TRETINOIN A PEPTIDE IN ANTI-AGING THERAPY: AN OVERVIEW.

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Abstract:

Tretinoin is a naturally occurring acid of retinol. Tretinoin binds to and activates retinoic acid receptors (RARs), thereby including changes in gene expression that lead to cell differentiation, decreased cell proliferation, and inhibition of tumorigenesis. Retinoids such as tretinoin are an important regulator of cell reproduction, proliferation, and differentiation, and are used in the treatment of acne and photodamaged skin and to manage keratinization disorders such as ichthyosis, keratosis follicularis. Topical tretinoin modifies fine wrinkles and certain other features of human skin damaged by exposure to the sun, but histologic changes do not account for this improvement. In mice photodamage induced by ultraviolet light, effacement of wrinkles by tretinoin is correlated with dermal collagen synthesis but not with histologic changes. Tretinoin minimizes the appearance of wrinkles, bolsters skin's thickness and elasticity, slows down the breakdown of collagen which helps keep skin firm, and lightens brown spots by sun exposure. Retinoids were first introduced to the market in the early 1970s as an aid in acne-fighting drugs. Since then they have been used to treat psoriasis, warts, wrinkles, and blotchiness caused by sun exposure and aged skin. This study provides an overview of the market trends regarding the use of peptides in anti-aging products, providing meaningful data for scientists involved in the development of new peptides to identify opportunities for innovation in this area to achieve desired results in making skin healthy.

- **INTRODUCTION:**

Skin: Fig.1. structure of the skin.

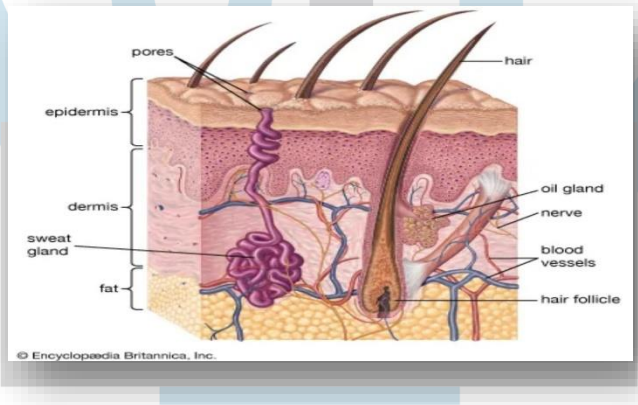
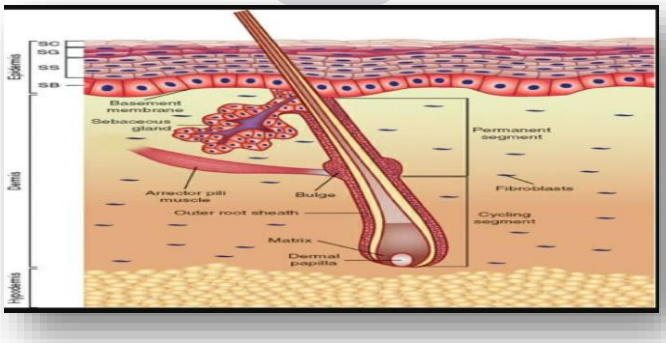


Fig.1. structure of the skin.

