



Introduction

Chemical peels have long been a key cosmetic practice to

improve the appearance of skin, especially on the face and neck. The American Society for Dermatologic Surgery defines the process by which "a chemical solution is applied to the skin that causes it to exfoliate and eventually peel off. The new, regenerated skin is usually smoother and less wrinkled than the old skin" [1]. Chemical peeling, sometimes known as chemical exfoliation, is an essential treatment that can promote cellular regeneration and improve skin health and appearance while avoiding the potential irritation caused by the debriding of skin cells through physical processes such as mechanical exfoliation.

Glycolic acid is a renowned active ingredient in skin care, utilized in a wide variety of dermal cosmetic applications and well-suited for use within chemical peels. Glycolic acid is a naturally-occurring α -hydroxy acid prized for its ability to effectively exfoliate skin though reactions with the epidermis. Reactions between glycolic acid and human skin remove the damaged or worn outer layers of the skin and expose the healthier, more vibrant skin cells beneath. As the smallest and simplest of the α -hydroxy acids, glycolic acid molecules are highly effective in penetrating between cells on the skin surface and chemically exfoliating the outermost layer of skin, or stratum corneum.

While the effectiveness of glycolic acid as a cosmetic chemical exfoliator is well-known and appreciated, in many cases the chemical and molecular mechanisms by which glycolic acid enhances the quality and health of human skin have not been fully elaborated.

Treatment with glycolic acid has shown to impart a number of benefits. In particular, research has shown that glycolic acid increases cellular turnover, increases skin smoothness and decreases levels of skin acne.



Increased Cellular Turnover

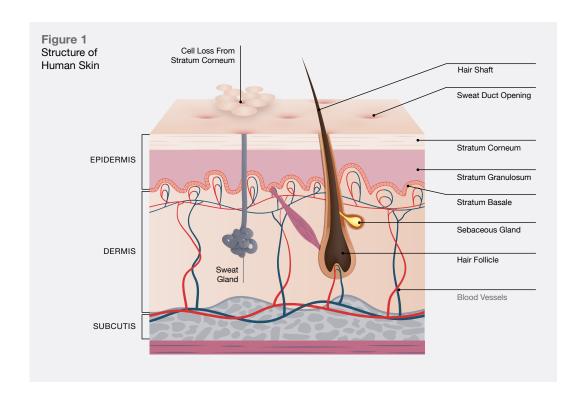
The Structure of Human Skin

Human skin, defined by the Encyclopedia Britannica as "the covering, or integument, of the body's surface that both provides protection and receives sensory stimuli from the external environment," is structured into three primary layers, the epidermis, dermis, and subcutis. As shown in Figure 1, these three layers interact to allow human skin to protect the rest of the human body, support itself, and self-replenish in response to aging or damage [2]. The **subcutis**, the deepest layer of the overall skin structures, is an adipose (fatty-tissue) layer below the dermis and above the skeleton. The subcutis primarily functions as "physical protection, as well as an energy reserve and source of insulation and thermal regulation" [3].

The **dermis**, meanwhile, is situated between the lowest layer, the subcutis, and the outermost layer, the epidermis. Composed of large quantities of connective tissues, the dermis comprises the bulk of the skin structure. The dermis also contains large quantities of blood vessels, though the structures of both the dermis and epidermis means that "[no blood] penetrates the living epidermis. The epidermis receives materials only by diffusion from below" [2]. Both the subcutis and the dermis provide nutrition and support to the epidermis, the outermost layer of the skin and the site of interactions between human skin and the environment.

The **epidermis** is the outermost layer of human skin and is primarily composed of two layers: the basal layer and an external layer composed of stratified squamous keratinized epithelium, or SSKE. Stratified squamous keratinized epithelium is an outer layer of epidermal cells exposed to regular physical abrasion. SSKE is composed of numerous layers of keratinized squamous cells specially structured to be waterproof, reduce evaporation from underlying tissues, and absorb physical abrasion from environmental factors [4]. In human skin, this outermost layer is typically known as the stratum corneum (SC).

