Review on Synthesis and Pharmacological Activities of Squalene and Related Compounds

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (B. Pharm.)

School of Pharmacy

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing a degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

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Ethics Statement

This project does not involve any kind of animal or human trial.

Abstract

This review article thoroughly analyzes the natural triterpene squalene, highlighting its importance in biology, cosmetics, and medicine. It describes the structure, biological functions (antioxidant, anti-inflammatory, and anti-aging), natural and synthetic sources, and methods of action of squalene in dermatology. Standard dermatological medications, new technology including nanocarriers, and plant-based cosmetic formulations are highlighted in the review article. It has been demonstrated that squalene and its derivatives, such as vitamins A, E, K, coenzyme Q10, and β-carotene, improve skin health, reduce inflammation, and guard against UV ray damage. Furthermore, squalene's promise as a multipurpose agent in cosmetic dermatology that supports skin protection, regeneration, and innovative therapeutics is confirmed by the synthesis routes, toxicological investigations, and both in vitro and in vivo studies.

Keywords: Squalene; Cosmetic dermatology; Synthesis; Coenzyme Q10; Emollient; Psoriasis.

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List of Acronyms

SQ	Squalene
AD	Atopic Dermatitis
CCID	Cell Culture Infectious Dose
CIR	Cosmetic Ingredient Review
DCW	Dry Cell Weight
DMAPP	Dimethylallyl Pyrophosphate
DNA	Deoxyribonucleic Acid
DXP	1-Deoxy-D-xylulose 5-Phosphate
DXS	1-Deoxy-D-xylulose-5-Phosphate Synthase
FDA	Food and Drug Administration
FPP	Farnesyl Pyrophosphate
FPS	Farnesyl Diphosphate Synthase
HDL	High-Density Lipoprotein
HMG	Hydroxymethylglutaryl
HSQ	Hydro Squalene
HSQS	Hydro Squalene Synthase
IDI	Isopentenyl Diphosphate Isomerase
IDS	Isopentenyl Diphosphate Synthase

Chapter 1

Brief Introduction to Squalene and Related Terpene Compounds

1.1 Squalene & Related Compounds

Squalene ($C_{30}H_{50}$) or 2, 6, 10, 15, 19, 23 - hexamethyetracosa - 2, 6, 10, 14, 18, 22 - hexane is a hydrocarbon characterized by six double bonds. This natural lipid, a member of the terpenoid family and featuring an isoprenoid, is an essential intermediate in the biosynthesis of phytosterols in many plants and cholesterol in most animal organisms. (Spanova & Daum, 2011)

The term "squalene" is derived from its discovery in shark liver oil, which is the most significant source of this compound. Squalene is a natural compound found abundantly in various sources, including olive, amaranth, wheat germ, palm, and rice bran. Squalene offers numerous benefits as a key component of the skin's surface and polyunsaturated lipids. It acts as an antioxidant, emollient, and hydrator and may possess potential antitumor properties. Squalene is used in many topical applications, such as nanostructured lipid carriers (NLCs) and hydrophobic emulsions. Additionally, Squalene is an uncommon triterpene compound that generates approximately 13% lipids present on the skin's surface. Its name originates from its initial extraction from shark liver oil (Squalus spp.), the richest source of this compound. Squalene is primarily concentrated in the skin but is widely distributed throughout human tissues. It is also commonly found in serum, especially in very low-density lipoproteins. (Huang et al., 2009)

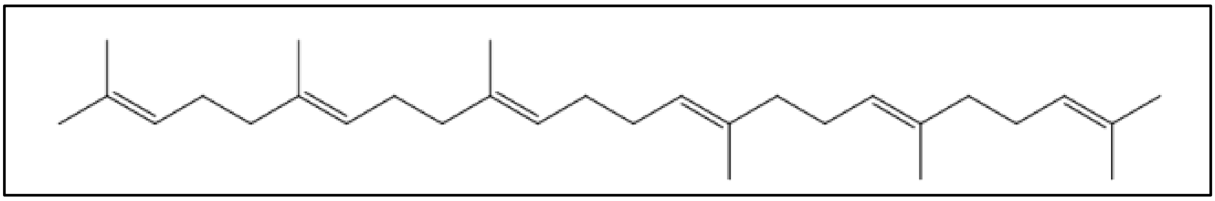

Figure 1.1: Chemical Structure of Squalene ($C_{30}H_{50}$). (Huang et al., 2009)

Squalene belongs to a member of the triterpene chemical class and is a lipophilic biomolecule. Since it comprises six isoprene components, it is an isoprenoid molecule consisting of 30 carbons and six double bonds ($C_{30}H_{50}$). The compound is a colorless, odorless liquid oil. Tsujimoto was the first to isolate it from shark liver oil, and subsequent research has found this compound in various plants through extraction methods. Squalene, found in eukaryotic cells, acts as a metabolic intermediate in the sterol biosynthetic pathway. Squalene synthase, located in the membrane of the endoplasmic reticulum, facilitates the synthesis of squalene through a two-step reaction that involves two units of farnesyl diphosphate. Squalene serves as a precursor to cholesterol in animals and phytosterols in plants, playing a vital role in the sterol biosynthesis of both organisms. (Micera et al., 2020)

A variety of polyprenyl compounds that resemble squalene play crucial biological roles. These include β-carotene, vitamins A, E, and K1, and co-enzyme Q10, all beneficial for skin health. For instance, prenyl groups are utilized by animals and form the side chain of coenzyme Q10, which contains ten prenyl groups. Other recognized compounds that contain prenyl groups for their synthesis also share structural similarities with squalene. (Huang et al., 2009)

Squalene exists in various cell types as it is an essential building block for the biosynthesis of eukaryotic sterols and bacterial hopanoids. More specifically, squalene and its oxidized forms, known as oxidosqualene and bis-oxidosqualene, form the initial structures of squalene, which are the basis for nearly two hundred different triterpenes. Some squalene-containing microorganisms, such as bacteria, can implement squalene as a carbon. The effectiveness of squalene consists of many facets: it possesses the qualities of an antioxidant, moisturizes the skin, and even takes part in vaccine adjuvants. In its constitution within olive oil, it has cancer preventive effects concerning breast cancer, anti-tumor, and cardio-protective, while at the same time giving a lowering effect on serum cholesterol. (Spanova & Daum, 2011)

1.2 Natural & Synthetic Sources of Squalene

Squalene is a particular marker of human sebum as it is not present in the sebum of most mammalian species. As a geared-up precursor of cholesterol and because it has been hastily transformed, it's found in nearly all cells in minute quantities. The main exception is the liver of the Squalidea family, which gets its name because it contains enormous amounts of squalene. The human sebaceous glands release natural squalene as they can no longer synthesize cholesterol. The human sebaceous glands consequently absolutely diverge from the ones of all mammalians, wherein sebum is uncommonly Cholesterol or Sterol-based. For example, Lanolin is found in sheep. (Huang et al., 2009)

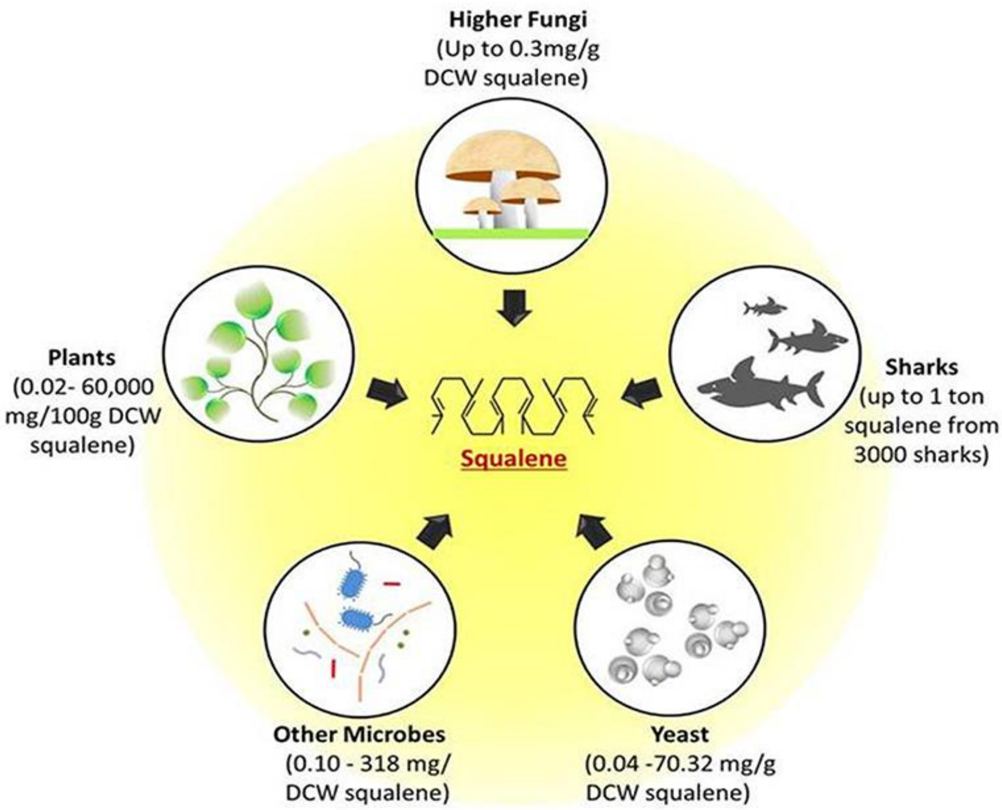

Figure 1.2: Natural sources of Squalene. (Ahmed & Husni Mhammad, 2023)

For instance, sources of squalene are divided into two distinct groups. They are as follows-

Endogenous sources of squalene

Squalene is present in various human organs, with the liver being the primary site for its synthesis and entry into circulation. Research indicates that the concentration of squalene can vary both locally in hepatocytes and systemically, particularly influenced by the synthesis of hepatic cholesterol. It is found in plasma, mostly within very low-density lipoproteins, while significant amounts are also present in low-density and high-density lipoproteins, correlated with triglyceride levels. (Micera et al., 2020)

Exogenous sources of squalene

Recent research highlights that exogenous squalene can originate from both synthetic and natural sources, with applications in food, pharmaceuticals, and supplements. Historically, squalene was derived from shark liver oil, which serves to regulate buoyancy and comprises about 40% of the oil content. Due to conservation regulations in the cosmetics industry, extracting squalene from mammals is now strictly controlled. Alternatively, squalene can be obtained from plants, which are primary precursors to phytosterols and various secondary metabolites. The concentration of squalene in plants is influenced by factors such as species, location, timing, and extraction methods. (Micera et al., 2020)

1.3 Biological Activities of Squalene & Its Analogs

Squalene is obtained in large quantities within the surface area of the skin, where it acts to defend from free radicals. In a substance extinguishing response of free radicals, the squalene atom consolidates the radical biochemically, creating squalene hydroperoxide – a new molecule. Squalene hydroperoxide isn't an antioxidant but a fantastic emollient that, within the skin, serves like a typical sunscreen and moisturizer. Squalene can alleviate, protect, nourish, and restore dry, sensitive skin harmony. Squalene can also be locally (on the skin) applicable, offering assistance to heal injury, helping prevent scarring, and providing a natural, effective moisturizer. Squalene keeps skin soft and smooth, helping to avoid fine lines and wrinkles. Because of its increased stability, squalane, a synthetic version of squalene, is employed in cosmetic applications. The skin is exposed to direct sunlight, which contains UVβ rays, which can cause free radicals and skin damage, in contrast to the interior mucosae. Several studies support Squalene's ability to shield skin from UV rays. (Spanova & Daum, 2011)

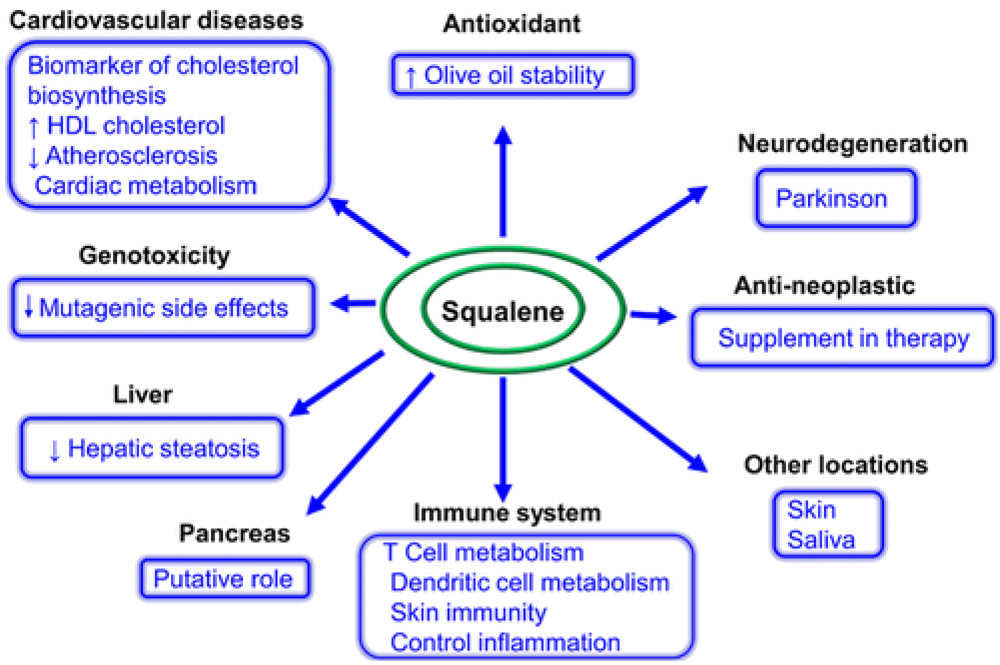

Figure 1.3- Biological Actions of Squalene. (Lou-Bonafonte et al., 2018)

Vitamins A, E, and K, β-carotene, and coenzyme Q10 are substances related to squalene, which also shows biochemical advantages for skin anatomy. (Huang et al., 2009)

- Acne treatment often involves substances derived from vitamin A. Vitamin A or retinol, is a popular anti-wrinkle ingredient in cosmetics.
- One of the potent lipophilic antioxidants in the body is Vitamin E, which is crucial for skin protection and against tumors caused by UV radiation and arsenic.
- Vitamin K has been applied topically to treat bruises, minimize pigmentation, and reduce the duration of purpura caused by laser treatments.
- Dietary intake of β-carotene can effectively shield human skin from UV light-induced erythema and lower the risk of developing skin cancers, excluding melanoma.
- Topical application of Coenzyme Q10 to human skin has been shown to reduce wrinkle depth effectively. It is one of the most popular antioxidants found in most skin care products, and it protects the skin from damage caused by free radicals. (Huang et al., 2009)

Chapter 2

Methodology

Emphasizing the synthesis pathways and pharmacological activities, particularly in cosmetic dermatology, this study used a methodical and organized methodology to collect, assess, and synthesize pertinent scientific material on squalene and its related compounds.