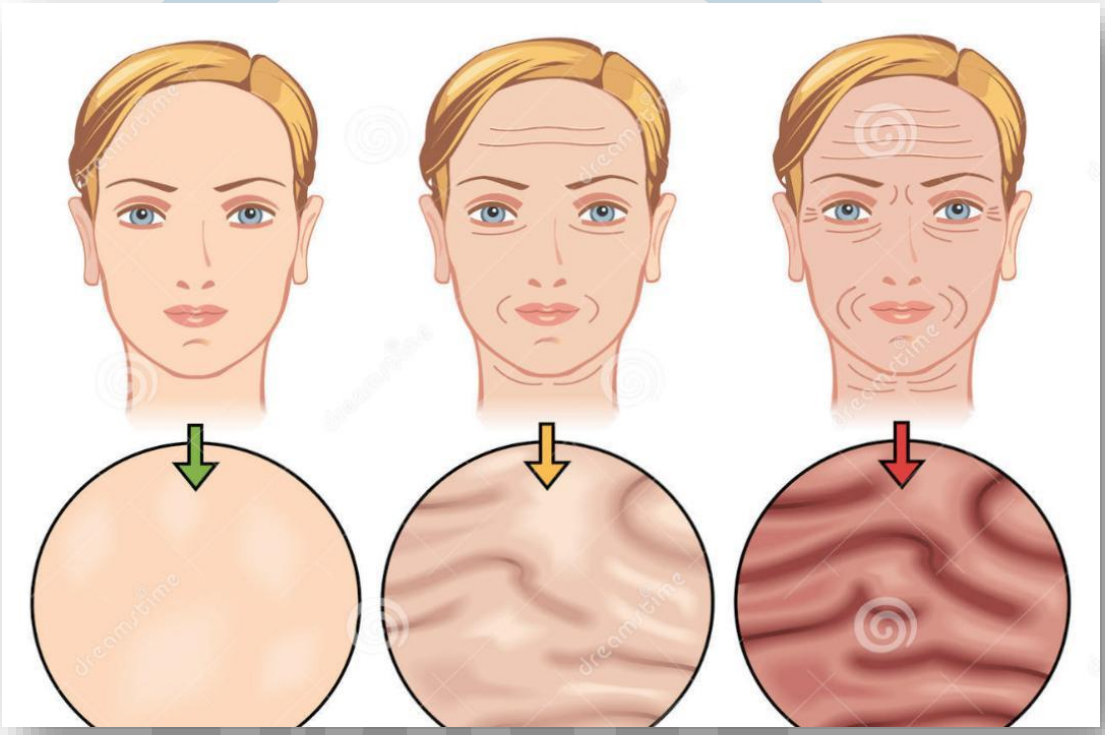
FIG 2: Verticle section of the skin



Skin the largest organ of the body protects all the other organs from the external environment. skin is a complex organ with multiple structures and cell types and is divided into three layers: epidermis, dermis, and subcutaneous tissue. The epidermis is mainly composed of keratinocytes, melanocytes, and antigens presenting Langerhans cells. A basement membrane separates the epidermis from the dermis which primarily contains extracellular proteins produced by the fibroblast below. the vascular supply and blood supply to the skin reside in the dermis. the subcutaneous tissue consists of adipose cells that underline the connective tissue. The other extracellular matrix proteins which are part of skin connective tissues are collagen (iii, iv, vii) elastin, proteoglycans, fibronectin, etc. type I procollagen is secreted into the dermal extracellular space where it undergoes enzymatic processing to arrange itself into a triple helix configuration which is a recent advancement in the cosmetology Skin is more than just a protective barrier between our insides and the environment – it also plays an active role in maintaining our health, such as regulating body temperature by sweating and flushing when we're hot, and raising goosebumps when we're cold. It can also produce Vitamin D, which is important for the health of our bones, Skin can vary greatly between species, and even between individual people! Here we will discuss the structure of human skin, the proper care of different skin types found among humans, and the functions of skin throughout the animal kingdom.

SKIN AGING:

Fig.3. skin aging.



With the aging of the skin, the natural rejuvenation process slows drastically and the skin becomes thinner, drier, and less elastic. Aging is a progressive physiological alteration in an organism that leads to senescence, or a decline of biological functions and of the organism's ability to adapt to metabolic stress. Aging takes place in cell tissues and organs, or the total organism with time. Aging is a process that goes on over the entire adult life period of any living thing. Gerontology is the scientific study of the aging process or old age, the process of aging is devoted to the understanding and control of all factors contributing to the finitude of individual life. Every species on the earth has a life history in which the individual life expectancy has an appropriate relationship to the reproductive life span and the mechanism of reproduction and the course of development. It is also important to differentiate between the purely physicochemical processes of aging and the accidental organismic processes of disease and injury that lead to death.

Gerontology, therefore, can be defined as the science of the finitude of life as expressed in the three aspects of longevity, aging, and death, examined from both evolutionary and individual (ontogenetic) perspectives. Longevity is the span of life of an organism. Aging is the sequential or progressive change in an organism that leads to an increased risk of debility, disease, and death. Senescence consists of these manifestations of the aging process.

The viability (survival ability) of a population is characterized by two actuarial functions:

the survivorship curve and the age-specific death rate, or the Gompertz function. The relation of such factors as aging characteristics, constitutional vigor, physical factors, diet, and exposure to disease-causing organisms to the actuarial functions is complex. There is, nevertheless, no substitute for them as measures of the aging process and the effect of environmental or genetic modify

Research has shown that telomeres are vulnerable to genetic factors that alter an organism's rate of aging. In humans, variations in a gene known as *TERC* (telomerase RNA [ribonucleic acid] component), which encodes an RNA segment of an enzyme known as

telomerase, have been associated with reduced telomere length and an increased rate of biological aging. Telomerase normally functions to prevent the shortening of telomeres, but in the presence
of *TERC* mutations, the enzyme's activity is altered. *TERC* also appears to influence the telomere length that individuals possess from the time of birth. Persons who carry *TERC* variations are believed to be several years older biologically compared with noncarriers of the same chronological age. This accelerated rate of biological aging is likely also influenced by exposure to environmental factors, such as smoking and obesity, which increase a carrier's susceptibility to the onset of age-related diseases relatively early in adult life.
Mutations of genes that affect telomere length lend support to another genetic theory of aging, which assumes that cell death is the result of "errors" introduced in the formation of key proteins, such as enzymes. Slight differences induced in the transmission of information from
DNA molecules of the chromosomes through RNA molecules (the "messenger" substance) to the proper assembly of the large and complex enzyme molecules could result in a molecule of the enzyme that would not "work" properly. This is precisely what happens in the instance of mutations in the *TERC* gene. Such mutations disrupt the normal function of the telomerase enzyme.
As cells grow and divide, a small proportion of them undergoes mutation. This change in the genetic code is then reproduced when the cells again divide. The "somatic mutation" theory of aging assumes that aging is due to the gradual accumulation of mutated cells that do not perform normally.
Skin aging is a complex biological process influenced by a combination of endogenous or intrinsic factors and exogenous or extrinsic factors. Because skin health and beauty are considered one of the principal factors representing the overall 'well-being' and the perception of ' health in humans. Several antiaging strategies have been developed during the last few years. This article intends to review the most important strategies that dermatologists have nowadays in hand, including preservative measurement, cosmetological topical and systemic therapeutic agents, and invasive procedures.

