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A Review on: Retinoids in cosmetics and dermatological treatment and its detrimental side effects.

Pranita Vasant Raut*[1], Dr. Pratima Shinde*[2]
*[1] M. Pharm, Department of Pharmaceutics, Siddhant College Of Pharmacy, Sudumbre, Pune, Maharashtra, India
*[2] Assistant Professor, Department/HOD Of Pharmaceutics, Siddhant College Of Pharmacy, Sudumbre, Pune, Maharashtra, India

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ABSTRACT: Vitamin A was the first vitamin to be approved by the Food and Drug Administration as an anti-wrinkle agent that improves the appearance of the skin's surface and has anti-aging properties. Vitamin A is a fat-soluble substance that belongs to the retinoids family. Aside from retinol, that group includes structurally related substances with retinol-like biological properties. Because the biological activity of the substances varies, it is given in retinol equivalents for standardisation. Vitamin A and its derivatives are among the most effective anti-aging agents. Cell apoptosis, differentiation, and proliferation are all regulated by retinoids. Retinoids' anti-wrinkle properties promote keratinocyte proliferation, strengthen the epidermis' protective function, limit transepidermal water loss, protect collagen from degradation, and inhibit metalloproteinase activity. In this analysis the overall study of retinol and derivatives in cosmetics and dermatological treatments is studied along with its common and detrimental side effects.
Keywords: vitamin A, retinol, retinoids, retinaldehyde.

I. INTRODUCTION

According to the IUPAC (International Union of Pure and Applied Chemistry) and IUBMB (International Union of Biochemistry and Molecular Biology), Retinoids are compounds with a head-to-tail structure made up of four isoprene units. Retinol, retinoic aldehyde, and retinoic acid are retinoids that have a non-aromatic -ionone fragment in their molecule. The word "retinoid" refers to both synthetic and natural vitamin A analogues. Retinoids are a group of compounds that are derived from or have structural and/or functional similarities to vitamin A. Retinoids are molecules that can bind to and activate the required nuclear receptors, as well as induce transcription of related genes either directly or after metabolic transformation, according to the latter description. Retinoids, a potent dermatological agent used in acne, psoriasis, and other skin disorders, are commonly used in cosmetics.

The objective of this study is to have an overview on retinol in cosmetics and dermatological products along with its side effects.

True, biologically active forms of vitamin A (retinol, retinal, and retinoic acid) as well as synthetic analogues of retinol make up retinoids (Figures 1, 2).Instead of cyclohexane, synthetic analogues have a benzene ring (etretinate, acitretin, tazarotene). Retinoids are classified into three generations based on their molecular structure and properties:

First generations: Retinol (vitamin A) and its metabolites – retinal, tretinoin, isotretinoin, and others – are normal retinoids, monoaromatic compounds obtained by altering polar groups at the end and side chain of the polyene vitamin that do not function selectively.

Second generations: Monoaromatic retinoids are synthetic analogues of vitamin A in which the cyclohexene ring is substituted by a benzene ring (etretinate, acitretin)

Third generations: polyaromatic retinoids (arotinoid, adapalene, tazarotene) formed by cyclization of the polyene side chain and characterised by receptor selectivity.

Vitamin A's biological properties are shared by retinol, retinal, and retinoic acid. Retinoids play a role in the development of the nervous system, liver, heart, kidneys, intestine, eyes, and limbs during embryogenesis. Since they are responsible for the proper functioning of the eye, retinoids are used in the treatment of so-called "night blindness." They are linked to the production of rhodopsin. They are used to treat conditions like acne and rosacea, psoriasis, cancer, hair follicle

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inflammation caused by bacteria, pyoderma, lupus erythematosus, and ichthyosis. Retinol has no biological effect on tissues, but it becomes active after being transformed into more active metabolites, the most prominent of which is retinoic acid, which has a multilateral action. Retinoic acid (RA) comes in two forms of isomers: the fully-trans form and the 9-cis form, which regulate the genes involved in cell proliferation and differentiation. Retinoids play a variety of roles in biology, including cellular development, cellular cohesion, immunomodulatory effects, and anti-tumor effects.

