Its mechanism of action includes: inhibiting the activity of sebaceous glands, normalizing the keratinization process within the pilosebaceous unit, exerting direct anti-inflammatory effects (inhibiting leukocyte chemotaxis), and secondary limitation of the growth of Cutibacterium acnes (formerly known as Propionibacterium acnes). Due to these actions, isotretinoin is the most effective method for treating common acne. It has been used since the 1980s for the treatment of severe and treatment-resistant forms of acne. Initially, isotretinoin was only used in the most severe cases of acne, but now it is also used for patients with milder forms of the disease who do not respond to previously used therapies, as well as for patients prone to scarring, acne fulminans, and those whose condition significantly impairs their quality of life [32, 33, 60].

Dosage

The recommended dosage of isotretinoin is from 0.5 to 1.0 mg per kilogram of body weight per day (up to 2 mg/kg/day), divided into two doses. If the patient does not comply with the instructions for divided dosing, the medication should be taken once a day. For moderate acne, lower doses of isotretinoin have been used in recent years (0.3 mg/kg, 0.4 mg/kg, or 20 mg, or 5 mg daily, or 20 mg every other day). The treatment should last from 15 to 24 weeks, up to a maximum of 9 months. The drug has a short half-life and is eliminated from the body within a few days. Studies suggest that acne improvement is typically observed with a cumulative dose of 100 to 150 mg per kilogram of body weight, and in some cases, a second course of pharmacotherapy may be necessary, starting 8 weeks after the first treatment course. Research also indicates that the majority of acne patients taking oral retinoids report improvement, with complete resolution of acne lesions observed in at least 40% of the subjects. Combining isotretinoin with an antihistamine medication may enhance its effectiveness and reduce side

effects. The medication should be taken with meals, preferably rich in fat, to optimize its bioavailability due to its lipophilic absorption profile [4,22].

Off-label use

Isotretinoin is not approved as a treatment for acne in children under 12 years of age. F. Sarazin et al. described a case of a 20-month-old girl who developed nodulocystic acne, which is not typical for infantile acne at that age, as it usually occurs between 6 and 16 months of age. The girl had no clinical or biological signs of hormonal disorders. Due to the lack of response to traditional first-line antibiotics, it was decided to initiate oral isotretinoin therapy. Remission was achieved after a seven-month treatment period. The clinical and biological tolerance of the treatment was good, with no growth disturbances in the patient. Isotretinoin can be used in cases of nodulocystic acne to reduce the risk of scarring [51].

Efficacy of oral isotretinoin compared to oral antibiotic therapy

Isotretinoin is recommended for the treatment of moderate to severe common acne, similar to orally administered antibiotics. Oral retinoids have an advantage over orally administered antibiotics. Patients taking isotretinoin experience fewer relapses, reducing the risk of scarring, which can worsen the appearance of the skin and lead to less emotional stress in teenagers. In the absence of absolute contraindications, isotretinoin should be the first-line treatment for moderate to severe inflammatory acne [65]. Isotretinoin can be used as monotherapy, while systemic antibiotics should only be used in combination with topical agents. The increasing problem with oral antibiotic therapy is the development of antibiotic resistance, which is why the therapy should be as short as possible, lasting a maximum of 12 weeks. These principles do not apply to selected resistant cases. After discontinuing systemic antibiotic therapy, topical retinoids should be used to maintain remission [5,43,65].

In the past, there was a belief that adolescent acne was an infectious disease, leading to antibacterial treatment being the main choice of specialists. However, in recent years, the prevailing theory suggests that acne is mainly associated with inflammatory skin conditions, which has led to a decrease in the use of oral antibiotics and an increasing preference for medications that reduce the severity of inflammation. Oral antibiotics should not be used in long-term maintenance therapy for common acne [38]. According to a meta-analysis conducted by I. Mavranezouli et al., the use of oral retinoids in the treatment of moderate to severe adolescent acne is associated with the highest treatment efficacy [39].