1. Search Strategy for Journal/Article

A comprehensive literature search was conducted using recognized scientific databases such as MDPI, PubMed, ScienceDirect, ResearchGate Google Scholar, Scopus, and CORE. The following keywords and Boolean combinations were used: "squalene", "squalene derivatives", "biosynthesis of squalene", "chemical synthesis of squalene", "squalene pharmacological activity", "cosmetic dermatology", "skin diseases and squalene", and "squalene in dermatology".

Filters were used to include only English-language publications published mostly between 2000 and 2024. The search focused on original research publications, reviews, and clinical trials that examine both natural and synthetic sources of squalene and its biological implications.

2. Criteria for Inclusion and Exclusion

- ❖ Inclusion Criteria:
  - ➢ Peer-reviewed papers and reviews released between 2000 and 2024
  - ➢ Studies on the therapeutic and cosmetic dermatological uses of squalene or its analogs
  - ➢ Articles addressing the chemical and biosynthetic production of squalene

- ➢ Research describing the pharmacokinetics, toxicity, and mechanisms of action of chemicals based on squalene

❖ Exclusion Criteria:

- ➢ Papers written in languages other than English are excluded.
- ➢ Articles that are not available in full text
- ➢ Research not connected to pharmacological or dermatological settings
- ➢ Non-peer-reviewed information, such as blogs or standard web pages

3. Data Extraction and Analysis

Titles and abstracts were used to filter relevant publications. For comprehensive details on chemical structure, synthesis pathways, biological activities, mechanisms of action, toxicological profiles, and formulation innovations, the full texts of the papers that made the short list were examined. Data and figures about molecular pathways, cosmetic applications, and in vitro and in vivo investigations were recorded and contrasted. The results from many investigations were compiled and interpreted using descriptive synthesis.

4. Ethical Consideration

Ethical approval was not required because this non-experimental review article was based solely on published data. All sources of information have been duly acknowledged and cited following academic standards.

Chapter 3

Standard Drugs in Cosmetic Dermatology

3.1 Introduction to Cosmetic Dermatology & its Role in Modern Skincare

The skin serves as the primary barrier between the human body and the environment, equipped with a sophisticated immune system that responds to foreign antigens. This cutaneous defense includes both innate and adaptive immunity, crucial for maintaining health against threats arising from skin barrier defects or alterations in skin flora. Comprising three main layers—the epidermis, dermis, and hypodermis—the skin features diverse innate immune cells, antimicrobial peptides, and phagocytes like neutrophils and macrophages that monitor the tissue through blood capillaries. The epidermis acts as a protective barrier primarily composed of keratinocytes, while the dermis provides nourishment, and the hypodermis assists in temperature regulation. The skin's resident cell groups effectively prevent water loss and protect against UV radiation and microbial infections. Immune cells traverse through the lymphatic system and blood vessels, adapting in number in response to skin irritation and various immune stimuli. (Lin et al., 2017)

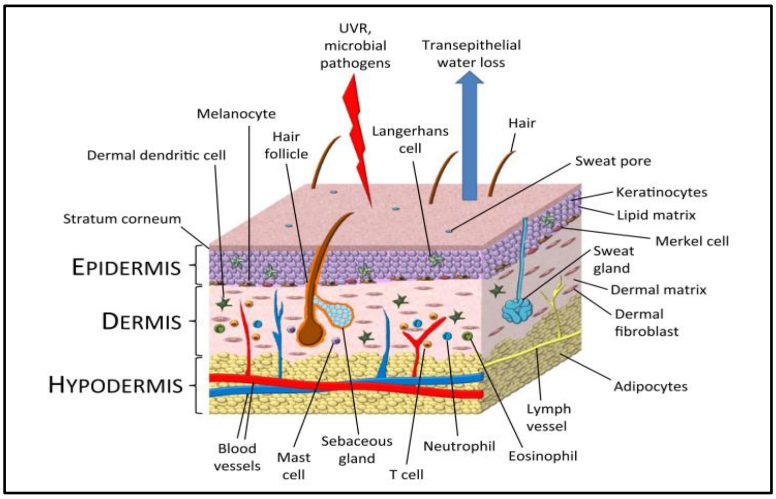

Figure 3.1: The 3D structure of the skin cellular constituents. (Zhou et al., 2018)

Skincare products are essential for maintaining healthy skin, providing benefits such as cleansing, hydration, and protection against environmental damage like UV rays. They contain active ingredients that enhance the skin’s natural functions, supporting moisture retention, metabolism, and overall balance. Key advantages include deep cleansing, moisture preservation, UV protection, antioxidant effects, and skin regeneration. Furthermore, these products can target specific issues such as acne, pigmentation, and aging, helping to minimize wrinkles, sagging, dark spots, and freckles, which leads to a brighter and more youthful appearance. (Kendall & Nicolaou, 2013)

The roles played by skincare cosmetics may include-

- Cosmetic dermatology is essential for maintaining skin balance and enhancing both aesthetics and health.
- It provides safe, effective anti-aging solutions, allowing individuals to embrace aging gracefully with treatments like Botox and laser therapy.
- Addresses various skin concerns beyond wrinkles, including stretch marks, scars from acne, and skin discolorations.
- Procedures are generally non-invasive and straightforward and promote quick recovery, typically within 2-3 days.
- Contributes to overall skin health by treating conditions such as acne and eczema while supporting long-term wellness. (Kendall & Nicolaou, 2013)

3.2 Common Skin Conditions that Need Cosmetic Dermatological Attention

Skin-related issues significantly impact global health, contributing to high mortality rates and representing the most common diseases among individuals of all ages. Due to their considerable socioeconomic effects, dermatological treatments are listed in the WHO's Essential Medicines. Major skin conditions include acne, psoriasis, eczema, fungal infections, and skin cancer, highlighting the need for prioritizing skin health globally. Skin disorders affect 30% to 70% of the population, transcending geographical and cultural boundaries. According to the Global Burden of Disease project (2013), the prevalence of skin diseases has increased by 46.8% since 1990, making them a critical public health concern. Skin conditions such as fungal infections, acne, and skin cancer impact individuals across all age groups, commencing as early as one year and often persisting into later life, particularly with issues like eczema and pruritus. These conditions detrimentally affect quality of life, contributing to decreased self-esteem and increased anxiety, especially among women and children who face more social challenges. (Maddheshiya et al., 2022)

Some common skin conditions that require Cosmetic Dermatological Attention are-

❖ **Eczema / Atopic Dermatitis:**

Atopic dermatitis (AD), commonly known as eczema, is a lifelong chronic inflammatory skin condition that notably impacts the quality of life in industrialized nations. It affects approximately 15-20% of children and 2.1-4.9% of adults globally. Characterized by dry and inflamed skin, lesions, and in severe cases, areas that may leak or drain, AD's onset is influenced by various genetic and environmental factors that compromise the skin barrier and immune responses. Effective management of AD requires a holistic approach aimed at reducing flare-ups, preserving skin integrity, and alleviating discomfort. (Maddheshiya et al., 2022)

❖ **Psoriasis / Skin Inflammation and Proliferation:**

Psoriasis is a chronic inflammatory skin condition of unknown origin, potentially influenced by genetic predisposition and environmental factors, including stress, infections, and certain medications. The disorder presents with inflammation of the skin and excessive proliferation of keratinocytes, leading to the formation of itchy, scaly plaques and heightened activity of T-cells. Psoriasis is a chronic skin disorder affecting over 13% of the global population. It is characterized by dysregulated immune responses. The most common form, plaque psoriasis or psoriasis vulgaris, constitutes 80% to 90% of cases. It presents with silver scales and red patches, often accompanied by irritation. Approximately 75% of patients experience persistent itching, which can intensify with the severity of the condition, potentially leading to discomfort or burning sensations. While psoriasis can impact both genders, it tends to be more severe and prevalent among women. (Maddheshiya et al., 2022)

- **Acne Vulgaris**

Acne vulgaris is a prevalent skin condition characterized by excessive sebum production and follicular hyper keratinization, leading to various inflammatory lesions known as comedones, often colonized by Propionibacterium acne. Affecting approximately 85% of the global population, acne presents in both inflammatory and non-inflammatory forms, including blackheads, whiteheads, papules, pustules, nodules, and cysts. The condition can result in permanent scarring and significant psychosocial repercussions, including sadness, social isolation, and suicidal ideation. Various factors contribute to its development, including genetics, hormonal changes, diet, pollution, climate, and other bacterial species, either independently or collectively. (Kendall & Nicolaou, 2013)

- **Fungal infection**

The prevalence of superficial fungal infections is rising, particularly among those with immunocompromised conditions like AIDS. Fungi can cause both superficial and deeper infections, with skin infections classified as superficial, cutaneous, or subcutaneous based on their tissue penetration. Dermatomycetes, including the genera Trichophyton, Epidermophyton, and Microsporum, are responsible for cutaneous infections affecting keratinized tissues. Noteworthy examples include Tinea spp. infections, such as var. faciei, var. barbae, var. capitis, and var. manuum. These infections are transmitted through personal contact with infected individuals, animals, soil, or contaminated surfaces. (Maddheshiya et al., 2022)

❖ Skin ageing

Skin aging is an inevitable process involving both internal and environmental causes, resulting in continuous changes in skin structure, function, and look. Aged skin is distinguished by its low lipid, NMF, and water content. According to some scientists, most aging effects are induced by extrinsic factors, with only 3% having an innate base. The most significant intrinsic elements influencing aging are gender, ethnicity, and genetic variability. Aging owing to natural causes is a physiological process that results in dry, wrinkled skin having fine lines. Basal cell growth is inhibited, resulting in a thin epidermal layer and a smaller interaction surface area over the dermis and epidermis. On the other hand, aging caused by external influences such as UV radiation, environmental pollutants, and poisons, and also deep wrinkles and hyperpigmentation, distinguish smoking. UV radiation accounts for around 80% of facial aging, also known as photoaging. (Maddheshiya et al., 2022)

❖ Contact dermatitis

Contact dermatitis is an IV-delayed allergic response characterized by the involvement of Th1 cells and CD8+ cytotoxic T cells, leading to symptoms such as itching and redness due to abnormal immune reactions mediated by cytokines and phagocytes. The immune response comprises an initial sensitization stage and a subsequent elicitation phase. Although research has primarily concentrated on the role of fatty acids in atopic dermatitis, recent findings indicate that a diet high in oleic acid can reduce contact hypersensitivity symptoms in mice. This is particularly significant as oleic acid does not operate through the eicosanoid pathway and is generally not associated with immune modulation. Furthermore, mice supplemented with fish oil also exhibited diminished contact hypersensitivity symptoms. These observations suggest that altering the balance of fatty acids in the skin may attenuate Th1-mediated responses, highlighting the potential role of fatty acids and their metabolites in modulating the immune responses involved in contact dermatitis. (Kendall & Nicolaou, 2013)

❖ **Skin cancer**

It is an abnormal proliferation of skin cells that can be classified according to the cell type involved. Basal and squamous cells are the most afflicted, and the condition is known as basal and squamous cell carcinoma, accordingly. Melanoma is a condition that impacts melanocytes. Squamous cell carcinomas, unlike basal cell carcinomas, are aggressive and potentially fatal if not treated promptly. Melanoma, on the other hand, is the most aggressive and deadly type of skin cancer. It comes in black, brown, blue, pink, white, and red spots. Skin carcinomas are typically caused by overexposure to UV radiation or sunbathing. (Maddheshiya et al., 2022)

3.3 Classification of Standard Drugs Used in Cosmetic Dermatology

Dermatological issues are treated by addressing the underlying causes with topically or orally administered treatments. Topical therapies with retinoids, antimicrobials, and antifungal medications are often favored. Oral antimicrobials, anticancer, and hormonal medicines are used to treat more serious infections. Nonetheless, the route of administration is determined by a variety of parameters, including the patient's age, convenience, site of infection, and disease severity. The most often used standard medications in cosmetic dermatology for treating diverse skin problems are listed below:

Retinoids: Tretinoin and Retinol are examples of topical retinoid therapy, which is the most common first-line treatment for inflammatory and non-inflammatory acne. Retinoids are mainly used for treating hyperpigmentation, fine lines, wrinkles, acne, and scarring, preventing the development of new acne lesions, controlling the growth of existing comedones, providing anti-aging benefits by reconstructing the damaged epithelium layer, and decreasing sebum levels. These Vitamin A derivatives are well-known for boosting skin cell turnover, resulting in smoother, more youthful skin. They function by increasing collagen production and hastening the exfoliation of dead skin cells, thereby reducing the visibility of fine wrinkles and improving skin texture. (Lin et al., 2017)

Sunscreens: Sunscreen is an essential component of any skincare regimen, providing critical protection from the sun's damaging rays. As dermatologists, we see firsthand the tremendous impact of constant sunscreen use, particularly those with Zinc Oxide and Titanium Dioxide, which are utilized to maintain skin health and vitality. Beyond cosmetic considerations, sunscreen protects the skin from UV radiation, preventing sunburn, lowering the risk of skin cancer, and slowing premature aging. Its use is not confined to sunny days; it should be a year-round habit, rain or shine. To preserve good skin health, individuals with cosmetic issues and everyone should apply sunscreen daily. Sunscreens can be found in a variety of formulations, including lotions, sprays, and tinted options, providing comfort and safety for all skin types. (Lin et al., 2017)

