ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Natural and synthetic retinoids in health and disease and role of pharmacists in preventing their side effects.

Tahani Al-Hajri, and Ladislav Novotny*.

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Kuwait University

ABSTRACT

Retinoids (other name for substances with vitamin A activity) are critical for human health. They are naturally occurring chemical substances that can also be chemically synthesized. These are substances that bind to retinoid receptors and elicit various biological responses. Retinoids have numerous significant function involving cellular differentiation, proliferation, and apoptosis. Furthermore, they are vital biomolecular for embryonic development, immune response, organogenesis, and vision. Also, they regulate expression of many genes through binding to specific nuclear transcription factors. Both, inadequate and excess intake of vitamin A can lead to many health problems. Additionally, retinoids used topically and orally for several conditions, such as some types of cancer and dermatological conditions. However, orally and topically administered retinoids have various mild to severe side effects that are normally controllable. Future scientific and clinical development of these compounds will the most likely concentrate on synthesis of new vitamin A-related compounds with different biological functions and activity, investigation of their interactions with different receptors or enzymes, and investigation of new application of vitamin A analog in patients with specific diseases.

Keywords: vitamin A, retinoids, naturally occurring retinoids, synthetic retinoids

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Vitamins are organic compounds that are important for normal metabolism. They are necessary in small amounts for growth, differentiation, function and development of a normal cell as they are involved in the regulation of many chemical reactions in the human body. Some vitamins (such as vitamin D, B_3 - niacin, B_7 – biotin and vitamin K) may be in small quantities synthesized in the human body. However, the human body obtains all the remaining vitamins only from various dietary sources. Vitamin are generally classified as fat soluble or water soluble. The fat soluble vitamins include vitamins A, D, E and K, while water soluble vitamins include B complex vitamins and vitamin C. Both, inadequate or excessive intake of any vitamin can lead to various diseases or disorders, such as broadly known rickets (lack of vitamin D), scurvy (lack of vitamin C) or beriberi (lack of vitamin B_1) [1].

Vitamin A is an organic fat-soluble substance. There are two types of vitamin A are available in human diet. The first type is represented by a substances with vitamin A activity called pre-formed or true vitamin A. The other name for the group of these compounds is 'retinoids'. They are found products of an animal origin, such as in dairy products, fish, meat, and liver. The second type of substances with a potential vitamin A activity are pro-vitamins A. They serve as a source of vitamin A for human but only after transformation in the human body. Provitamins A are also known as carotenoids. Carotenoids are present in plant-based foods, such as fruits and vegetables [1].

VITAMIN A UPTAKE AND METABOLISM

As mentioned earlier, human obtain vitamin A from the diet either as retinoids from animal sources or as carotenoids from plant sources. In the body, retinoids exist primarily in one of two chemical forms either as retinol or retinyl esters. Both of these possess essential roles in the uptake, metabolism, storage, and transfer of vitamin A to tissues. In the intestinal lumen, retinyl esters are hydrolyzed into retinol by pancreatic and intestinal enzymes. After that, free retinol is taken up by the enterocytes and re-esterified by lecithin retinol acyltransferase (LRAT) and retinyl esters are formed. Retinyl esters are then incorporated into chylomicrons that are secreted into lymphatic system and transferred to the liver. In the liver, the chylomicrons are taken absorbed by hepatocytes (stellate cells) and that is the site of the storage of retinoids in the form of retinyl esters. When retinol needs to be released to the blood stream, retinyl esters are hydrolyzed. Transportation of retinol is achieved *via* a retinol-binding protein (RBP) and transthyretin (TTR) complex. The RBP-TTR complex formation is necessary due to lipophilicity of retinol molecule. Inside target cells, retinol is bound to a cellular retinol-binding protein (CRBP) and oxidized reversibly by retinol dehydrogenases (ROLDH) into retinal. Additionally, retinal is oxidized in irreversible manner to retinoic acid (RA) through retinal dehydrogenase (RALDH) [2].

BIOLOGICAL ROLES OF RETINOIDS AND THEIR IMPORTANCE FOR HEALTH

Retinoids have very important biological roles in human. Sporn and Roberts defined retinoid as "a substance that can elicit specific biological responses by binding to and activating a specific receptor or set of receptors" [3]. Retinoids fulfill numerous significant function in the organism. Cellular differentiation, proliferation, and apoptosis [4] belong among them. Retinoids represent essential substances for embryonic development, reproduction, immune response, and epithelial growth [5]. Additionally, they are vital cofactors for the growth of B lymphocytes, T-helper (Th)-cell differentiation, activation and proliferation of T lymphocytes [6]. Moreover, retinoids regulate the development and regeneration of many organs such as lens, heart, lung, and central nervous system. Also, they represent a critical element for visual formation and regulation of expression for several genes. Gene expression is modulated by retinoids through their binding to nuclear transcription factors that are known as retinoic acid receptors (RAR) and retinoid X receptors (RXR) [5, 6].

CHEMICAL NATURE OF RETINOIDS AND CLASSIFICATION OF SYNTHETIC SUBSTANCES

Structurally, all natural retinoids consist of a monocyclic (β-ionone ring) parent structure that contains five carbon-carbon double bonds and a polyunsaturated side chain with an alcohol, aldehyde, carboxylic acid or ester end group that is by its nature more polar than the rest of the molecule. The side chain, also called polyene side chain, is composed of four isoprenoid units (diterpene) joined in a head-to-tail manner. This forms a sequence of conjugated double bonds in *trans*- or *cis*-configuration. Retinoids are naturally occurring chemical

substances but they may also be prepared *via* various synthetic routes in laboratory. Several classes of retinoids are formed by changing the side chain or end group [6].

