Retinoids: active molecules influencing skin structure formation in cosmetic and dermatological treatments

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Abstract
Vitamin A is the first vitamin approved by the Food and Drug Administration as an anti-wrinkle agent that changes appearance of the skin surface and has anti-aging effects. Vitamin A is in a group of fat-soluble substances and belongs to the category of retinoids. Apart from retinol, that group includes structurally related substances with the biological properties of retinol. Since the biological activity of the substances differs, for the purpose of standardization, it is given in retinol equivalents. Vitamin A and its derivatives are among the most effective substances slowing the aging process. Retinoids regulate the cell apoptosis, differentiation and proliferation. Anti-wrinkle properties of retinoids promote keratinocytes proliferation, strengthen the protective function of the epidermis, restrain transepidermal water loss, protect collagen against degradation and inhibit metalloproteinases activity. Retinoid activity is related to high affinity for nuclear receptors: RAR – retinoid acid receptors and RXR – retinoid X receptors.

Key words: vitamin A, retinol, retinoids, skin aging, dermatology.

Introduction
According to the IUPAC (International Union of Pure and Applied Chemistry) and IUBMB (International Union of Biochemistry and Molecular Biology), retinoids are compounds containing four isoprene units with a head-to-tail structure [1]. Retinol, retinoic aldehyde and retinoic acid belong to retinoids with a non-aromatic fragment of β-ionone in their molecule. The term "retinoid" refers to the synthetic and natural analogues of vitamin A. Retinoids are a class of compounds derived from vitamin A or showing structural and/or functional similarities to vitamin A. According to the latter definition, retinoids are molecules that can bind to and activate the appropriate nuclear receptors and to induce transcription of relevant genes either directly or after metabolic transformation [2]. Retinoids are widely applied in cosmetics being a potent dermatological agent used in acne, psoriasis as well as other skin diseases.

The objective of this study is to introduce and compare different types of retinoid uses in cosmetic and dermatological treatments. Moreover, this paper should address the issue of the cellular activity of retinoids.

Retinoids are compounds of both natural, biologically active forms of vitamin A (retinol, retinal and retinoic acid) as well as synthetic analogues of retinol (Figures 1, 2). Synthetic analogues have a benzene ring instead of cyclohexane (etretinate, acitretin, tazarotene). Based on the molecular structure and properties, retinoids can be divided into three generations:

– First generation – natural retinoids, monoaromatic compounds obtained by modifying polar groups at the end and side chain of the polyene vitamin that do not act selectively – retinol (vitamin A) and its metabolites – retinal, tretinoin, isotretinoin,
– Second generation – monoaromatic retinoids, synthetic compounds in which the cyclohexene ring is replaced by a benzene ring; synthetic analogues of vitamin A (etretinate, acitretin),
– Third generation – polyaromatic retinoids formed as a result of cyclization of polyene side chain and characterized by selective activity towards receptor (arotinoid, adapalene, tazarotene) [3].

Retinol, retinal and retinoic acid have the same biological features as vitamin A. Retinoids are involved in the process of embryogenesis during development of the nervous system, liver, heart, kidneys, intestine, eyes and limbs. Retinoids are used in treatment of the so-called “night blindness” because they are responsible for proper functioning of the organ of sight. They are
associated with formation of rhodopsin. They are used in pharmacotherapy of diseases such as acne and rosacea, psoriasis, cancer, inflammation of hair follicles with bacterial aetiology, pyoderma, lupus erythematosus and ichthyosis. Retinol does not exert a significant biological effect on tissues but becomes active after transformation into three active metabolites, the most important one being the retinoic acid characterized by its multilateral action. Retinoic acid (RA), occurs in the form of two isomers: the fully-trans form and the 9-cis form that affects proliferation and differentiation of cells by regulating the respective genes. Retinoids are involved in diverse biological activities including cellular growth, cellular cohesion, immunomodulatory effects, and anti-tumour functions.