Skin aging is a part of a natural human 'aging mosaic' that becomes evident and follows different trajectories in different organs tissues and cells with time. While the aging signs of internal organs are masked from the ambient eyes., the skin provides the first obvious marks of the passing time. Skin aging is a complex biological process influenced by the combination of intrinsic (genetics, cellular metabolism hormone, and metabolic process) and extrinsic (chronic light exposure, pollution, ionizing radiation, chemicals, toxins) factors.in contrast to thin, atrophic, finely wrinkled, and dry intrinsically aged skin, premature photoaged skin typically shows a thickened epidermis, discoloration of the skin, deep wrinkles, laxity, dullness, and roughness. Sun-exposed aged skin is characterized by solar elastosis.

Sparse distribution and decrease in the collagen concentration in the skin can be due to the degradation of various metalloproteinases, serines, and other proteases irrelevant to the same collagen production. In older skin, the collagen looks irregular and disorganized, and the ratio of col-3: col-1 has been shown to increase significantly because of the loss of col-1. the collagen content per unit area of the skin surface is known to decline by approximately 1% per year. GAGS are among the primary dermal skin matrix constituents that help in the binding of water. The total hyaluronic acid(HA) level in the dermis of the skin that age intrinsically remains stable but epidermal HA markedly.

Aging represents biological attrition at the cellular level resulting in reduced reserved capacity and ability to perform normal functions that occur throughout an organism's life period increasing the likelihood of death. It is thus the result of the genetic clock that is implanted in the genetic makeup of each living being. Skin aging is triggered by most factors including genetics, environmental exposure like UV exposure, xenobiotics and mechanical stress, hormonal changes, and metabolic process generation of reactive chemical compounds such as activated oxygen species, sugars, and aldehyde. All factors together act on the alterations of skin structure function and appearance.
Aging represents biological attrition at the cellular level resulting in decreased reserve capacity and ability to perform normal functions occurs throughout an organism's life span increases the likelihood of death. Aging is thus the result of a genetic program or a clock that is implanted in the genetic makeup of each species. One must also remember that cumulative damage to the genes and proteins derived thereof, results in compromised function and homeostatic failure. This leads the organism towards premature aging and death, which in turn shall depend on its repair systems.
The somatic cells have telomeres at the terminal portion of the eukaryotic chromosomes which consist of many hundreds of tandem short sequence repeats (TTAGGG) predetermining the number of times the cell can divide before it senesces. The enzyme DNA polymerase that replicates cellular chromosomes during mitosis cannot replicate the final base pairs of each chromosome, resulting in progressive telomere shortening with each cellular division. A critically short telomere will compromise gene transcription and signal cellular senescence which is otherwise better known as "apoptosis" (Yaar and Gilchrest 2001). Human keratinocytes approach replicative senescence after 50–100 population doublings in culture and remain permanently arrested in the G1 phase of the cell cycle.
The telomere is just one of the three molecules which were found to be crucial for replicative senescence. In addition, keratinocytes have an increased resistance to apoptosis, thus giving a time window for DNA and protein damage to accumulate (Rheinwald et al 2002).
The skin, being the ultimate protective barrier between the internal organs and the environment, is exposed to ultraviolet (UV) irradiation and a lesser extent to other DNA damaging agents such as cigarette smoke, automobile exhaust, and professional exposure. UV irradiation causes the formation of pyrimidine dimers and the benzo[a]pyrene from cigarette smoke causes the formation of guanine base pair adducts. All this moves hand-in-hand with damage from endogenous agents such as reactive oxygen

and nitrogen species (ROS/RNS) generated by all aerobic cell species as part of their routine metabolic processes (Yaar and Gilchrest 2001).

Amino acid racemization and interaction of amino acid groups with reducing sugars (Maillard reaction) result in an altered or total loss of protein functions which does the dermal collagen proteins (Yaar and Gilchrest 2001).

Intrinsic /chronological aging :

Intrinisic /chronological aging is defined by the clinical, histological, and physiological decrements that occur in the sun-protected skin, affecting the rate of epidermal turnover, clearance of chemical substances from the dermis, dermal thickness and cellularity, thermoregulation, rate of re-epithelialization after wounding, mechanical protection, immune responsiveness, sensory perception, sweat and sebum production, capacity for vitamin D synthesis and vascular reactivity. Clinically, the intrinsically aged skin is atrophic, which may result in the prominence of vasculature and loss of elasticity. The stratum corneum remains relatively unchanged but the epidermis thins with a flattening of the dermo-epidermal junction expressing an increased fragility of the skin. There is a considerable decrease in dermal thickness and vascularity as well as a reduction in the number and biosynthetic capacity of the fibroblast resulting in delayed wound healing. With increasing age, there is a progressive decline in the response of keratinocytes and fibroblasts to growth factors, decreasing the proliferative capacity (Gilchrest 1996). A decreased immune responsiveness is seen with aging since there is a decrease in the number and abnormal morphology seen in the antigen-presenting cells. Another important function that decreases with aging is the formation of vitamin D3 due to decreased formation of 7-dehydrocholesterol in the reduced epidermal cells (Yaar and Gilchrest 2001).