The detailed information accumulated about cellular retinoid receptors contributed significantly to the development of synthetic retinoids that may interact in specific manners with specific receptors (or classes of receptors), such as RAR or RXR. The development of synthetic retinoids resulted in modifying original definition of retinoids of natural origin. These are recognized now "as compounds that are structurally similar to retinol with or without biological activity or that can elicit specific biologic responses by binding to and activating a specific receptor or set of receptors" [6]. Retinol, retinal, retinoic acid and retinyl ester belong among retinoids of natural origin. Additionally, at present, three generations of synthetic retinoids that developed gradually by modification of parent chemical structure are available to scientists and clinicians at present.

- The first-generation of synthetic retinoids contains non-aromatic substances and is represented by isotretinoin and alitretinoin.
- The second-generation of synthetic retinoids that are mono-aromatic in nature includes etretinate and acitretin.
- The third poly-aromatic generation of synthetic retinoids is represented by tazarotene, adapalene and bexarotene.

CHEMICAL PROPERTIES OF NATURAL RETINOIDS

Retinol

Retinol also called all-trans-retinol or vitamin A alcohol (Fig. 1A). It is a terpenoid that contains a 20-carbon with primary alcohol. It has a molecular formula of $C_{20}H_{30}O$. (2E,4E,6E,8E)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraen-1-ol is the IUPAC name for retinol [7].

Retinyl esters

Retinyl acetate (Fig. 1B) and retinyl palmitate (Fig. 1C) are the most common ester forms of vitamin A. Retinyl acetate or acetate ester of retinol, also known as vitamin A acetate, is a natural form of vitamin A. It has a chemical formula of $C_{22}H_{32}O_2$. The IUPAC name of retinyl acetate is (2*E*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl) nona-2,4,6,8-tetraen-1-yl acetate [8]. Retinyl palmitate is also an ester of retinol with palmitic acid, the most common saturated fatty acid. It has a chemical formula of $C_{36}H_{60}O_2$. The IUPAC name of retinyl palmitate is [(2E,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohexen-1-yl) nona-2,4,6,8-tetraenyl] hexadecanoate [9].

Retinal

Retinaldehyde (or retinal) is the aldehyde form of vitamin A. Retinal in nature exists as different isomers (all-*trans* and 11-*cis*) at the double bond at position 11 (Fig. 1D and 1E) (other isomers are also possible). In the retina, these isomers are responsible for converting the energy of photons into electrical impulses. Retinal (all isomers) has a molecular formula of $C_{20}H_{28}O$. (2E,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohexen-1-yl) nona-2,4,6,8-tetraenal is the IUPAC name for retinal [10,11].

Retinoic acid (Tretinoin)

Tretinoin, also known as all-*trans*-retinoic acid (ATRA) or vitamin A acid, is the carboxylic acid form vitamin A (Fig. 1F). It is available as oral and topical form. As mentioned above, retinoic acid is synthesized from retinol via two enzymatic reactions, including first reversible oxidation of retinol to retinal, and then a second irreversibly oxidation to retinoic acid. It has molecular formula of $C_{20}H_{28}O_2$. The IUPAC name for retinoic acid is (2E,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohexen-1-yl) nona-2,4,6,8-tetraenoic acid [12].

Alitretinoin

Alitretinoin (9-cis-retinoic acid) (Fig. 1G) is a naturally occurring retinoid that binds to and activities both RAR and RXR. It is a monocyclic compound with an aliphatic tail that contains nine carbon atoms with one

carboxyl groups. It has a chemical formula of $C_{20}H_{28}O_2$. IUPAC name of alitretinoin is (2E,4E,6Z,8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohexen-1-yl) nona-2,4,6,8-tetraenoic acid [13].

CHEMICAL STRUCTURE OF SYNTHETIC RETINOID DERIVATIVES

Below are shown the most important examples of synthetic molecules possessing biological activity similar to the activity of natural retinoids. Often, they differ from naturally occurring retinoids in their chemical structure but they are very important in clinical medicine.

Isotretinoin

Isotretinoin, also known as 13-cis retinoic acid, is a first-generation synthetic retinoid (Fig. 2A). It is an aliphatic monocyclic compound with carboxylic acid moiety. It binds to and activates RARs (retinoic acid receptors) and is marketed as Accutane [14] or Roaccutane [15]. As it is the 13-*cis* isomer of retinoic acid, it has the same molecular formula of retinoic acid which is $C_{20}H_{28}O_2$. The IUPAC name of isotretinoin is (2Z,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohexen-1-yl) nona-2,4,6,8-tetraenoic acid [16].

Tazarotene

Tazarotene is a third generation retinoid (polyaromatic) and an ethyl ester of tazarotenic acid (Fig. 2B). It has selective binding affinity to retinoic acid receptors RARβ and RARγ. It contains a pyridine ring bonded to a carboxylic acid group and a sulfur-containing heterocycle connected to a benzene ring and with two methyl substituent. Consequently, it is an aromatic hetero-polycyclic compounds with retinoids activity. The IUPAC name of tazarotene is ethyl 6-[2-(4,4-dimethyl-2,3-dihydrothiochromen-6-yl) ethynyl] pyridine-3-carboxylate. It has a chemical formula of $C_{21}H_{21}NO_2S$ [17].

Adapalene

Adapalene (Fig. 2C) differs significantly from the structure of retinoic acid. It is formed by naphthalene substituted with a phenyl ring (three aromatic rings) and an adamantyl substituent to the phenyl ring. Additionally, it contains methoxy and carboxylic substituents. It has higher binding affinity to RAR β and RAR γ. It is a synthetic naphthalene derivative (polycyclic) with retinoid activity. Its chemical formula is $C_{28}H_{28}O_3$ and IUPAC name 6-[3-(adamant-1-yl)-4-methoxyphenyl] naphthalene-2-carboxylic acid [18].