Rosacea is an inflammatory skin condition affecting adults. Its papulopustular subtype is mainly treated with topical and oral antibiotics. A study conducted by A. Shemer et al.

compared the effectiveness of treatment for rosacea by taking oral isotretinoin in one group of patients and oral antibiotic therapy (minocycline) in another group. For mild to moderate severity of the lesions, the efficacy of treatment with isotretinoin at a dose of 20 mg per week (in a single undivided dose) was compared to minocycline at a dose of 100 mg per day. The therapies lasted for 4 to 7 months. Both medications showed comparable treatment efficacy. For severe rosacea, isotretinoin at a dose of 40 mg per week was more effective. This study demonstrates that using weekly low-dose isotretinoin is an effective treatment option for papulopustular rosacea, including patients with a severe form of the disease [53].

Anti-aging

Skin aging involves the loss of its physical and biological properties, influenced by various factors. Skin aging can be divided into exogenous and endogenous aging. Exogenous aging is influenced by external factors such as lifestyle, diet, tobacco smoking, mechanical stress, xenobiotics, and solar radiation (known as photoaging or sun-induced aging). Endogenous aging, also known as natural aging or chronological aging, is related to factors such as age, hormonal changes, genetic factors, metabolic processes, etc. Undoubtedly, UV solar radiation is the main factor responsible for skin aging [50].

Table 1. The effect of external retinoids on the skin.

The action of external retinoids on the skin.
Regulation of the skin cell renewal processes: loosening of connections between epidermal cells and facilitating keratinization
Enhancement of epidermal renewal, accelerated proliferation of basal layer cells of the epidermis
Strengthening the protective functions of the epidermis, reducing excessive transepidermal water loss
Stimulation of collagen fiber production and increased elastin synthesis
Inhibition of the activity of collagen and elastin-degrading enzymes
Influence on the increase in the quantity and activity of fibroblasts
Anti-acne action, regulating the process of sebum secretion in the sebaceous gland ducts
Influence on the proper and even distribution of melanin in the skin
Stimulation of angiogenesis

Source: [2,8,27,66].

Through their comprehensive action, retinoids contribute to improving the appearance and overall condition of the skin by smoothing and increasing its elasticity, improving hydration, eliminating fine wrinkles and reducing deep ones, lightening pigmentation, and reducing the number of blackheads [23].

This is clearly illustrated by Jang et al. in a long-term study comparing the effectiveness and speed of action of different concentrations of retinol (1500-6600 IU) on middle-aged women. Low concentrations of retinol (1500-2500 IU) had a significantly greater impact on the color, brightness, and elasticity of the skin, as well as a faster improvement in skin brightness and elasticity compared to high concentrations (3300-6600 IU). High concentrations of retinol had a significantly greater impact on wrinkles, skin density, and pores, as well as a faster improvement in wrinkles, skin texture, pores, and desquamation compared to low concentrations [28].

Similarly, a double-blind study conducted by Randhawa et al. evaluated the efficacy and safety of using 0.1% stabilized retinol on photodamaged skin during a one-year treatment. The authors demonstrated in their results that after 52 weeks of retinol therapy, there was a 44% reduction in fine lines and an 84% reduction in mottled pigmentation. Over 50% of the participants reported a significant subjective improvement in their skin condition. Furthermore, histochemical data in the 52nd week confirmed the clinical results, as increased expression of type I pro-collagen, hyaluronan, and Ki67 were observed in skin biopsies of the treated patients [48].

The initial effects of topical retinoid use can be seen after a few weeks. Currently, there are no limitations regarding the duration of retinoid use in photodamage prevention. With proper care, topical retinoids can be used continuously for several years [23].

Despite promising results in skin aging therapy, light sensitivity and irritating reactions such as burning, peeling, or skin inflammation associated with retinoid therapy limit their acceptance by patients. Various new drug delivery systems have been developed to minimize these side effects. Nanoparticles, in particular, have shown great potential in improving the stability, tolerance, and effectiveness of retinoids. It is possible to employ a slightly different approach to formulating cosmetics containing retinol by using formulations such as liposomes, microsponges, microemulsions, and inclusion complexes with cyclodextrins [54].