Photoaging:

Photoaging is the superimposition of photodamage on intrinsically aged skin generally bringing about premature aging. This specific damage occurs by chronic (multiple) exposures of the skin to UV light. Clinically, the skin becomes coarse; the epidermis thickens (hyperplasia) initially and then thins (atrophy), there is laxity, sallowness with wrinkles, irregular hyperpigmentation, lentigines, and telangiectasias (Gilchrest 1996). The pores of the skin are larger, filled with horny material, and tend to develop Favre-Racouchot's syndrome (nodular elastosis with cysts and comedones). There is also an increase in the development of benign neoplasms (seborrheic keratosis, fibroma, acrochordon, and ruby spots), "premalignant" lesions (actinic keratosis, lentigo maligna), and malignant lesions (basal and squamous cell carcinomas and malignant melanomas) on chronically exposed skin found in the face, hands and neck regions (Torras 1996, Oppel and Korting 2004).

In severely damaged skin, there is a loss of epidermal polarity (orderly maturation) and individual keratinocytes may show atypia, especially in the lower epidermal layers. More profound changes occur in the dermis, where photodamage is characterized by degeneration of collagen and deposition of abnormal elastotic material, reflected by wrinkles, furrows, and yellow discoloration of the skin. The greater the photodamage, the more the accumulation of thickened, tangled, and degraded elastic fibers (Gilchrest 1996). The surface roughness is not only attributed to the changes in the stratum corneum but also to the changes in the glycosaminoglycan (GAG) content of the skin. With the increase in age, there is a decrease in the GAG content. Contradictorily, Bernstein and Uitto (1995) found that there is an increase in the GAG content in the photoaged skin. Yet GAG does not deposit in the papillary dermis, instead, it accumulates on the abnormal elastotic material, which makes it unavailable as a source of hydration resulting in a dull, leathery appearance of the skin (Kang, Fisher, et al 2001). Microcirculation is also affected by sun exposure. Blood vessels become dilated and twisted (telangiectasia) and finally very sparse, while their walls are initially thickened and later thinned (Gilchrest 1996).

UV irradiation of the skin increases the reactive oxygen species and decreases the endogenous antioxidant enzymes. The superoxide anion is produced by energy transfer from several endogenous UV-absorbing chromophores including NADH−/NADPH, tryptophan, riboflavin, or transurocanic acid (Rittié and Fisher 2002) in the presence of molecular water present within the cell. The superoxide anion is then converted to hydrogen peroxide, which in the presence of transition metal ions such as iron and copper undergoes conversion to a highly reactive hydroxyl radical. This increased production of ROS alters gene and protein structure and function leading to skin damage.

The aging of the skin is an intricate biological process consisting of two types. While intrinsic or chronological aging is an inevitable process, photoaging involves the premature aging of the skin occurring due to cumulative exposure to ultraviolet radiation. Chronological and photoaging both have clinically different manifestations. Various natural and synthetic retinoids have been explored for the treatment of aging and many of them have shown histological and clinical improvement, but most of the studies have been carried out in patients presenting with photoaged skin. Amongst the retinoids, tretinoin possibly is the most potent and certainly the most widely investigated retinoid for photoaging therapy.

Although retinoids show promise in the treatment of skin aging, irritant reactions such as burning, scaling, or dermatitis associated with retinoid therapy limit their acceptance by patients. This problem is more prominent with tretinoin and tazarotene whereas other retinoids mainly represented by retinaldehyde and retinol are considerably less
irritating. To minimize these side effects, various novel drug delivery systems have been developed. In particular, nanoparticles have shown good potential in improving the stability, tolerability, and efficacy of retinoids like tretinoin and retinol. However, more elaborate clinical studies are required to confirm their advantage in the delivery of topical retinoids.

- **LITERATURE REVIEW:**

The use of peptides in antiaging cosmetics increased by 7.2%, while the number of peptide combinations in products has increased by 88.5%. the most used peptides in the antiaging formulation are palmitoyl oligopeptide, acetyl hexapeptide, and palmitoyl tetrapeptide-7. In 2011, the majority of peptides and skincare proteins were obtained from synthesis, while in 2018, biotechnology processing was the dominant source. This study provides an overview of the market trends regarding the use of peptides in anti-aging products, providing meaningful data for scientists involved in the development of new peptides to identify opportunities for innovation in this area.

The anti-aging market is expected to be grown worldwide on large scale at an approximate 8% compound annual growth rate between 2018 and 2021, reaching a value of USD 271.0 billion by 2024. As the competition increases among cosmetic brands in the anti-aging market, new products claim to contain the ultimate innovations to stand out, the challenges often advertising new active ingredients. Glutathione was the first biologically active peptide synthesized in the laboratory, development of new synthetic methods allowed for the synthesis of longer peptide chains, such as oxytocin and insulin. Although peptides are differentiated from proteins by their length, the cut-off number of amino acids to establish the classification as the peptide is arbitrary.

