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The Skin Aging Process and Anti-Aging Strategies

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Abbreviations: ROS: Reactive Oxidative Species; H_2O_2: Hydrogen Peroxide; BTX: Botulinum Toxin; HA: Hyaluronic Acid; PRP: Platelet-Rich Plasma; TGF: Transforming Growth Factor; PDGF: Platelet-Derived Growth Factor; GF: Growth Factor; RARE: Retinoic Acid Response Elements; AA: Ascorbic Acid; NLP: Nano-Lipidic Particle

ABSTRACT

Aging can be seen as the accumulation of changes in cells and tissues as a result of increased disorderliness of biological regulatory mechanisms. Alteration of intrinsic factors like hormone processes, genetics, and cellular metabolism in conjunction with exposure to extrinsic factors like UV radiation, pollution, and other chemicals are responsible for structural and physiological changes of the skin that result in the formation of fine lines, wrinkles, and other blemishes. Both preventive and treatment methods can be used when combating factors responsible for the degradation of skin integrity over time. Proper nutrition and protection from UV rays are important methods in remaining pro-active against excessive damage from Reactive Oxidative Species (ROS). Minimally invasive cosmetic procedures like Botox and fillers are popular as muscle relaxers and skin plumpers to restore volume and fullness in the face and diminish facial lines. In drug treatment, active ingredients have become a keystone in the management of the aging process with proven ability to repair skin damage through stimulation of collagen production and removal of ROS. Through further medical and scientific intervention, researchers hope to advance and refine anti-aging strategies to minimize this visualization of the aging process and maintain youthful looks throughout lengthening life spans. This paper will review the process by which the structure of skin deteriorates as well as several types of treatment methods that can be used to address this deterioration and how they function at the cellular level to accomplish rejuvenation.

Keywords: Skin Barrier System; Collagen Synthesis; Reactive Oxygen Species; Transdermal Drugs

Introduction

Appearances play a vital role in society as it is how one communicates to others their identity and it strongly influences how one is perceived. Moreover, when living in the age of social media, influencers, and photoshop, the average person is now exceedingly aware of their physical appearance. It is easy to fall victim to setting unrealistic expectations for oneself, especially when comparing the average person to the meticulously retouched images of celebrities posted to the public. Filters used to smooth out wrinkles on Instagram posts, fillers injected to plump up tissue to diminish laugh lines, [1] and makeup to cover up any sunspots that have developed all show a marked aversion to aging in their picture-perfect society. In 2012, a survey conducted by the market research company NPD Group found that women between the ages of 18 and 24 found that fewer than 20% considered anti-aging skin care to be important. However, a survey of the same demographics in 2018 by beauty consumer analysts discovered that this statistic rose to more than 50% of women adding products in their routine to

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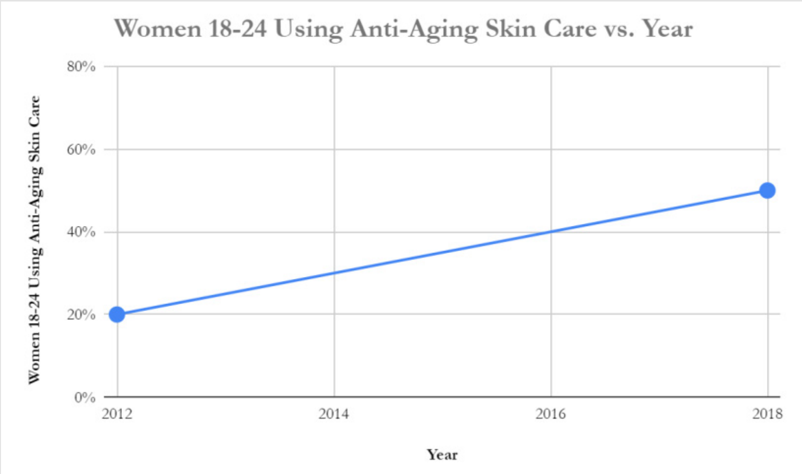
defy wrinkles [2] (Graph 1). The notable 150% increase in utilizing preventive skin care is reflective of the generation's growing unwillingness to show the physical signs of aging. Nonetheless this attempt to delay the aging process is not unique to Millennials or Gen Z.



Graph 1.