Corticosteroids: Corticosteroid formulations, both systemic and topical, are frequently prescribed for patients to treat inflammation, redness, and specific skin disorders such as eczema, psoriasis, and dermatitis. When acute hypersensitivity disorders, connective tissue diseases, immunological blistering diseases, and common dermatoses are severe and widespread, oral steroids can help. Topical steroid formulations are primarily used to treat various forms of dermatitis, although they are also beneficial for psoriasis and other skin conditions. Topical corticosteroids (TCs) constitute the foundation of medicinal skin care. (Kendall & Nicolaou, 2013)

Antifungals: Antifungal medications are crucial for treating dermatophytosis and are available in both systemic and topical forms. Systemic antifungal agents are categorized into four groups—polyenes, azoles, echinocandins, and nucleoside analogs—based on their action within pathogens. Topical formulations, including creams, ointments, lotions, and powders, are commonly employed for infections like ringworm and athlete's foot, with frequently used agents like Amphotericin B, Ketoconazole, Clotrimazole, and Terbinafine. These medications not only target fungi on the skin and nails but also play a vital role in minimizing spore transmission. The effectiveness of topical antifungals is significantly influenced by their ability to penetrate deeper skin layers, alleviating symptoms such as itching and redness, regardless of the formulation's properties. (Lin et al., 2017)

Antibiotics: Topical antibiotics, such as clindamycin and erythromycin, are frequently utilized for the treatment of mild to moderate inflammatory acne due to their ability to reduce bacteria and inflammation. However, their application is limited by negative side effects and lack of efficacy. The combination of topical retinoids and benzoyl peroxide with topical antibiotics is preferred to enhance effectiveness and mitigate bacterial resistance. In cases of inflammatory moderate-to-severe acne that does not respond to topical therapies, oral antibiotics become necessary. Common oral options include macrolides, fluoroquinolones, and tetracyclines, which impede the growth of P. acnes and inflammatory mediators. Among these, minocycline and doxycycline are favored for their superior anti-inflammatory effects and better lipid solubility, facilitating effective targeting of P. acnes. (Kendall & Nicolaou, 2013)

Hydroquinone: Hydroquinone is a chemical widely utilized for skin lightening, particularly in treating hyperpigmentation conditions such as melasma and age spots. It functions by inhibiting melanin production through the suppression of the enzyme tyrosinase. Available in over-the-counter 2% concentrations and stronger prescription formulations, hydroquinone is frequently combined with topical retinoids and corticosteroids to improve treatment outcomes. Despite its effectiveness, oral hydroquinone may cause adverse effects, including liver toxicity, while retinoids can lead to skin irritation and heightened sun sensitivity. Prolonged hydroquinone application can result in various skin issues, such as irritation, ochronosis, thinning skin, and stretch marks. Although combination therapies often yield better results, they come with increased risks of side effects. (Kendall & Nicolaou, 2013)

3.4 Recent Advancements in the Treatment Approaches of Cosmetic Dermatology

Cosmetics serve to enhance appearance and address body odors while promoting skin health. The evolution of skincare formulations has led to a focus on the functional components of cosmetic products and their efficacy and safety. Despite advancements, challenges such as limited solubility and low skin penetration persist. Lipid carriers present a promising solution for improving the solubility and stability of these products. Moreover, biotechnology and nanotechnology emerge as pivotal areas for innovation, enabling the development of biocompatible treatments and effective delivery systems. Topical dermatological therapies show potential due to reduced systemic side effects, yet overcoming the barrier posed by the stratum corneum remains essential. Research into particulate carrier systems, including liposomes, solid lipid nanoparticles, and nanostructured lipid carriers, offers valuable insights for enhancing dermal penetration.

Recent progress in treatment methods for cosmetic dermatology includes-

- **Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC)**

Solid lipid nanoparticles (SLN), introduced in the early 1990s, serve as a novel delivery system that offers several advantages for topical medicinal and cosmetic uses, such as compound stabilization, controlled release, and skin occlusivity. Additionally, nanostructured lipid carriers (NLC) represent a more advanced option with enhanced loading capacity and potential for triggered release. This article discusses the creation of concentrated lipid nanoparticle dispersions with a lipid content between 30-80% and positions SLN and NLC as sophisticated delivery mechanisms in pharmaceuticals and cosmetics. While the initial applications may predominantly be in cosmetics due to regulatory ease, further research on lipid particle formation, surfactant interactions, and human subject studies is crucial for real-world applicability. The article emphasizes the need for increased focus on this field, paralleling the advancements seen in oral and parenteral lipid nanoparticle applications. (Fang et al., 2008)

❖ Nanocarrier Technology-Based Active Cosmetic Ingredients

Nanocarrier technology has transformed medication and cosmetic delivery by overcoming the limitations of traditional formulations. This advancement enhances the absorption and retention of active ingredients, particularly in skincare, where it improves the stability, solubility, and penetration of components for sustained release to address various skin conditions. Despite its benefits, the complexity of creating nanocarriers requires meticulous attention to component characteristics and formulations to ensure stability and permeability. Challenges such as Ostwald ripening, potential drug leakage, and material degradation obstruct the large-scale production of some nanocarriers. Additionally, converting these carriers into suitable cosmetic forms complicates quality control due to the introduction of excipients affecting particle size and drug release. Consequently, optimizing formulations and advancing preparation technologies remain critical areas for further research and development in nanocarrier technology. (Zhou et al., 2021)

❖ The potential role of essential oils in skin problems

The World Health Organization identifies medicinal plants as a vital source of pharmaceuticals, with nearly 80% of individuals in impoverished nations relying on traditional herbal remedies for health issues. The appeal of natural medicine lies in its cost-effectiveness, lower side effects, and higher acceptance among patients. Evidence suggests that natural products can effectively manage various disorders that resist conventional treatment, prompting research into herbal medicine for skin conditions ranging from mild irritation to severe cancers.

Essential oils (EOs), derived from plants, are valuable in the cosmetics, fragrance, and pharmaceutical sectors. These volatile compounds, responsible for a plant's unique scent or flavor, are produced by special cells within the plant. Significant components of EOs are those present in higher quantities (20-70%), while trace elements are considered insignificant. The composition of essential oils is influenced by factors such as geographical location, harvest timing, plant maturity, and species variety, with terpenes and terpenoids as the primary constituents, largely composed of isoprene units. (Maddheshiya et al., 2022)

- **The role of current synthetic and possible plant and marine phytochemical compounds**

Current research explores the efficacy of synthetic compounds and phytochemicals from plant and marine sources in treating acne, a chronic skin condition characterized by clogged hair follicles. Historically noted in ancient civilizations and traditionally managed with various folk remedies, acne is currently treated in women using antibiotics, keratolytics, corticosteroids, and hormone therapies, all of which may lead to significant side effects. This underscores the need for safe, natural alternatives. Therapeutic phytochemicals found in plants demonstrate antibacterial, antioxidant, anti-inflammatory, keratolytic, and sebaceous-reducing properties. Important compounds such as terpenes, flavonoids, alkaloids, and essential oils can be extracted from different parts of plants and utilized in formulations to enhance skin absorption. Furthermore, bioactive substances sourced from marine environments may also play a role in acne treatment strategies.

Chapter 4

Potential Uses and M/A of Squalene & Related Compounds in Cosmetic Dermatology

4.1 Potential Uses of Squalene in Cosmetic Dermatology

In plants, a secondary metabolite found in the unsaponifiable fraction of the contained lipids is squalene, contributing to cell membrane stability. It plays a significant part in how plants adjust to biotic stress and synthesize phytosterols, precursors of growth hormones. In skin, squalene is synthesized and discharged by the sebaceous organ and has be a significant constituent of the surface lipids of skin (human). It is one of the significant components of sebum, up to 12%, and has the most softening, moisturizing, and adjusting the lipid substance of the skin layers, antioxidant, emollient, UV defender. In skin physiology, squalene functions as an antioxidant, hydrator (moisturizer), and topical carrier while also addressing skin conditions such as seborrheic dermatitis, acne, psoriasis, or atopic dermatitis, in addition to helping prevent skin aging. (Lou-Bonafonte et al., 2018)

It is utilized as an adjuvant in vaccines and drugs within the pharmaceutical industry, increasing the item's biocompatibility and solidness. Within the (dermato-cosmetic) industry, it is used as an emollient, antioxidant, and UV protectant and encourages the infiltration of dynamic fixings into the skin. Advertising for squalene is projected to reach 184 million dollars by 2025, mainly due to growing demand from the pharmaceutical industry, which utilizes it as an adjuvant in drugs and vaccinations for antibodies. Squalene arranged in emulsion, either as one fixing or in combination with other components, can move the instrument of activity of medicines and immunizations forward by activating a favorable, safe reaction against the exogenous antigen. (Knox & O’Boyle, 2021)

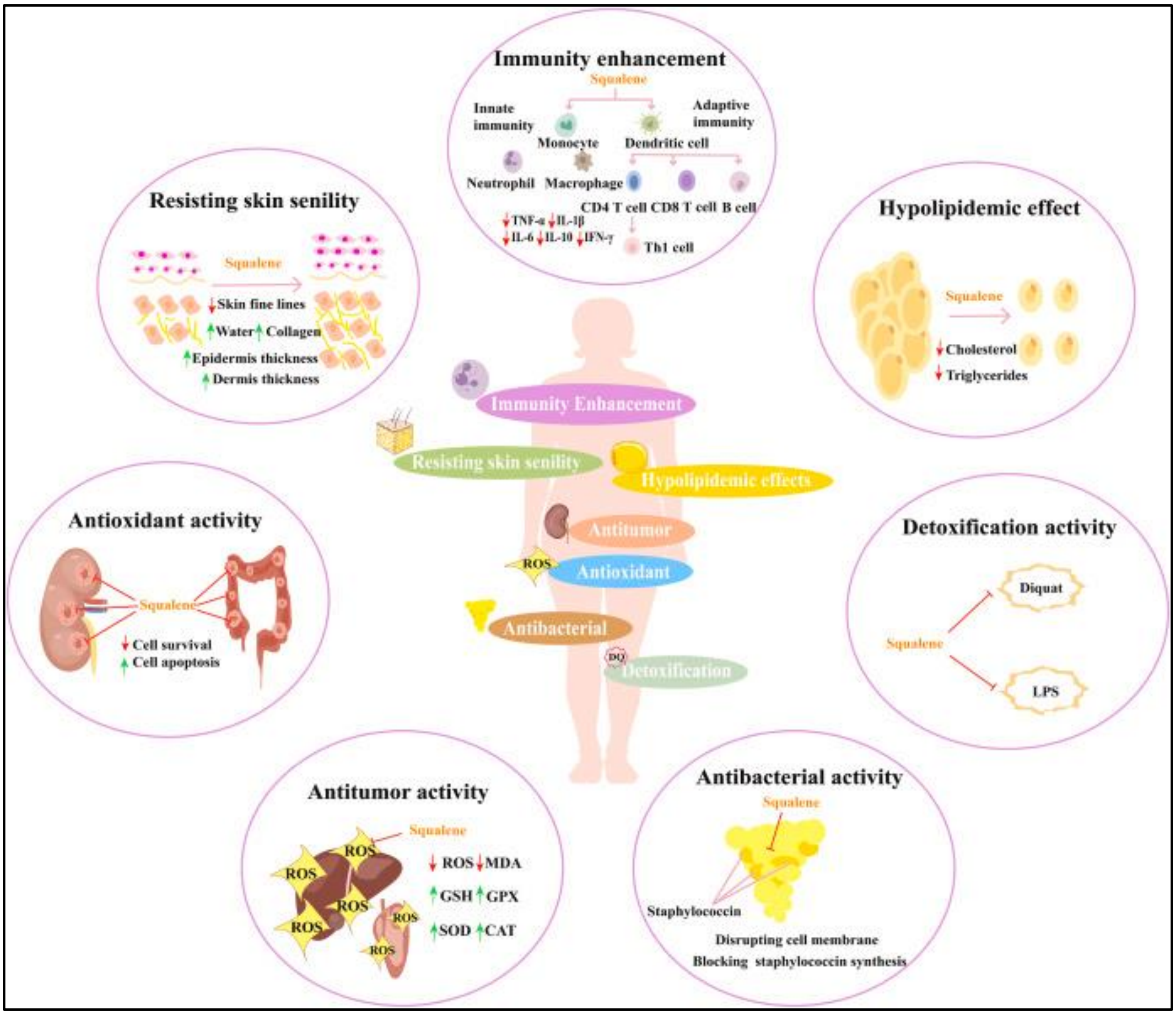

Figure 4.1: Potential Uses of Squalene. (Cheng et al., 2024)

Squalene in Skincare

Squalene is commonly incorporated into pharmaceutical products as a potent skin moisturizer and helps prevent aging or cancer-related wrinkles and fine lines. A wide range of cosmetic items containing squalene can be found in markets globally. In addition to being colorless and odorless, its characteristics such as excellent spreading ability, light texture, stability across various temperatures, non-greasy feel, quick absorption through the skin, ability to restore skin softness, formation of a moisture barrier, healing of dry and cracked skin, antibacterial effects, and promotion of cell regeneration make squalene a superb skin protector. Squalene is applicable in areas such as anti-aging, wrinkle prevention, eczema treatment, damaged hair care, dry scalp, and brittle nail repair. (GNES, 2013)

Squalene emulsions

Squalene is commonly utilized in emulsions as either the main ingredient or a secondary lipid. While squalene emulsions are created for a variety of applications, they are often employed to deliver vaccines and medications into the body. For this purpose, squalene functions as an immunological adjuvant, remaining safe and non-toxic for the host while modulating or boosting the immune reaction against the adjuvant. When used for antigen delivery, squalene is emulsified with various other substances. It is instrumental in developing vaccines with significant transfection efficiency as well as in producing stable and viscous emulsions of adjuvants that have been rendered quite soluble with small droplets. (Knox & O'Boyle, 2021)

Squalene as Moisturizer

Squalene is one of the most important hydrating agents found in nature. It quickly and efficiently absorbs into the skin, enhancing elasticity and restoring flexibility without leaving an oily film. Squalene also has an occlusive impact that gives it vital moisturizing properties by anticipating trans epidermal water misfortune and maintaining the moisturizing adjustment within the profound layers of the skin. Additionally, it has an oil–balancing impact by avoiding the compensatory overproduction of sebum when the dryness of the skin increases due to environmental conditions. (GNES, 2013)

Protective effects of squalene

Shark liver oil, rich in squalene and alkylglycerol, is recognized for its protective effects against bacterial and fungal infections, particularly in those with atopic dermatitis and psoriasis-related skin lesions. Squalene, which constitutes about 12% of skin lipid secretion, has demonstrated a protective role against UV radiation damage in animal studies conducted by Hashim et al.