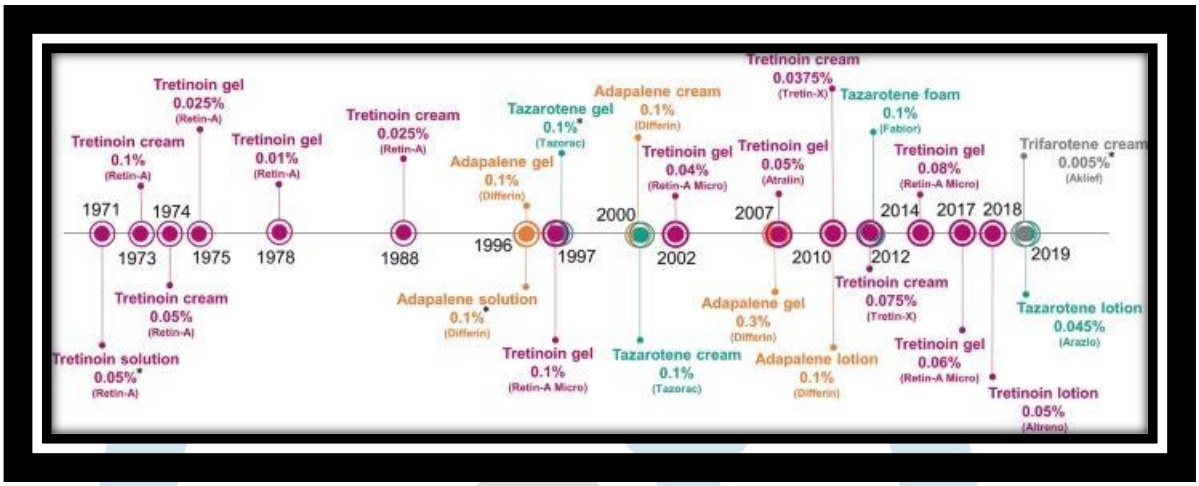
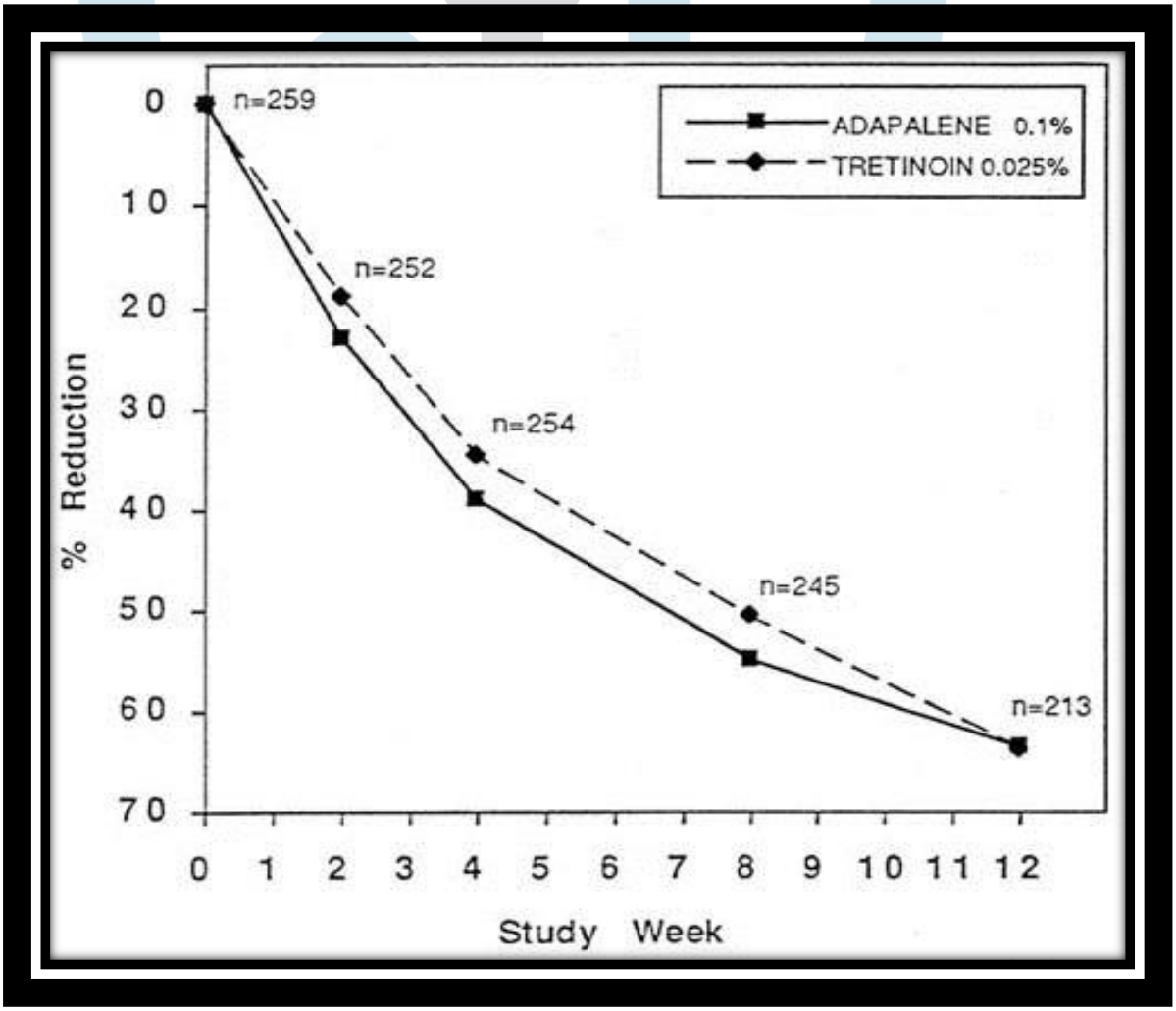


Fig.4 Usage of tretinoin throughout the years.