As early as 30 BC, Cleopatra was known to take daily baths in donkey-milk for the anti-aging and skin-softening properties of the hydroxy acids in the milk and during the Tang-dynasty, Empress Wu Zlitan maintained her famed beauty through the years by washing her face with powdered Chinese motherwort and cold water [3] Since then, science and technology has advanced to be able to identify the specific active compounds that made these treatments effective. In doing so, these compounds are able to be purified for higher efficacy in treatment. Furthermore, the development of new treatment methods for the purpose of anti-aging have taken the world by a storm. A study done by the American Society of Plastic Surgeons reported that 3.4 million injections of soft tissue filler were done in 2020 alone. This value is second only to Botox injections being the most popular minimally invasive cosmetic procedure with a total of 4.4 million procedures done. In addition to fillers, other popular anti-aging methods include serums, resurfacing creams, "vampire facials'' and more that claim to help create a smoother and fuller appearance of the skin.

As concerns about the physical manifestation of aging grow and people continue to take an active role in either the prevention or reversion of aging skin, treatment methods have become more accessible and normalized in the modern world. While anti-aging claims are an effective marketing tool in drawing consumers to a product or procedure, these claims must be backed up with actual mechanisms that work to rejuvenate the skin - whether it is through stimulation of collagen production or the removal of damaging reactive oxidative species. There are so many products on the market with varying ingredients and price points, so it is important to know which ones are actually effective in producing anti-aging results and which ones are pointless. While there is not yet a proven effective product capable of eliminating all signs of aging, there are products and treatments that are clinically proven to have wrinkle-reducing effects and work to visibly reduce signs of aging.

Aging Process

Graying hair, shrinking stature, and cracking joints are all tell-tale signs of aging everyone hopes to escape, with the most famous indication being the appearance of fine lines and wrinkles on the skin. Wrinkles are the creases and folds that form in the skin as a by-product of the aging process as the skin loses its elasticity over time. As the separation of the body from the outside environment, the skin is impacted by aging factors that are both intrinsic and extrinsic. Intrinsic aging is determined genetically and describes the unavoidable physiological process resulting in the development of fine wrinkles in thin, dry skin. Extrinsic aging factors encompass environmental factors such as sun exposure, air pollution, and smoking that produce rough textured skin and the formation of deeper, coarse wrinkles [4]. To protect from these external factors, the skin has multiple layers to serve as a defense against pathogens, UV light, physical injuries, and more. The 3 most commonly known layers of the skin are the epidermis, dermis, and hypodermis - all varying in structure and function. Lesser known is that each of these layers has several sublayers aiding in the functionalities of the skin.

The outermost layer, the epidermis, is divided into the stratum Basale, stratum spinosum, stratum granulosum, stratum lucidum, and the stratum corneum [5]. Of these, the skin barrier has been located primarily at the intercellular lipid matrix of the uppermost layer of the epidermis, the stratum corneum. The stratum corneum consists of 20-30 cell layers of keratin and horny scales (made up of anucleate squamous cells, or dead keratinocytes) as well as the crucial lipid matrix containing cholesterol, free fatty acids, and ceramides. These compounds making up the lipid matrix are together known as a "natural moisturizing factor" as they function to keep the deeper layers of skin, such as the dermis and hypodermis, well-nourished and hydrated. The primary purpose of the skin barrier is to remain as tight as possible and in doing so, it plays three vital roles. First, it protects the body from external stressors such as UV radiation, pollution, and chemicals. Second, the barrier functions to retain water in the skin and maintain healthy levels of hydration through the prevention of excessive trans epidermal water. Trans epidermal water loss refers to the amount of water that passively evaporates via the surface of the skin, and it is a good measure of effectiveness of the skin barrier system [6].

Third, the skin barrier is responsible for transporting nutrients through itself and into the skin to preserve the health of the major organ. Ultimately, these tasks in conjunction operate to maintain homeostasis among the body's many systems [7]. If the skin barrier does not work as, it should, the epidermis will become vulnerable to damage and unable to fight off external aggressors, such as free radicals that can result in the formation of discoloration and premature wrinkles. In fact, up to 90% of visible skin aging is due to environmental factors, such as sun exposure [8]. Over time, with improper care, the skin barrier will become impaired and result in less hydrated skin that is more susceptible to harm. With normal, healthy skin, the top layer is continually shed as it is being renewed by a self-replenishing pool of stem cells existing in the basal layer. However, as people age, this pool of stem cells becomes diminished resulting in slower cell turnover rates [9]. This slowing divide of cells causes the dermis layer to thin. The dermis consists of interwoven elastin and collagen fibers, offering support and elasticity. As the interconnected fibers loosen with time, depressions are created on the skin surface that are unable to heal, resulting in the development of wrinkles [10].