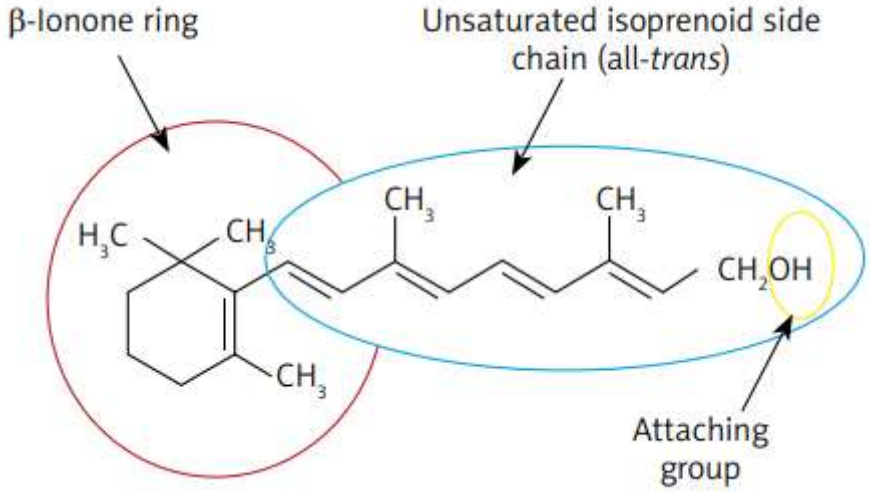

Figure 1: Chemical structure of Retinol (Vitamin A)

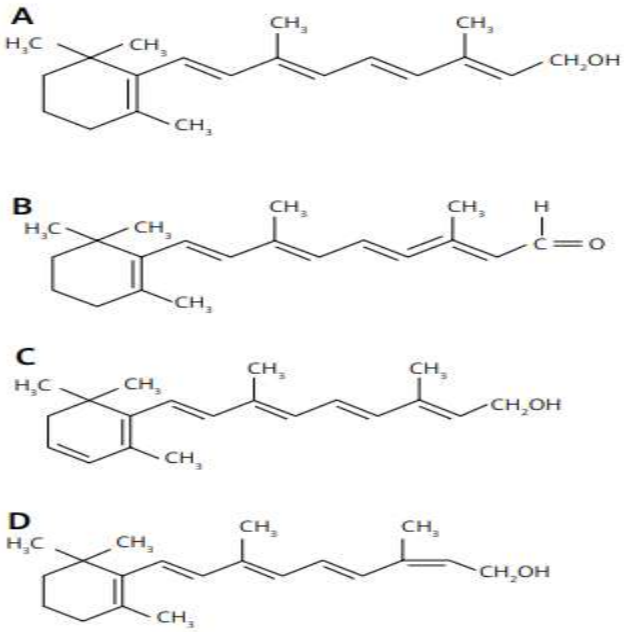

Figure 2: Structural formula for (A) retinol, (B) retinal, (C) 3-dehydroretiol (vitamin A2), (D) 13-cis-retinol.

Mechanism Of Action

Because of their ability to regulate epithelial cell growth and differentiation, retinoids are widely used in cosmetics. The ability of retinoids, which are lipophilic molecules, to diffuse across cellular membranes causes this effect. They

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bind to particular nuclear receptors once within the cells and modulate the expression of genes involved in cellular proliferation and differentiation. Retinoids are found in the skin naturally, with retinol and retinyl esters being the most common. In the small intestine, retinol is formed by one of two mechanisms: hydrolysis of retinyl esters or oxidation of carotenoids. The active form of retinol is formed by oxidising retinol to retinaldehyde, which is then oxidised to form tretinoin.

Retinol

Retinol, which is a precursor to retinaldehyde and retinoic acid, is commonly used in cosmetics, but there is no evidence that supports its effectiveness in the treatment of photoaging. Kang et al compared topical retinol, retinoic acid, and a vehicle alone in a randomised, double-blind sample. A small group of healthy volunteers were given the agents to apply to their buttock skin, and biopsies were taken at 0, 6, 24, and 96 hours. In contrast to retinol, which caused no or just trace erythema, retinoic acid caused severe erythema in the clinic. Retinol has been shown to induce epidermal thickening in the same way as retinoic acid does. CRABP-2 mRNA and protein levels were also increased by retinol. With retinol use, there was also a large accumulation of epidermal retinyl ester, according to the report. Topical retinol, on the other hand, had no effect on retinoic acid levels.