In Expression of Corneodesmosin in the Granular Layer and Stratum Corneum of Normal and Diseased Epidermis, Haftek et al. detail how "Owing to its relative impermeability to water and water-soluble substances, the SC prevents the loss of physiological liquids. Its physical resistance combined with the constant renewal of the [stratum corneum] offer a screen against physical (e.g. ultraviolet radiation, rubbing), chemical (e.g. detergents, solvents, allergens) and biological (e.g. bacteria, fungi) aggressions" [5]. The human stratum corneum, as the outermost layer of the epidermis and the skin as a whole, comprises the visible portion of the skin and is the part of the skin that most directly interacts with most personal care products.



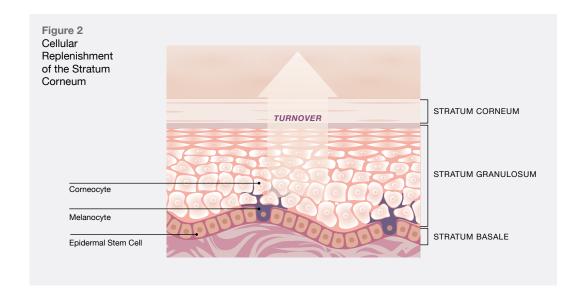
Natural Replenishment of the Stratum Corneum

The **stratum corneum**, as the external layer of human skin, is primarily composed of keratinized, non-living cells adapted to form the outer protective coating of the skin. This layer works to protect and shield the skin against physical damage. In *The Stratum Corneum:* Structure and Function in Health and Disease, Harding states that "the SC is essentially impermeable to water except for a small but vital flux that serves to maintain its hydration, and thereby, its flexibility" [6]. These cells are constantly faced with chemical and mechanical stresses that can damage and/or disrupt the structure of the stratum corneum layer. As such, the SC is perpetually undergoing des-

quamation, or the shedding of dead skin cells, to replace worn-out or degraded keratinocytes.

As stated by Harding, the SC is also key in regulating moisture loss where "Hydration of the surface layers is also critical to facilitate desquamation" [6]. Under normal circumstances, desquamation of the stratum corneum is offset by replenishment from keratinocytes (skin cells) that develop in the stratum basale, a lower layer within the epidermis (Figure 2). These keratinocytes differentiate into stratum corneum-specific corneocytes upon reaching their final destination as part of the stratum corneum layer.

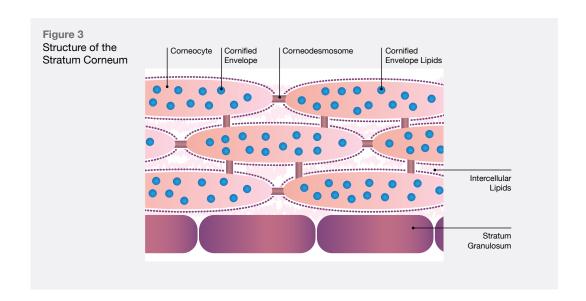
The **cornecytes** comprising the stratum corneum are embedded in an intercellular



matrix composed of a combination of ceramides, fatty acids, and cholesterol [7]. In [6], Harding states, "the overall integrity of the SC itself is achieved primarily through large numbers of specialized intercellular protein structures called corneodesmosomes, which effectively rivet neighboring corneocytes together both in the plane of the SC layer and in adjacent layers" [6]. This cell-matrix structure of the SC allows it to be degraded by proteases and slough naturally over time. As cells are shed from the stratum corneum, keratinocytes that have formed within the stratum basale migrate towards the skin surface and differentiate to replace lost SC corneccytes. Keratinocyte cells typically migrate through the epidermis towards the stratum corneum in a journey that of roughly fourteen days [8]. This process, however, is not uniform and can be affected by localized skin irritation or damage.

Properties of Carboxylic Acids

Carboxylic acids are a class of acids containing carboxyl groups and include α -hydroxy acids such as glycolic acid. Carboxylic acids are polar molecules containing hydrogen-bond acceptors (the carbonyl functional group) as well as hydrogen-bond donors (the hydroxyl functional group), and can therefore function in hydrogen bonding. These characteristics make carboxylic acids, including the α -hydroxy acids, well-suited for use in dermal cosmetic applications. In Alpha-hydroxyacids and carboxylic acids, Yu et al. states "[α -hydroxy acids] are organic hydroxyacids, a group of natural and physiological substances which can modulate skin keratinization and increase biosynthesis of dermal components" [11].