Aging and Role of Collagen

Collagen is the most abundant protein present in mammalians, serving as one of the main building blocks for a range of tissue types including bones, skin, muscles, and hair. The 3 parallel polypeptide strands are found in a left-handed, polyproline II-type helical formation with a one-residue stagger forming a right-handed triple helix [11]. This stagger contains a special amino acid sequence specifying that every third amino acid must be glycine while the 2 remaining residues are often either proline or hydroxyproline [12]. This structure results in incredible stability and versatility of the protein, allowing it to play key roles throughout the body in various forms. In the skin, collagen fibers are found in the dermis layer to form fibroblasts where new cells can grow in addition to playing a role in replacing and restoring dead skin cells [13]. As one ages not only does the body produce less collagen, causing a decline in the structural integrity of the skin, but this process can be hastened by exposure to harmful extrinsic factors like ultraviolet rays and smoking. The breakdown of the complex network of fibers leads to wrinkles as the layers underneath the epidermis lose their firmness. This is visualized in the diagram below through the comparison of the many layers shown as the collagen-elastin network progresses from younger skin to aging skin [14] (Figure 1).

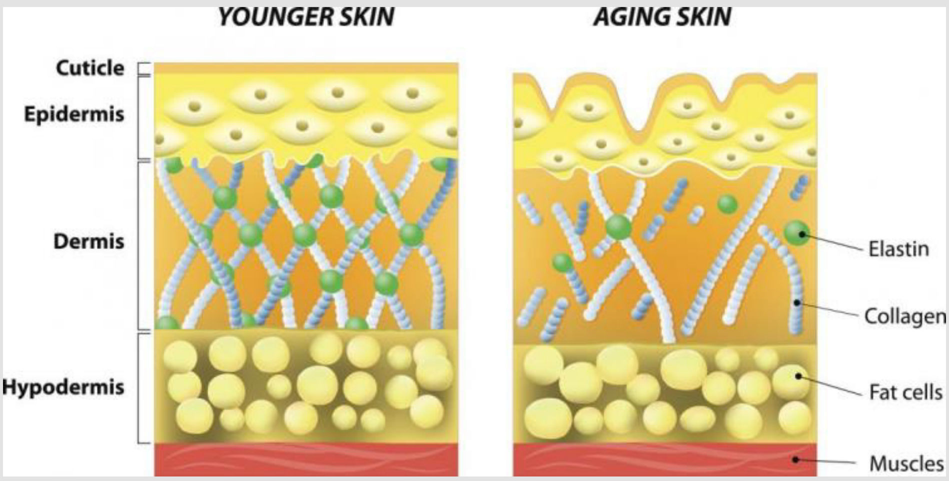


Figure 1.

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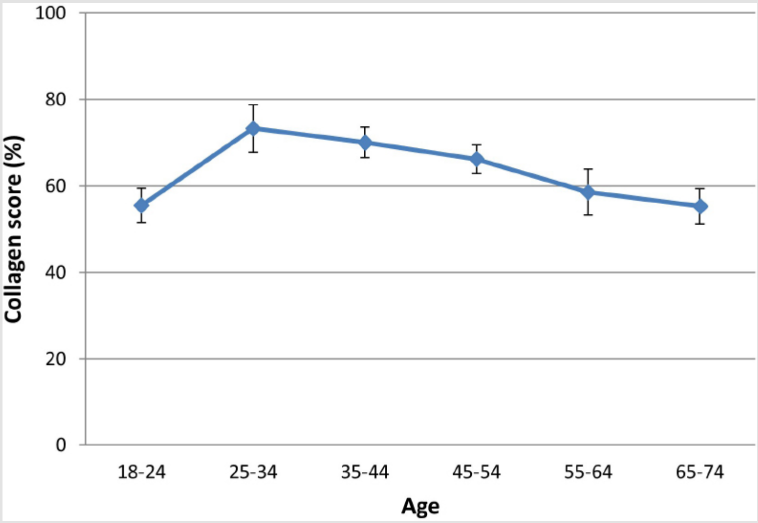
Not only is overall collagen production reduced, but the type of collagen being also produced is different in aging skin as well. Currently, there are a total of 28 different forms of collagen in the body including both fibril-forming as well as non-fibril forming proteins. Of these, the most predominant types of collagens are Type I, Type II, and Type III. Type I is the most common type of collagen, making up 80-90% of skin, hair, and nails and is composed of two α1 chains and one α2 chain coiled around each other [15]. Type II is mainly found in cartilage to support joint health and it contains three identical α1-polypeptide chains of 1,060 amino acid residues [16]. Type III supports Type I collagen in maintaining skin and bone health and it is made of three α1(III) chains supercoiled in a right-handed triple helix to form a homotrimer. In older skin, the collagen structure will look irregular as the proportion of collagen types in the skin changes with age. While young skin is composed of 80% Type I collagen and 15% Type III collagen, aging skin has shown an increase in the ratio of Type III to Type I collagen - largely due to the loss of Type III collagen [17]. With age, overall collagen content per unit area of skin surface is said to decline at a rate of approximately 1% per year as fibroblasts become less active [13]. In fact, a study conducted by MINERVA Research Labs reported that peak collagen content was identified between the ages of 25-34, followed by a gradual decline over the coming decades [18] (Graph 2).