Vitamin A and its derivatives, particularly retinol, are substances slowing the aging process most effectively. Fat soluble retinol penetrates the stratum corneum and it slightly penetrates into the dermis. When retinol reaches a keratinocyte, it enters its interior and binds to an appropriate receptor. There are four groups of receptors with high affinity towards retinol (CRBP) [4, 5]. Retinol stimulates the cellular activity of keratinocytes, fibroblasts, melanocytes and Langerhans cells. Retinol, by interacting with receptors inside keratinocytes, promotes their proliferation, strengthens the epidermal protective function, reduces transepidermal water loss, protects collagen against degradation and inhibits the activity of metalloproteinases which are responsible for degradation of the extracellular matrix. Moreover, it enhances remodelling of reticular fibres and stimulates angiogenesis in the papillary layer of the dermis. Irritant properties of vitamin A and its derivatives as well as their instability are factors that limit their application in cosmetic and pharmaceutical products [6].

Retinoids: a mode of action

Retinoids, as compounds that are sparingly soluble in body fluids (lipophilic compounds), need specialized proteins to transport them (complex with Transthyretin – (prealbumin) is a retinol binding protein (vitamin A). Results of the study by Hyung et al. proved new applications of RBP and retinoids as stabilizers of transthyretin [7]. These are proteins such as RBP and CRBP Cytosolic retinol binding protein (CRBP), which is present in cytoplasm, shows affinity for retinol, while cytosolic retinoic acid binding protein (CRAPB) has affinity for retinoid acid. There are two subtypes of both groups of receptors: CRBP I and II and CRAPB I and II. Intracellular concentration of retinoids depends on their binding to cellular CRAPB I and II. Studies show that CRAPB II (it is the main form present in the epidermis) is much more abundant in the skin than CRAPB I (modulates the level of retinoic acid in different tissues) [8]. These proteins activate appropriate nuclear receptors, thanks to which retinoids exert their biological effect on particular tissues, organs and cells.
by retinoids. Receptor expression is not regular and is described in only some tissues and organs, including the epidermis, dermis, sebaceous glands and hair follicles, or in cells of the immune system.

Vitamin A and its derivatives are involved in embryogenesis. Retinoids take part in development of the nervous system, liver, heart, kidneys, intestine, eyes and limbs. Two-step oxidation occurring in the target organ cells results in conversion of retinol to its active form – retinoic acid. After entering the cell, retinol dehydrogenase (RDH) or alcohol dehydrogenase (ADH) catalyse the oxidation of retinol to retinal. This reaction may be reversed by the same enzyme because oxidation of retinol to retinoic aldehyde is a reversible process. Moreover, many enzymes can catalyse the reverse reaction, i.e. the conversion from retinamide to retinol. It indicates the presence of an additional mechanism which regulates the local retinol concentration in the tissues [4]. Subsequently, retinol is oxidized to retinol acid by retinaldehyde dehydrogenase (RALDH) or some enzymes of the CYP family (belonging to the cytochrome P450 family). This reaction is irreversible; the product formed is a natural ligand of nuclear receptors and it reflects the activity of vitamin A. Further oxidation of the retinoic acid by CYP26 enzyme results in obtaining inactive vitamin A metabolites.