Bexarotene

Bexarotene (Fig. 2D) is a third-generation synthetic retinoid that is selectively binds to and activates retinoid X receptors (RXRs). It is an aromatic polycyclic compound with retinoids activity. It contains benzene ring fused to a cyclohexane, propene substituent bound to a phenyl group, and one carboxylic acid substituent. It has a chemical formula of $C_{24}H_{28}O_2$ and IUPAC name 4-[1-(3,5,5,8,8-pentamethyl-6,7-dihydronaphthalen-2-yl)ethenyl]benzoic acid [19].

PHYSIOCHEMICAL PROPRIETIES OF RETINOIDS

Retinoids are yellow to orange crystalline solids with floral odor. They are soluble in most organic solvents (acetone, chloroform, dimethyl sulfoxide, ether, ethanol, hexane, isopropanol, methanol), fats, and in mineral oils. In addition, they are unstable compounds. This is a result of the presence of conjugated double bonds of the isoprenoid chain. Also, they are practically insoluble in water because of the presence of a large hydrophobic moiety (0.06 micromole/L). As an illustration of their properties: Retinol has molecular weight of 286.45 Da, melting point of 62-64 °C and boiling point of 137-138 °C, whereas retinal has molecular weight of 284.44 Da and melting point of 64-65 °C. Esters palmitate of vitamin A, which exists in the form of yellow oil, has molecular weight of 524.90 Da and melting point of 28-29°C, while retinyl acetate has molecular weight of 328.49 Da and melting point of 57-58 °C. Additionally, retinoic acid has molecular weight of 300.44 Da and melting point of 180-182 °C [7,8,9,10,12].

Similarly, synthetic retinoids are also insoluble in water and sparingly soluble in alcohol. Isotretinoin, a yellow-orange to orange crystalline powder, has molecular weight of 300.44 Da and melting point of 174-175

°C, adapalene has a molecular weight of 412.52 Da and melting point of 319-322 °C. Tazarotene has molecular weight of 351.46 Da and melting point of 174-175 °C. In general, retinoids exists as crystalline solids sensitive to oxygen, heat, light and heavy metals. Consequently, any manipulation with these substances should be done in inert atmosphere and the substances and their formulations should be transported and stored at low temperatures in cool dark places with the temperature below 20°C [16-18].

PHARMACOLOGICAL ACTIVITIES OF RETINOIDS

All-trans retinoic acid (ATRA) and 11-cis retinal are the key substance for mediating biological activities of retinoids. ATRA is responsible for signaling that regulates transcription of many genes necessary for development, while 11-cis retinal is essential element for visual functions [5]. ATRA binds to the retinoic acid receptors (RAR) then forms heterodimers with the retinoid X receptors (RXR). This results in the initiation of gene transcription. The complex of RAR and RXR then binds to DNA sequence called retinoic acid response element (RARE) or retinoid X response elements (RXREs) located in the promoter region of target genes and activates the target genes [5,6]. RAR recognizes both ATRA and 9-cis retinoic acid, whereas RXR recognizes only 9-cis retinoic acid [4, 5].

Retinoids are important for both early embryonic development and maintenance of epithelial differentiation in the adults [20]. Retinoic acid is a pleiotropic activation factor that participates in regulating gene associated with different biological processes, such as cell differentiation, proliferation, and apoptosis. It is an important morphogen involved in regulating germ layer formation, body axis formation and hindbrain pattern. Studies show that it interacts with Nodal signaling to regulate dorsoventrally axis formation. Moreover, it regulates the expression of Neurog2 and hence promotes neural differentiation. Several studies have revealed the important roles of retinoic acid in various physiological processes. These include limb, eyes, and ears development and regeneration. Also, it includes in central nervous system development, reproduction, and hematopoiesis. Moreover, RA involves in both hepatic and pancreatic formation and the development of lung and heart [5]. Retinoids also play essential roles in various pathological conditions, such as skin diseases, cancer, premature birth, and osteoporosis [6].

Retinal plays an important role in visual cycle as 11-*cis*-retinal. It is generally known that the retina of the eye has two types of photoreceptor cells that are known as rod and cone cells. All-trans-retinol is transported to retinal pigment epithelium (RPE) cells of retina through circulation. In RPE cells, all-*trans*-retinol is esterified to form a retinyl ester, which can be stored. When required, retinyl ester is hydrolyzed and isomerized to 11-*cis*-retinol. Then, 11-*cis*-retinol is oxidized to form 11-*cis*-retinal. After that, 11-*cis*-retinal is transported to rod photoreceptor cell, where it is covalently bound to protein called opsin to form a visual pigment called rhodopsin. When photon of light is absorbed by rhodopsin, the 11-*cis*-retinal is isomerized to all-*trans*-retinal. The photo-isomerization activates signal transduction cascades, leading to the generation of a nerve impulse. Optic nerve carries the electrical signal to the brain's visual cortex, where it processes the signal into an image. To complete the visual cycle, all-*trans*-retinal is reduced to all-*trans*-retinol and transported back to RPE cells [21].