Graph 2.

This, created by MINERVA Research Labs depicts the increase of collagen content until the mid-20s. Shortly after begins the progressive loss of collagen equating to an almost 25% decrease over the span of 4 decades. The synthesis of collagen fibers is primarily done by the fibroblasts of the skin, meaning that the rejuvenation of this biomatrix can only be efficiently improved with a supply of supplemental nutrients via the bloodstream. As the skin's natural collagen supply diminishes, the introduction of collagen via injection, topical treatment, or oral ingestion can work to replenish the collagen that has been lost or even stimulate the production of more collagen after absorption. A randomized, placebo-controlled, blind study by Bloke was used to investigate the effects of drinking a test product containing a blend of 2.5 grams of collagen peptides, acerola fruit extract, biotin, vitamin C, and other compounds. Performed on women 35 years and older, this study, in conjunction with others totaling a pool of 805 patients, demonstrated that collagen supplements are effective in increasing hydration, dermal collagen density, and elasticity of the skin [19]. Another study done by Porsche et al. reported that the intake of 2.5 grams of collagen a day over an 8 week period produced an increase in procollagen Type I as well as elastin, leading to a significant reduction in eye wrinkle volume [20]. Although the formation of wrinkles is inevitable as a byproduct of the aging process, researchers are actively working to find ways to minimize the appearance of these fine lines. While there are developing treatment methods, a second way to combat wrinkles is through preventive measures.

Preventive Measure as Anti-Aging Efforts

A popular preventive measure for reducing or delaying the appearance of wrinkles is through nutrition to combat the effects of reactive oxygen species (ROS). Reactive oxygen species are generated as by-products when molecular oxygen is utilized by aerobic organisms to perform essential metabolic reactions within the body. ROS is a term used to define any oxygen-containing reactive including hydrogen peroxide (H_2O_2), hydroxyl radicals ($^{\cdot}OH$), peroxyl radicals ($LOO^{\cdot}$), and more [21]. In addition to involvement in metabolic processes, ROS also play important roles in wound healing, inflammatory responses, and apoptosis. As the skin functions as a barrier to protect from external harmful agents, when the skin becomes inflamed high levels of ROS are generated for the purpose of removing and destroying invading microorganisms and breaking down any damaged tissue. As mediators of inflammatory responses, ROS activate cell signaling to increase the production and release of proinflammatory cytokines to instigate inflammatory responses.

In the presence of nitric oxide, calcium, and pathogens within human cells, the balance between oxidant and antioxidants is affected and results in the generation and accumulation of ROS in cells. The resulting imbalance between oxidative and antioxidative events induces oxidative stress, leading to oxidative reactions. ROS are reactive species that show molecular aggregation and are capable of causing serious damage to biomolecules including lipids, nucleic acids and proteins. This deterioration to DNA and other biomolecules can also induce other structural and functional damages leading to cell and tissue injury. As DNA, lipid, and protein structures are altered, there is a resulting dysregulation of cell-signaling pathways that trigger downstream signaling cascades to alter cytokine release. As the cytokines are not released regularly, the induced inflammatory response is prolonged and causes tissue damage and the exacerbation of inflammatory skin diseases [22]. To defend against these attacks, a series of antioxidant defenses have been developed to protect vital biomolecules from ROS damage. Antioxidants perform their duties by 3 major modes of action:

(a) Directly scavenging already-formed ROS,

(b) Inhibit formation of ROS from cellular sources,

(c) Remove or repair harm caused by ROS.