Vitamin A and its derivatives, particularly retinol, are among the most effective substances delaying the process of aging. Fat-soluble retinol penetrates into the stratum corneum and, to a small extent, into the dermis. It is important to increase penetration of retinol, thus increasing its spectrum of activity, and to control a potential action in laboratory tests, and then to enhance the procedure effectiveness. Retinol, after reaching keratinocyte, penetrates into its interior and binds to an appropriate receptor. Cytosolic retinol binding protein receptors show high affinity for retinol [5, 6]. In epidermis, retinoids may influence secretion of transcription and growth factors. They are responsible for proliferation of the living layer of the epidermis, strengthening of the protective function of epidermis and reduction in excessive transepidermal water loss (TEWL). Moreover, retinoids protect against degradation of collagen and inhibit activity of metalloproteinases, enhances angiogenesis in the papillary layer of the dermis [9, 10]. The irritant effect of vitamin A and its derivatives and their instability are factors limiting their use in cosmetic and pharmaceutical products. Intracellular penetration is the main way of transport during which molecules move through the intercellular cement structure composed of ceramides, sterols, phospholipids and fatty acids. Intercellular cement has a lamellar structure, the lipid layer and hydrophilic layer are arranged alternately [8, 11]. Further studies on retinol activity in various cosmetic formulas are required in order to select the one that is best tolerated by the skin and to determine whether the concentration significantly influences the effect it exerts on the skin. Natural retinoids have a positive effect on the skin parameters. They are characterized by good absorbability (they are fat-soluble) which improves the skin function. Retinoids boost production of epidermal proteins and accelerate the process of keratinization, forming a layer of keratin which is more developed. Retinol penetrates into the basal layer of the epidermis (composed of living (nucleated) cells that are constantly producing new cells) as well as to a small extent, into the dermis and marginally to the subcutaneous tissue. In the case of retinol applied topically, there is an interaction with specific nuclear receptors. Retinol makes the connections between epidermal cells more loose and facilitates keratosis. What is more, it enhances epidermis turn-over and accelerates proliferation of the basal layer of epidermal cells and the stratum corneum. In keratinocytes, proliferation AP-1 transcription factor, exposed to various stimulants, growth factors and cytokines, plays a major role. In retinol-treated aged human skin, AP-1 complex is comprised of c-Jun/c-Fos and c-Jun transcription factor was increased [12]. Due to the fact that retinoids exert anticomedogenic effects, they regulate the process of shedding within sebaceous glands ducts. What is most important, retinoids decrease activity of enzymes participating in lipogenesis and block differentiation and cellular divisions of sebocytes [12]. Moreover, they reduce discoloration of the skin, reduce its pigmentation by about 60% and contribute to a proper distribution of melanin in the skin. Topically applied retinoids also influence the function of melanocytes, providing regular arrangement of melanin in the epidermis. They also block transport of melanin to epidermal cells and diminish the activity of stimulated melanocytes. An increase in synthesis and activity of tyrosinase, disturbances in subsequent steps of melanogenesis or a decrease in the amount of melanocytes is related to inhibition of melanogenesis. Retinoids are also commonly known as biologically active anti-aging molecules. Retinol stimulates fibroblasts to synthesize collagen fibres (stimulates the activity of fibroblasts and increases their number), improves skin elasticity (removes degenerated elastin fibres) and promotes angiogenesis [13]. Some studies indicate that retinol also enhances production of elastin fibres [14]. Moreover, retinol inhibits matrix metalloproteinases (MMPs) and enhances synthesis of tissue inhibitors of metalloproteinases (TIMPs) [15]. Changes within collagen and elastin fibres are associated with photoaging. It leads to occurrence of wrinkles and loss of the skin firmness and elasticity. Collagen fibres atrophy is caused by an increased expression of collagenases (MMP-1), gelatinases (MMP-2) and stromelysin-1 [16] as well as enhanced expression of elastase and MMP-9 associated with degradation of elastin fibres. Retinol counteracts development of precancerous conditions as a result of hampering the activity of atypical cells, which has been proved by the results of studies [17]. ECM-producing cells...
commonly used tretinoin concentration in anti-acne ther-
ulating the tissue inhibitor of MMPs (TIMP1). The most
inhibition of MMPs results from blocking AP-1, not upreg-
also causes dispersion of melanin granules. Tretinoin’s
tretinoin increases the epidermal cellular turnover, it
itive form among retinoids applied topically to the skin.
apy varies from 0.01% to 0.4%. It comes in the form of gel
and nail disorders [13, 20]. They are widely used externally in the treatment of
acne, psoriasis, excessive dryness, skin keratosis and hair
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and hair disorders [13, 20].

Application in cosmetology and dermatology (Table 1)
Tretinoin (all trans-retinoic acid) is the most bioac-
tive form among retinoids applied topically to the skin. Tretinoin increases the epidermal cellular turnover, it
also causes dispersion of melanin granules. Tretinoin’s inhibition of MMPs results from blocking AP-1, not upreg-
ulating the tissue inhibitor of MMPs (TIMP1). The most
commonly used tretinoin concentration in anti-acne ther-
apy varies from 0.01% to 0.4%. It comes in the form of gel
or cream applied topically. Retinoic acid may have differ-
ent formulas: gel (0.01%, 0.25%), cream (0.025%, 0.05%, 0.1%), new technology microspheres (0.04%, 0.1%), solution (0.05%), and emollient (0.05%) [21, 22].
Retinol is most frequently used in cosmeceutical treatment. It is very stable in product formulations and
well tolerated. It provides better effects than retinoic
acid applied in equivalent doses. Retinoic acid proves
to be approximately 20 times more powerful than reti-
ol. Firstly, retinol is converted to retinoic acid through a two-step oxidation process. Retinol has an ability to
bind to the retinoic acid receptors. The process begins
when free retinol is combined with a specific cytoplas-
mic protein that binds retinol. The resultant complex is
a substrate for retinol dehydrogenase, an enzyme that
catalyses the conversion of retinol to retinaldehyde. Ret-
inaldehyde is oxidized to retinoic acid by retinaldehyde
oxidase [23]. Retinaldehyde is used in cosme-
ticals, however, its efficacy in the skin treatment is
limited. Similarly to retinyl esters, it is a stable derivative
of vitamin A but it only mildly improves wrinkles and the
skin texture. As compared to retinoic acid, it is less irri-