NOTE ON PREFERENTIAL METHODS FOR ANALYTICAL DETERMINATION OF RETINOIDS

Investigation of retinoids and their chemical, biological properties and therapeutic potential were significantly helped by development of new instrumental analytical techniques. Retinoids are essential as dietary and therapeutic compounds. Therefore, identification and quantification of retinoids in diet and biological tissues are essential [22]. Reversed phase high performance liquid chromatography (HPLC) has become the preferred technique for analysis of retinoids. This technique allows small volume extracts of retinoids to be analyzed qualitatively and quantitatively in a short time [22,23] and is compatible and suitable for separating and analyzing light, heat, and oxygen sensitive retinoids. Also, it is rapid method that allows separation of geometric isomers and metabolites within a wide polarity range. Ultra-violet (UV) and visible light absorbance detectors are the most commonly used detectors in HPLC chromatography of retinoids as retinoids absorb light at UV and visible wavelengths because of the conjugated polyene chain in their structure. The light absorption region of UV/visible spectrum is around 325-380 nm with high molar extinction coefficients. On the other hand, gas chromatography is rarely used for retinoids analysis because of their thermal instability and limited volatility.

Mass spectrometry coupled with HPLC (LC-MS) is another powerful analytic technique for identification and quantification of retinoids. Fluorescence detectors are often used for analysis of retinol and retinyl esters in

biological samples because retinol and retinyl esters are fluorescent, while other retinoids, such as retinal, retinoic acid, and most of the synthetic retinoids are not. Additionally, nuclear magnetic resonance (NMR) is another technique used for structural determination and assignment of *cis* and *trans* isomers [23].

ISSUES RELATED TO THE INADEQUATE OR EXCESSIVE RETINOIDS SUPPLEMENTATION

Vitamin A deficiency (VAD) is a critical nutritional concern and a public health problem in more than half of all countries. The problem is aggravated in developing countries, especially in South-East Asia and Africa [24]. The World Health Organization (WHO) has classified VAD as one of the top three most common worldwide deficiencies. In 2012, the WHO stated that about 250 million preschool children are vitamin A deficient. The main underlying cause of VAD is insufficient intake of foods high in vitamin A or beta-carotene precursors. VAD and associated disorders mainly affect children, women of reproductive age, and pregnant women. Other groups at risk of VAD are those with insignificant absorption of lipids as a result of impaired pancreatic or biliary secretion, alcoholism, Crohn's disease, and celiac disease. VAD is often defined by serum retinol concentrations lower than 0.70 µmol/l (20 µg/dl). Severe VAD is defined as serum concentrations of retinol below 0.35 µmol/l [25]. Low vitamin A intake is associated with health consequences and there are many symptoms of VAD through indicating low levels of vitamin A in the body. One of the earliest symptoms are nyctalopia (night blindness) and xerophthalmia [26]. Nyctalopia is a delayed adaptation to the dark, while xerophthalmia is the excessive dryness of conjunctiva and cornea. VAD is associated with loose goblet cells on the conjunctiva and the formation of keratin debris, which in turn may lead to an infection. If not properly treated, the infection will eventually lead to blindness as result of corneal damage. Moreover, Bitot's spots, which represent an ocular manifestation of VAD, can also develop. Bitot's spots are triangular white foamy patches that develop due to keratinization of conjunctiva of the eye [26,27]. Additionally, VAD leads to anemia because of impaired iron use and red blood cell formation. VAD is a base of a nutritionally acquired immunodeficiency disease that has a higher rate of respiratory complications and diarrhea. It also has a higher degree of mortality from measles compared to children taking sufficient amount of vitamin A [12].

Vitamin A toxicity (VAT), also called hypervitaminosis, is relatively rare in the general population. It is caused by overconsumption of vitamin A, which is rapidly absorbed and slowly eliminated from the body. VAT is classified as acute or chronic hypervitaminosis. Acute toxicity results from consuming large amounts of vitamin A over a short period of time, usually within a few hours or days. On the other hand, chronic toxicity results from building up of vitamin A in the body over a long period of time. Acute VAT symptoms include headache, abdominal pain, nausea and vomiting. Moreover, loss of appetite, drowsiness, peeling of skin, hair loss, and blurred vision are common in acute VAT. Whereas, symptoms of chronic toxicity are desquamation of the skin, pain and tenderness of the bones, restricted movement, and anorexia. In addition, increased CSF pressure, papillary oedema, hepatomegaly, and splenomegaly may occur in VAT [28].

In the USA, the recommended dietary allowance (RDA) of vitamin A for adults is 900 micrograms daily (3,000 IU) for men and 700 micrograms daily (2,300 IU) for women. For pregnant women 19 years old and older, the RDA is 770 micrograms daily (2,600 IU) and for lactating women is 1,300 micrograms daily (4,300 IU) [29].

USEFULNESS OF SELECTED RETINOIDS AND ANALOGS IN THERAPIES OF DIFFERENT PATHOLOGICAL STATES OR DISEASES

Retinoids have essential roles in many pathological conditions, such as dermatology and oncology conditions, premature birth, and measles [6]. They have significant activity in the treatment of a variety of cancer, including cutaneous T-cell lymphoma, acute promyelocytic leukemia, AIDS-related Kaposi's sarcoma, dermatological conditions and other.

ATRA A and acute promyelocytic leukemia

Acute promyelocytic leukemia (APL) represents a subclass of acute myeloid leukemia (AML) and the most curable subtype of AML [30]. APL is characterized by a translocation between chromosomes 15 and 17 as t(15;17) [31]. The t(15;17) translocation leads to a fusion protein of the PML gene on chromosome 15 and the Urara on chromosome 17 [32]. This PML/RARa fusion dimerizes and recruits co-repressors, which results in repression of target genes and inhibition of PML protein function as a

tumor suppressor [31,33]. The PML/RARa fusion gene blocks myeloid cells maturation and differentiation at the promyelocytic stage. ATRA, as a form of differentiation therapy, with chemotherapy is the standard therapy for APL [32,33]. ATRA trigger a conformational change of the fusion protein, resulting in the release of corepressors and the recruitment of coactivators [32]. It induces rapid onset of differentiation of promyelocytes into mature granulocytes, triggers PML/RARa degradation and activates apoptosis of APL cells that express PML/RARa [31,33].

