Retinol (Vitamin A) and Its Derivatives: Synthesis and Applications

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Abstract. This paper systematically reviews the synthesis methods of retinol (Vitamin A) and its derivatives, along with their applications in skincare and pharmaceuticals. By examining traditional chemical synthesis pathways such as the Roche, BASF, and Rhone-Poulenc routes, as well as modern biological synthesis pathways, the paper highlights the advantages and limitations of each method, particularly in terms of improving synthesis efficiency, reducing production costs, and minimizing environmental impact. The paper also analyzes the application of retinol derivatives in skincare, including their roles in anti-aging, skin barrier repair, skin whitening, and even tone. Additionally, the paper discusses methods to enhance the stability and bioactivity of retinol. Future directions include further innovation in synthesis techniques, the development of new derivatives, and new pharmaceutical applications of retinol. The paper concludes that retinol and its derivatives hold great promise in the beauty and health sectors, though further research is needed to overcome current challenges and promote wider application.

Keywords: Retinol, derivatives, synthesis pathways, skincare applications.

1. Introduction

Retinol, also known as Vitamin A1, is a fat-soluble vitamin first identified by American scientists Elmer McCollum and Thomas Osborne in 1913. This vitamin is characterized by its unique chemical structure, which includes a β-ionone ring and a long-chain unsaturated side chain, with a hydroxyl group connected to the 15th carbon atom. This molecular structure enables retinol to play diverse physiological roles in the body, including its crucial function in the visual system, regulation of cell growth and differentiation, enhancement of immunity, and maintenance of skin and bone health [1].

Retinol's applications in skincare and medicine are particularly extensive. It is a key component in the synthesis of rhodopsin, essential for night vision and dark adaptation. A deficiency in retinol can lead to night blindness and other vision problems [2]. Additionally, retinol regulates gene expression and the cell cycle, promoting normal cell differentiation and proliferation, supporting embryonic development, and tissue repair. It also plays a role in regulating the growth and keratinization of skin cells, maintaining the skin barrier function, reducing dryness and roughness, and promoting skin repair and regeneration [3]. Moreover, retinol contributes to enhancing immune function and supporting bone health [4]. Due to these significant biological functions, retinol and its derivatives have become focal points of research in skincare and pharmaceuticals.

Despite the extensive research on retinol, unresolved issues remain regarding its synthesis pathways, derivative development, and stability and safety in practical applications. Current research focuses on improving synthesis efficiency, reducing production costs, and developing stable, less irritating retinol derivatives to meet market demands. Therefore, this study aims to review the existing synthesis methods of retinol and its derivatives, explore their practical applications in skincare and pharmaceuticals, and propose potential directions for future research.

The objectives of this paper include the following: first, to comprehensively summarize the main synthesis pathways of retinol, covering both traditional chemical and modern biological synthesis methods; second, to analyze the development of retinol derivatives and their applications in skincare and medicine; and third, to discuss the limitations of current synthesis technologies and propose potential research directions for further development in this field.

2. Synthesis Pathways of Retinol

2.1. Chemical Synthesis Pathways

Since the mid-20th century, retinol has been synthesized using several classic routes, with the Wittig reaction being the most widely applied method. Through the Wittig reaction, β-ionone reacts with phosphonium salts to produce retinol, a method favored for its readily available raw materials, low cost, and high yield. Additionally, the Wittig reaction is environmentally friendly, reducing the use of harmful chemicals and thus minimizing the environmental impact of production. However, the Wittig reaction also faces challenges, such as handling intermediate products and purifying the final product. Building on this, alternative methods such as the Julia and Horner-Wadsworth-Emmons reactions have been widely studied. The Julia reaction uses thioalkylation as an intermediate step to produce retinol, showing excellent selectivity and yield. The Horner-Wadsworth-Emmons reaction, which involves reacting phosphonate compounds with aldehydes or ketones to produce alkenes, has also been widely applied in retinol synthesis due to its mild conditions and high stereoselectivity [5].

2.2. Modern Chemical Synthesis Pathways

With advances in chemical synthesis technology, flow chemistry has become an important technique in retinol synthesis. Flow chemistry, which utilizes microchannels or small reactors under precisely controlled conditions, significantly improves reaction efficiency and safety. Compared to traditional batch synthesis, flow chemistry reduces reaction time and energy consumption, as well as waste generation. Flow chemistry can also integrate multi-step reactions, simplifying synthesis processes and reducing the difficulty of separating and purifying intermediates [6]. This technology is particularly suitable for multi-step synthesis and sensitive chemical transformations of retinol, effectively enhancing synthesis efficiency and product quality. In addition, modern synthesis techniques include the use of advanced catalysts and novel solvent systems, further improving retinol synthesis efficiency. For example, using nanocatalysts or ionic liquids as reaction media can achieve efficient chemical transformations under milder conditions, reduce by-product formation, and increase product purity. These combined technologies not only optimize the retinol synthesis process but also provide more possibilities for green chemistry practices [7].