To reduce the risk of oxidative stress-related issues one could implement a plant-based diet with high volumes of intake of fruits, vegetables, and other foods rich in antioxidants. A meat-based diet is low in antioxidants while plant-based foods are antioxidant rich due to the presence of thousands of bioactive food constituents. These constituents - including flavonoids, tannins, stilbenes, phenolic acids, and lignans - are called phytochemicals that are redox active molecules and function as antioxidants. When comparing the meats versus plant-based foods, plants have 5 to 33 times higher mean antioxidant content when compared to the values for animal-based foods [23]. Long-term exposure to UV radiation is also a major cause of skin aging that can be reduced through preventive measures. Photoaging causes alterations in the structure of skin such as epidermal stratum corneum integrity, skin thickness, hydration and lipidation leading to the development of wrinkles and skin relaxation. UV exposure can lead to the generation of excess ROS in the skin that then in turn activate pathways related to skin aging including: "MMP1-mediated aging, MAPK/AP-1/NF-kB/tumor necrosis factor (TNF)-α/IL-6-mediated inflammation-induced aging, and p53/BAX/cleaved caspase-3/ cytochrome c-mediated apoptosis-induced aging [24].

"The activation of transcription factors like NF-kB promote inflammation-induced signaling and create oxidative stress by increasing ROS production to lead to skin cell apoptosis [25]. UVB-induced ROS generation is capable of activating the MAPK pathway leading to the expression of MMPs. MMPs are able for the degradation of the extracellular matrix in the skin, leading to the formation of wrinkles [26]. As the risks that come with overexposure to UV radiation become abundantly clear, so is the importance of using protection against the sun's rays. It is recommended to stay out of the sun from 10:00 am to 2:00 pm when the sun's rays are the strongest, and when going outside, one should dress to protect by wearing covering materials such as a long-sleeved shirt, a hat, and sunglasses. On skin that is not covered, the FDA recommends to wear a sunscreen offering broad-spectrum protection that is SPF 30 or higher [27]. Sunscreens can be made with organic filters that absorb UV radiation energy to convert into unnoticeable infrared energy. The structure responsible for this absorption is chromophore, consisting of electrons engaged in multiple bond sequences between atoms. Upon absorption, the UV photon holds enough energy to result in an electron transfer to a higher energy orbit within the chromophore molecule [28]. From this excited state, different relaxation processes occur dependent on the ability of the UV filter to convert the absorbed energy in order to bring it down to the ground state energy. Inorganic filters are also used in sunscreens as pigment grade powders of metal oxides like zinc oxide in conjunction with organic filters to enhance sun protection. Unlike organic filters, these metal oxides work by reflecting and diffusing UV radiation so that it only reaches the skin, rather than becoming absorbed past it [29].

Changing the Perception

When considering anti-aging, there are two ways of looking at it: perception versus making real changes to the skin. To simply change perception, multiple methods can be used such as filters for a blurring effect or the use of makeup like foundation and concealers to lessen the appearance of any unwanted fine lines. It is important to note that many makeup brands will advertise their products as having the ability to "reduce the appearance of wrinkles" which is important to distinguish from "will reduce wrinkles". The difference is that the former is a cosmetic claim whereas the latter is a drug claim. The FDA defines cosmetics as "articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced to, or otherwise applied to the human body...for cleansing, beautifying, promoting attractiveness, or altering the appearance" [30]. For example, mica is an earth-derived silicate mineral that is included in many cosmetic products to provide a shimmering effect on the skin surface. In doing so, it not only provides protection against the sun's rays, but it also diffuses reflected light off of the skin so that wrinkle lines are not as pronounced [31]. While mica is able to fulfill the cosmetic claim of reducing the appearance of wrinkles, there are other treatment options that work to reduce the physical presence of wrinkles. One such example is Botulinum Toxin (BTX).

While it cannot entirely discontinue the aging process of the skin, regular injections are able to slow down the visible effects of aging by helping manage the further stimulation of dynamic wrinkles. BTX-subtype A (BTX-A) is a potent neurotoxin that blocks the presynaptic release of acetylcholine at the neuro-muscular junction to produce temporary chemical denervation [32]. The toxin binds to presynaptic neurons of the pre-selected muscles within an hour and clinically reversible chemical denervation and paralysis begin after 24 to 48 hours of the injection [33]. It is only on Day 28 that the nerve sprouts are able to mediate partial restoration and new neuro-muscular junctions begin to form near the site of the old junction and by Day 62-91 there is complete recovery of muscle function. As the muscular changes achieved through BTX-A are completely reversible, treatment should be repeated every 3 to 4 months to maintain results [34]. Like Botox, dermal fillers can be injected, but they differ in function by adding fullness to areas that have thinned due to age. Biodegradable fillers, like collagen and Hyaluronic Acid (HA) fillers are reabsorbed by the body and typically have effects lasting 6 to 18 months [35].