Kafi et al investigated the efficacy of topical 0.4 percent retinol in improving the symptoms of naturally aged upper arm skin in a randomised, double-blind, vehicle-controlled trial. The 24-week trial was completed by 23 patients in their study. After four weeks of therapy, their findings showed clinical improvement in fine wrinkles, according to two blinded dermatologists. Glycosaminoglycan expression and collagen output were found to be higher in their patients' biopsies. The authors suggested that major improvement take at least two to three months of care based on their findings.

Retinol derivatives:- To improve retinol's chemical stability, retinol derivatives have been produced. Instead of retinol, retinol derivatives such as retinyl acetate, retinyl propionate, and retinyl palmitate have been commonly used in cosmetic items. In reality, after the discovery that retinyl propionate induces epidermal thickening in mouse tails and promotes collagen formation in UV-irradiated mice, retinol derivatives were thought to be useful for the treatment of photoaging. Based on positive results, a 48-week double-blind, randomised, placebo-controlled trial (n = 60) was conducted. Unfortunately, no statistically significant change in either of the measured histopathological or clinical symptoms of photoaging was seen when topical retinyl propionate cream (0.15 percent) was compared to placebo. Actinic keratoses were reduced to almost zero in a small number of subjects after 48 weeks, but this effect was not statistically important. Han and colleagues (2003) created retinol derivatives that improved the photostability of retinol while maintaining its anti-aging properties. They discovered that the N-formyl aspartame derivative of retinol has a high potential to act as an anti-aging agent (Figure3) due to its excellent photostability. Furthermore, human fibroblasts tolerated it well, and it reduced collagenase production (an indicator of anti-aging activity) just as well as retinol. Extensive studies to demonstrate its in vivo efficacy are still required.

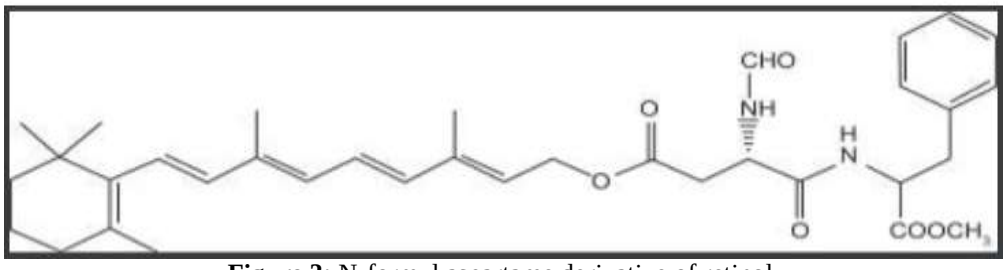

Figure 3: N-formyl aspartame derivative of retinol.

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Retinol contains a variety of benefits for the skin and can help:

- Treat acne
- Clear pores
- Amp up cellular turnover
- Increase collagen
- Promote elasticity
- Decrease hyperpigmentation
- Brighten skin
- Diminish and prevent fine lines and wrinkles
- Refine skin texture and tone

Common and Detrimental Side Effects of Retinol:

- Redness
- Irritation
- Burning
- Itching
- Dry skin
- Flaking and peeling of the skin
- Increased sensitivity to the sun
- Skin cancer

1. Pregnancy Complications

Aside from topical applications such as creams or moisturisers, retinol can also be obtained through diet. Pregnancy necessitates an increased intake of retinol. The average daily vitamin A intake is 700 micrograms (mcg) of retinol activity equivalent (RAE) During pregnancy, the average daily intake rises to 750 mcg RAE, and during lactation, it rises to 1,200 mcg RAE. One International Unit (IU) of retinol equals 0.3 mcg RAE. In adults over the age of two, the average daily dietary vitamin A intake is 607 mcg RAE. Retinol contains vitamin A, which means it aids in glucose metabolism. It is involved in immune system function, vision, and organ maintenance. Preformed Vitamin A, which includes retinol, and provitamin A carotenoids are the two types of Vitamin A that can be consumed. Dairy products, fish, and meat all contain preformed vitamin A.

