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HealFast

HealFast Skin Health

Rejuvination and Regeneration

Scientific Review

INTRODUCTION

Skin is the largest organ in a human body. Adults carry an average of 8 pounds (3.6 kilograms) and 22 square feet (2 square meters) of it. As an organ - skin is complex, containing almost 500 genes and an elevated pattern of expression in the skin. Unlike most other organs, skin is exposed to the outside world, maintains homeostasis, and acts like a wall and a defense against the outside world.

To accomplish these tasks, skin has a multifaceted barrier system which comprises of the stratum corneum, tight junctions, the microbiome, the chemical barrier, and the immunological barrier. For a substance to be absorbed through the skin it must first bypass these barriers along with the skin's 7 layers.

For generations, topical applications such as skin creams have been applied for the maintenance and improvement of skin health, however the absorption and utility of many of these interventions have been questioned.

Current studies show that skin health is often a reflection of overall health, environmental factors, and stress. Many metabolic and internal factors affect the skin, and novel scientific research is emerging to characterize how skin can be optimized for regeneration and rejuvenation through internal metabolic mechanisms. This trend in maintaining skin health is dubbed "Beauty From Within"; i.e., the notion that in order to truly deliver nourishment and factors for skin health, one must optimize their overall metabolism and physiology. Since skin regenerates itself approximately every 27 days, a focus on the importance of nourishing this organ with orally absorbed and bioavailable ingredients should be held in order to maintain the health and vitality of skin.

This white paper will review, generally, skin structure and function, the concept of "Beauty from Within" (BFW), and delve into the most evidence based orally-consumed bioavailable ingredients that have been shown to improve skin structure, function, and regenerative ability. We will also highlight some of the results that have been achieved using these interventions.

BACKGROUND

Generally, in order to understand how to improve skin and it's appearance, one must understand the basics of skin structure and function.

1. SKIN STRUCTURE

Skin is composed of 3 main layers.

1. Epidermis: The outer layer. The epidermis is the thinnest layer and is responsible for protecting the body from the harsh outside environment. It contains 5 layers and hosts different types of cells including:

- Keratinocytes: produces keratin and extracellular matrix, the main component of the epidermis that protects the skin and provides skin texture and structure
- Melanocytes: provides melanin, a skin pigment
- Langerhans cells: prevent particles from getting into your skin.

2. Dermis: The middle layer. The dermis layers provides the skin with fullness and plumpness. Age and the sun can damage the dermis and lead to wrinkles. The dermis is a complex layer, containing blood vessels, hair follicles, sebaceous (oil) glands, as well as extracellular matrix.

One of the main synthetic cells located in this layer are fibroblasts. These cells manufacture collagen, elastin, heparan sulfate and hyaluronic acid which play key roles in the health and appearance of your skin. As your skin ages, the number of functional fibroblast cells begins to decline, and the remaining cells typically slow down production of collagen, hyaluronic acid and heparan sulfate.

These changes typically lead to skin thinning, fragility, fine lines, wrinkles, easy bruising and sagging of skin.

Many topically applied skin creams attempt to address these changes but do not penetrate down into this layer. External stem cells, peptides, hyaluronic acid and other ingredients applied topically do not penetrate down into the dermal skin layer.

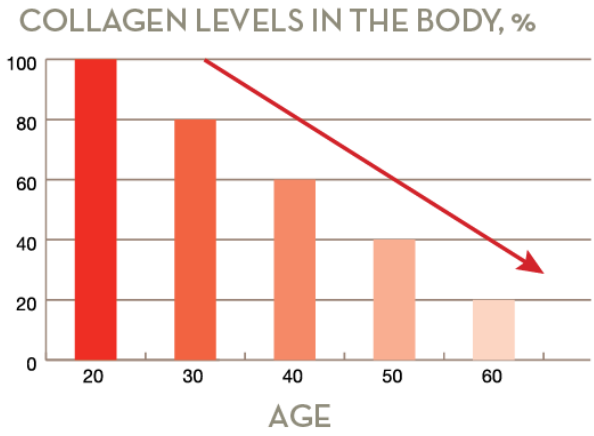
3. Hypodermis: The fatty layer. This layer is also known as the subcutis. It hosts sweat glands and fat and collagen cells, and is responsible for conserving your body's heat and protecting vital inner organs. Reduction of tissue in this layer contributes to sagging skin.

2. SKIN MATRIX – KEY COMPONENTS

In these three layers, there are several cellular components that maintain skin structure. These components reside in the extracellular matrix. Extracellular matrix (ECM) is a three-dimensional network of extracellular macromolecules, such as collagen, enzymes, and glycoproteins, keratin, elastin, and hyaluronic acid that provide structural and biochemical support of surrounding cells.

The main four to know understand further are collagen, elastin, keratin, and hyaluronic acid.