Molecular Interactions between Glycolic Acid and the Stratum Corneum

Glycolic acid is the smallest and simplest of the α -hydroxy acids, and its chemical and molecular properties allow it to interact with the stratum corneum and exfoliate keratinocytes in the epidermal layer. In Interaction Between Bovine Collagen and Glycolic Acid Peeling: A Proposal of a New Protocol, Sito and Sorrentino explains, "[glycolic acid's] action mechanism is concentration-dependent. At low concentrations (5-10%), the keratocyte cohesion decreases and this interferes with the ionic bonding between corneocytes. The resulting thinning of the keratin strata allows greater penetration of the other substances and a fresher, more luminous appearance of the skin" [9]. The molecular geometry of glycolic acid, along with its size, facilitate the insertion of glycolic acid into the stratum corneum and

allow it to interact with molecular matrices within the SC, weakening corneocyte adhesion in the uppermost layers. This cohesion-oriented approach is supported by studies of structural adhesion in the SC, which implicate the corneodesmosome matrix as the primary intercellular adhesive structures within the stratum corneum. In *The stratum corneum: structure and function in health and disease*, Harding discusses how "Ultimately... it is the corneodesmosomal structures that represent the primary cohesive force and which must be degraded to facilitate desquamation" [6].

As illustrated in **Figure 3**, the application of glycolic acid to the stratum corneum thus weakens corneodesmosome cohesion by binding within the corneodesmosome matrix and preemptively disrupting normal corneocyte adhesion. As detailed by Babilas et al. in Cosmetic and Dermatologic Use of Alpha Hydroxy Acids, "AHAs induces desquamation,



sensitivity, physical abrasion, or chemical stress, to be uniformly shed and replaced with newer, healthier SC layers. This is confirmed in Functional Changes in Human Stratum Corneum Induced by Topical Glycolic Acid: Comparison with All-trans Retinoic Acid, where Effendy et al. state that glycolic acid "signifi-

cantly decreased stratum corneum turnover time" [12]. Thus, glycolic acid, in essence, streamlines the natural skin replenishment process by accelerating the rate at which corneocytes are shed, independent of non-universal factors such as localized damage.

Increased Skin Smoothness

Skin Wrinkling and Fatigue

The formation of wrinkles in human skin is a common symptom of damage related to skin ageing. In Interaction Between Bovine Collagen and Glycolic Acid Peeling: A Proposal of a New Protocol, skin ageing is described as "a physiological phenomenon which involves a number of etiopathic factors," where wrinkling of the skin is "caused by a decrease in the keratocyte turnover which in turn reduces the spontaneous, physiological desquamation" [9]. Wrinkling is also shown to be related to the level of collagen present within the skin, where due to "progressive atrophy of the collagen and elastic fiber bundles... the dermis becomes less elastic, the skin sags and is more prone to wrinkling" [9]. Wrinkling increases as the skin ages, where accumulating damage and fatigue to skin tissue leads to an increasing prevalency of skin wrinkles.

In Aging as a Consequence of Misrepair – A Novel Theory of Aging, Wang et al. further elaborate on the process by which wrinkling proliferates as skin ages. The authors claim that, when tissues are subjected to traumas, "damage drives the aging process by triggering Misrepair" [13]. As the human body responds to damage to the epidermis, repair and replenishment processes work to replace damaged collagen fibers, move new keratinocytes to the surface, and restore the original functionality of the skin. Wrinkling happens, however, when the original configuration of the damaged skin is not

restored. Naturally-occurring errors in the repair process replace damaged collagen fibers with incorrectly-sized replacements and damaged regions of the stratum corneum are replaced with misordered corneocytes. Such misrepairs decrease both the cosmetic appearance of the skin as well as the ability of the stratum corneum to protect against physical, chemical and biological damage [5]. Batisse et al. in Influence of age on the wrinkling capacities of skin describe how wrinkling that "appears progressively as a function of age could in fact be due to the presence of a rigid stratum corneum, the mechanical support of which (i.e. living epidermis/upper epidermis) is weakened by the gradual alteration of collagen bundles" [14]. Thus, a combination of accumulated damage to the skin alongside errors in the repair of both the stratum corneum and collagen fibers lead to the increasing prevalency of wrinkles in human skin as the body ages.