| Retinoids | Functions/mechanism of action | Application in cosmetic and dermatological treatment |
|-----------|-------------------------------|---------------------------------------------------|
| Retinol (all-trans retinol) | Inhibits collagenase and MMP expression; stimulates collagen type 1 and GAGs synthesis | Anti-wrinkle treatments, improvement of texture, dyspigmentation, dryness, and fine lines |
| Retinoic acid (all-trans retinoic acid, tretinoin) | Stimulates the process of epidermal cell proliferation, accelerates the elimination of sebum remaining in ducts, therefore reducing inflammation in sebaceous glands; loosens connections among cells in stratum corneum and inhibits keratosis | Acne, psoriasis, chronic inflammation of hair follicles and sebaceous glands |
| Retinyl esters (retinyl acetate and palmitate) | First converts to retinol by cleavage of the ester bond, and then converts into retinoic acid, stimulates the epidermal cell proliferation, inhibits keratin | Antioxidant, wrinkles, stabilising properties |
| Retinaldehyde | First oxidizes to retinoic acid by retinaldehyde dehydrogenases (e.g., RALDH2) or some enzymes of the CYP family and then stimulates the epidermal cell proliferation | Stabilising properties, wrinkles, texture |
| Adapalene (naphthalene carboxylic acid) | Changes gene expression and mRNA synthesis; it is a strong modulator of keratinization of hair follicle cells, modifies keratinocyte metabolism, increases their proliferation, and thus has a keratolytic effect | Acne vulgaris, psoriasis, chronically photodamaged skin, photoprotection from sunlight |
| Tazarotene | Receptor-specific retinoid regulates down markers of keratinocyte differentiation, keratinocyte proliferation and inflammation | Acne vulgaris, psoriasis, chronically photodamaged skin, photoprotection from sunlight |
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Recent scientific articles on retinol describe the combination of 4% hydroquinone with 1% retinol in a 24-week therapy of the skin with sun damage (photoaging) and melasma [27] and combinations of lyophilized retinoic acid and hydroquinone used in treatment of melasma. The lyophilized form of the acid is used to increase penetration efficiency in the case of a sensitive skin [28]. Scientists from the Johnson & Johnson Skin Research Centre reported that a stabilized form of retinol stimulated the synthesis of hyaluronic acid in the skin and influenced the expression of genes stimulating the synthesis of macromolecules [29]. Retinol in the form of retinyl palmitate, retinol and β-carotene is most commonly used in cosmetics [30, 31]. Recent studies of Kim et al. focus on the low stability of retinol in cosmetic formulas (due to its sensitivity to light, temperature, etc.). They analysed triple encapsulated emulsions with retinol containing poly-caprolactone, lecithin and silica and five biomimetic cosmetic emulsions O/W in order to find solutions against the decomposition of retinol. The results of their study have confirmed that retinol stability depends not only on the temperature, but also on the type of substrate used and the method of emulsion preparation.

Conclusions

Retinol and their active metabolites such as retinal, retinoin, isoretinoin and allaretinoin belong to a group of first-generation retinoids. Retinol has the ability to effectively penetrate the stratum corneum (lipophilic nature of retinoids). Age, cellular metabolism, cardiovascular function, stratum corneum thickness, level of hydration and analysed area of the face are important factors in mature skin therapies. The number of scientific reports on the activity of retinoids was the reason for this study.

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Conflict of interest

The authors declare no conflict of interest.

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