Furthermore, squalene and phenolic compounds in olive oil are noted for their substantial protective effects against coronary heart disease and aging. However, prolonged exposure to UV radiation can lead to photo-oxidized squalene, potentially causing ongoing inflammation and heightened skin metabolism, particularly in oily skin types. This form of squalene may also act as a target for preventing and treating UV-related skin disorders. High doses of squalene (over 13.5 g daily) have shown positive effects on aging skin, enhancing wrinkle appearance, increasing type I procollagen, and reducing DNA damage from UV exposure. Additionally, emerging research underscores the protective properties of squalene against skin cancer. (Chugh, 2003)

4.2 Potential Uses of Squalene-Related Compounds in Cosmetic Dermatology

Compounds associated with squalene, including β-carotene, coenzyme Q10, and vitamins A, E, and K, also demonstrate advantages for skin health.

Vitamin A

Acne treatment often involves substances derived from vitamin A. Additionally, retinoids are used as chemotherapeutic agents and chemo preventive for different types of cancer. In vitro and in vivo studies significantly influence the development and differentiation of normal cells compared to premalignant and epithelial malignant or cancerous cells. Vitamin A, or retinol, is a popular anti-wrinkle ingredient in cosmetics. However, using it in traditional cosmetic formulations poses challenges due to its instability in light and the potential for skin irritation.

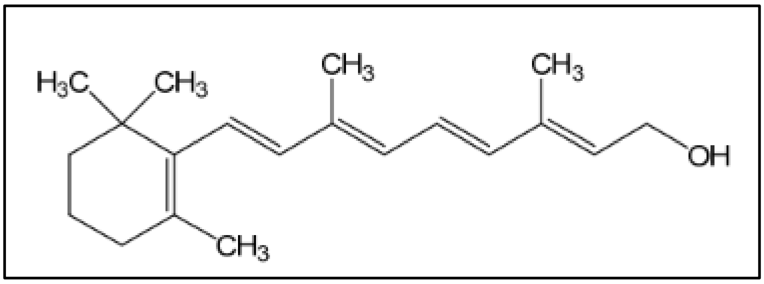

Figure 4.2: Chemical Structure of Vitamin A (retinol). (Huang et al., 2009)

Retinol is commonly formulated as a gel or an oil-in-water emulsion to enhance its effectiveness during application. Research has investigated retinol absorption levels in both in vitro and in vivo models, focusing on fuzzy rats. These studies demonstrated that after 24 hours, there was a significant skin reservoir for retinol measured at 0.3% in human skin. The findings from this research help clarify the significance of the in vitro retinol reservoir in human skin when assessing systemic absorption. (Huang et al., 2009)

Vitamin E

One of the potent lipophilic antioxidants found in the body is Vitamin E, which is crucial for skin protection. A study by Uddin et al. investigated how vitamin E protects against tumors caused by UV radiation and arsenic. In this research findings showed that vitamin E decreased the occurrence of tumors in mice exposed to UV light and arsenic. This research indicates that vitamin E can mitigate the carcinogenic effects of arsenic in conjunction with UV exposure.

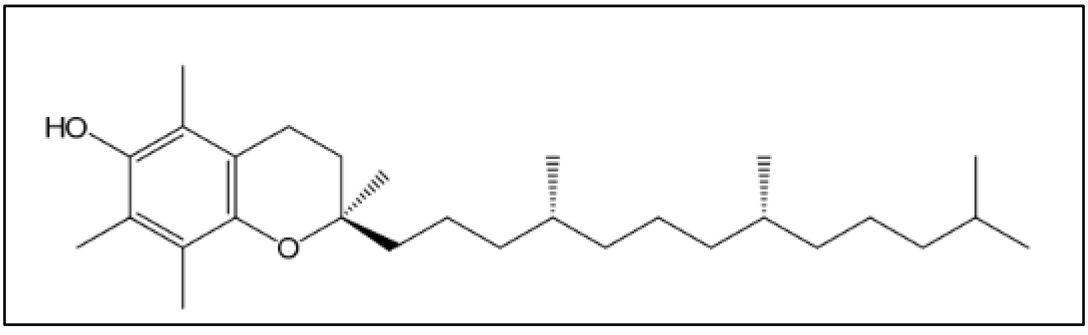

Figure 4.3: Chemical Structure of Vitamin E. (Huang et al., 2009)

Recent research by Ekanayake-Mudiyanselage et al. has shown that products that include α-tocopherol at levels under 0.2% can elevate vitamin E levels in the stratum corneum of human skin and prevent lipid peroxidation in live subjects. Consequently, skincare products containing α-tocopherol at concentrations between 0.1% and 1% are expected to be potentially effective formulations that boost the skin barrier's antioxidant protection. (Morgan et al., 2024)

Vitamin K

An additional compound linked to squalene that promotes skin health is vitamin K. A topical cream with vitamin K leads to faster healing from purpura that can reduce the duration of purpura caused by laser treatments. Additionally, topical application of vitamin K has been employed to treat bruises and minimize pigmentation.

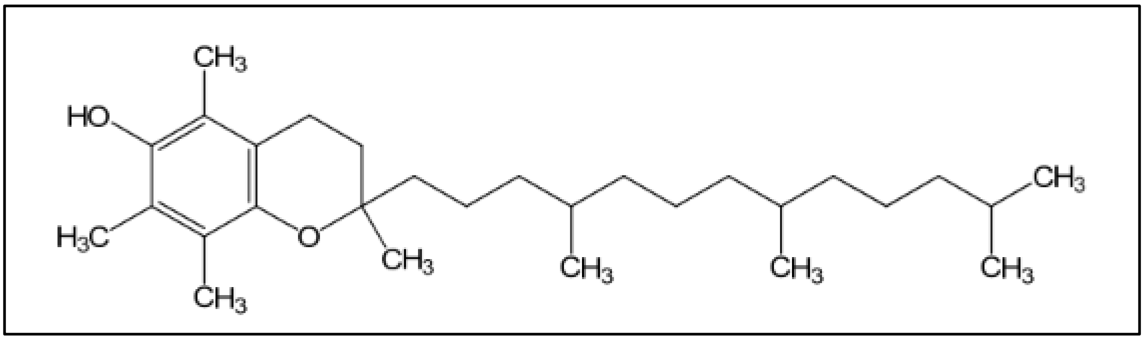

Figure 4.4: Chemical Structure of Vitamin K_1. (Huang et al., 2009)

Lopes et al. investigated the potential of systems for delivering drugs based on lipids to improve the transdermal absorption and in vitro penetration of vitamin K at a concentration of 2.5% (w/w). Their experimental results revealed that vitamin K incorporated into a lipophilic carrier showed inadequate topical distribution. (Morgan et al., 2024)

β-Carotene

Many compounds, including polyphenols, share a similar chemical structure with squalene and are vital for various organic processes. It is widely recognized that β-carotene serves as an effective oxygen quencher and behaves as an exclusive scavenger of free radicals. Numerous in vivo studies identified the oxidation products of β-carotene to elucidate how it protects against UVA-induced skin damage.

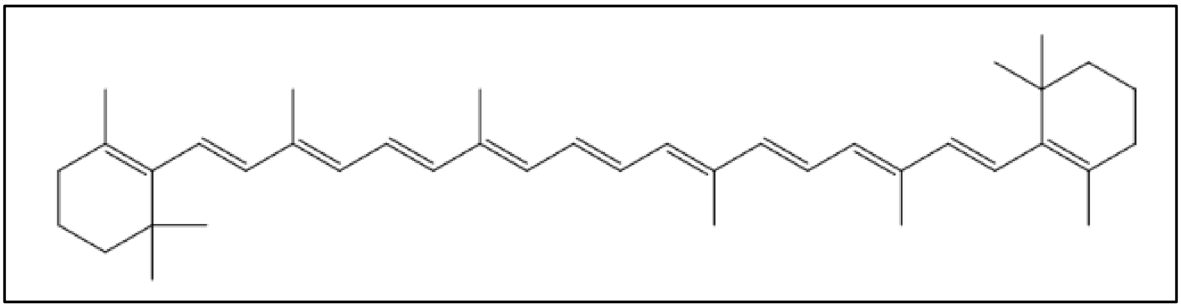

Figure 4.5: Chemical Structure of β-Carotene. (Huang et al., 2009)

Dietary intake of β-carotene can effectively shield human skin from UV light-induced erythema; Topical β-carotene is transformed into esters of retinyl within the epidermis, acting as a precursor for vitamin A in the skin, which is vital for preserving youthful and resilient skin. An excited oxygen (O2) state is considered a key liaison of erythropoietic protoporphyria, a photosensitivity condition largely resolved by β-carotene. Research has demonstrated that higher serum levels of β-carotene are linked to a lower risk of developing skin cancers, excluding melanoma. Experimental studies on UV-induced cancer formation have revealed that β-carotene offers protective benefits for the skin. (Huang et al., 2009)

Coenzyme Q10

An essential lipid-soluble antioxidant produced by the human body is coenzyme Q10. Therefore, topical coenzyme Q10 therapy can be suggested as a proper pharmaceutical technique in dermatology and cosmetics. As people age, their skin contains less coenzyme Q10 than others. Coenzyme Q10, when applied topically to human skin, has been shown to reduce wrinkle depth effectively. One of the studies suggests that consuming coenzyme Q10 raises the amount of the enzyme in the epidermis, which may be required to minimize wrinkles and other advantages associated with the skin's potent antioxidant and invigorating properties.

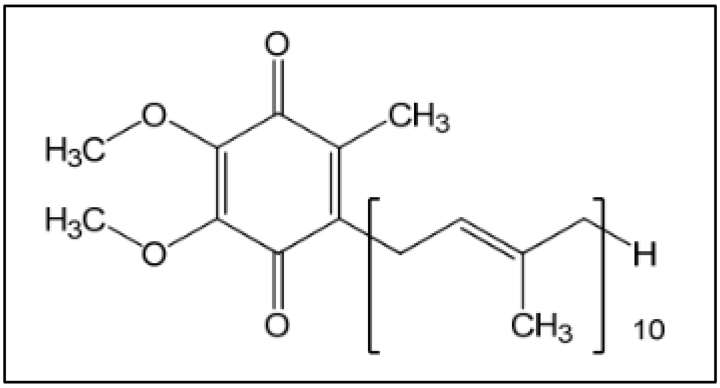

Figure 4.6: Chemical Structure of Coenzyme Q10. (Huang et al., 2009)

Coenzyme Q10 is one of the most popular antioxidants found in most skin care products, and it protects the skin from damage caused by free radicals. It has been suggested that topical skincare products containing carotenoids and the coenzyme Q10 may provide better protection against irritation and premature aging brought on by exposure to sunlight. (Morgan et al., 2024)

4.3 Mechanism of Action of Squalene in Cosmetic Dermatology

(A) Moisturization and Skin Barrier Protection

❖ **Role:**

- Squalene/squalane integrates into the lipid bilayer of the stratum corneum, reinforcing the skin's protective barrier.
- It prevents transepidermal water loss (TEWL) by forming a semi-permeable barrier
- It provides an occlusive effect, reducing water evaporation from the skin.
- Enhances skin hydration, elasticity, flexibility, and softness without clogging pores (non-comedogenic). (Lou-Bonafonte et al., 2018)

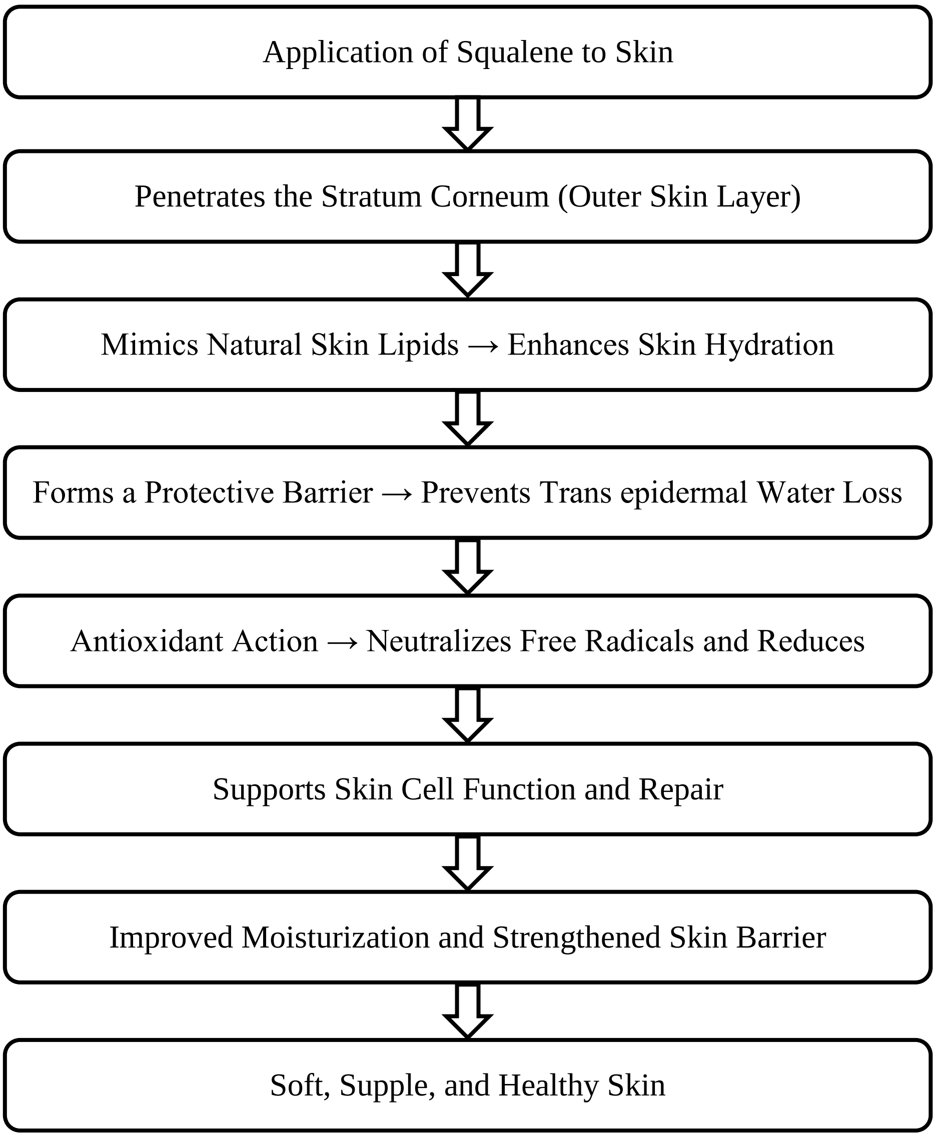

Figure 4.7: M/A of Squalene in Moisturization and Skin Barrier Protection. (Lou-Bonafonte et al., 2018)

❖ **Cosmetic Application:**

- Used in moisturizers, serums, and facial oils for dry and sensitive skin.
- Suitable for acne-prone and oily skin due to its lightweight texture.