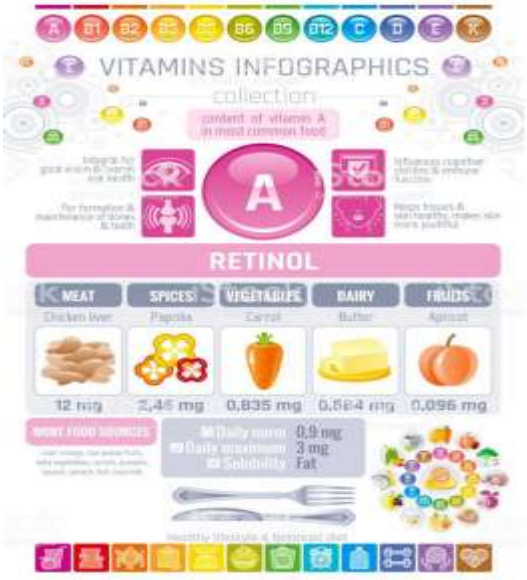

Figure 4: Retinol can be obtained through diet, specifically Vitamin A rich foods .

Provitamin A carotenoids are also found in milk and eggs. Tomato juice, carrots, pistachios, and peppers are also high in Vitamin A. Once ingested, retinol levels are measured using plasma or blood samples. Pregnant women, people with cystic fibrosis, and premature infants are at the greatest risk of Vitamin A deficiency.

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2. Polycystic Ovarian Syndrome

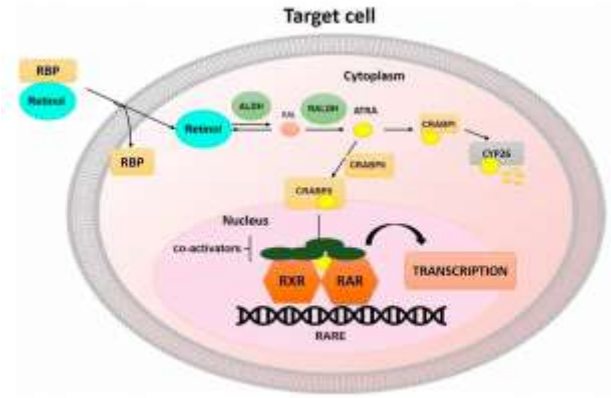

Figure 5: Regulation of Retinoid and RBP4 levels in cells is crucial to preventing Polycystic Ovarian Syndrome

RBP4 is also thought to be responsible for polycystic ovarian syndrome. Polycystic ovarian syndrome (PCOS) is a hormonal disorder that affects women of reproductive age. The condition is characterised by irregular or excessive menstrual cycles. The ovaries fail to release eggs in women who have PCOS. High RBP4 levels in PCOS women are thought to be influenced by androgen hormones. Androgen hormones, including testosterone, are more commonly associated with male hormones, despite the fact that they are produced in females as well, and high levels of androgens inhibit egg release. Male hormones, when combined with oestrogen, help women maintain proper bone mass and reproductive tissues. In females aged 19 and up, the appropriate amount of testosterone is between 8 and 60 nanograms per deciliter. In contrast, the average amount of testosterone in males is 240-950 nanograms per deciliter. Retinoic acid receptors in stem cells help with hematopoiesis, or the formation of blood cellular structures found in bone marrow. Retinoid signalling plays a role in the meiosis of germ cells found in mammalian foetal ovaries. As a result, abnormal retinoid signalling is thought to play a role in the onset of polycystic ovarian syndrome. Retinoid levels in the ovary can be controlled at the molecular level, allowing for molecular control of ovarian development and oocyte maturation. Acne is a less severe but common side effect of having too much androgen. PCOS in women can lead to other life-threatening health problems such as endometrial cancer and stroke. Race and ethnicity have no effect on a person's risk of PCOS, but a family history of obesity does. Women can avoid PCOS complications during pregnancy by maintaining a healthy blood sugar level prior to and during pregnancy, as well as a healthy weight.