Smoothness via Exfoliation and Replenishment

As detailed in the analysis of increased cellular turnover, the stratum corneum is perpetually undergoing desquamation to replace damaged corneocytes. Research has shown that α -hydroxy acids, such as glycolic acid, are capable of mediating this process and stimulating replenishment of the outer epidermal layers. Applications of hydroxy acids: classification, mechanisms, and photoactivity describes how "topically applied HAs are capable of interact-

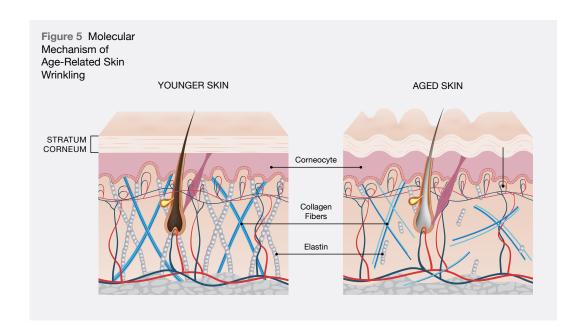
Figure 4 Number of Corneocyte Layers in the Stratum Corneum of Glycolic Acid— and Vehicle—Treated Skin

SUBJECT NO.	GLYCOLIC ACID	VEHICLE
1	17	17–18
2	18–20	24
3	18–20	17–19
4	21–22	20–22

ing with many basic biological processes that occur in mammalian skin... they can affect and modify the processes of cell proliferation, cytokine excretion, and induction of apoptosis and can act as antioxidant/chelators, influence the skin barrier function, and act as moisturizers" [15]. When applied topically to the skin, α-hydroxy acids can jump-start the cellular replacement process, bringing newly-formed layers of corneccytes to the surface of the SC. This process allowed improperly-aligned regions of the stratum corneum to be replaced by properly-structured tissue. Such replacement decreases the disruptions to skin texture caused by misordered cells and leads to increased smoothness of the epidermis.

Experiments conducted by Fartasch et al. in Mode of action of glycolic acid on human stratum corneum: ultrastructural and functional evaluation of the epidermal barrier further illustrate how the exfoliation of the stratum corneum leads to replacement of misordered stratum corneum layers without compromising the structural integrity of the stratum corneum as a protective barrier. In the test, "a 4% glycolic acid formulation (pH 3.8) or the vehicle formulation as a cosmetic lotion were applied

to the volar forearm twice daily for three weeks," with a goal of the test being an analysis of the skin post application to determine "which structural entities in the SC are targets for the action of AHA" [16]. The experiment found that desmosome breakdown and loss of cohesion was localized to the stratum disjunctum, defined up the outermost layers of the SC. This supports experimental data (Figure 4) collected by Yu and Van Scott in [11], which confirm that, in contrast to topical salicylic acid formulations, which are shown to decrease overall skin thickness, "AHAs... on topical application can modulate keratinization and stimulate biosynthesis... leading to increased skin thickness, which can be measured by micrometer callipers and also determined by histological analysis" [11]. The authors of [16] also noted that "in clinically normal skin, the effects of $[\alpha$ -hydroxy acids] (at the low concentration tested) is to smooth the skin surface by removing the randomly retained squames of the stratum disjunctum," with disruption of the stratum corneum and the epidermis limited to the outermost layers, preserving the integrity of the SC as a whole [16].