The duration of the filler is dependent on the source and extent of cross-linking, as well as the concentration and size of each product. As hyaluronic acids are linear polymeric dimers of N-acetyl glucosamine and glucuronic acid, the degree and methods of chain cross-linking, the uniformity and size of particles, and concentration of particles will all vary and impact the clinical effects of the filler. With greater cross-linking and concentration, the viscosity, elasticity, and resistance to degradation all increase. Additionally, larger particle products in high concentrations will absorb more water and increase the degree of tissue swelling following injection [36]. Unlike biodegradable fillers, non-biodegradable fillers work by provoking a foreign body reaction to stimulate the fibroblastic deposition of collagen surrounding nonabsorbable microspheres. One example of this type of filler is Silikon®1000 which is a medical-grade pure form of silicon - upon injection, the body will form collagen around these silicone particles to increase volume in the tissue [37]. However, owing to the permanent nature of these fillers, complications are much more difficult to treat. Another treatment that is a popular treatment for skin rejuvenation is Autologous Platelet-rich Plasma (PRP).

PRP is made from fresh whole blood containing high concentrations of platelets. In these platelets there are α-granules that secrete various growth factors including transforming growth factor (TGF), insulin-like growth factor (GF), and platelet-derived growth factor (PDGF) [38]. These factors are responsible for regulating processes such as cell migration, proliferation and differentiation, and promoting extracellular matrix accumulation. In this way, PRP is also capable of inducing collagen synthesis by stimulating the activation of fibroblasts, which can then in turn rejuvenate the skin [39].

Some of the Useful Approved Drugs

The Food and Drug Administration defines a drug as "articles (other than food) intended to affect the structure or any function of the body of man or other animals" [30]. To do so, active ingredients are used to produce desired biological or chemical effects. For example, retinoids vitamin A derivatives that have been proven clinically to reduce acne, prevent wrinkles, reverse the effects of sun damage, and more. As lipophilic molecules, retinoids are able to diffuse through phospholipid membranes such as the cell membrane where it is able to bind to various receptors. The resulting ligand-receptor complexes are able to directly bind to specific DNA sequences called "retinoic acid response elements" (RARE) as transcription factors or by indirectly repressing the transcription factor AP-1.31-33 [40]. The activation of RARE and the repression of AP-1 expression allows retinoids to act as powerful agents able to regulate gene expression to influence cellular differentiation and proliferation. Following treatment with retinol and retinoic acid, there is a resulting epidermal thickening due to the inhibition of collagen degradation and an increase in collagen synthesis. To determine the molecular mechanism for these changes, the expression of 12 genes were determined.

After retinol and retinoic acid treatment, there were increases in the gene expression of COL1A1 and COL3A1 responsible for the production of procollagen I and procollagen III proteins. The retinol treatment resulted in a 1.34-fold increase in COL1A1 gene expression and a 1.43-fold increase in COL3A1. After retinoic acid treatment, there was a 2.48-fold increase in the expression of the COL1A1 gene and a 2.77-fold increase for COL3A1. A facial wrinkle analysis conducted after 12 weeks of treatment showed a significant reduction in wrinkle scores: at the cheeks the scores were reduced by 63.74% and the eye areas were reduced by 38.74% [41]. Vitamin C is another compound that can be found in serums, as topical creams, or ingested to play a metabolic role in collagen synthesis and as an antioxidant. Ascorbic acid (AA) is an alpha-keto lactone that exists as a monovalent hydroxyl anion at physiologic pH levels. As an antioxidant, ascorbate undergoes a stepwise donation of 2 electrons where the intermediate compound following the donation of 1 electron is the ascorbate free radical. This radical functions as an effective free radical scavenger and suppresses matrix-metalloproteinases associated with collagen degradation

[42]. AA also functions as a cofactor in the production of 2 enzymes required for collagen synthesis. Prolyl hydroxylase stabilizes the collagen molecule while lysis hydroxylase gives structural strength via intermolecular cross-linking - AA is consumed non stoichiometrically during translation within ribosomes for the formation of both of these enzymes [43].