The Impact of Retinoid Use on Stretch Marks

Stretch marks are linear atrophic skin changes that most commonly occur in young, healthy women [7, 21, 35, 36]. They can develop both in physiological states such as pregnancy and rapid growth during adolescence, as well as in pathological conditions such as Cushing's syndrome or Marfan syndrome [36]. The etiology of their formation is not entirely clear, but the most frequently mentioned factors in the literature are hormonal imbalances, especially excess cortisol, mechanical stress, and genetic predispositions [7,36]. Stretch marks result from skin scarring and epidermal thinning. In the dermis, a decrease in extracellular matrix components such as collagen, fibrillin, elastin, and fibronectin is observed [19,42,56,61]. Clinically, two stages of stretch mark development can be observed. The initial stage is characterized by raised, erythematous, and inflammatory changes, while the second stage involves white, depressed, and wrinkled changes [12,19]. Stretch marks often lead to a deterioration in mental well-being, especially in women and professions where physical appearance is of great importance [21,36].

Currently, there are many methods available for treating stretch marks, although none of them can completely eliminate them. The treatments aim to increase collagen production, reduce redness, or enhance pigmentation [19,36].

Table 2: Methods for treating stretch marks.

Stretch mark treatment methods
Laser therapy
Light-based therapies
Radiofrequency (ablation and non-ablative)
Galvanopuncture
Carboxytherapy
Microdermabrasion
Platelet-rich plasma injections
Microneedling
Topically applied substances

Source: [19,36].

Table 3: Topically applied substances in the treatment of stretch marks.

Topically applied substances
Tretinoin and retinoic acid
Centellaasiatica extract
Hyaluronic acid
Silicones
Chemical peels containing glycolic acid or trichloroacetic acid
Ascorbic acid
Cocoa butter
Plant oils
Pirfenidone

Source: [19,36].

One of the treatment methods involves the use of tretinoin and retinoic acid on the affected skin. These substances are believed to act by stimulating fibroblasts, leading to an increase in collagen levels in the tissues, particularly in early-stage stretch marks [1]. Studies have shown that tretinoin has demonstrated greater effectiveness in treating red stretch marks, while its efficacy is limited in the case of white stretch marks [49, 62].

In a study conducted by Rengel O., 20 women with stretch marks in the abdominal area associated with pregnancy participated. They applied a 0.1% tretinoin cream daily for three months. One specific lesion was analyzed and assessed using a six-point scale. Significant improvement was observed in all women at the 12th week compared to the initial state, with a reduction in the length of the selected lesion by approximately 20% [49].

Kang S. and colleagues conducted a double-blind, randomized trial involving 22 patients. Ten of them used a 0.1% tretinoin cream (the experimental group), while the remaining 12 used a placebo (the control group). Both groups applied the cream daily to the affected areas. The results were evaluated through monthly physical examinations and analysis of stretch mark biopsies, comparing them with untreated normal skin. After just two months, patients using

tretinoin showed significant improvement in the severity of stretch marks compared to those in the placebo group. At the end of the therapy, 80% of patients treated with tretinoin showed noticeable improvement, while only 1 patient (8%) in the control group experienced improvement. The group using tretinoin demonstrated a reduction in the average length and width of stretch marks by 14% and 8%, respectively, whereas the group using the placebo experienced an increase in the dimensions by 10% and 24%, respectively. No significant differences were noted in the measurements of skin collagen and elastin content in the stretch marks between the two groups [29].

Lu H. and colleagues conducted a meta-analysis to assess the effectiveness of different therapies for treating stretch marks. They analyzed 14 studies involving a total of 651 participants. The clinical efficacy and patient satisfaction rate were evaluated for the following treatment methods: topical agents, microdermabrasion, laser therapy, light therapy, needle therapy, radiofrequency device therapy, platelet-rich plasma injections, and combination therapies. The combination of bipolar radiofrequency and tretinoin showed the highest likelihood of favorable results in terms of both clinical efficacy and patient satisfaction. The second most effective treatment was bipolar radiofrequency as a monotherapy. Fractional CO2 laser demonstrated much better clinical efficacy and higher patient satisfaction compared to other laser procedures. According to the authors, topical tretinoin exhibited the lowest effectiveness considering the evaluated aspects [37].