Example:

1. Nature Derma 100% Squalene Face Oil

- Active ingredients: Squalane*, Amaranth oil, and Natural Biome Boost Solution
- Uses: hydrates the skin, improves texture, and potentially reduces the appearance of wrinkles, scars, and hyperpigmentation.

*Squalane is a saturated version of squalene that works better in cosmetics since it is less likely to oxidize.

2. Squalene + Zinc Oil-Free Moisturizer
    - Active ingredients: Squalene & Zinc
    - Uses: Prevents dryness & hydrates the skin for a long duration of time, controls excessive sebum production.

(B) Anti-Inflammatory Effects

❖ **Role:**

- Squalene has anti-inflammatory effects, reduces inflammation in conditions such as acne, eczema, and rosacea
- Modulates inflammatory mediators by inhibiting NF-kB and cytokine release (TNF-a, IL-6, IL-1ß).
- Restores skin barrier function in inflammatory conditions.
- Enhances wound healing by promoting keratinocyte proliferation and migration, as well as lipid restoration. (Lou-Bonafonte et al., 2018)

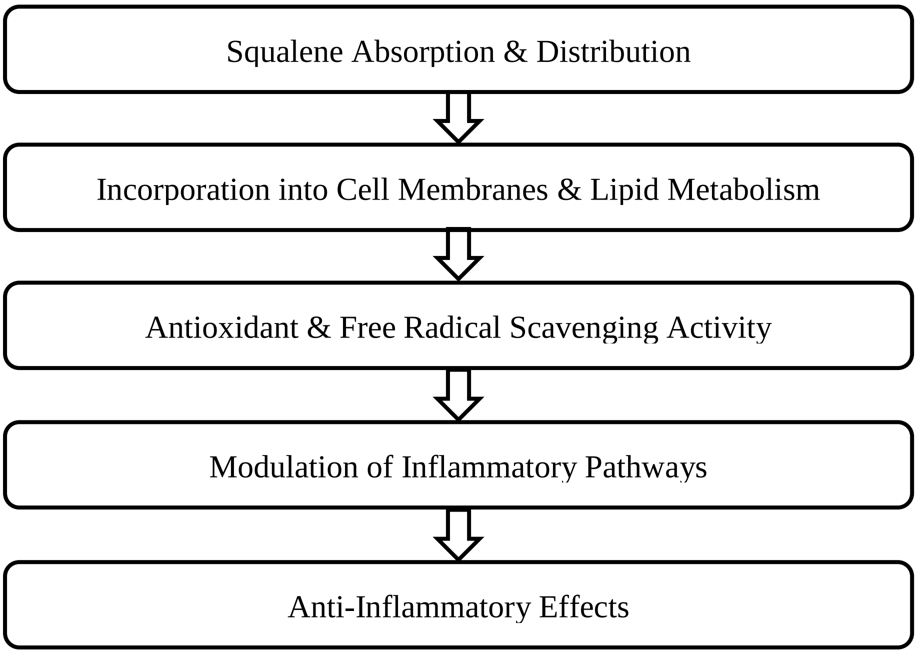

Figure 4.8: M/A of Squalene in Anti-inflammatory effect. (Lou-Bonafonte et al., 2018)

❖ **Cosmetic Application:**

- Used in formulations for sensitive, acne-prone, or irritated skin.
- Used in post-procedure skincare (chemical peels, laser treatments).

Examples:

1. Biossance 100% Squalane Oil
    - Active ingredients: Squalane*
    - Uses: Prevents dryness, treats irritation, and cures sun-damaged skin.

*Squalane is a saturated version of squalene that works better in cosmetics since it is less likely to oxidize.

2. La Roche Posay Toleriane Ultra Soothing Repair Moisturizer
    - Active ingredients: Squalane* & shea butter
    - Uses: nourish and hydrate, provides quick relief from irritated, inflamed, or dehydrated skin.

(C) Antimicrobial and Acne-Fighting Properties

❖ Role:

- Inhibits the growth of acne-causing bacteria and supports healthy skin microbiota.
- Farnesol (terpene alcohol) disrupts bacterial cell membranes, reducing colonization of Propionibacterium acnes (P. acnes).
- Reduces biofilm formation, preventing clogged pores.
- Acts as a non-comedogenic emollient, reducing pore congestion.
- Squalene is naturally produced in sebaceous glands and contributes to skin homeostasis.
- Oxidized squalene can trigger inflammation and acne formation. Using squalane prevents lipid peroxidation. (GNES, 2013)

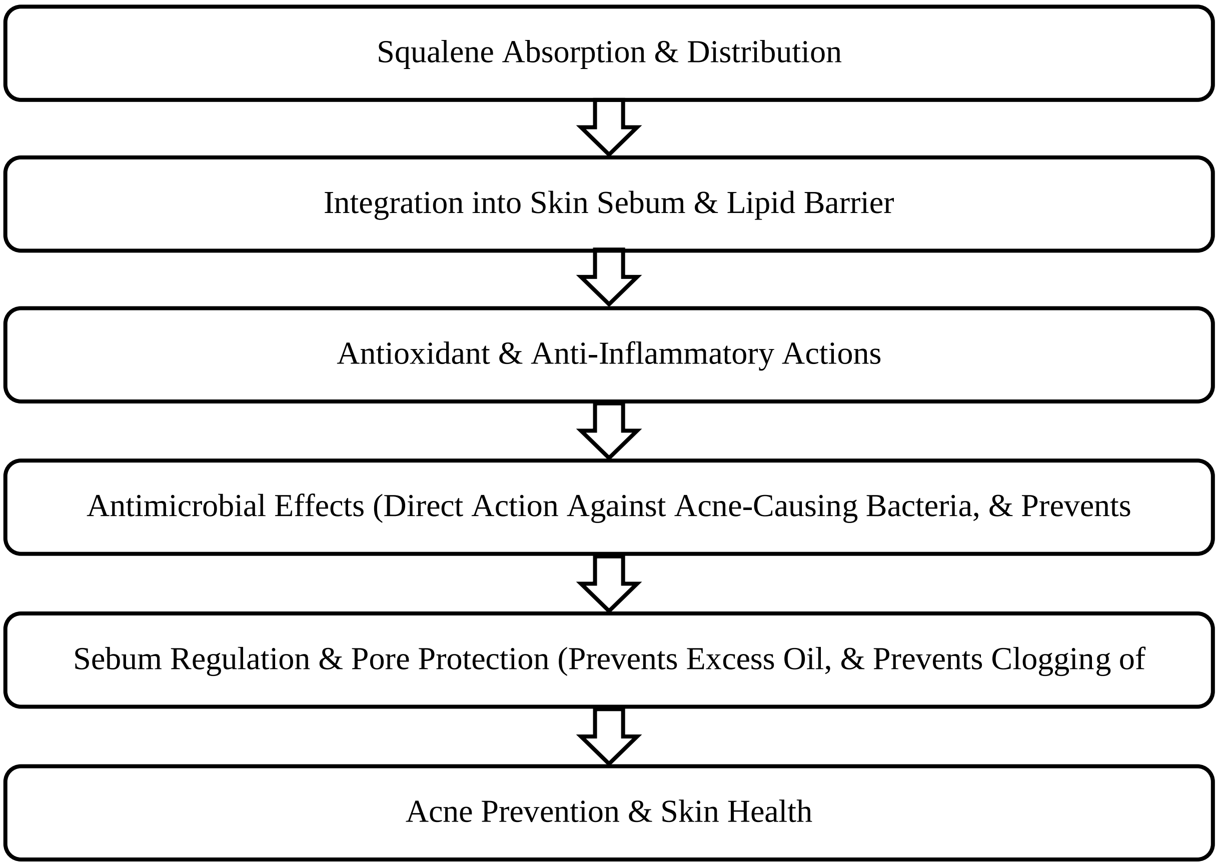

Figure 4.9: M/A of Squalene in Antimicrobial and Acne-Fighting Properties. (GNES, 2013)

- ❖ **Cosmetic Application:**
  - ➢ Found in acne treatments, toners, and oil-balancing serums.
  - ➢ Works well with ingredients like niacinamide for regulating sebum.

Examples:

1. AXIS-Y Dark Spot Correcting Glow Serum
    - Active ingredients: Squalane* & Niacinamide
    - Uses: targets and fades dark spots, post-acne discoloration, and overall unevenness, paving the way for clearer, more radiant skin.

*Squalane is a saturated version of squalene that works better in cosmetics since it is less likely to oxidize.

2. Belora Paris Vegan Squalene Moisturizer
    - Active ingredients: Stearic Acid, Propylene Glycol, Glyceryl Monostearate, and Squalene.
    - Uses: Improves skin texture by repairing the skin's natural barrier, treats acne, reduces age spots and blemishes, restores microbial balance.

(D) Antioxidant and Anti-Aging Action

❖ Role:

- Protects against oxidative stress and prevents premature skin aging.
- Squalene is a potent lipid peroxidation inhibitor.
- Enhances the efficacy of other antioxidants, such as vitamin E.
- Protects collagen and elastin from degradation, preventing wrinkles and fine lines. (GNES, 2013)

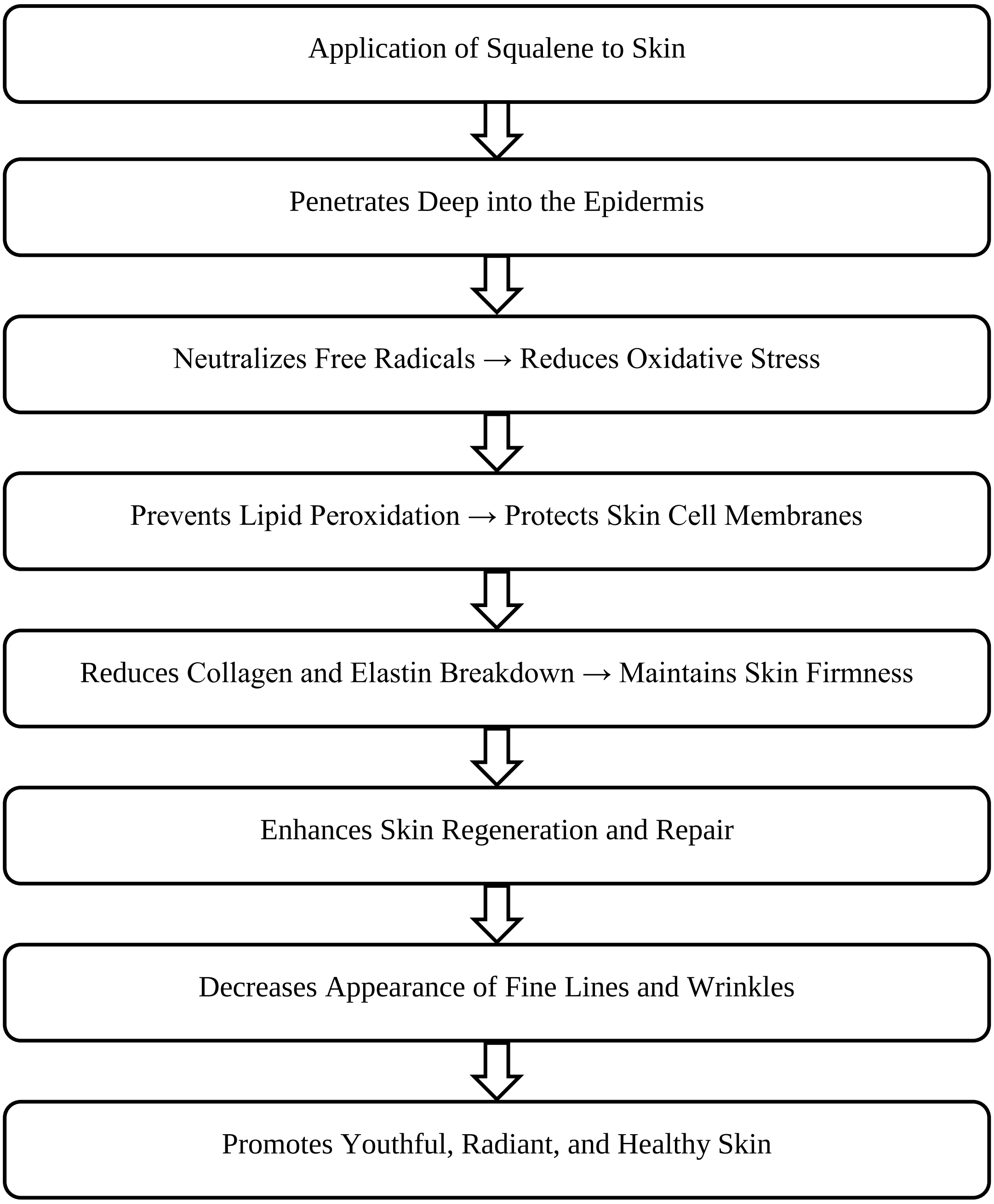

Figure 4.10: M/A of Squalene in Antioxidant and Anti-Aging Action. (GNES, 2013)

❖ **Cosmetic Application:**

- Found in anti-aging creams, serums, and sunscreens to combat fine lines, wrinkles, and UV-induced skin damage.
- Helps reduce hyperpigmentation and oxidative damage.