Smoothness via Collagen Production

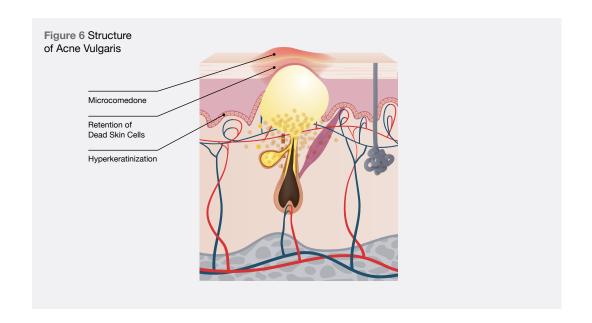
Glycolic acid has also been shown to decrease wrinkling and increase skin smoothness by stimulating the production of collagen. Sito and Sorrentino note that as the skin ages, there is atrophy of collagen bundles accompanied by disruptions to the typical spatial orientation of such bundles [9]. As depicted in Figure 5, decreases in collagen levels within the skin, as well as replacement of damaged collagen fibers with incorrectly-sized or oriented replacements, can lead to losses of the rigidity and structural stability typically provided by collagen to the skin. In an experiment conducted by Batisse et al. in Influence of age on the wrinkling capacities of skin, a study of skin wrinkling was conducted. In the test, regions of skin on test subjects were analyzed in order to measure the

width of skin folds. Subsequently, ultrasound imaging was used to delineate between various skin layers, with mathematical scores being assigned representing the amount of wrinkling as a function of age. In the analysis, Batisse et al. noted that "the upper dermis of elderly subjects is more transparent to ultrasound waves than that of young subjects, which could be explained by recent data indicating that, in elderly skin, exposed to sunlight, regular and relatively isotropic bands of collagen are replaced by randomly orientated fine fibers" [14]. Together, decreases in collagen levels coupled with misrepair of damaged collagen strands further exacerbate wrinkling of skin by compromising the structural and functional ability of collagen within the skin.

Topical application of α -hydroxy acids, and glycolic acid in particular, has been experimen-

tally shown to encourage increased production of collagen. In Cosmetic and dermatologic use of alpha hydroxy acids, it is noted that in prior testing, treatment of skin samples with α -hydroxy acids led to "improved quality of elastic fibers, and increased density of collagen according to their results" [10]. This is supported by observations made in Alphahydroxyacids and carboxylic acids, where the authors note that when applied to the skin, α-hydroxy acids can increase the production within the skin of glycosaminoglycans (GAGs), including hyaluronic acid and collagen fibres, resulting in increased skin thickness [11]. Research has shown that increased production of glycosaminoglycans is a key indicator of heightened levels of collagen synthesis. In Glycolic Acid Treatment Increases Type I Collagen mRNA and Hyaluronic Acid Content of Human Skin, Bernstein et al. state that "although GAGs make up only about 0.1-0.3% of the dry weight of normal dermis, they can bind up to 1000 times their weight in water. Thus, relatively small alterations in the amount of dermal GAGs may result in large changes in epidermal and dermal hydration" [17]. The authors go on to further state that increased GAG expression results in the creation of a larger and more stable matrix, composed primarily of collagen, for the replenishment and repair of skin. These sources indicate that treatment with glycolic acid leads to increased production of collagen in the skin by amplifying the expression of glycosaminoglycans.

In [15], the authors state that "glycolic acid not only directly accelerates collagen synthesis by fibroblasts, but that it also modulates matrix degradation and collagen synthesis through keratinocyte-released cytokines" [15]. As alvolic acid molecules bond with the corneodesmosome structure of the stratum corneum and exfoliate the outer SC layers, the skin releases immunological signals to stimulate the creation of new keratinocytes and collagen matrices. This generalized immune response creates new stratum corneum layers and leads to greater production of collagen, lessening wrinkles. In Interaction Between Bovine Collagen and Glycolic Acid Peeling: A Proposal of a New Protocol, the process is described as "a bland inflammatory reaction in the dermis" that "stimulates new collagen and elastic fiber synthesis, new synthesis of glycosaminoglycans and neovascularisation" [9]. The bonding of glycolic acid molecules into the outer stratum corneum layers signals the synthesis of increased amounts of GAGs in response to microscopic "damage" (the exfoliation of the stratum disjunctum) and induces overexpression of collagen as a means to repair the lost layers of the epidermis. This overexpression of collagen subsequently replaces and restores damaged or absent collagen in the epidermis.