Fig.5. Comparative study of the efficacy of tretinoin and adapalene.



PEPTIDES:

Peptides and proteins are amino acid derivatives, derived from the word Pepto which means digested in Greek. if the chain of amino acids is less than 20 then it is referred to as oligopeptides and that includes dipeptides, tripeptides, and tetrapeptides. A polypeptide is a long, continuous, unbranched chain of peptides. That is the reason peptides are categorized under the broad chemical class of biological polymers and oligomers, alongside nucleic acids, oligosaccharides, polysaccharides, etc. polypeptides containing more than 50 amino acids in the structure are known as proteins. Proteins are one or more polypeptides arranged in a biologically functional way, often bound to ligands such as coenzymes, and cofactors or to any other protein that can be macromolecule like DNA or RNA or to a complex macromolecular assembly. A molecule of water is released every time the formation of an amide bond between two amino acids. All peptides have an N- terminal amine group and C-terminal carboxylic acid group except cyclic peptides.

Naturally occurring human peptides are known to perform cellular communication, such as protein regulation, cell proliferation, inflammation, cell migration, angiogenesis, and melanogenesis., which results in a broad variety of physiological processes including defense, immunity, stress, growth, homeostasis, and reproduction. The first-ever peptide was described by Emil Fischer and Fourneauin. Fischer described the first peptide as glycyl glycine and this explained more peptide structures like dipeptide, tripeptide, and polypeptides. besides the advancing knowledge about natural and synthetic peptides, different synthetic peptides were developed .copper glycine histidine lysine was developed in 1973 by Loren Pickard.

In the late 80s, the first copper peptide was incorporated into skin cosmetics and other products. After that, the peptide development proceeded slowly until the beginning of 2000 when palmitoyl pentapeptide-4 was established. Since then the research and the industries have developed many short, stable, and synthetic peptides that have a role in extracellular matrix stimulation, pigmentation, innate immunity, and inflammation. These peptides are used for collagen stimulation and wound healing. Botox-like wrinkle-smoothing, as well as antioxidative antimicrobial, whitening effects, and moisturizing.

Topical cosmeceutical peptides and proteins can be classified as signal peptides, carrier peptides, neurotransmitter inhibitor peptides, enzyme inhibitor peptides, etc. cosmeceutical peptides have certain features to obtain good effects. historically it has always been presumed that because of the skin barrier, the molecular weight of the peptide should be less than 500Da, otherwise the peptides couldn't cross the barrier named skin. Newer studies have shown that larger peptides can travel the skin barrier, especially in cases of dry and aged skin. some peptides are used in cosmetic products like carnosine, copper tripeptide, trifluoroacetic-tripeptide-2, hexapeptide, pentamidine-6, manganese tripeptide -1, soybean peptide, silk fibroin peptide, black rice oligopeptides, keratin peptide, tretinoin peptide.

As the competition increases among cosmetic brands in the anti-aging market, new products claim to contain the ultimate innovations to stand out, the challenges often advertising new active ingredients. Glutathione was the first biologically active peptide synthesized in the laboratory, development of new synthetic methods allowed for the synthesis of longer peptide chains, such as oxytocin and insulin. Although peptides are differentiated from proteins by their length, the cut-off number of amino acids to establish the classification as the peptide is arbitrary.

According to the Food and Drug Administration (FDA), which is responsible for the regulation of health products, proteins are amino acid congeners with a specific defined sequence that is greater than 40 amino acids in size. Peptides became popular in cosmetic products due to their bioactive properties, as they can interact with skin cells by multiple mechanisms to fight against skin problems, present high potency at a low dosage and because their size is minimum thought to achieve a moderate penetration into the upper skin layers. Due to their hydrophilic properties, chemical modifications such as esterification with alkyl chains may be mandatory to achieve penetration through the skin.

Bioactive peptides are defined as peptide sequences within a protein, usually 2 to 20 amino acids, that exert an effect on human health which are beneficial beyond their known nutritional value. These peptides impact a broad spectrum of human health and exhibit pharmacological activities including cardioprotective, antimicrobial, antioxidant, and mineral binding properties, all collectively improving lifespan. Owing to their nature of the ability to attenuate the implying basis of aging, the use of bioactive peptides has gained attention as nutraceuticals and functional foods. The anti-aging action of dietary peptides has also revealed an intricate network of interacting cell communication pathways and higher-order molecular processes. As the emergence of the aging population and consciousness of health gradually deepens people pay more attention to their skincare.

A series of bioactive peptides such as plant extracts, microbial metabolites, minerals, and vitamins are useful to make skin desirable. according to a previous literature survey, some bioactive compounds like proteins and peptides can regulate various biological processes in the skin epidermis, and dermis to affect the different functions of the skin by increasing the production of collagen, instead of the lost extracellular matrix and improving skin wrinkles, fine lines, and tone. Currently, there is a wide range of peptides in cosmeceuticals which are categorized according to their mechanism of action.