Bexarotene in cutaneous T-cell lymphoma

Cutaneous T-cell lymphoma (CTCL) is a type of non-Hodgkin lymphoma (NHL) that mainly affects the skin. Bexarotene is a selective retinoid X receptor (RXR) agonist, which is approved by the Food and Drug Administration (FDA) for the treatment of CTCL in patients that are refractory to at least one of the systemic therapy. Clinical studies show that oral therapy with bexarotene is effective for refractory early and advanced stage CTCL [34,35,36]. The mechanism of action of bexarotene in CTCL is a complex one based on blocking cell cycle progression, inducing apoptosis and differentiation and inhibiting angiogenesis and metastasis. Therefore, it has anti-proliferative, pro-apoptotic, anti-angiogenic, and anti-metastasis properties [37].

Alitretinoin in AIDS-related Kaposi's sarcoma

Alitretinoin, also known as 9-*cis*-retinoic acid, is a first-generation topical retinoid that is approved by the FDA for the local treatment of skin lesions in patients with AIDS-related Kaposi's sarcoma (KS). It binds to all retinoid receptors (RAR and RXR). It promotes apoptosis through acting on RXR and induces cell differentiation and diminishes cell proliferation by acting on RAR. Moreover, alitretinoin blocks neo-angiogenesis of KS cells and reduces tendency for malignant deterioration [38,39].

Retinoids in *acne vulgaris*

Oral and topical retinoids are used in the treatment of acne vulgaris. Oral isotretinoin is indicated for severe acne because it affects all four pathogenic factors for acne. It directly suppresses abnormal keratinization of sebaceous follicle and sebum production and reduces the colonization by *Propionibacterium acnes* and the associated inflammation [30,40,41]. On the other hand, topical tretinoin, adapalene, and tazarotene are used as first-line therapy for treatment of inflammatory and non-inflammatory acne over many years [42]. Topical retinoids act by reducing inflammation and inflammatory lesions, increase desquamation and normalize abnormal keratinocyte differentiation. Moreover, they down-regulate the expression of toll-like receptor (TLR)-2, which is associated with the inflammatory response in acne, and enhance the penetration of other topical acne medications [42]. Tretinoin binds to RAR alpha, beta, and gamma, while tazarotene and adapalene are selectively bind to RAR beta and gamma. It is important to note that because of the teratogenic effects of all three drugs, all female patients of childbearing age should be properly instructed about the pregnancy risks when starting retinoid therapy [43].

Retinoids in therapy of psoriasis and related disorders

Psoriasis is a chronic disease that can affect the quality of life. Various topical and systemic treatments are available for the treatment of psoriasis. The selection of the treatment is depended on severity of disease, comorbidities, efficacy and patient response and preference. Oral acitretin is used for the treatment of severe psoriasis, including pustular, erythrodermas, and in patients with HIV-associated psoriasis. It is usually combined with other medications, such as corticosteroids, coal tar, vitamin D_3 derivatives, or with phototherapy. It has immunomodulatory and anti-inflammatory activities. It also modulates epidermal proliferation and differentiation and inhibits the excessive cell growth and keratinization. Additionally, it reduces the thickening of the skin, plaque formation, and scaling. Because of teratogenicity side effects, women of childbearing age should use effective birth control not only for the duration of acitretin therapy but also for 3 years after discontinuing the agent [30]. Also, topical tazarotene can be used for the treatment of psoriasis. It selectively binds to RARs without any affinity for RXRs. It inhibits the proliferation of psoriatic keratinocytes and decreases epidermal inflammation. In addition, tazarotene is effective in decreasing psoriatic plaque lesions and achieving remission. Studies show that combination of tazarotene with low potency corticosteroids increase the overall therapeutic potential and decrease local irritation [40,43-45].

Vitamin A in measles

Vitamin A deficiency and blindness have been associated with children diagnosed with measles. Vitamin A deficiency affects the severity of illness, increases rate of post-measles complications and deaths, delays recovery, and precipitates xerophthalmia and blindness. As a result, vitamin A deficiency is consider a risk factor for severe measles. Therefore, Vitamin A is used for the treatment of measles, reducing the severity of infection, and preventing the consequent of developing secondary infection and eye damage or blindness. The WHO recommendation is to administer two doses of vitamin A supplements, 24 hours apart, to all children in developing countries diagnosed with measles. The most important benefit of vitamin A supplementation is based in reducing morbidity and mortality from measles by 50% [46-49].

ADVERSE EFFECTS OF RETINOIDS AND POSSIBLE ROLES OF PHARMACISTS (OR OTHER HEALTH PROFESSIONALS) IN PREVENTING THESE EFFECTS

There are several topical retinoids available which are tretinoin, adapalene, and tazarotene. Topical retinoids are prescribed for treating acne, psoriasis, and wrinkles. Common side effects of topical retinoids are local reactions, including skin irritation, burning, erythema, pruritus, and xeroderma (dryness of the skin). Increased sensitivity to UVB light or sunlight, skin pigmentation, and peeling or blistering of the skin are also possible side effects of topical retinoids. The pharmacist should advice the patient to moisturize their skin in order to reduce the dryness of skin. Also, they should educate the patient to avoid applying topical retinoids to sensitive areas, such as eyes, mouth, mucus membrane, broken or sunburned skin. Moreover, the patient should avoid expose to UV light, including sun light, and apply sun screen to the exposed skin in the morning. Patients should wear protective clothing to reduce photosensitivity reaction of topical retinoids. Pharmacist should educate patients to avoid the concomitant use of irritating products with topical retinoids, such as harsh soaps, astringents, and abrasive cleaners in order to minimize irritation. The lower pH of synthetic detergents, such as Cetaphil, is recommended for minimization of skin irritation and dryness. Additionally, patient should use water-based lotions, cosmetics, or hair products because these products are less comedogenic than oil-based products [35,50].