Decreased Skin Acne

Dermal Nature of Acne

Acne, also known as acne vulgaris, is a common skin condition characterized by inflammation and blocked skin pores. Acne vulgaris is caused by a combination of heredity genetic factors, hormones, and bacterial deposits on the skin. A key component in the development of acne is hyperkeratinization, a disorder of the skin cells surrounding follicles and pores (Figure 6). An increased production of sebum, or skin oils, lead to dead skin cells sticking together and clogging the pore. This results in the formation of a blockage, referred to as the microcomedone. In Emerging Drugs for the Treatment of Acne, Aslam et al. describe hyperkeratinization as one of the primary causes of acne vulgaris as it is "directly responsible for initiating microcomedone formation" [18]. The authors explain that "the bacteria P. acnes... can enter the clogged pore and start multiplying rapidly. This consequently triggers an inflammatory response by the surrounding skin" resulting in pustules and irritation that characterizes skin suffering from acne [18].

Treating Acne via Exfoliation

The abnormal buildup of keratinocytes on the skin surface during acne vulgaris, one of the root causes of the skin disorder, offers a key way by which acne vulgaris can be treated. In *Alpha-hydroxyacids and carboxylic acids*, the authors state that "Since acne lesions initially involve retention of follicular corneocytes, $[\alpha-hydroxy\ acids]$ can be therapeutically effec-

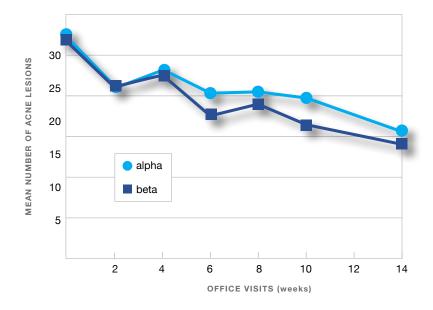
tive for topical treatment of acne" [11]. The well-documented ability of α -hydroxy acid, including glycolic acid, to weaken keratinocyte adhesion offers a promising avenue for acne prevention and treatment. Kessler et al, in Comparison of α - and β -Hydroxy Acid Chemical Peels in the Treatment of Mild to Moderately Severe Facial Acne Vulgaris, describe how "Superficial chemical peels are frequently performed as adjuvants for the treatment of facial acne" [19]. As acne vulgaris typically involves blockages within the upper layers of the skin, treatments that loosen the outermost layers of the skin can combat acne by freeing the blockages that lead to microcomedones. Glycolic acid, as a commonly-used active ingredient in desquamation formulations, is ideally suited to treat acne vulgaris, with Kessler et al. stating that "This desquamation reduces corneocyte cohesion, keratinocyte plugging, and enables the extrusion of inflammatory contents. This process helps to prevent further comedone formation" [19].

Treatment of acne vulgaris via glycolic acid relies on the principles by which glycolic acid induces exfoliation of the top layers of the stratum corneum. In *Glycolic Acid and its Use in Dermatology*, the authors relate how, "Lower concentrations of glycolic acid cause a reduction of cohesion of follicular corneocytes... The use of glycolic acid 50% or 70% solutions, repeated weekly or every two weeks has demonstrated a substantial improvement in patients affected by comedonic and papulo-pustolar forms of acne" [20]. Glycolic acid interacts ionically with extracellular matrix structures adhering deposited corneocytes together, weakening the forces holding follicle

and pore blockages closed allowing for more effective cleansing of the skin surface. Babilas et al. further describe how the "keratolytic effects suggested the use of AHAs for acne or acne-prone skin as well as for peelings. The higher the concentration of the acid and the lower the pH of the product, the faster keratolysis is induced" [10]. The ability of α -hydroxy acid to bond with the stratum corneum and induce peeling of the outermost layers, coupled with glycolic acid's status as the smallest and simplest of the α -hydroxy acid, make it an ideal candidate for use in the treatment of acne vulgaris.