2.3. Biological Synthesis Pathways

Biological synthesis pathways are becoming an important direction for retinol production. Through genetic engineering, microorganisms such as Escherichia coli and Saccharomyces cerevisiae are engineered to efficiently produce retinol or its precursors. Advances in synthetic biology enable researchers to design more efficient biosynthetic pathways, such as constructing engineered strains that can directly synthesize retinol by introducing the β-carotene synthesis pathway and key enzyme genes. This method not only reduces dependence on petrochemical raw materials but also lowers the environmental burden of production [8]. Additionally, extracting retinol from natural resources is another important biosynthesis strategy. Although extracting retinol from animal tissues is costly and complex, optimizing fermentation and extraction conditions makes microbial synthesis a more sustainable alternative. This method can significantly increase yield while reducing impurity formation through optimized fermentation processes, thus improving product purity and quality [9].

Future research will focus on further optimizing these synthesis pathways to increase yield, reduce costs, and develop more environmentally friendly processes to meet the growing market demand. By combining the advantages of chemical and biological synthesis, it is expected that more efficient and economical methods of retinol production will be developed, promoting its widespread application in pharmaceuticals and cosmetics.

3. Development of Retinol Derivatives

Retinol's wide range of applications extends beyond its original form, involving the development and use of various derivatives. These derivatives exhibit unique bioactivities and applications in cosmetics and pharmaceuticals. Due to limitations in retinol's application, such as photosensitivity, instability, and potential skin irritation, researchers are synthesizing different retinol derivatives to overcome these issues and enhance its effectiveness in specific areas.

3.1. Retinal

Retinal, also known as Vitamin A aldehyde, is the aldehyde form of retinol and is a major metabolite with significant bioactivity. In skincare, retinal is noted for its lower irritation and higher anti-aging efficacy. Retinal can be converted to retinoic acid in the skin, regulating cell proliferation and differentiation. However, retinal is chemically unstable and prone to degradation when exposed to light and air, making stabilizing retinal for practical applications a key area of research [10]. Scientists are developing various methods to stabilize retinal, such as encapsulating it in microspheres or liposomes to reduce its exposure to environmental factors and prolong its activity. Additionally, chemical modifications or combining retinal with other active ingredients may further enhance its efficacy and stability, making it more promising for anti-aging skincare products.

3.2. Retinoic Acid

Retinoic acid is the active form of retinol, directly involved in regulating gene expression and plays a vital role in cell growth, differentiation, and tissue repair. As a treatment for acne and photodamage, retinoic acid is widely used in dermatology. However, its potency also comes with a high potential for skin irritation and side effects, limiting its use in everyday skincare products. To address these issues, researchers have developed various retinoic acid derivatives, such as all-trans retinoic acid (tretinoin) and 13-cis retinoic acid (isotretinoin), to reduce irritation and increase skin tolerance [11]. Additionally, novel retinoic acid-like molecules are being designed and tested to retain or enhance retinoic acid's therapeutic effects while minimizing side effects. These derivatives offer more options for safe and effective skin treatments.

3.3. Retinyl Esters

Retinyl esters are esterified forms of retinol with fatty acids, such as retinyl palmitate, retinyl linoleate, and retinyl acetate. These esterified retinol forms are popular in cosmetics because they are generally more stable and less irritating than retinol itself [12]. Retinyl esters gradually release retinol in the skin, which is then further converted into retinoic acid to exert its biological activity. Due to their mild action, these derivatives are well-suited for long-term care products like anti-aging lotions and serums. The development of retinyl esters not only expands retinol's applications in skincare but also provides effective solutions to the instability and irritation issues associated with retinol [13].

3.4. Other Retinol Derivatives

In addition to retinal, retinoic acid, and retinyl esters, scientists have developed other types of retinol derivatives to achieve more desirable properties. For example, conjugated molecules combining retinol with other antioxidants or anti-inflammatory agents can protect the skin while enhancing retinol's anti-aging effects [14]. Moreover, through molecular modifications, new retinol derivatives that better penetrate the skin and gradually release retinol over time have become a focus of recent research.