- Signal peptides: work by stimulating matrix protein production such as elastin and collagen, helping in cell growth and metabolic functions.
- Carrier peptides: which may act as transportation peptides or facilitators for the important substance or trace elements inside the cell such as copper and magnesium.
- Neurotransmitter inhibiting peptide: targets the expression of wrinkles by inhibiting the acetylcholine release at the neuromuscular junction by acting on distinct molecular targets.
- Enzyme-inhibiting peptides reduce the activity of an enzyme that participates in skin aging. E.g. silk fibroin peptide, soybean peptide, rice peptides.
- Peptides derived from structural protein digestion:e.g keratin-based peptide, tretinoin

TRETINOIN:

Tretinoin (all-trans-retinoic acid), a vitamin A derivative, induces cellular differentiation in several hematological precursor cell lines and cells from patients with acute promyelocytic leukemia. Drug treatment with tretinoin is associated with morphological and functional maturation of leukemic promyelocytes and a progressive reduction in the occurrence of the characteristic t(15;17) chromosomal translocation.

For acne, it is applied as a cream, gel, or ointment. For leukemia, it is taken by mouth for up to three months. tretinoin was patented in 1957 and approved for medical use in 1962. It is on the world health organizations' list of essential medicine. Tretinoin is available as a generic medicine. Oral isotretinoin (13-cis-retinoic acid) is a retinoid derived from vitamin a. it was synthesized in 1955, but it was only in 1973 that studies on its use in psoriasis, genetic disorders of keratinization, cystic acne, and basal cell carcinoma began. Isotretinoin act as a prodrug, being converted into all-trans-retinoic acid (ATRA) in the cytoplasm of cells to be transported to the nucleus, where it binds to the nuclear retinoic acid receptors (RAR) isoform a, b, and g.

BIOSYNTHESIS:

it is synthesized from beta carotene. the beta carotene is firstly cleaved into beta carotene 15-15`monooxygenase through the site 1 double bond oxidized to epoxide. The epoxide is attacked by water to form a diol in site 1. NADH, as a reduction agent, reduces the alcohol group to aldehyde. Tretinoin was co-developed for its use in acne by James Fulton and Albert Klingman when they were at the University of Pennsylvania in the 1960s phase 1 trial, the first concluded on human subjects was performed on an inmate at Holmes burg prison during a long-running regime of nontherapeutic and unethical testing**.**

Topical tretinoin has been approved for use in dermatology for 40 years and is currently approved for the treatment of acne vulgaris and photodamage. During this time topical tretinoin has accumulated significant efficacy and safety data in the treatment of acne and skin aging due to photodamage. the diverse effect may be due to the complex underlying mechanism of action of tretinoin, including keratolytic activity, and collagenases. Retinoids, as compounds that are sparingly soluble in body fluids (lipophilic compounds), need specialized proteins to transport them (complex with Transthyretin – (prealbumin) is a retinol-binding protein (vitamin A). Results of the study by Hyung *et al.* proved new applications of RBP and retinoids as stabilizers of transthyretin. These are proteins such as RBP and CRBP.

Cytosolic retinol-binding protein (CRBP), which is present in the cytoplasm, shows an affinity for retinol, while cytosolic retinoic acid-binding protein (CRABP) has an affinity for retinoic acid. There are two subtypes of both groups of receptors: CRBP I and II and CRABP I and II. The intracellular concentration of retinoids depends on their binding to cellular CRABP I and II. Studies show that CRABP II (it is the main form present in the epidermis) is much more abundant in the skin than CRABP I (which modulates the level of retinoic acid in different tissues) These proteins activate appropriate nuclear receptors, thanks to which retinoids exert their biological effect on particular tissues, organs, and cells. Retinoid nuclear receptors (RNR, which represent a steroid thyroid hormone receptor) include:

- RA receptors (RAR), its natural ligand is retinoic acid (RA), and
- Retinoid X Receptors (RXR), its natural ligand is 9-*cis*-retinoic acid.

Within these receptors, there are three types of isotypes: α, β, and g (RARα, RARβ, RARγ). They may be further divided into isoforms. The human skin mainly contains RXRg and RARα. Retinoids activate receptors in the form of dimers which in turn bind to the appropriate RARE element, i.e. the domain of the DNA response. They are located near the gene promoter sequences regulated by retinoids. Receptor expression is not regular and is described in only some tissues and organs, including the epidermis, dermis, sebaceous glands, hair follicles, or cells of the immune system.

Long-term studies on tretinoin were carried out as short-term studies showed that the skin condition continued to improve in appearance over time. Additionally, another objective was to assess the long-term benefit-to-risk ratio of the tretinoin formulations. For suitability of understanding, we have divided long-term studies into 6-months studies and studies involving more than 6 months. The ability of long-term (more than 6 months) tretinoin treatment to maintain improvement in photoaging was first evaluated by Ellis and colleagues (1990) in a 22-month study carried out on 16 patients with photoaged skin. All the subjects used 0.1% tretinoin for the first 4 months. Thereafter, 3 patients continued this regimen, 8 were changed to alternate day treatment for the last 12 months, and the remaining used 0.05% tretinoin for 5 months and then reduced to alternate day application till the end of therapy. It was observed that the improvement of wrinkling continued up to the 10th month and was maintained thereafter. The stratum corneum and epidermal thickness returned to normal during treatment. In another trial, Green and colleagues (1993) studied the effect of 0.05% tretinoin emollient cream applied daily for 12 months. Tretinoin treatment showed significant improvement in the clinical signs of photoaging. However, the major degree of changes occurred after 6 months and later on, they tended to remain stable as observed in the earlier study. Extension of the study for 6 more months with either weekly or thrice weekly application showed further improvement in overall signs of photoaging.