Hexsel et al. compared the effects of superficial dermabrasion and topical application of a tretinoin cream on early red stretch marks. In the first group, superficial and localized dermabrasion were applied for 16 weeks, while the second group daily applied a cream with a 0.05% concentration of tretinoin. The stretch marks were evaluated using photographic documentation and their dimensions were measured before the trial and at 4, 8, 12, and 16 weeks. Both groups showed a reduction in the width and length of the evaluated stretch marks at the end of the treatment. There were no significant differences between the results of the two groups. All study participants reported improvement from the treatment [25].

In their research, Listiawan focused on late-stage white stretch marks. They compared standard treatment with a cream containing 0.1% tretinoin to combination therapy using fractional micro-needle radiofrequency and fractional CO2 laser. Each of the studied groups consisted of 11 patients. The length and width of the lesions were measured for all patients, and the percentage of collagen surface area was assessed. The first evaluation was conducted before the study, and another one was done 4 weeks after the completion of the therapy. The group using the tretinoin cream did not observe a reduction in the size of the stretch marks,

while the group receiving combination therapy showed a decrease in the size of the white stretch marks. The change in the length of the stretch marks was not statistically significant. The collagen surface area increased in both groups [35].

Bakuchiol - a natural retinoid?

Bakuchiol is a compound that is gaining increasing interest in cosmetology. The first studies on this substance were conducted in the 1970s, but difficulties in extraction delayed the availability of bakuchiol-based cosmetics until 2007 [10,40]. Since then, it has become a popular natural alternative to retinoids, which are considered the foundation of anti-aging skincare and therapy.

Bakuchiol is functionally similar to retinol - although these substances do not have strict structural similarities, they have been shown to exhibit similar gene expression and protein synthesis stimulation, suggesting similar in vivo bioactivity. Bakuchiol belongs to the group of natural meroterpenoid phenols, primarily isolated from plants such as Psoraleacorylifolia, P. grandulosa, P. drupaceae, P. otholobium, and P. longum. It has wide applications in Chinese and Indian medicine. Bakuchiol has been shown to have anti-inflammatory, anticancer, antioxidant, antibacterial, cytotoxic, and hepatoprotective properties [9,11].

Cosmetics containing retinol can cause adverse effects such as redness, itching, burning, dryness, increased skin cell turnover, increased perspiration, hair loss, or photosensitivity. However, these adverse effects have not been observed with the use of bakuchiol, which is gentler on the skin, causing minimal irritation and allergic reactions [1,55]. Furthermore, compared to retinol, bakuchiol exhibits greater photochemical stability and ease of formulation with emollients and solubilizers [64]. It is also noteworthy that the ease of using bakuchiol-based cosmetics - its application does not require dermatological consultation or a gradual introduction into routine skincare. It can be used throughout the year without concerns about photosensitivity, and it can also be used during pregnancy and breastfeeding [1,45].

In a study by S. Dhaliwal et al. in 2018, the effects of 0.5% retinol and 0.5% bakuchiol on a group of 44 individuals were compared. The reduction in wrinkles, hyperpigmentation, and adverse effects were evaluated. During the 12-week study period, both bakuchiol and retinol showed comparable effects in the first two parameters. However, bakuchiol, despite transient redness, was better tolerated than retinol, with fewer patients reporting peeling, burning, and itching [15].

Chaudhuri and Bojanowski conducted a study in 2014 using an in vitro skin model called EpiDerm-FT, in which they demonstrated that both bakuchiol and retinol similarly increased the expression of CDH1 and AQP3 genes associated with water transport, ensuring adequate skin hydration and homeostasis. The study also assessed the content of collagen types I, III, and IV in the skin, and it was found that bakuchiol stimulated collagen production to a greater extent, indicating better regenerative properties [9].

Bakuchiol appears to be a remarkable natural ingredient that acts comprehensively yet gently on the skin. Its properties encourage further research to determine optimal doses, establish safety, and explore the possibilities of using bakuchiol not only in cosmetology but also in dermatology and pharmacology.

Summary

Retinoids, derived from vitamin A, regulate the processes of skin renewal, strengthen its protective functions, stimulate collagen and elastin production, have anti-acne effects, and promote angiogenesis. They are successfully used in skin conditions such as acne vulgaris, rosacea, and psoriasis. Additionally, retinoids have anti-aging effects, reducing fine lines and improving skin elasticity.