These new derivatives not only show great potential in cosmetics but may also offer new options for treating skin diseases in the pharmaceutical field. These advances highlight the broad prospects of retinol derivative development and provide important directions for future research.

3.5. Market Applications and Prospects

The application of retinol and its derivatives in the skincare market is rapidly expanding, driven by increasing consumer demand for anti-aging products. As technology advances, particularly in improving product stability and reducing side effects, retinol and its derivatives are expected to play an increasingly important role in the global skincare and pharmaceutical markets. Overall, the development of retinol derivatives not only enriches the variety of skincare and pharmaceutical products but also overcomes some of the limitations of original retinol. As research deepens, these derivatives will continue to play a key role in the beauty and health industries.

4. Applications of Retinol and Its Derivatives in Skincare

Retinol and its derivatives are widely used in skincare products due to their excellent bioactivity, improving skin health and appearance. Below are their applications in anti-aging, skin barrier repair, skin whitening, even tone, formulation technology, and stability.

4.1. Anti-Aging Effects

Since the FDA approved retinol for use in anti-aging cosmetics in 1996, it has been widely applied in skincare. Retinol stimulates fibroblasts to synthesize collagen and inhibits matrix metalloproteinase activity while promoting the synthesis of tissue inhibitors of metalloproteinases, preventing collagen fiber breakdown and increasing skin elasticity [15]. Studies have shown that using 0.1% retinol cream effectively improves the appearance of photodamaged skin, reducing fine lines and wrinkles and enhancing skin firmness and elasticity. Long-term studies have further found that continuous use of retinol products for one year can result in sustained improvement in signs of skin aging [16].

4.2. Skin Barrier Repair

Retinol compounds are lipophilic molecules capable of penetrating the stratum corneum and reaching the epidermis, with some even penetrating the dermis, effectively repairing the skin barrier and improving skin smoothness. Retinoids influence transcription factors and growth factor secretion, stimulating the proliferation of basal epidermal cells, enhancing the skin’s protective function, and reducing transepidermal water loss [17]. Additionally, retinol promotes the expression of hyaluronic acid in skin cells, increasing skin elasticity. An experiment showed that using a 0.4% retinol lotion for 24 weeks significantly improved skin roughness in participants [18]. This further demonstrates the effectiveness of retinol in repairing the skin barrier and improving skin texture.

4.3. Skin Whitening and Even Tone Effects

Retinol and its derivatives also show significant effects on skin whitening and even tone. Experimental studies have found that retinol can inhibit tyrosinase activity in the B16 melanoma cell model and reduce melanin transport, thereby decreasing melanin content in cells and making skin pigmentation more uniform [19]. Clinical trials further indicate that retinoids can even out skin tone, reduce hyperpigmentation, diminish spots, and help distribute melanin evenly. Using a 0.1% retinol moisturizer significantly improved spotted hyperpigmentation, making the skin tone more uniform [16].

4.4. Stability and Formulation Technology

Although retinol and its derivatives have significant effects in skincare, their stability is poor, easily degrading under light exposure, temperature changes, acidic environments, or contact with other chemicals, thus affecting their activity and efficacy [20]. In cosmetic development, retinol's shelf life is extended by selecting appropriate packaging materials, reducing exposure to air and light, and using strict sealing measures during production. However, simply adding sunscreens or light blockers is limited; studies have shown that adding yellow pigments that absorb blue light can significantly enhance retinol's stability [21]. As retinol and retinyl esters degrade over time and are sensitive to light, temperature, heavy metals, and acids, further improving their stability and bioactivity remains a key focus in skincare formulation research.

5. Future Development Directions

5.1. Innovation in Synthesis Techniques

Since O. Isler and his colleagues at Roche completed the total synthesis of all-trans Vitamin A acetate using β-ionone as a raw material in 1947, Vitamin A synthesis technology has continued to evolve. Roche first achieved the industrial production of Vitamin A acetate in 1948, and in 1971, BASF advanced the industrialization of Vitamin A through the Wittig reaction [22]. By 1991, Roche, BASF, and Rhone-Poulenc produced 3,000 tons annually. Today, German company BASF and Dutch company DSM account for 60% of global Vitamin A production.

In recent years, optimizing the acetylation of Vitamin A intermediates catalyzed by Aspergillus oryzae WZ007 cells has made the Roche synthesis pathway more economical and environmentally friendly, further reducing Vitamin A synthesis costs [23]. Moreover, numerous studies aim to optimize the synthesis pathways of retinol intermediates and the overall synthesis process, striving to increase yields while achieving more environmentally friendly and efficient production. These innovations provide more economical and sustainable solutions for the production of Vitamin A and its derivatives and help meet the growing market demand.