Oral retinoids side effects are controllable and reversible most of the time on discontinuation of therapy. These side effects include dryness of skin and dryness of mucus membrane. These include cheilitis (dryness of lips), blepharitis, conjunctivitis (dryness of eyes), and epistaxis (nose bleeding). Additionally, itching, headache, hair loss, and photosensitivity are also side effects of oral retinoids. Musculoskeletal symptoms such as myalgia and arthralgia, which is transient and dose depended, are another adverse effect of oral therapy. Increase levels of lipids, both of triglycerides and cholesterol, and also an increase in liver enzymes activities (serum transaminases) are associated with oral use of retinoids. Moreover, thrombocytopenia, neutropenia, and anemia are also a possible side effect. Mood alteration, such as depression, aggressive behavior, or anxiety, and increased suicide behavior are a rare but possible risk related to retinoids therapy [30, 50].

Oral and topical retinoids are teratogenic and should be avoided in pregnant women or women planning to get pregnant. Pharmacist play an important role in educating patients to avoid blood donation during treatment and for at least 1 month after treatment. Also, patients should be advised to avoid UV light, including sunlight, and use sunscreen with a sun protection (SPF) of at least 15 and to wear protective clothing to reduce photosensitivity caused by oral retinoids. Moreover, pharmacists counsel the patient on the use of emollient, eye lubricants, and lip balm preparation from the start of treatment. Pharmacist (or physician) should warn patients to avoid wax epilation because of possibility of epidermal stripping. Also, patients should avoid laser skin treatment during treatment and for at least 6 months after stopping the treatment that included retinoids because of probability of scaring. In addition, laboratory monitoring is very important and the patient's hepatic function, serum lipids, and CBC should be measured before treatment, one month after starting therapy, and then every three months. Also, monitoring patient's mood change(s) and depression before, during, and after treatment is very important. Pregnancy should be avoided in women of child bearing age. Females of child-bearing age undergoing retinoid therapy should perform pregnancy test every month during treatment and five weeks after stopping this treatment [30,50].

ISSN: 0975-8585

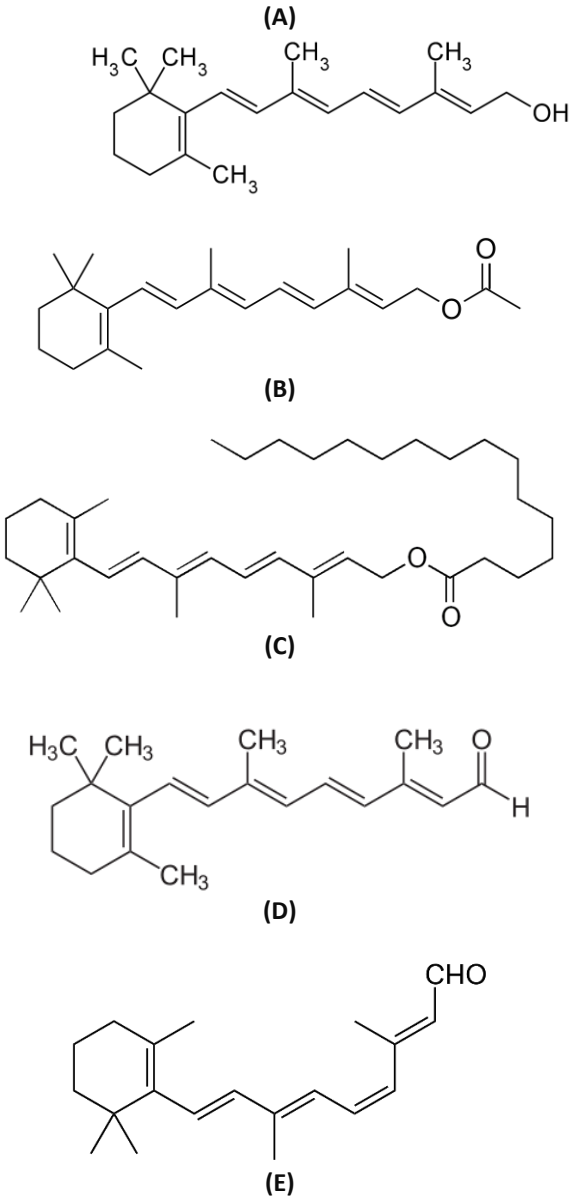
POSSIBLE FUTURE DEVELOPMENT IN THE FIELD OF RETINOIDS

There are several possible directions in scientific and clinical development of vitamin A-related compounds. These are the following:

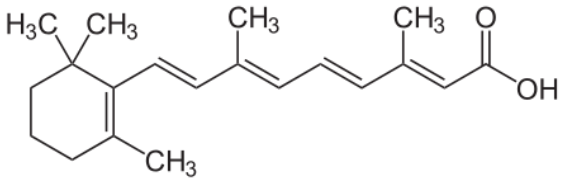
- Synthesis of new compounds that would be similar-in-structure to vitamin A and other currently available biologically active molecules with vitamin A activity or other biological activity. The new compounds may be various new analogs, derivatives or 'biosimilars'.

- More detailed investigation of various interactions of vitamin A and vitamin A-like structures with biological targets, i.e. receptors, enzymes etc. will be performed to elucidate various aspects of biological or therapeutics activity of vitamin A and related compounds.
- Obtained new scientific information may lead to new applications of vitamin A-like compound in therapies of various pathological states or in finding new ways for benefiting patients and also healthy subjects (new dosing, new drug forms etc.).