FOOTNOTES

Author's contribution

Conceptualization, M.Z.; methodology, M.Z.; validation, M.Z.; formal analysis, M.Z.; investigation, M.Z.; writing - original draft preparation, M.Z.; writing - review and editing, A.Hunek; supervision, A.Hunek, K.K., K.C., K.T., K.W-S.,M.D., A.Hapon.

All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Statement of Informed Consent

Not applicable.

Data Availability Statement

Not applicable.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References:

1. Adarsh Krishna TP., Edachery B., Athalathil S. 2022. Bakuchiol - a natural meroterpenoid: structure, isolation, synthesis and functionalization approaches. *RSC Adv*. 12(14):8815-8832.

2. Kaźmierska A., Bolesławska I., Przysławski J. 2019. Effect of retinoids on the skin and prevention of side effects. *Hygeia Public Health*. 54(3): 165-172.

3. Andrea L. Zaenglein, Arun L. Pathy, Bethanee J. Schlosser, Ali Alikhan, Hilary E. Baldwin, Diane S. Berson, Whitney P. Bowe, Emmy M. Graber, Julie C. Harper, Sewon Kang, Jonette E. Keri, James J. Leyden, Rachel V. Reynolds, Nanette B. Silverberg, Linda F. Stein Gold, Megha M. Tollefson, Jonathan S. Weiss, Nancy C. Dolan, Andrew A. Sagan, Mackenzie Stern, Kevin M. Boyer, Reva Bhushan. 2016. Guidelines of care for the management of acne vulgaris, *Journal of the American Academy of Dermatology*, Volume 74, Issue 5, Pages 945-973.e33

4. Bagatin E, Costa CS. 2020. The use of isotretinoin for acne - an update on optimal dosing, surveillance, and adverse effects. *Expert Rev Clin Pharmacol.* 13(8):885-897.

5. Bienenfeld A, Nagler AR, Orlow SJ. 2017. Oral antibacterial therapy for acne vulgaris: an evidence-based review. *Am J Clin Dermatol.*18(4):469-490.

6. Bojarowicz H, Płowiec A. 2010. Wpływ witaminy A na kondycję skóry. *Problemy Higieny i Epidemiol*, 91(3): 352-356.

7. Borrelli MR, Griffin M, Ngaage LM, Longaker MT, Lorenz HP. 2021. Striae Distensae: Scars without Wounds. *Plast Reconstr Surg*.;148(1):77-87.

8. Boryczka M, Pasker B, Sosada M. 2010. Retinoidy jako substancje czynne produktów leczniczych, kosmetyków i suplementów diety. *Farm Prz Nauk*, 8(67): 8-16.

9. Chaudhuri RK, Bojanowski K. 2014. Bakuchiol: a retinol-like functional compound revealed by gene expression profiling and clinically proven to have anti-aging effects. *Int J Cosmet Sci.* 36(3):221-30.

10. Chaudhuri, Ratan K., et al. 2015. Bakuchiol: a retinol-like functional compound, modulating multiple retinol and non-retinol targets. *Cosmeceuticals and active cosmetics*, 1-18.

11. Chen, Zhe; Jin, Ke; Gao, Lingyan; et al. 2010. Anti-tumor effects of bakuchiol, an analogue of resveratrol, on human lung adenocarcinoma A549 cell line. *European Journal of Pharmacology,* 643(2–3): 170–9.

12. Cho S, Park ES, Lee DH, Li K, Chung JH. 2006. Clinical features and risk factors for striae distensae in Korean adolescents. *J Eur Acad Dermatol Venereol.* 20(9):1108-13.

13. Cunliffe WJ, Poncet M, Loesche C, Verschoore M. 1998. A comparison of the efficacy and tolerability of adapalene 0.1% gel versus tretinoin 0.025% gel in patients with acne vulgaris: a meta-analysis of five randomized trials. *Br Journal of Dermatology*; 139 Suppl 52: 48– 56.