5.2. New Applications of Retinol in Medicine

Retinol's new applications in medicine also show great promise. Research indicates that retinol positively affects human umbilical cord mesenchymal stem cells (UCMSCs), promoting the production of epidermal growth factor (EGF), stem cell factor (SCF), colony-stimulating factor 1 (CSF1), and leukemia inhibitory factor (LIF), which are directly related to the self-renewal and differentiation of hematopoietic stem cells and male germ cells, as well as nerve regeneration. In addition, retinol derivative development aims to improve stability, controlled release, and functionality, with commercialization expected by 2024.

Research on supramolecular retinol also shows potential. Supramolecular technology prepares retinol-active compound nanocarriers, increasing transdermal absorption and reducing retinol's irritation through controlled release while enhancing its anti-wrinkle effects. These new applications and research advancements suggest that retinol will have significant economic value and investment potential in the pharmaceutical field. As technology advances, retinol and its derivatives will play an increasingly important role in drug development and clinical treatment [24].

6. Conclusion

This paper comprehensively reviews the synthesis pathways, practical applications, and future development directions of retinol and its derivatives. Through an analysis of existing literature and research findings, we explored the chemical and biological synthesis methods of retinol, provided a detailed overview of its broad applications in skincare and medicine, and highlighted the challenges and opportunities related to stability, efficacy, and safety. In terms of synthesis, traditional Roche, BASF, and Rhone-Poulenc routes still dominate. These pathways have been widely applied in industrial production, particularly by Roche and BASF. However, these methods still face challenges in actual production, particularly concerning yield and environmental pollution, especially in waste treatment.

With the rapid development of biotechnology, new microbial synthesis pathways have emerged, such as using lipase from Aspergillus oryzae to synthesize Vitamin A derivatives or employing engineered yeast cells to synthesize retinol derivatives from xylose. These biological synthesis techniques not only reduce production costs but also significantly decrease pollutant emissions, embodying the principles of green chemistry and providing more environmentally friendly and sustainable solutions for retinol production.

Retinol and its derivatives have demonstrated significant commercial and medical value in various fields. In the daily chemical industry, retinol has been widely used in cosmetic, skincare, and health supplement industries, especially in anti-aging, skin texture improvement, and skin tone evenness. Additionally, retinol also plays an important role in medicine, such as maintaining normal vision, promoting growth and development, enhancing immunity, protecting mucosal health, and maintaining reproductive function. Despite this, retinol and its derivatives' applications also come with certain risks and challenges, particularly regarding potential adverse reactions and irritations during use, which require further research and optimization.

Future research should continue to explore the biological mechanisms and practical applications of retinol and its derivatives. Although retinoids have been widely studied over the past few decades, many mechanisms have not been fully elucidated, especially at the histological and molecular levels in the skin. Current research indicates that retinol and its derivatives have great potential in anti-aging, and future studies should focus on their specific roles in skin repair, antioxidation, and cellular metabolism. Additionally, developing new retinol derivatives, optimizing existing synthesis pathways, and exploring their potential applications in other medical fields will pave the way for the comprehensive application of retinol. These efforts will not only advance scientific development but also bring safer and more effective products to market, contributing more significantly to human health and beauty.

Reference

[1] Vahlquist, A. (1982). Vitamin A in human skin: I. Detection and identification of retinoids in normal epidermis. *The Journal of Investigative Dermatology, 79* (2), 89-93.

[2] Kiser, P., Golczak, M., & Palczewski, K. (2013). Chemistry of the Retinoid (Visual) Cycle. *Chemical Reviews, 114*, 194-232.

[3] Zasada, M., & Budzisz, E. (2019). Retinoids: active molecules influencing skin structure formation in cosmetic and dermatological treatments. *Advances in Dermatology and Allergology/Postępy Dermatologii i Alergologii, 36*, 392-397.

[4] Yee, M. M. F., Chin, K. Y., Ima-Nirwana, S., & Wong, S. K. (2021). Vitamin A and bone health: a review on current evidence. *Molecules, 26*(6), 1757.

[5] Parker, G. L., Smith, L. K., & Baxendale, I. R. (2016). Development of the industrial synthesis of vitamin A. *Tetrahedron, 72*(13), 1645-1652.

[6] Salom, E. (2019). Continuous flow systems for multicatalytic processes based on supported ionic liquids. *1*.