3. Maternal Anemia and Night Blindness

A cross-sectional study published in the Journal of Obstetrics and Gynecology investigated how a lack of Vitamin A during pregnancy could increase the risk of maternal anaemia and delivery complications. Anemia, or a low red blood cell count, complicates pregnancies because there aren't enough red blood cells to allow oxygen to flow from the mother to the baby. This study looked at 736 women during their third trimester of pregnancy, and the factors used to assess the women's health included night blindness, hypertension levels, and the infant's gestational age. The women came from all socioeconomic backgrounds, which was important when it came to access to proper nutrients, specifically Vitamin A. The women were divided into two groups, and their socioeconomic status was determined based on their highest level of education, annual income, property holdings, and occupation. According to the findings of this cross-sectional study, 2.9 percent of the women suffered from night blindness. Night blindness was assessed using a questionnaire, and it was determined that all of the women who suffered from night blindness came from low-income families. Thirty-five percent (35%) of the women had low retinol concentrations, and 41.2 percent had moderate to severe anaemia. During the study, 15.7 percent (15.8 percent) of the women developed

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hypertension. The authors also suggested that low vitamin A levels increased susceptibility to infection, so low retinol concentrations cause pregnancy anaemia and contribute to other conditions such as night blindness and hypertension. Excessive Vitamin A consumption, on the other hand, has risks. High levels of vitamin A during pregnancy are associated with liver damage. Vitamin A is fat soluble and is stored in the liver. When it accumulates in large amounts, it causes irreversible liver damage. Retinol interacts with the hormones thyroxine and transthyretin when used. Thyroxine is synthesised in the thyroid gland and released into the bloodstream. Thyroxine and transthyretin combine to form a complex that prevents the retinol binding protein from reaching the kidney. Thyroxine enters the bloodstream and travels to the liver.

Furthermore, women who use topical isotretinoin have an increased risk of birth defects in their children, particularly those affecting the eyes and lungs. Retinol is currently classified as pregnancy category X in the United States, which means that studies have revealed signs of foetal complications when pregnant women are exposed to retinol.

Table: Retinoid uses in cosmetic and dermatological skin care treatments.

Retinoids	**Functions/mechanism of action**	**Application in cosmetic and dermatological treatment**
Retinoic acid (all-trans retinoic acid, tretinoin)	Stimulates epidermal cell proliferation, accelerates the elimination of sebum remaining in ducts, reducing inflammation in sebaceous glands; loosens connections between cells in the stratum corneum and inhibits keratosis	Acne, psoriasis, chronic inflammation of hair follicles and sebaceous glands
Retinol (all-trans retinol)	Collagenase and MMP expression are inhibited; collagen type 1 and GAG synthesis are stimulated.	Anti-wrinkle treatments, improvement of texture, dyspigmentation, dryness, and fine lines
Retinaldehyde	Retinaldehyde dehydrogenases (e.g., RALDH2) or some CYP family enzymes first oxidise it to retinoic acid, which then stimulates epidermal cell proliferation.	Stabilising properties, wrinkles, texture
Retinyl esters (retinyl acetate and palmitate)	By cleaving the ester bond, it first converts to retinol and then to retinoic acid, which stimulates epidermal cell proliferation and regulates sebum production.	Antioxidant, wrinkles, stabilising properties

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Adapalene (naphthalenecarboxylic acid)	Changes gene expression and mRNA synthesis; it is a strong modulator of hair follicle cell keratinization, modifies keratinocyte metabolism, increases keratinocyte proliferation, and thus has a keratolytic effect.	Acne, inflammation, excessive keratosis
Tazarotene	Receptor-specific retinoid suppresses keratinocyte differentiation, proliferation, and inflammation markers.	Acne vulgaris, psoriasis, chronically photodamaged skin, photoprotection from sunlight

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III. CONCLUSION:

Retinol can effectively penetrate the stratum corneum due to the lipophilic nature of retinoids. Age, cellular metabolism, cardiovascular function, stratum corneum thickness, hydration level, and face analysis area are all important factors in mature skin therapies. Individuals with prior health conditions that may affect their body's response to retinol consumption should be taken into account. This meta analysis drew from a variety of sources, but the information found is somewhat limited given the short time frame in which this meta analysis was constructed. The studies included in this analysis were published in various countries around the world. The reason for this study was the large number of scientific reports on the activity of retinoids.

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