Examples:

1. Paula's Choice Ultra-Rich Moisturizer
    - Active ingredients: squalene, glycerin, ceramides.
    - Uses: Prevents dryness of the skin, makes it soft and glowing.
2. Joy Revivify Squalene & Green Tea Oil-Free Mattifying Face Moisturizer
    - Active ingredients: Squalene & Green Tea
    - Uses: promote healthy skin, maintain cellular health, fight skin damage, and prevent ageing by reducing free radicals.

Chapter 5

Synthesis of Squalene & Related Compounds

5.1 Squalene distribution in Nature

Squalene is found in a variety of biological sources, including animals, plants, and microorganisms such as yeast and marine microalgae. While it can be extracted from several sources, the overall yield is low compared to its abundance in shark liver oil (80%) and amaranth oil (80mg/g). In humans, squalene is produced at approximately 1.5 grams daily and is present in fish and various plant oils, including amaranth and olive oil. Notably, human sebaceous materials contain higher concentrations of squalene, which is synthesized predominantly in the liver and skin. Around 60% of human squalene comes from dietary sources, while a significant amount is secreted by sebaceous glands, comprising about 12% of skin-secreted sebum. The daily secretion rate from the skin ranges from 125 to 475 mg and acts as a precursor for cholesterol synthesis. (Maxim et al., 2024)

Natural Sources of Squalene

Natural sources of squalene are divided into two distinct groups. They are as follows-

- ➢ Endogenous sources
- ➢ Exogenous source

Endogenous sources of squalene

Squalene is a compound present in various organs and tissues within the human body, with the liver being the primary site for its synthesis and entry into circulation. Research on mammals demonstrates that the concentration of squalene may be affected both locally in liver cells and systemically by the modulation of hepatic cholesterol production. Squalene is found in plasma, mainly within very low-density lipoproteins (VLDL), but is also present in both low-density

(LDL) and high-density lipoproteins (HDL), with its levels correlated to triglyceride content. Due to its hydrophobic characteristics, adipocytes can store squalene at a concentration of 0.275 µg/mg. Furthermore, squalene constitutes about 12% of the lipid content on the epidermal surface of human skin, a phenomenon likely linked to the need for added protection against UV radiation in hairless skin. Notably, epithelial tissues exhibit heightened concentrations of squalene (approximately 0.475 µg/mg), suggesting that sebaceous glands may serve as a potential source for its synthesis. (Micera et al., 2020)

Exogenous sources of squalene

Recent research indicates that squalene, derived from both synthetic and natural sources, is commonly incorporated into food, medications, and nutritional supplements. Traditionally, squalene was extracted from shark liver oil, which constituted about 40% of the total oil content. As squalene plays a role in regulating shark buoyancy, its extraction is now governed by strict regulations due to conservation concerns. Alternatively, plants and their derivatives offer a viable source of squalene, which is a precursor to phytosterols and other secondary plant metabolites. The concentration of squalene in plant oils varies with factors such as species, cultivation location, timing, and extraction methods. (Micera et al., 2020)

Due to the severe pollution of the marine environment by various persistent pollutants (polychlorinated biphenyls, polychlorinated diphenyl ethers, dioxins, heavy metals, and other chemical pollutants) contained in purified squalane extracted from shark livers, but also due to overexploitation of fisheries, which has led to a severe decline in shark populations, interest in finding alternative sources of squalene has increased exponentially. Today, we are increasingly looking for sustainable alternative sources that do not significantly impact the balance of the food chain. The scientific literature indicates the following alternative sources of squalene:

1. Plants (0.02-60000mg/100g squalene DCW);

2. Higher fungi (up to 0.3mg/g squalene DCW);
3. Yeast (0.04-70.32 mg/g squalene DCW);
4. Other microorganisms (.1-318 mg/DCW squalene)

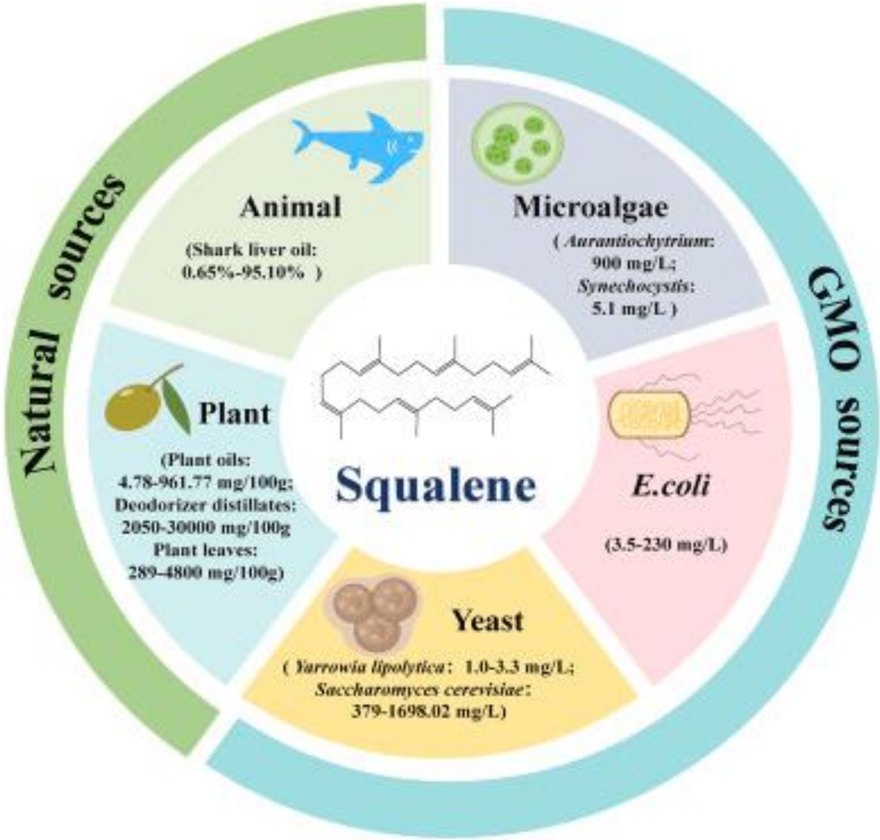

Figure 5.1: Biochemical Sources of Squalene. (Cheng et al., 2024)

The most significant plant sources of squalene include oils from amaranth, olive, rice, wheat germ, grape seed, peanut, and soybean. While various factors influence the amount of squalene present in these extracts, the promising findings in this area of research provide strong evidence for the potential use of plant-derived squalene in the nutritional, cosmetic, and pharmaceutical industries. Studies on both humans and animals have examined the bioavailability of dietary squalene and the fate of exogenous squalene in the gastrointestinal system, highlighting that around 60% of the chemical is absorbed. After squalene is primarily removed in the feces, the gut bacteria most likely digest the remaining unabsorbed squalene. However, further study is needed to comprehend this process entirely. (Maxim et al., 2024)

5.2 Biosynthesis of Squalene

Squalene is a naturally occurring polyprenyl compound classified as an isoprenoid, which is widely found in living organisms and is crucial to cellular metabolism. In plants, isoprenoids facilitate essential biological functions including photosynthesis and respiration, and they regulate metabolism, growth, and development. They also play roles in transcription, meiosis, apoptosis, and intracellular signaling. Chemically, squalene belongs to the triterpenoids group and serves as a lipophilic precursor for various phytosterols and steroids, as well as terpenes such as ubiquinones and gibberellins. Its broad involvement in biochemical pathways underscores the significance of isoprenoids in plant physiology. (P. Senbagalakshmi, 2019)

Squalene is a crucial intermediate in the biosynthesis of hopanoids, phytosterols, and over 200 essential triterpenes found in cell membranes. Its synthesis involves the isopentenyl units, specifically isopentenyl diphosphate (IPP) from mevalonate (MVA) and dimethylallyl diphosphate (DMAPP) from the methylerythritol phosphate (MEP) pathway. The process begins with the conversion of three acetyl-CoA molecules into MVA through multiple reactions, ultimately leading to the production of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) via enzymes such as balsamic-acetyl-CoA synthase and HMG-CoA synthase (Figure 5.2).

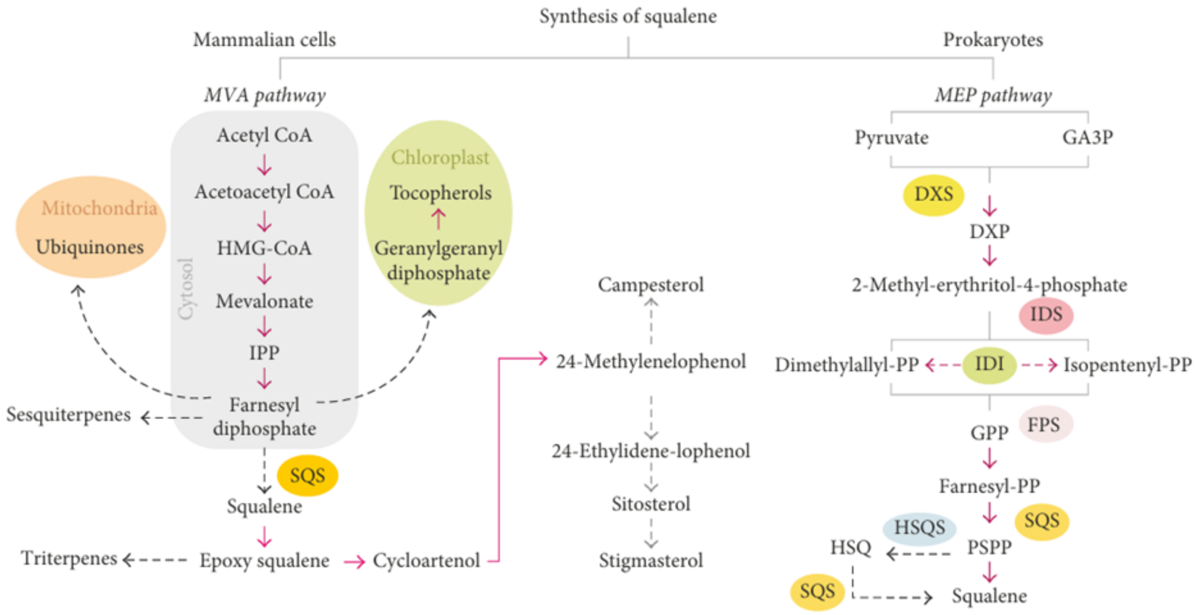

Figure 5.2: Biosynthetic Pathway of Squalene. (P. Senbagalakshmi, 2019)

[MVA = Mevalonate; MEP = methylerythritol phosphate; Acetyl CoA = acetyl coenzyme A; HMG-CoA = hydroxymethyl glutaryl coenzyme A; IPP = isopentenyl diphosphate; SQS = squalene synthase; DXP = desoxicelulose 5-phosphate; DXS = desoxicelulose 5-phosphate synthase; IDI = isopentenyl diphosphate isomerase; IDS = isopentenyl diphosphate synthase; FPS = farnesyl diphosphate synthase; GPP = geranyl diphosphate; HSQS = hydrosqualene.]

The metabolic pathway of HMG-CoA leads to the synthesis of mevalonate (MVA), which is subsequently phosphorylated to form MVA-5-diphosphate. This compound, in the presence of ATP, decarboxylates to yield isopentenyl pyrophosphate (IPP). Enzymatic action by IPP isomerase converts IPP into dimethylallyl pyrophosphate (DMAPP), while additional condensation of IPP produces geranyl pyrophosphate (GPP). The combination of GPP with another IPP results in a 15-carbon diphosphate that is eventually reduced to squalene, a precursor for phytosterol biosynthesis. The conversion of squalene into phytosterols involves cyclization processes initiated by ionic species or specific triterpene enzymes, such as squalene cyclase and oxidized-squalene cyclase. These enzymes catalyze reactions that produce a diverse array of terpenes vital for the structural integrity and functional components of cell membranes. (P. Senbagalakshmi, 2019)

Squalene synthesis occurs in various prokaryotic and eukaryotic organisms, including E. coli and specific yeasts and fungi, utilizing the MEP pathway. The process begins with the synthesis of 1-deoxy-D-xylulose-5-phosphate (DXP) and involves several enzymes leading to the formation of isoprenoid precursors, namely IPP and DMAPP. These precursors are combined by farnesyl-diphosphate-synthase to produce GPP and subsequently FPP, essential for squalene production. Recent findings suggest that the synthesis pathway includes a three-step process facilitated by PSPP-synthase, HSQ-synthase, and squalene synthase (SQS), with some debate regarding the linearity of this sequence. The commercial application of this biosynthetic pathway is being explored through metabolic engineering and fermentation techniques; however, current yields (14.5-160.2 mg/L) fall short of commercial viability, and cost considerations remain underexplored. (P. Senbagalakshmi, 2019)

5.3 Chemical Synthesis of Squalene

Synthetic routes to squalene focus on mimicking the biosynthetic dimerization of farnesyl compounds, primarily Farnesyl halides. Farnesyl halides, including farnesyl chloride and farnesyl bromide, are organic synthesis compounds derived from farnesol, which consists of 15 carbon atoms in an isoprenoid structure. Farnesyl halides feature a halogen atom, such as chlorine or bromine, bonded to the farnesyl group, characterized by its 15-carbon isoprenoid chain. Here is a possible chemical synthesis of Squalene by Farnesyl Halides:

- **Step 1: Preparation of Farnesyl Halide**

  Farnesol is converted into farnesyl bromide via bromination:

  $$\text{Farnesol} + \text{PBr3} \rightarrow \text{Farnesyl Bromide} + \text{HBr}$$

  The –OH group in Farnesol is swapped out for a bromine atom in phosphorus tribromide (PBr_3) and produces a reactive electrophile that is prepared for coupling, farnesyl bromide.