14. Czarnota, A., 2018. Retinoidy. mechanizm działania, właściwości oraz zakres stosowania w dermatologii i kosmetologii. *Kosmetologia estetyczna.* vol 7,371-376.

15. Dhaliwal, S., Rybak, I., Ellis, S., Notay, M., Trivedi, M., Burney, W, Sivamani, R. K. 2019. Prospective, randomized, double-blind assessment of topical bakuchiol and retinol for facial photoaging, *British Journal of Dermatology*, Volume 180, Issue 2, Pages 289–296.

16. Dominguez J, Hojyo MT, Celayo JL, Dominguez-Soto L, Teixeira F. 1998. Topical isotretinoin vs. topical retinoic acid in the treatment of acne vulgaris. *International Journal of Dermatology*; 37: 54– 55.

17. Draelos, Z. D., & Peterson, R. S. 2020. A Double-Blind, Comparative Clinical Study of Newly Formulated Retinol Serums vs Tretinoin Cream in Escalating Doses: A Method for Rapid Retinization With Minimized Irritation. *Journal of drugs in dermatology: JDD*, 19(6), 625–631.

18. Elbaum D. J. 1988. Comparison of the stability of topical isotretinoin and topical Tretinoina and their efficacy in acne. *Journal of the American Academy of Dermatology*, 19(3), 486–491.

19. Elsedfy H. 2020. Striae distensae in adolescents: A mini review. *Acta Biomed.* 91(1):176-181.

20. Ertl, G. A., Levine, N., & Kligman, A. M. 1994. A comparison of the efficacy of topical tretinoin and low-dose oral isotretinoin in rosacea. *Archives of dermatology*, 130(3), 319–324.

21. Forbat E, Al-Niaimi F. 2019. Treatment of striae distensae: An evidence-based approach. *J Cosmet Laser Ther.*;21(1):49-57.

22. Greydanus DE, Azmeh R, Cabral MD, Dickson CA, Patel DR. 2021. Acne in the first three decades of life: An update of a disorder with profound implications for all decades of life. *Dis Mon.* 67(4):101103.

23. Glenc-Ambroży M., Piejko L.. 2020. Retinoids in the prevention of photoaging. *Aesthetic Cosmetology and Medicine*. 9(6):489-493.

24. Gupta AK, Lynde CW, Kunynetz RA, Amin S, Choi K, Goldstein E. 2003. A randomized, double-blind, multicenter, parallel group study to compare relative

efficacies of the topical gels 3% erythromycin/5% benzoyl peroxide and 0.025% tretinoin/erythromycin 4% in the treatment of moderate acne vulgaris of the face. *Journal of Cutaneous Medicine and Surgery*; 7: 31– 37.

25. Hexsel D, Soirefmann M, Porto MD, Schilling-Souza J, Siega C, Dal'Forno T. 2014. Superficial dermabrasion versus topical tretinoin on early striae distensae: a randomized, pilot study. *Dermatol Surg.* 40(5):537-44.

26. Honeybrook, A., & Bernstein, E. 2020. Oral isotretinoin and photoaging: A review. *Journal of cosmetic dermatology,* 19(7), 1548–1554.

27. Janda K, Chwiłkowska M. 2014. Trądzik pospolity – etiologia, klasyfikacja, leczenie. *Ann Acad Med. Stetin*, 60(2): 13-18.

28. Jang S., Jung Y., Suk J., Lee S., Han J., Suh B., Kim E. 2022. A long term study of the difference in efficacy and effect rate of various concentrations of retinol (1500-6600 IU) in middle aged women. *Arch Dermatol Res.*

29. Kang S, Kim KJ, Griffiths CE, Wong TY, Talwar HS, Fisher GJ, Gordon D, Hamilton TA, Ellis CN, Voorhees JJ. 1996. Topical tretinoin (retinoic acid) improves early stretch marks. *Arch Dermatol*. 132(5):519-26. PMID: 8624148.

30. Kong, R., Cui, Y., Fisher, G. J., Wang, X., Chen, Y., Schneider, L. M., & Majmudar, G. 2015. A comparative study of the effects of retinol and retinoic acid on histological, molecular, and clinical properties of human skin. *Journal of Cosmetic Dermatology, 15(1), 49–57.*

31. Korting HC, Braun-Falco O. 1989. Efficacy and tolerability of combined topical treatment of acne vulgaris with treti-noin and erythromycin in general practice. *Drugs under Experimental and Clinical Research*; 15: 447– 451.