- **Collagen:** Collagen is the main structural protein in the extracellular space in the various connective tissues including skin. As the main component of connective tissue, it is the most abundant protein in mammals, making 25% to 35% of the whole-body protein content and over 80% of dry skin weight.

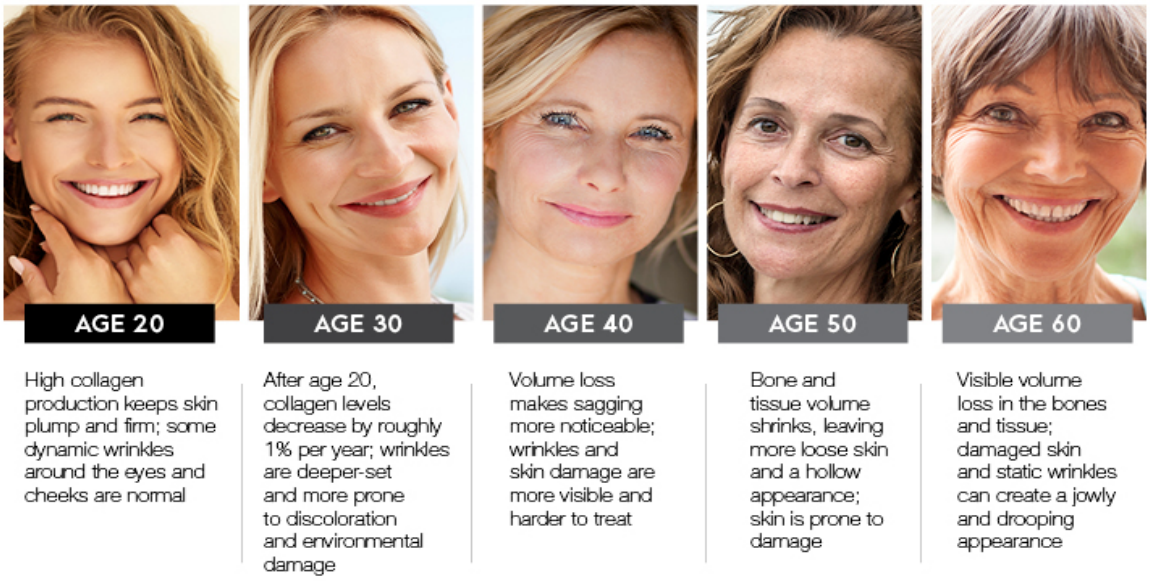


There are many types of collagen, but over 90% of the collagen in the human body, is type I collagen. It is the substance that holds the body together. Collagen forms a scaffold to provide strength and structure. In fact, some types of collagen fibrils, gram-for-gram, are stronger than steel. Collagen production declines with age and exposure to factors such as smoking and UV light. Collagen as a molecule is very large, and does not penetrate the skin from the outside.

- **Elastin:** Elastin is the component of the skin responsible for elasticity or bounce back of the skin. Skin sags when elastin levels go down in the skin. After puberty, the skin begins to produce less and less elastin, which is why older skin is not as supple and elastic as younger skin. Elastin is formed as a precursor called tropoelastin which then must be modified by the cell to form mature elastin which is complexed with other elastin fibers.

- **Hyaluronic acid:** Hyaluronic acid (HA) is a specific type of sugar that is naturally present in skin. It has the ability to bind to and retain up to 1,000 times its weight in water molecules. It plumps the skin and gives it volume. Although widely available, formulations of topical hyaluronic acid do not actually penetrate into the skin because the molecule is too large.

- **Keratin:** Keratins are the major structural proteins of the vertebrate epidermis. Keratin confers rigidity of skin and helps with the barrier protection that your skin offers. Together with actin microfilaments and microtubules, keratin filaments make up the cytoskeletons of epithelial cells.
  These filaments impart mechanical strength to a keratinocyte, without which the cell becomes fragile and prone to rupturing upon physical stress. In additional to skin, Keratins are also found in high concentrations in hair shafts, cuticles, and nails



BEAUTY FROM WITHIN

As apparent from the structure and function of the skin, the skin is an incredibly complex organ. One of the main functions of this organ is one of a barrier from the outside world. Components of the skin, hair, and nails are synthesized by our bodies, using substrate that we ingest through our gastrointestinal tract.

Although creams can confer some benefit, the skin is not able to absorb the nutrients this organ requires to maintain and regenerate its appearance and function.

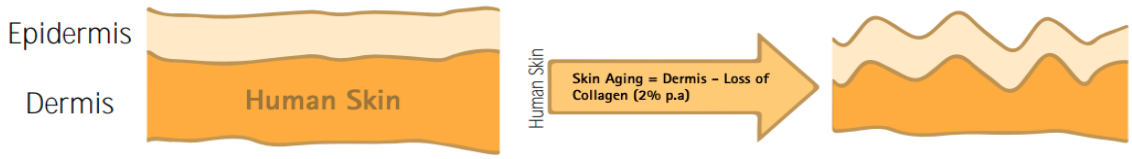
Evolving scientific studies have depicted that in order to effectively regenerate and support skin as an organ, nutrients must be taken orally and metabolized.