  This step provides a reactive electrophilic intermediate.

- **Step 2: Coupling of Farnesyl Halides**

  Two molecules of farnesyl bromide undergo coupling in the presence of a strong reducing agent such as sodium metal or organometallic catalysts (e.g., Grignard reagents or lithium aluminum hydride):

  $$2\ \text{Farnesyl Bromide} + \text{Na} \longrightarrow \text{Squalene} + 2\ \text{NaBr}$$

  As a reducing agent, sodium metal helps two farnesyl bromide molecules to the homocouple. Squalene, a 30-carbon linear triterpene composed of six isoprene units, is the result of the coupling. (P. Senbagalakshmi, 2019)

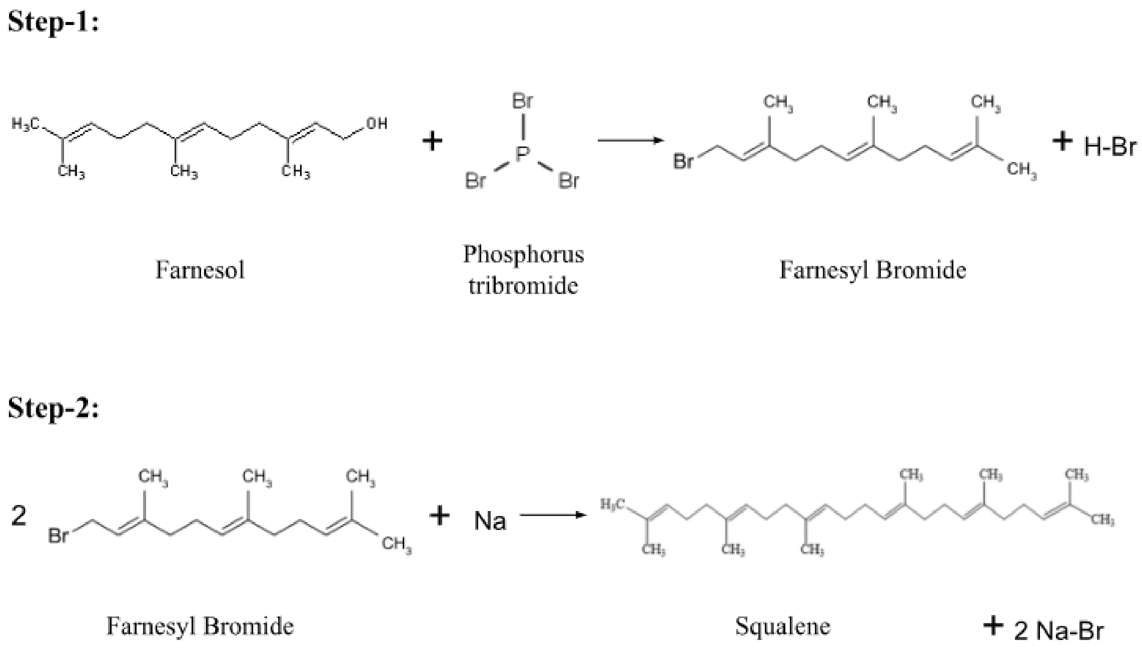

Figure 5.3: Chemical synthesis of squalene.

5.4 Strategies for increasing squalene production in natural producers

The biosynthetic pathway and the biotechnological generation of squalene have garnered significant attention from researchers due to its positive impact on human health and its use in the pharmaceutical and cosmetic sectors. To date, extracting squalene from natural producers under optimized media conditions has proven to be the most effective method for enhancing squalene production. It is essential to devise strategies that identify alternative squalene producers exhibiting elevated levels of squalene.

Microorganisms hold significant promise as sources for the production of squalene. Ongoing research aims to enhance the squalene levels within these microorganisms. Various approaches such as exploring alternative sources, optimizing fermentation processes, and employing metabolic engineering techniques, have been utilized to boost squalene production.

Some strategies for increasing squalene production:

- ➢ Exploration of squalene-producing sources
- ➢ Optimization of media and fermentation conditions
- ➢ Metabolic engineering
- ➢ Production of Squalene Using a Microbial Cell Factory

Utilizing microorganisms like S. cerevisiae and E. coli as hosts allows for the targeting of specific genes, which facilitates squalene production through distinct biochemical pathways. Although the results achieved so far are encouraging, the yields remain inadequate for commercial viability. Enhancing the production of precursors by incorporating foreign pathways or inhibiting branch pathways, as well as improving the yield of target-soluble proteins through techniques that minimize stress, could be viable strategies for boosting metabolic engineering effectiveness in squalene production. Key questions that remain unanswered include whether the yields are constrained by carbon flux through the pathways or if there are additional, yet-to-be-identified, physiological factors that may hinder squalene accumulation in the modified strains. Investigating strains that naturally produce high amounts of squalene could provide valuable insights. (Maxim et al., 2024)

Chapter 6

In Vitro and In Vivo Studies on Squalene and Related Compounds

Introduction Squalene, a naturally occurring polyunsaturated triterpene, is commonly found in nature, especially in shark liver oil, olive oil, wheat germ, and amaranth seeds. It plays a crucial role as an intermediate in the biosynthesis of sterols, such as cholesterol, in both humans and animals. Because of its various biological properties, including antioxidant, anti-inflammatory, and anticancer effects, numerous in vitro and in vivo studies have been performed to assess its potential therapeutic uses. This essay examines these studies, concentrating on the pharmacological and biological impacts of squalene and its associated compounds. (Smith, 2020)

6.1 In Vitro Studies on Squalene and Related Compounds

1. Antioxidant Properties Several studies conducted in vitro have shown that squalene can effectively scavenge free radicals and protect against oxidative damage. For example, research by Zhang et al. (2021) indicated that squalene demonstrated strong antioxidant capabilities in lipid peroxidation tests, which are crucial for safeguarding skin and cellular health. (Kim et al., 2023)
2. Anti-inflammatory Effects Squalene has been found to influence inflammatory pathways. In an in vitro investigation using human macrophage cells, squalene reduced the levels of pro-inflammatory cytokines, including TNF-a and IL-6. These results imply its potential role in the treatment of inflammatory diseases. (Gao et al., 2022)

Anticancer Potential Squalene and its derivatives have been examined for their potential anticancer effects. In vitro research involving breast cancer cell lines (MCF-7) showed that squalene triggered apoptosis via the mitochondrial pathway. (Lee et al., 2023) Moreover, related compounds like squalane exhibited comparable anti-proliferative effects in melanoma and lung cancer cells. (Martinez et al., 2022)

3. Antimicrobial Activity Squalene has been found to possess antimicrobial properties against a range of pathogens. In an in vitro study, squalene displayed notable inhibitory effects on Staphylococcus aureus and Escherichia coli by compromising bacterial membrane integrity. (Fernandez et al., 2021).

6.2 In Vivo Studies on Squalene and Related Compounds

1. Cardioprotective Properties Research has shown that squalene possesses cardioprotective effects in animal studies. An in vivo investigation involving hyperlipidemic rats revealed that squalene supplementation in their diet led to a notable decrease in LDL cholesterol and an increase in HDL cholesterol levels. This indicates a possible role in the prevention of cardiovascular diseases. (Kim et al., 2023)
2. Neuroprotective Properties Recent in vivo studies suggest that squalene may contribute to neuroprotection. A study done on a mouse model of Alzheimer's disease indicated that squalene administration led to a reduction in amyloid-ß buildup and an enhancement of cognitive function. (Torres et al., 2022)
3. Skin Protection and Wound Recovery Squalene is commonly utilized in dermatological applications due to its skin-protective attributes. In vivo research has indicated that applying squalene topically sped up the wound healing process in rats by fostering fibroblast growth and collagen formation. Additionally, its ability to protect against UV-induced skin damage has been confirmed in relevant models. (Nguyen et al., 2021

4. Hepatoprotective Properties Squalene has also been shown to have hepatoprotective capabilities. An experiment involving rats with chemically induced liver damage found that squalene supplementation significantly lowered liver enzyme levels (AST, ALT) and improved histological indicators of liver health. (Wang et al., 2023)
5. Immunomodulatory Properties Squalene and its derivatives have been investigated for their impact on the immune system. It has been discovered that squalene can enhance immune responses when utilized as an adjuvant in vaccine formulations. A study involving mice that received an influenza vaccine adjuvanted with a squalene-based emulsion (MF59) showed increased antibody production and T-cell activation compared to those that received vaccines without the adjuvant. (Brito et al., 2020)

Comparison of In Vitro and In Vivo Findings In vitro research has played a crucial role in uncovering the molecular mechanisms behind squalene's bioactivity, while in vivo studies demonstrate its physiological significance and therapeutic potential. For example, although in vitro studies reveal squalene's capacity to neutralize free radicals, in vivo research further substantiates its protective effects in models of diseases such as cardiovascular and neurodegenerative conditions. Nonetheless, in vitro research often overlooks metabolic changes, bioavailability, and pharmacokinetics, aspects that are thoroughly investigated in in vivo studies.

Challenges and Future Directions Despite encouraging outcomes, several hurdles exist in translating the advantages of squalene into clinical settings. These challenges include concerns regarding bioavailability, optimal dosing, and long-term safety. Future research should prioritize Nano-formulation strategies to improve squalene's bioavailability and targeted delivery. Furthermore, additional clinical trials are necessary to confirm preclinical results and evaluate possible adverse effects.

Squalene and its derivatives display a variety of biological activities, such as antioxidant, anti-inflammatory, anticancer, cardioprotective, neuroprotective, and immunomodulatory properties. Laboratory studies have shed light on the molecular mechanisms that underpin these effects, while animal studies have corroborated their therapeutic potential. Nonetheless, additional research is necessary to refine formulations and improve bioavailability, as well as to confirm clinical effectiveness. With its wide range of pharmacological properties, squalene continues to be a promising candidate for future therapeutic uses.

Chapter 7

Toxicological Study and Chemical Inhibitors of Squalene in Cosmetic Dermatology

Squalene, a naturally occurring triterpene, is commonly utilized in cosmetic dermatology due to its moisturizing, antioxidant, and anti-inflammatory effects. However, a thorough understanding of its toxicological profile is essential for ensuring its safety in skincare products. Moreover, there has been increasing interest in chemical inhibitors that target the synthesis of squalene, as they play a significant role in addressing dermatological issues such as acne, fungal infections, and skin aging. This essay examines the toxicological implications of squalene in dermatology and the different chemical inhibitors that influence its biosynthesis.

7.1 Toxicological Profile of Squalene in Dermatology

1. General Toxicity: Squalene is typically regarded as safe (GRAS) for external application, with minimal reported toxicity. However, its toxicity may depend on the formulation, concentration, and individual skin sensitivities:

- **Dermal Toxicity:** Squalene, along with its hydrogenated form, squalane, is non-irritating and does not clog pores, making it suitable for all skin types. Nonetheless, oxidized squalene has been linked to the development of acne in rare instances.
- **Ocular and Mucosal Irritation:** Research suggests that formulations containing squalene have a low potential for irritation, making them safe for delicate areas such as the eye region.

- **Allergic Reactions:** While rare, some individuals may develop contact dermatitis as a result of impurities or oxidized products in squalene-based formulations. (Nagaraja et al., 2020)

2. Oxidative Stress and Lipid Peroxidation: A significant concern about the toxicity of squalene in dermatology is its tendency to oxidize. When squalene is oxidized, it can:

- Produce free radicals that result in oxidative stress and inflammatory skin issues.
- Play a role in the development of acne by facilitating conidiogenesis when it accumulates within sebaceous glands.
- Diminish the effectiveness of skincare products by breaking down other active components. To address these concerns, formulators frequently opt for squalane (the hydrogenated variant of squalene), which is more stable and less prone to oxidation. (Nagaraja et al., 2020)

7.2 Chemical Inhibitors of Squalene in Dermatology

Squalene biosynthesis plays a crucial role in skin health; however, excessive production can lead to skin disorders like acne and fungal infections. In dermatology, chemical inhibitors that target squalene and its metabolic pathways are employed for their therapeutic effects.

1. Squalene Synthase Inhibitors (SSIs) in Dermatology: Squalene synthase inhibitors (SSIs) obstruct the transformation of farnesyl pyrophosphate (FPP) into squalene, which decreases sebum production and cholesterol synthesis in the skin. (Nagaraja et al., 2020)

Examples:

- ➢ **Lapaquistat (TAK-475):** This compound has been studied for its cholesterol-lowering effects, as well as its potential impact on sebum regulation in dermatological applications.
- ➢ **Zaragozic acids (Squalestatins):** These inhibitors, derived from fungi, reduce squalene synthesis and could potentially be used to address oily skin and acne. (Nagaraja et al., 2020)

2. Inhibitors of Squalene Epoxidase (SQLE) in Dermatology: Squalene epoxidase converts squalene into 2, 3-oxidosqualene, representing a crucial step in the synthesis of sterols. Inhibition of this enzyme results in the accumulation of squalene, which can be harmful to fungal cells, thus making SQLE inhibitors significant for the treatment of dermatophytic infections. (Ottaviani et al., 2006)

Examples:

- ➢ Terbinafine: An antifungal agent commonly used that compromises fungal cell membranes by raising intracellular squalene levels, effectively addressing conditions like athlete's foot and ringworm.
- ➢ Butenafine and Naftifine: Utilized in topical antifungal formulations for the management of dermatophyte infections. (Ottaviani et al., 2006)

3. Inhibitors of Squalene Monooxygenase in Dermatology: Squalene monooxygenase (SMO) plays a crucial role in the synthesis of sterols. Researchers are looking into inhibitors that target this enzyme for potential dermatological uses. (Eudier et al., 2019)

Examples:

- ➢ **NB-598:** Being studied for its effectiveness in decreasing sebum production and addressing oily skin issues.
- ➢ **Itraconazole:** A medication used to treat fungal infections, which also influences sterol biosynthesis, thus proving beneficial for fungal skin conditions. (Eudier et al., 2019)

7.3 Potential Uses and Hazards of Squalene Inhibitors in Dermatology

Although squalene inhibitors offer potential benefits for dermatological treatments, they also come with specific risks:

- **Sebum Disruption:** Excessive inhibition of squalene production may result in heightened dryness and weaken the skin's protective barrier.
- **Irritation and Sensitivity:** Certain inhibitors, like terbinafine, can lead to skin irritation, redness, or hypersensitive reactions.
- **Microbial Resistance:** Continued use of antifungal squalene inhibitors may lead to the development of drug-resistant fungal strains. (Rastogi & Anjali Gholap, 2023)

Squalene and its derivatives are essential for maintaining healthy skin, but their toxicological characteristics require careful formulation to prevent oxidative harm and skin irritation. Chemical agents that inhibit squalene biosynthesis hold promise for treating acne, fungal infections, and seborrheic conditions. Nevertheless, potential risks such as disruption of the skin barrier and microbial resistance emphasize the necessity for controlled application and additional research in cosmetic dermatology. Future developments should aim at creating targeted inhibitors that have minimal side effects to maximize their therapeutic advantages in skincare products.