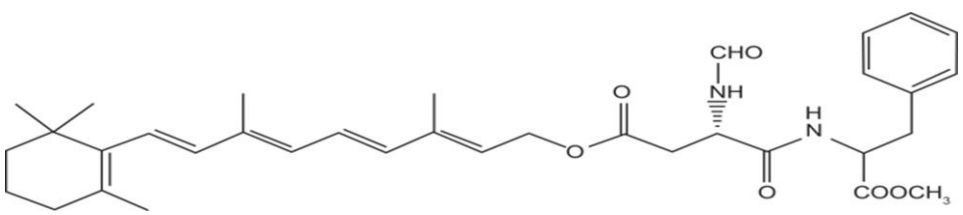


Fig.6. Structure of tretinoin.

Tretinoin alone does not eradicate the leukemic clone and consolidation chemotherapy is recommended as a follow-up. The use of reverse transcription-polymerase chain reaction (RT-PCR) provides a sensitive and specific technique to assist in the prediction and monitoring of a patient's response to treatment and to help detect the presence of residual or recurrent disease.

The use of tretinoin is potentially limited by the rapid and almost universal development of drug resistance and the occurrence of the often severe retinoic acid syndrome. Useful strategies have been described to manage these effects but current and future efforts must be directed at elucidating the mechanisms involved and determining the optimal therapeutic management.

In summary, results to date indicate that the combination of tretinoin and intensive chemotherapy is more effective than chemotherapy alone and appears to improve the prognosis of newly diagnosed patients with acute promyelocytic leukemia. Further information on the relative efficacy of various induction and post-remission strategies in subsets of patients will help determine the optimum use of this promising agent in the management of acute promyelocytic leukemia.

Pharmacokinetic properties:

The oral bioavailability of tretinoin is approximately 50% and, after single-dose administration, plasma drug concentrations remain within the range required for in vitro differentiation of acute promyelocytic leukemia cells for about 4 hours. Tretinoin is distributed rapidly and extensively to tissues but has not been detected in cerebrospinal fluid. Repeated dose administration results in a marked reduction in plasma drug concentration and area under the plasma concentration-time curve which is associated with relapse in treated patients.

Tretinoin undergoes oxidative metabolism via the cytochrome P450 enzyme system in the liver, glucuronide conjugation, and elimination in urine and bile. Tretinoin appears to undergo capacity-limited (saturable) elimination with a terminal elimination half-life of less than 1 hr

Tolerability:

Compared with standard antineoplastic chemotherapy, which is cytotoxic to normal hemopoietic and leukemic cells, tretinoin induces remission in patients with acute promyelocytic leukemia without causing bone marrow hypoplasia or exacerbation of the frequently occurring hemorrhagic syndrome. Many trials have reported that bleeding complications associated with this disease resolve within 4 to 6 days of patients starting drug treatment.

A potentially serious consequence of tretinoin therapy is the development of retinoic acid syndrome. This syndrome, which is characterized by fever, respiratory distress, interstitial pulmonary infiltrates, pleural effusions, and weight gain may occur in up to 25% of patients and can be fatal if not promptly recognized and treated. It has been successfully managed with high-dose corticosteroids and/or the addition of standard chemotherapy to tretinoin therapy, although additional data are needed to determine the efficacy and appropriate use of these strategies.

In common with other retinoids, adverse events with tretinoin often involve the skin and mucous membranes. Dryness of the skin, nasal and/or other mucosal membranes, and/or cheilitis occur in 24 to 65% of patients but respond to symptomatic treatment. Similarly, headaches, bone pain, and arthralgias are frequently reported but are alleviated by analgesics.

- **MARKETED FORMULATION OF TRETINOIN:**

1. Twyneo tretinoin
2. Retin-A®
3. Tretin-X®
4. Refissa®
5. Renova®
6. Avita

Fig.7. Fig.8.

Fig.9.

APPLICATION OF TRETINOIN:

Tretinoin is used to treat acne or other skin diseases as determined by your doctor. It works partly by keeping skin pores clear. One of the tretinoin creams is used to treat fine wrinkles, dark spots, or rough skin on the face caused by the damaging rays of the sun. Tretinoin comes in topical forms, such as gels and creams, or as an oral medication called isotretinoin. The Food and Drug Administration (FDA) approves topical forms of tretinoin for treating acne vulgaris. The FDA also approves the use of oral tretinoin, or isotretinoin, to treat severe nodular acne.

- **BENEFITS OF TRETINOIN:**

❖ Reducing the appearance of fine lines and dark spots.
❖ Improving skin texture.
❖ Reducing the frequency and severity of acne outbreaks.
❖ Clearing up existing acne.
❖ Retinoids, such as tretinoin, stimulate the generation of skin cells, meaning they grow and divide quicker. This accelerates the removal of dead skin cells and keeps the pores clear of bacteria and other irritants.

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