[7] Khalifeh, R., Zarei, Z., & Rajabzadeh, M. (2020). Imidazolium-based ionic liquid immobilized on functionalized magnetic hydrotalcite (Fe3O4/HT-IM): as an efficient heterogeneous magnetic nanocatalyst for chemical fixation of carbon dioxide under green conditions. *New Journal of Chemistry*.

[8] Han, M., & Lee, P. (2021). Microbial production of bioactive retinoic acid using metabolically engineered Escherichia coli. *Microorganisms, 9*.

[9] Harada, H. (2021). Pathway engineering using Escherichia coli to produce commercialized carotenoids. *Advances in Experimental Medicine and Biology, 1261*, 191-199.

[10] Sorg, O., & Saurat, J. (2014). Topical retinoids in skin ageing: A focused update with reference to sun-induced epidermal vitamin A deficiency. *Dermatology, 228*, 314-325.

[11] Chivot, M. (2005). Retinoid therapy for acne. *American Journal of Clinical Dermatology, 6*, 13-19.

[12] Guaratini, T., Gianeti, M., & Campos, P. (2006). Stability of cosmetic formulations containing esters of vitamins E and A: chemical and physical aspects. *International Journal of Pharmaceutics, 327*(1-2), 12-16.

[13] Bjerke, D., Li, R., Price, J., Dobson, R., Rodrigues, M., Tey, C., Vires, L., Adams, R., Sherrill, J., Styczynski, P., Goncalves, K., Maltman, V., Przyborski, S., & Oblong, J. (2020). The vitamin A ester

retinyl propionate has a unique metabolic profile and higher retinoid-related bioactivity over retinol and retinyl palmitate in human skin models. *Experimental Dermatology, 30*, 226-236.

[14] Pavlík, V., Machalová, V., Čepa, M., Šínová, R., Šafránková, B., Kulhánek, J., Drmota, T., Kubala, L., Huerta-Ángeles, G., Velebný, V., & Nešporová, K. (2022). Retinoic acid grafted to hyaluronic acid activates retinoid gene expression and removes cholesterol from cellular membranes. *Biomolecules, 12*.

[15] Geiger, J. M., Hommel, L., Harms, M., et al. (1996). Oral 13-cis retinoic acid is superior to 9-cis retinoic acid in sebosuppression in human beings. *Journal of the American Academy of Dermatology, 34*(3), 513-515.

[16] Tucker-Samaras, S., Zedayko, T., Cole, C., et al. (2009). A stabilized 0.1% retinol facial moisturizer improves the appearance of photodamaged skin in an eight-week, double-blind, vehicle-controlled study. *Journal of Drugs in Dermatology, 8*(10), 932-936.

[17] Zasada, M., & Budzisz, E. (2019). Retinoids: active molecules influencing skin structure formation in cosmetic and dermatological treatments. *Advances in Dermatology and Allergology, 36*(4), 392-397.

[18] Kafi, R., Kwak, H. S. R., Schumacher, W. E., et al. (2007). Improvement of naturally aged skin with Vitamin A (Retinol). *Archives of Dermatology, 143*(5), 606-612.

[19] Sato, K., Morita, M., Ichikawa, C., et al. (2008). Depigmenting mechanisms of all-trans retinoic acid and retinol on B16 melanoma cells. *Bioscience Biotechnology & Biochemistry, 72*(10), 2589-2597.

[20] Yan, J., Ren, G., Lai, M., et al. (2010). Stability and thermal degradation kinetics of vitamin A esters. *Science and Technology of Food Industry, 31*(9), 30-33.

[21] Carlotti, M. E., Rossatto, V., Gallarate, M. (2002). Vitamin A and vitamin A palmitate stability over time and under UVA and UVB radiation. *International Journal of Pharmaceutics, 240*(1-2), 85-94.

[22] Konig, H., Lammerhirt, K., Paust, J., et al. (1974). Chemistry and galenics of tretinoin. *Arzneimittel-Forschung, 24*(8), 1184-1187.

[23] Zheng, J. (2015). Separation, purification, gene cloning, expression and application of Aspergillus oryzae lipase in the synthesis of vitamin A (PhD dissertation). Zhejiang University of Technology.

[24] Pierard-Franchimont, C., Castelli, D., Cromphaut, I. V., et al. (1998). Tensile properties and contours of aging facial skin: A controlled double-blind comparative study of the effects of retinol, melibiose-lactose and their association. *Skin Research and Technology, 4*, 237-243.