32. Kurokawa I, Layton AM, Ogawa R. 2021. Updated Treatment for Acne: Targeted Therapy Based on Pathogenesis. *Dermatol Ther (Heidelb)*. 11(4):1129-1139.

33. Kurokawa I, Danby FW, Ju Q, Wang X, Xiang LF, Xia L, Chen W, Nagy I, Picardo M, Suh DH, Ganceviciene R, Schagen S, Tsatsou F, Zouboulis CC. 2009. New developments in our understanding of acne pathogenesis and treatment. *Exp Dermatol.* 18(10):821-32.

34. Lavker RM, Leyden JJ, Thorne EG. 1992. An ultrastructural study of the effects of topical tretinoin on microcomedones. *Clinical Therapeutics*; 14(6): 773 –780.

35. Listiawan MY, Prakoeswa CRS, Astari L, Zulkarnain I, Sawitri, Rahmadewi, Wardhani PH, Harnanti DV. 2021. A comparison study of the 0.1% tretinoin cream versus fractional microneedle radiofrequency combination with fractional CO2 laser for the treatment of striae alba in Indonesian patients*. J Cosmet Laser Ther*. 19;23(3-4):81-86.

36. Lokhande AJ, Mysore V. 2019. Striae Distensae Treatment Review and Update. *Indian Dermatol Online J*. 10(4):380-395.

37. Lu H, Guo J, Hong X, Chen A, Zhang X, Shen S. 2020. Comparative effectiveness of different therapies for treating striae distensae: A systematic review and network meta-analysis. *Medicine (Baltimore).* 25;99(39):e22256.

38. Marson JW, Baldwin HE. 2019. An Overview of Acne Therapy, Part 2: Hormonal Therapy and Isotretinoin. *Dermatol Clin*. 37(2):195-203.

39. Mavranezouli I, Daly CH, Welton NJ, et al. 2022. A systematic review and network meta-analysis of topical pharmacological, oral pharmacological, physical and combined treatments for acne vulgaris. *Br J Dermatol*. 187(5):639-649.

40. Mehta G., Nayak U.R., & Dev, S. 1973. Meroterpenoids—I : Psoralea corylifolia Linn.—1. Bakuchiol, a novel monoterpene phenol. *Tetrahedron, 29*, 1119-1125.

41. Mills OH, Jr., Kligman AM. 1978. Treatment of acne vulgaris with topically applied erythromycin and tretinoin. *Acta Dermato- Venereologica*; 58: 555– 557.

42. Mitts TF, Jimenez F, Hinek A. 2005. Skin biopsy analysis reveals predisposition to stretch mark formation. *Aesthet Surg J.* 25(6):593-600.

43. Oge' LK, Broussard A, Marshall MD. 2019. Acne Vulgaris: Diagnosis and Treatment. *Am Fam Physician*.100(8):475-484.

44. Padlewska K. 2014. *Medycyna estetyczna i kosmetologia*, 20-22, 28, 41-42, 62, 166-172.

45. Park Sarah Jaehwa. 2022. A Comprehensive Review of Topical Bakuchiol for the Treatment of Photoaging.

46. Placek W., Szepietowski J., Kapińska-Mrowiecka M., Kaszuba A., Langner A., Wolska H., Matusiak Ł. 2016. Trądzik zwyczajny: patogeneza i leczenie. Konsensus Polskiego Towarzystwa Dermatologicznego. *Przegląd Dermatologiczny*, *103*, 1–12.

47. Placek W. 2016. *Dermatologia estetyczna*, Termedia, 233-245.

48. Randhawa M., Rossetti D., Leyden J., Fantasia J., Zeichner J., Cula G., Southall M., Tucker-Samaras S. 2015. One-year topical stabilized retinol treatment improves photodamaged skin in a double-blind, vehicle-controlled trial. 14(3):271-80.