Glycolic acid's effectiveness in the treatment of acne vulgaris has been demonstrated through testing by Kessler et al. (Figure 7) in Comparison of α - and β -Hydroxy Acid Chemical Peels in the Treatment of Mild to Moderately Severe Facial Acne Vulgaris. In this article, the authors conducted a test in which an α -hydroxy acid, glycolic acid, was compared to a β -hydroxy acid, salicylic acid. In this experiment, "the efficacy of α -hydroxy acid and β -hydroxy acid peels in the treatment of mild to moderately severe facial acne vulgaris" was compared [19]. The experiment assigned subjects testing sites for both the glycolic and salicylic acid samples, with "one side of the face to receive the 30% glycolic acid... peel and the contralateral side to receive the 30% salicylic acid" [19]. The test showed that both the glycolic and salicylic acid peels were successful in significantly decreasing the number of patients' acne lesions by the second treatment. Additionally. patients demonstrated continued reduction in acne lesions through the first month of follow-up after the treatment period. Kessler et al.

Figure 7 Skin Acne Lesions After Chemical Peel Treatments



performed an independent groups t-test to statistically verify the collected data. This test confirmed similar performances by the two chemical peels from subject baseline through the 1-month follow-up. This analysis verifies that " α - and β -hydroxy acid peels were similarly effective against acne lesions," while demonstrating the validity of glycolic acid as an effective topical acne vulgaris treatment via exfoliation [19]. The authors discerned that "Patients noted a greater degree of desquamation associated with the glycolic acid peel compared with the salicylic acid peel in their self-assessments" [19]. This observation substantiates the chemical and molecular effectiveness of glycolic acid treatments for acne vulgaris via decreased corneocyte cohesion and greater penetration of the other substances through skin surface deposits. {4}

Preventing Acne via Exfoliation

While glycolic acid has shown to be effective in treating acne by loosening skin-surface keratinocytes and freeing microcomedone deposits, the exfoliating properties of the α -hydroxy acid and in particular glycolic acid make it a convenient preventative measure against acne vulgaris as well. Cotellessa et al. state in Glycolic Acid and its Use in Dermatology that, "Low concentrations of glycolic acid produce diminished cornecyte cohesion and subsequent prevention of stratum corneum thickening" where at the same time, "the daily use of low concentrations [of glycolic acid] can help to prevent the re-occluding of follicles" [20]. Regular treatment of acne-prone skin with glycolic acid formulations can be effective in encouraging a consistent turnover of stratum corneum cells, mitigating hyperkeratinization and expediting the desquamation of excess corneccytes that would otherwise be retained and cause pore and follicle blockages.



Conclusion

In this study, an explanation of the chemical and mechanical effects of glycolic acid on human skin has been developed through a comprehensive analysis of available research. Glycolic acid has long been recognized as a naturally-occurring effective chemical exfoliator, and has commonly been used in skin care formulations within the personal care industries. In general, however, results from a wide array of scientific data have not been incorporated into a holistic picture of the molecular mechanisms for the benefits glycolic acid seen in skin care applications.

This study has shown that interactions on a molecular level between human skin stratum corneum and glycolic acid is crucial in understanding the health benefits of glycolic acid topical treatments. The three-dimensional orientation of molecular matrices in the stratum corneum and the chemical composition of the corneodesmosome complex are well-suited to bond with glycolic acid. Research has demonstrated that glycolic acid's small size and relative stability, along with its bonding capabilities, allow it to enter the stratum corneum, ionically-bond with and loosen the matrix holding the outer-layer corneccytes in place. This allows the outer layers of the stratum corneum to be uniformly shed in a controlled manner and replaced with newer and healthier skin cell layers. When exposed to damage from ageing or the environment, the stratum corneum can become fatigued, disrupted, or damaged. Glycolic acid's ability to induce repair of the stratum corneum through corneocyte

matrix bonding is evidence of its efficacy as a skin therapy within personal care. Additionally, the small size of the glycolic acid molecule when compared to other α -hydroxy and carboxylic acids permit more effective penetration of the stratum corneum, leading to more comprehensive and total skin exfoliation.

Overall, it can be seen that the molecular nature of glycolic acid gives it singular effectiveness in the treatment and replenishment of human skin health. Improvements in characteristics of the skin such as increased cellular turnover, increased skin smoothness, and decreased levels of skin acne can all be obtained through the use of glycolic acid treatments. The data analyzed in this study shows that the chemical effects from the addition of glycolic acid to skin care products provide benefits to both healthy and damaged skin.

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