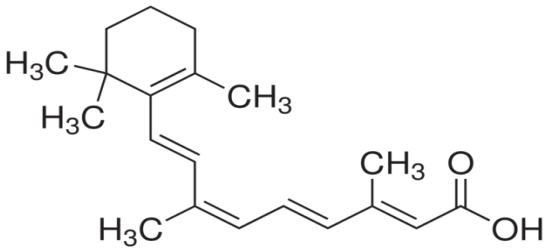
Fig. 1. Chemical structures of naturally occurring retinoids: retinol (A), retinyl acetate (B), retinyl palmitate (C), all-*trans*-retinal (D), cis-retinal (E), all-*trans*-retinoic acid (F) and alitretinoin (G).



ISSN: 0975-8585

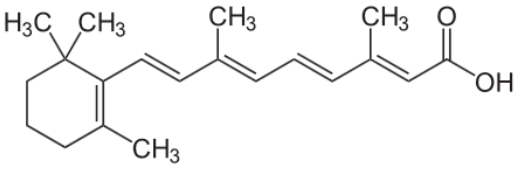


(F)

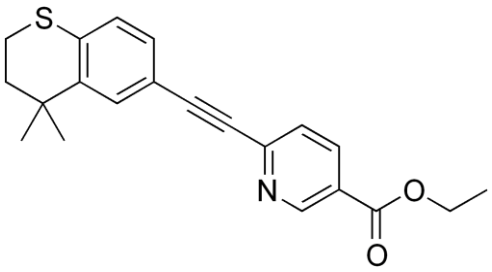


(G)

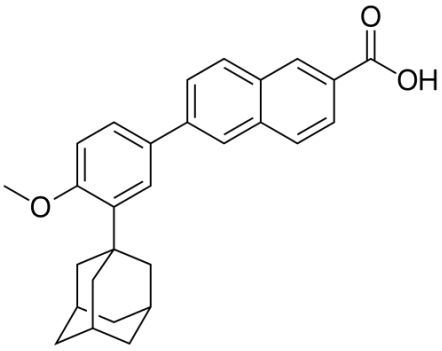
Fig. 2. Chemical structures of synthetic retinoid derivatives and analogs: 13-cis-retinoic acid – isotretinoin (A), Tazarotene (B), Adapalene (C), Bexarotene (D) and Alitretinoin (E).



(A)

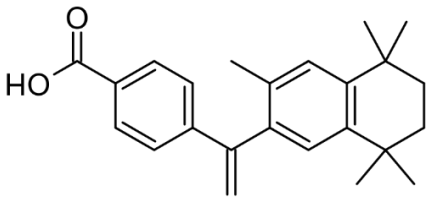


(B)

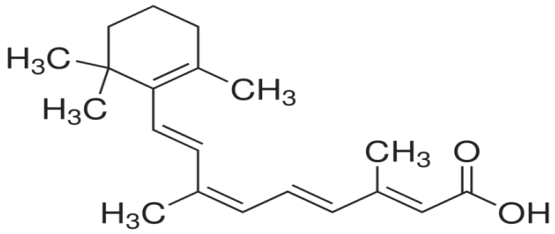


(C)

ISSN: 0975-8585



(D)



(E)

CONCLUSION

In conclusion, vitamin A is an essential fat-soluble compound. It is found in animal products and as carotenoids in fruit and vegetables. Retinoids are defined as compounds that are structurally similar to vitamin A or substances that exhibit vitamin A activity through binding to and activating a specific receptor or set of receptor. They have essential roles in many biological processes during embryogenesis and also during the adult period of life. Their chemical structure derives from monocyclic compound with four isoprenoid units joined in a head to tail manner in a polyunsaturated side chain. It contains five carbon-carbon double bond with a polar terminal functional group at the end of polyunsaturated side chain. Vitamin A deficiency is common in poorer countries and mainly affects children, women of reproductive age, and pregnant women. It is characterized by numerous ocular manifestations and inability of immune system to fight infection. These include nyctalopia, xerophthalmia, Bitot's spots, respiratory complications, and diarrhea. On the other hand, hypervitaminosis or vitamin A toxicity is rare and caused by overconsumption of preformed vitamin A. It is characterized by many manifestations and classified to acute or chronic hypervitaminosis. Recommended Dietary Allowance (RDA), depending on age and gender, allows sufficient intake of vitamin A to meet the nutrient requirements for healthy people. Retinol, retinal, and retinoic acid are the three active forms of vitamin A. Retinoic acid is important for regulation of transcription of many genes that is necessary for development, while retinal plays an essential role in visual cycle. Retinoids are used in the treatment of various diseases, including cancer, dermatological conditions, and measles. They have several side effects ranging from mild to severe but they are manageable most of the time. Retinoid therapy is teratogenic therefore it should be avoided in pregnant women or women planning to get pregnant. Pharmacists and other health care professionals should play an active role in ensuring that the patients benefit from the retinoid therapy while minimizing potential side effects of this therapy. Future development in this field is warrantied.