While the use of vitamin C alone functions to remove ROS, combining the additional active ingredient vitamin E can provide maximal anti-aging and brightening effects. When vitamin C and E work synergistically, the elimination of free radicals is much more efficient as vitamin C is able to regenerate oxidized vitamin E into its reduced form. Furthermore, vitamin E possesses lipid-soluble properties allowing it to pass down via sebaceous gland secretions into the deepest layers of the stratum corneum to occupy cell membranes and provide protection from oxidative stress [44]. The effectiveness of this synergistic anti-aging process is proven as the topical use of 15% L-ascorbic acid with 1% alpha-tocopherol provides significantly more protection withstanding sunburn cell formation when compared to the use of either active ingredient alone [45]. Peptides are amino acids that structure the specific proteins necessary for the skin. Studies have shown that the ingestion of collagen peptides with other active compounds can rejuvenate skin and other damaged tissues. As peptides travel throughout the body, they will encounter sites with fibroblasts, stimulating them to produce more compounds like collagen, elastin, and hyaluronic acid. With long term use, there is noticeable improvement in skin elasticity and hydration leading to more youthful, firmer-looking skin [15].

Antiaging Cosmeceuticals

While active ingredients are proven to work, they are only as effective as how far they are going into the skin. Topical treatments are meant to reduce systematic exposure and the ingredients mainly only go as deep as the epidermis to address whatever issue must be solved. However, when creating products with the purpose of anti-aging the problem with topical presentation is getting enough of the active ingredient past the top layers of the skin and to the target tissue. The penetration of actives further into the skin or penetration to a specified layer of the skin can maximize the effectiveness of these active ingredients. Derma zone is a cosmeceutical company that integrates its nanotechnology platform and science to perform transformative skin care through more effective delivery of active compounds [46]. As a cosmeceutical company, beyond the transient appearance of skin enhancement Derma zone formulas contain pure and potent bio-active ingredients to provide in-depth penetration of the epidermis and make true changes to the biochemical processes to impact the mechanisms of aging. Derma zone technology provides innovative delivery and deeper penetration of these active ingredients and botanicals. Transdermal drugs describe a vast category of drugs that serve as vessels for delivering drugs for both local and systemic mechanisms [47].

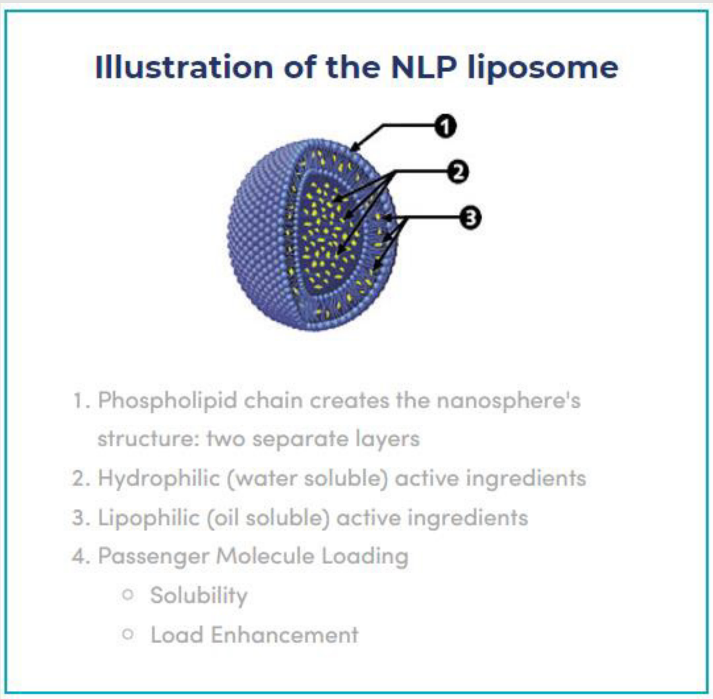


Figure 2.