Chapter 8

Safety Assessment for using Squalene compounds

8.1 Safety Assessment for Using Squalene in Cosmetic Dermatology

Squalene is a naturally occurring lipid present in human sebum, a range of plant oils, and shark liver oil. Its significance in cosmetic dermatology has grown due to its emollient and antioxidant characteristics, making it an important component in moisturizers, serums, and anti-aging products. Nevertheless, its extensive application requires a comprehensive safety evaluation to ensure that consumers are not subjected to any dangers. This essay explores the safety profile of squalene in cosmetic dermatology by analyzing its toxicology, ability for dermal absorption, potential for irritation, and overall safety, as assessed by various scientific research studies. (“Final Report on the Safety Assessment of Squalane and Squalene,” 1990)

Chemical Properties and Role in Dermatology: Squalene is an unsaturated hydrocarbon that is essential for keeping skin hydrated and defending against oxidative damage. Its ability to closely resemble the skin's natural lipids makes it a popular choice as an emollient in skincare products. Nevertheless, in its original form, squalene is susceptible to oxidation, resulting in the creation of peroxides, which can be detrimental to the skin. To address this issue, squalane, a hydrogenated and more stable version of squalene, is frequently used in cosmetic products. (“Final Report on the Safety Assessment of Squalane and Squalene,” 1990)

Toxicological Profile: A variety of toxicological studies have established that squalene is safe for use in cosmetic formulations. Evidence suggests that both squalene and squalane demonstrate minimal acute toxicity when introduced through different administration routes, such as the skin and orally. Research involving both animals and humans has found that squalene is absorbed poorly from the gastrointestinal tract and has a slow absorption rate through the skin. Furthermore, no significant adverse effects have been reported, even at elevated concentrations, which further supports its safety for topical application. (“Final Report on the Safety Assessment of Squalane and Squalene,” 1990)

Dermal Absorption and Metabolism: Squalene is found naturally in human skin, making up to 11% of the total lipids present. When applied topically, it does not interfere with normal skin functions but instead improves the integrity of the skin barrier. Research in animals indicates that squalene is absorbed gradually through the outer layer of the skin, which limits systemic exposure and decreases the chances of negative side effects. Additionally, since squalene is a precursor to cholesterol and other sterols, any amount that is absorbed is quickly metabolized by the body, further confirming its safety. (“Final Report on the Safety Assessment of Squalane and Squalene,” 1990)

Skin Irritation and Sensitization Potential: Comprehensive dermatological studies have demonstrated that squalene is both non-irritating and non-sensitizing for human skin. Clinical patch tests involving subjects with various skin types, including those with sensitive skin, have shown no significant adverse reactions. Only minor and temporary inflammatory responses were noted in instances where undiluted squalene was applied to the skin, with these reactions resolving without any lasting effects. Moreover, formulations that include squalene at concentrations of up to 50% are considered safe for repeated application, and there have been no instances of allergic sensitization or contact dermatitis reported. (“Final Report on the Safety Assessment of Squalane and Squalene,” 1990)

Phototoxicity and Comedogenicity: One major issue related to squalene is its vulnerability to oxidation when exposed to air and ultraviolet (UV) light. Oxidized squalene is known to contribute to conidiogenesis, especially in individuals prone to acne. However, research suggests that this risk is significantly reduced when squalene is effectively stabilized within cosmetic products. Additionally, studies on squalane, the fully saturated form of squalene, show that it is non-comedogenic and does not promote the development of acne. ("Final Report on the Safety Assessment of Squalane and Squalene," 1990)

Regulatory Status and Safety Evaluations: The Cosmetic Ingredient Review (CIR) Expert Panel has conducted multiple evaluations regarding the safety of squalene and squalane. In their latest assessment, the panel determined that both substances are safe for cosmetic use given their current concentrations and application conditions. Regulatory agencies, including the U.S. Food and Drug Administration (FDA) and the European Commission's Scientific Committee on Consumer Safety (SCCS), have also deemed squalene to be a safe ingredient for cosmetics. Additionally, global standards guarantee that the squalene utilized in cosmetics is obtained sustainably, which helps alleviate ethical and environmental issues linked to shark-derived squalene.

The existing scientific research robustly confirms the safety of squalene within cosmetic dermatology. Its low level of toxicity, minimal absorption through the skin, and lack of significant irritation or sensitivity make it an ideal component for skincare products. Although there are concerns regarding oxidation and potential clogging of pores, these risks can be effectively managed through appropriate formulation strategies and the employment of stabilized derivatives such as squalane. Based on the available information, squalene continues to be a safe and advantageous ingredient in contemporary skincare products, enhancing skin hydration and overall wellness. ("Final Report on the Safety Assessment of Squalane and Squalene," 1990)

Chapter 9

Impact of the Review Article and Future Direction

The review article Biological and Pharmacological Activities of Squalene and Related Compounds: Potential Uses in Cosmetic Dermatology offers an in-depth examination of the diverse biological functions of squalene and its applications in dermatology. The research not only emphasizes squalene's antioxidant, emollient, and anti-cancer characteristics but also investigates its role as a delivery system in topical products. The significance of this review goes beyond the analysis of squalene alone, as it sheds light on related compounds including ß-carotene, coenzyme Q10, and vitamins A, E, and K. This essay discusses the importance of the review in the context of scientific research and clinical uses, as well as its potential impact on future studies, while also pinpointing avenues for additional research.

9.1 Impact of the Review Article

Scientific Contribution and Knowledge Expansion

The review article is essential for summarizing the current understanding of squalene's biological roles, especially in the context of skin physiology. It brings together findings from a range of experimental and clinical investigations, creating a comprehensive view of how squalene and its derivatives support skin health. By outlining squalene's functions in reducing oxidative stress, enhancing skin hydration, and serving as an antitumor agent, the article lays a solid groundwork for future research in dermatology. Additionally, the exploration of squalene's use in lipid emulsions and nanostructured lipid carriers (NLCs) highlights its significance in drug delivery and cosmetic products, thus expanding its scientific and industrial importance. (Boughton et al., 1955)

Implications in Cosmetic and Pharmaceutical Industries

The review article is crucial for encapsulating the current knowledge of squalene's biological functions, particularly concerning skin physiology. It synthesizes results from various experimental and clinical studies, forming a thorough understanding of how squalene and its derivatives contribute to skin health. By detailing squalene's roles in mitigating oxidative stress, improving skin hydration, and acting as an antitumor agent, the article establishes a strong foundation for future dermatological research. Furthermore, the discussion of squalene's application in lipid emulsions and nanostructured lipid carriers (NLCs) underscores its importance in drug delivery and cosmetic formulations, thereby broadening its scientific and commercial relevance.

Advancing Clinical Applications

In addition to its cosmetic uses, the review highlights squalene's potential role in clinical dermatology, especially for the prevention and treatment of skin conditions. The examination of its antitumor effects indicates that squalene might warrant further investigation as a supplementary option in cancer treatments. Although initial studies in animals have yielded encouraging outcomes, the review also warns against directly applying these results to humans without additional clinical validation. This emphasizes the need for more comprehensive human trials to confirm squalene's therapeutic effectiveness. (Boughton et al., 1955)

9.2 Future Directions in Squalene Research

Exploration of Mechanistic Pathways

Although the review thoroughly examines the biological functions of squalene, a more in-depth investigation into its mechanistic pathways is required. Gaining insight into the specific molecular interactions that allow squalene to produce its antioxidative and antitumor effects would improve its therapeutic applications. Future research might utilize cutting-edge biochemical and molecular biology methods to clarify these mechanisms more comprehensively.

Long-Term Clinical Trials and Human Studies

Although initial results are encouraging, the review underscores the necessity for extensive long-term human studies to confirm the efficacy and safety of squalene. Upcoming clinical trials should aim to identify the best dosages, methods of administration, and possible side effects associated with its use in skin care treatments. Additionally, comparative studies that evaluate squalene's effectiveness in relation to other well-known skincare ingredients would help clarify its position in dermatology. (Boughton et al., 1955)

9.3 Development of More Stable and Efficient Formulations

Considering the review's exploration of squalene's instability when subjected to environmental influences, it is essential for research to concentrate on creating formulations that are more stable. This could include the application of encapsulation methods, such as nanoemulsions or polymer-based delivery systems, to improve the stability and bioavailability of squalene. Furthermore, integrating squalene with other beneficial compounds like vitamins and polyphenols may boost its effectiveness and lessen the risk of oxidative degradation.

Potential in Systemic Health Benefits

Although the review mainly emphasizes dermatological uses, squalene in food sources implies possible overall health advantages. Exploring its influence on heart health, immune response, and metabolic conditions might reveal new opportunities for therapeutic purposes. Interdisciplinary research incorporating nutrition, pharmacology, and dermatology could yield a more thorough understanding of squalene's complete potential.

The review article makes a significant contribution to the scientific community by compiling research on squalene and its related compounds, especially in the field of dermatology. Its significance also reaches the cosmetics and pharmaceutical sectors by offering evidence-based knowledge for product development and therapeutic uses. Nonetheless, the necessity for additional research is clear, particularly in clarifying its exact mechanisms, carrying out long-term clinical studies, and creating more stable formulations. Future research should focus on closing these gaps, guaranteeing that squalene's full potential is effectively utilized in both dermatological and overall health applications. As research advances, squalene could become a fundamental component in skincare and medical treatments, underscoring its relevance in both scientific and commercial areas.

Chapter 10

Conclusion

Squalene, a naturally occurring triterpene, has attracted considerable interest due to its diverse functions in dermatology, pharmaceuticals, and cosmetics. This review has examined its biological roles, natural and synthetic origins, biochemical pathways, therapeutic uses, and possible safety concerns. As a core component of sterol biosynthesis, squalene is essential for skin health, offering antioxidant, anti-inflammatory, and moisturizing properties. Additionally, its presence in human sebum highlights its biological significance in shielding the skin from oxidative damage and preserving barrier function. (Reddy & Couvreur, 2009)

The extensive availability of squalene from both natural and artificial sources has led to its growing application in cosmetic and pharmaceutical products. Historically, it has been extracted from shark liver oil; however, recent advancements have directed attention toward plant-derived and microbial sources to promote sustainability and mitigate environmental issues. Alternative sources such as amaranth oil, olive oil, rice bran, and microbial fermentation have demonstrated encouraging yields, providing ethical and environmentally friendly alternatives for commercial production. Nonetheless, refining extraction techniques is vital for enhancing yield efficiency and ensuring high-purity formulations. (Reddy & Couvreur, 2009)

In dermatology, squalene has shown notable therapeutic promise in addressing a variety of skin issues, such as acne, eczema, psoriasis, and atopic dermatitis. Its antioxidant properties make it a beneficial component in anti-aging products, guarding the skin against oxidative harm from environmental pollutants and UV rays. Furthermore, its function as a skin moisturizer and emollient enhances its value in cosmetic formulations. The hydrogenated variant, squalane, is commonly used in skincare due to its greater stability and non-comedogenic attributes, rendering it appropriate for all skin types. (Reddy & Couvreur, 2009)

In addition to skincare, squalene has been explored for its pharmacological benefits, especially concerning cardiovascular health, immune modulation, and cancer prevention. Laboratory studies indicate its potential to lower LDL cholesterol levels, boost immune functions, and slow tumor development. Nevertheless, even with encouraging preclinical findings, clinical validation is crucial to confirm specific therapeutic uses and improve its pharmacokinetic characteristics. (Reddy & Couvreur, 2009)

Squalene is typically considered safe for both topical and oral use; however, there are some concerns about its oxidation and its possible role in promoting acne. The oxidative stress leading to the formation of squalene peroxide could exacerbate inflammatory skin issues, highlighting the importance of developing stable formulations that prevent the peroxidation of lipids. Moreover, certain chemical inhibitors that target the biosynthesis of squalene, such as squalene synthase and squalene epoxidase inhibitors, have shown promise in treating disorders associated with excessive oil production, like acne and fungal infections. Upcoming research should aim to improve the bioavailability and stability of squalene-containing products while exploring innovative delivery methods such as nanocarriers and lipid-based formulations. Furthermore, the incorporation of biotechnology and synthetic biology techniques in microbial fermentation may lead to more economical and environmentally friendly production. Clinical trials are essential for converting preclinical observations into useful therapeutic interventions, ensuring that squalene and its derivatives can be used safely and effectively in cosmetic dermatology and other fields. (Reddy & Couvreur, 2009)

In conclusion, squalene is an important bioactive substance widely used in skincare, healthcare, and various industries. Its potential therapeutic advantages, along with continuous progress in sustainable sourcing and formulation techniques, establish it as a significant component for upcoming innovations in cosmetics and pharmaceuticals. With ongoing studies and advancements in technology, squalene could transform dermatological therapies and improve skin health overall. (Reddy & Couvreur, 2009)

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