REFERENCES

[1] Low Dog T. Fortify Your Life: Your guide to vitamins, minerals, and more. National Geographic Society, 2016, pp. 1-338.
[2] Perusek L, Maeda T. Nutrients 2013;5:2646-2666.
[3] Sporn MB, Roberts AB. Princess Takamatsu Symp. 1985;16:149-158.
[4] Li Y, Wongsiriroj N, Blaner WS. Hepatobiliary Surg Nutrition 2014;3:126-139.
[5] Kam RKT, Dent Y, Chen Y, Zhao H. Cell Biosci 2012;2:11.
[6] Blomhoff R, Blomhoff HK. J Neurobiol, 2006;66:606-630.
[7] PubChem. https://pubchem.ncbi.nlm.nih.gov/compound/445354#section=Top (Accessed on 7 November 2016).
[8] PubChem. https://pubchem.ncbi.nlm.nih.gov/compound/638034 (Accessed on 7 November 2016).
[9] PubChem. https://pubchem.ncbi.nlm.nih.gov/compound/5280531 (Accessed on 7 November 2016).
[10] PubChem. https://pubchem.ncbi.nlm.nih.gov/compound/638015 (Accessed on 7 November 2016).

[11] PubChem. https://pubchem.ncbi.nlm.nih.gov/compound/5280490 (Accessed on 7 November 2016).
[12] PubChem. https://pubchem.ncbi.nlm.nih.gov/compound/444795#section=Top (Accessed on 7 November 2016).
[13] PubChem. https://pubchem.ncbi.nlm.nih.gov/compound/449171#section=Top (Accessed on 8 November 2016).
[14] Accutane. Drugs.com. https://www.drugs.com/accutane.html (Accessed on 8 November 2016).
[15] Roaccutane. News, Medical Life Sci. http://www.news-medical.net/drugs/Roaccutane.aspx (Accessed on 8 November 2016).
[16] PubChem. https://pubchem.ncbi.nlm.nih.gov/compound/5282379 (Accessed on 8 November 2016).
[17] PubChem. https://pubchem.ncbi.nlm.nih.gov/compound/5381#section=Top (Accessed on 8 November 2016).
[18] PubChem. https://pubchem.ncbi.nlm.nih.gov/compound/60164#section=Top (Accessed on 8 November 2016).
[19] PubChem. https://pubchem.ncbi.nlm.nih.gov/compound/82146#section=Top (Accessed on 8 November 2016).
[20] Ross SA, Mc Caffery PJ, Drager UC, De Luca LM. Physiol Rev. 2000;80:1021-1054.
[21] von Lintig, J, Kiser PD, Golczak M, Palczewski K. Trends Biochem Sci. 2010;35:400-410.
[22] Van Breemen, RB, Huang CR. FASEB J. 1996;10:1098-1101.
[23] Furr HC. J Nutr. 2004;134:281S-285S.
[24] World Health Organization. http://www.who.int/nutrition/topics/vad/en/ (Accessed on 8 November 2016).
[25] WHO. Global prevalence of vitamin A deficiency in populations at risk 1995-2005: WHO global database on vitamina A deficiency. WHO Press, Geneva 2009.
[26] Gilbert C. Community Eye Health, 2013;26:66-67.
[27] Sharma A, Aggarwal S, Sharma V. Int J Prev Med. 2014;**5**:1058-1059.
[28] Blomhoff R., Alexander J. Nordic Council of Ministers, 2003. Tidsskr Nor Laegeforen. 1993;113:3037-3039.
[29] Mayo Clinic. http://www.mayoclinic.org/drugs-supplements/vitamin-a/dosing/HRB-20060201 (Accessed on 9 November 2016).
[30] Poon Bickert B, Hartfield Seung A. In: Pharmacotherapy: A Pathophysiologic Approach 9/E. (Eds: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells GB, Posey LM), McGraw-Hill Education, USA, 2014, Chapter 111, p. 2255-2276.
[31] Pitha-Rowe I, Petty WJ, Kitareewan S, Dmitrovsky E. Leukemia 2003;17:1723-1730.
[32] Pandolfi PP. Hum Mol Genet. 2001;10:769-775.
[33] Ablain, J, de The H. Blood 2011;117: 5795-5802.
[34] Huber MA, Staib G, Pehamberger H, Scharffetter-Kochanek K. Am J Clin Dermatol.
[35] 2006;7:155-169.
[36] Dummer R, Beyer M, Hymes K, Epping MT et al. Leuk Lymphoma. 2012;53:1501-1508.
[37] Gniadecki R, Assaf C, Bagot M, Dummer R et al. Br J Dermatol. 2007;157:433-440.
[38] Qu L, Tang X. Cancer Chemother Pharmacol. 2010;65:201-205.
[39] Gonzalez de Arriba A, Perez-Gala S, Goiriz-Valdes R, Rios-Buceta L, Garcia-Diez A. Actas Dermosifiliogr. (English Edition) 2007;98:50-53.
[40] Bubna AK. Indian J Dermatol. 2015;60:520.
[41] Zouboulis CC. Skin Pharmacol Appl Physiol. 2001;14:303-315.
[42] Zouboulis CC. Hautarzt. 2014;65:733-747.
[43] Zaenglein AL, Pathy AL, Schlosser BJ, Alikhan A et al. JAm Acad Dermatol. 2016;74:945-973.e33.
[44] Zouboulis CC, Bettoli V. Br J Dermatol. 2015;172 Suppl 1:27-36.
[45] Leonardi CL. Semin Cutan Med Surg. 2016;35(4 Suppl 4):S65-66.
[46] Choo W. Int J Pharm Compd. 2016;20:6-10.
[47] Huiming Y, Chaomin W, Meng M. Cochrane Database Syst Rev. 2005;(4):CD001479.
[48] Bello S, Meremikwu MM, Ejemot-Nwadiaro RI, Oduwole O. Cochrane Database Syst Rev. 2014;(1):CD007719.
[49] WHO. Wkly Epidemiol. Rec. 1999;74:1-6.
[50] WHO. Wkly Epidemiol. Rec 1997;72:329-331.
[51] Joint Formulary Committee. British National Formulary, 65th Ed, London, UK 2013.