True transdermal medication is the application of a drug through the skin with the intent to drive the compound into the bloodstream to promote systemic exposure across the skin. However instead of driving the active ingredients through the epidermal layer and into the bloodstream, Derma zone transdermal technology seeks to transport ingredients to the depths of the epidermis to depot there for a slow release rather than breaking into the dermis. At this layer, the capsule is broken to release the active compounds that are now free to interact with viable cells [48]. In the transportation of active compounds, Derma zone uses materials that are bioavailable to the skin to encapsulate the active ingredients in a lipophilic outer membrane that is able to efficiently penetrate the skin and be delivered to the target area. For this purpose, Derma zone has developed Nano-Lipidic Particle (NLP) nanotechnology to serve as transport. The process of making this patented NLP nanotechnology can be done in 3 phases. In Phase I, there is the development of an NLP precursor, to which water and ethanol are added to complete Phase II. Then in Phase III, the NLP liposome is completely formed with the addition of water and the active ingredient it is meant to transport (Figure 2) [49]. When fully formed, the NLP liposome will look like the illustration below. With this technology, Derma zone is able to encapsulate almost any compound. Not only are the ingredients to form NLP natural to biological organisms, it is also easily incorporated into existing processes of manufacturing and yields a more efficient and economic delivery of active ingredients. The only limitation is that the capsules are less than 200 nm, so compounds larger than a few thousand Dalton are unable to fit in the NLP liposome. Nonetheless, active ingredients such as acetyl hexapeptide-8, vitamin C, geranium maculatum oil, octanoate, and many others are able to be encapsulated and are used in the products sold through Derma zone's brands including Cleome®, Kara Vita®, and Hyssop Health® [50].

Conclusion

As the largest organ and a physical barrier between the internal human body and harmful microbes and chemicals, the skin plays an essential role as the body's first line of defense and in maintaining homeostasis among the many systems and biological mechanisms that keep us alive. Not only is it impacted by intrinsic factors that change as the aging process advances, but it must also bear the damage inflicted by years of exposure to unavoidable damaging external factors producing visible blemishes like wrinkles, age spots, and rough patches of skin. Furthermore, as people age the slowing of cell turnover rates and reduction in collagen production result in thinner skin with irregular depressions as the elastin-collagen network of fibers breaks down and loses its structural integrity. To combat these effects, both preventive and treatment measures can be undertaken to minimize the appearance of wrinkles. As vital metabolic reactions proceed within the body and UV radiation infiltrates from outside the body, reactive oxygen species are generated that have the ability to degrade biomolecules like DNA when produced in excess leading to oxidative stress. Preventive methods like consuming a healthy diet rich in antioxidants and minimizing sun exposure by covering up and the application of daily sunscreen can reduce the negative effects of excess ROS.

While reflective creams and cosmetic foundation can be used to hide the perception of aging externally, minimally invasive cosmetic treatments like Botox, dermal fillers, and platelet-rich plasma each work in unique ways to lessen the appearance of wrinkles internally [51]. Even more effective in treating aging skin is the use of drugs that are capable of affecting the behavior of cells and processes within the body to reverse aging at a cellular level which manifests in a physical form of more pliable skin, better barrier integrity, and reduction of fine lines. Such compounds include retinoids, vitamins, and peptides. To be effective defenses against skin aging at a cellular level, these compounds must first be able to penetrate the living and nonliving layers of skin to interact with target molecules and processes. To move further than topical treatment, transdermal drugs like the NLP liposome, can be utilized to transport active ingredients and aid in deeper penetration for higher efficacy in reducing the effects of the aging processes.

Future Trends

The maintenance of cellular health is coordinated by gene-regulatory pathways and a number of cell biological processes. It was once thought that aging is an inevitable process and the natural result of entropy on the cells, tissues, and organs of the body, bringing about the gradual decline of many bodily functions [52] Now, rather than seeing aging as a process of life, scientists are beginning to view physical aging as a disease process. Both the cellular and molecular mechanisms by which aging occurs reveal intricate series of signals and pathways that are responsible for the monitoring and control of lifespan of a cell as it ages. This information reveals that the breakdown of cellular processes is in fact the result of a programmatic decision by the cell to either continue or discontinue maintenance procedures with age. As a result, it only makes sense that cellular reprogramming can be used to reverse the aging leading to the decline in activities and function of mesenchymal stem/stromal cells (MSCs). Through the in-depth studying of these molecular events and pathways, the science of antiaging will be furthered and come another step closer to reversing the aging process. In fact, Dr. Wan-Ju Li is the lead of one such study. When comparing non-rejuvenated parental MSCs to reprogrammed MSCs, scientists were able to recognize the GATA6/SHH/FOXP1 pathway as a key mechanism in the regulation of MSC aging and rejuvenation [53]. The continuation of identifying the underlying mechanisms controlling cell aging-related activities will help improve understanding of the causes of aging and play significant roles in the future of regenerative medicine.

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