49. Rangel O, Arias I, García E, Lopez-Padilla S. 2001. Topical tretinoin 0.1% for pregnancy-related abdominal striae: an open-label, multicenter, prospective study. *Adv Ther.* 18(4):181-6.

50. Rittié L, Fisher GJ. 2002. UV-light-induced signal cascades and skin aging. Ageing Res Rev. 1(4):705-20.

51. Sarazin F, Dompmartin A, Nivot S, Letessier D, Leroy D. 2004. Treatment of an infantile acne with oral isotretinoin. *Eur J Dermatol.* 14(1):71-72.

52. Shao, Y., He, T., Fisher, G. J., Voorhees, J. J., & Quan, T. 2016. Molecular basis of retinol anti-ageing properties in naturally aged human skin in vivo. *International Journal of Cosmetic Science, 39(1), 56–65.*

53. Shemer A, Gupta AK, Kassem R, Sharon N, Quinlan EM, Galili E. 2021. Low-dose isotretinoin versus minocycline in the treatment of rosacea. *Dermatol Ther*. 34(4):e14986.

54. Siddharth Mukherjee, Abhijit Date, Vandana Patravale, Hans Christian Korting, Alexander Roeder, Günther Weindl. 2006. "Retinoids in the treatment of skin aging: an overview of clinical efficacy and safety". *Clin Interv Aging,* 1(4): 327–348.

55. Spierings NMK. 2020. Cosmetic commentary: Is bakuchiol the new "skincare hero"? *J Cosmet Dermatol.* 19(12):3208-3209.

56. Stamatas GN, Lopes-DaCunha A, Nkengne A, Bertin C. 2015. Biophysical properties of Striae Distensae evaluated in vivo using non-invasive assays. *Skin Res Technol.* 21(2):254-8.

57. Sumita, J. M., Leonardi, G. R., & Bagatin, E. 2017. Tretinoin peel: a critical view. *Anais brasileiros de dermatologia*, 92(3), 363–366.

58. Thielitz, A., Abdel-Naser, M. B., Fluhr, J. W., Zouboulis, C. C., & Gollnick, H. 2008. Topical retinoids in acne--an evidence-based overview. *Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG*, *6*(12), 1023–1031.

59. Thielitz, A., Abdel-Naser, M. B., Fluhr, J. W., Zouboulis, C. C., & Gollnick, H. 2010. Topical retinoids in acne--an evidence-based overview. *Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG*, 8 Suppl 1, S15–S23.

60. Thielitz, A., Krautheim, A., & Gollnick, H. 2006. Update in retinoid therapy of acne. *Dermatologic Therapy*, 19(5), 272–279.

61. Tong PL, Qin J, Cooper CL, Lowe PM, Murrell DF, Kossard S, Ng LG, Roediger B, Weninger W, Haass NK. 2013. A quantitative approach to histopathological dissection of elastin-related disorders using multiphoton microscopy. *Br J Dermatol.* 169(4):869-79.

62. Ud-Din S, McGeorge D, Bayat A. 2016. Topical management of striae distensae (stretch marks): prevention and therapy of striae rubrae and albae. *J Eur Acad Dermatol Venereol.* 30(2):211-22.

63. Wójcik, A., Bartnicka, E., Namieciński, P., & Rotsztejn, H. 2015. *Influence of the complex of retinol-vitamin C on skin surface lipids. Journal of Cosmetic Dermatology, 14(2), 92–99.*

64. Wysocka M. 2023. Bakuchiol - a plant-based retinol. The review article. *Aesthetic Cosmetology and Medicine.* 11. 10.52336/acm.2022.031.

65. Zaenglein AL, Pathy AL, Schlosser BJ, et al. 2016. Guidelines of care for the management of acne vulgaris [published correction appears in J Am Acad Dermatol. 2020 Jun;82(6):1576]. *J Am Acad Dermatol*. 74(5):945-73.e33.

66. Zasada, M., & Budzisz, E. 2019. Retinoids: active molecules influencing skin structure formation in cosmetic and dermatological treatments. *Postepy dermatologii i alergologii*, 36(4), 392–397.

67. Żaba R. Bezpieczeństwo stosowania retinoidów. 2006. Przewodnik Lekarza, 7(9):62-77.