Below we will review some of the known skin repair mechanisms and detail the level of evidence for various orally-taken ingredients.

1. COLLAGEN

Collagen, as reviewed above, is the main structural protein of the connective tissue including skin. In fact, it comprises about 80 % of its dry weight. Collagen production declines with age and exposure to factors such as smoking and UV light.

Specific peptides contained in the HEALFAST formulation, VERISOL (described below), have been shown to improve skin elasticity, reduce fine lines, wrinkles, maintain skin tone, and support skin healing after surgery and injury in a little as 4 weeks.



1.1 ABSORPTION, BIOAVAILABILITY, AND MECHANISM OF ACTION

Collagen as a molecule is very large and is not absorbed topically. In it's intact large form it is not absorbed by the gastrointestinal either; thus collagen needs to be broken down into smaller components by a process known as enzymatic hydrolysis.

Studies show that, hydrolyzed collagen, on the other hand, has a 90% rate of digestion/absorption and is available in the bloodstream within an hour. Collagen is absorbed in two ways, one via dipeptides and tripeptides, and also intact hydrolyzed amino acid peptide (up to 30 amino acids). From the bloodstream, these peptides are transported to tissue including skin, bones, and cartilage. (1-7).

Once in the bloodstream, collagen peptides act via a dual mechanism in the skin. First, they stimulate fibroblasts via integrilin and other receptors to produce more collagen and extracellular matrix (8) and they provide the ideal mixture of amino acids as building blocks for collagen production (8).

However, not all collagen is created equal. The process and result of the hydrolysis and enzymatic breakdown of collagen influences the bioavailability and stimulatory effect of the resulting peptide. Depending on the process used, molecular weight, amino acid composition and sequence play a role in bioavailability and ability to provide a stimulatory effect on the fibroblasts.

To date, the most effectively studied peptide is VERISOL, which contains a unique peptide profile, average molecular weight 2kDa. This unique collagen peptide has been shown to have the highest effect in triggering extracellular matrix formation (collagen and proteoglycans) than other collagen peptides of very similar specification. (9) These bioactive peptides also have been found to have increased affinity towards connective-tissue cells, higher than individual amino acids (19)

Summary Key Points on HEALFAST VERISOL Collagen

- Bioactive Collagen Peptides® are polypeptides of unique shape and amino acid composition that are absorbed in intact form, to some extent.

- The rare single helical structure of Bioactive Collagen Peptides®, formed by frequent Proline–Hydroxyproline–Glycine repeats, provides the favorable folding and stability that facilitate gut permeability.

- Bioactive Collagen Peptides® are remarkably rich in the amino acid Proline (1⁄4) and it is known that Proline forms strong peptide bonds that are more resistant to be broken down by digestive enzymes.

- The true digestibility of Bioactive Collagen Peptides® is very high (98.4%) (18). Amino acids are important products of peptide digestion, as they are the protein building blocks of new connective tissue. Approximately 10% of the Bioactive Collagen Peptides® stay intact during digestion (good bioavailability) and have a direct stimulatory impact on cell metabolism.

Verisol is acquired by an enzymatic hydrolysis process to produce Bioactive Collagen Peptides® from the parent collagen protein. The process is similar to human digestion, however it is much more specific and consistently produces precise bioactive sequences that have been shown to have the most stimulatory effect by in-vivo and in-vitro studies.

The results of a series of preclinical trials performed by manufacturer GELITA have demonstrated that minimal differences in peptide molecular weight and structure ultimately have major effects on the efficacy of Bioactive Collagen Peptides®

Although gut digestion can break down collagen into peptides, the digestion is random and does not always cleave the collagen protein into the desired active sequences (10-12).

The absorption of HEALFAST VERISOL is confirmed by a number of studies *in-vivo* tested the concept that small, but physiologically significant quantities of polypeptides, ranging in chain length from 3 to 51 amino acids, or even small proteins of nearly 200 amino acids, can be absorbed intact through the adult gut and produce biologic effects at the tissue level. (13-14)

Specifically Bioactive Collagen Peptides® (BCP) HEALFAST VERISOL are resistant to gastrointestinal degradation due to high levels of Proline-Hydroxyproline-Glycine repeats in collagen gives BCPs a functional shape and resistance to hydrolysis, so that BCPs do not encounter the same permeability issues as the broader class of nutritional polypeptides.

Interestingly, polypeptides that survive hydrolysis in the gut are usually those that are high in the amino acid Proline. Proline and Hydroxyproline represent 1⁄4 of all the amino acids in collagen peptides, a remarkably high proportion not seen in any other protein source. (15)

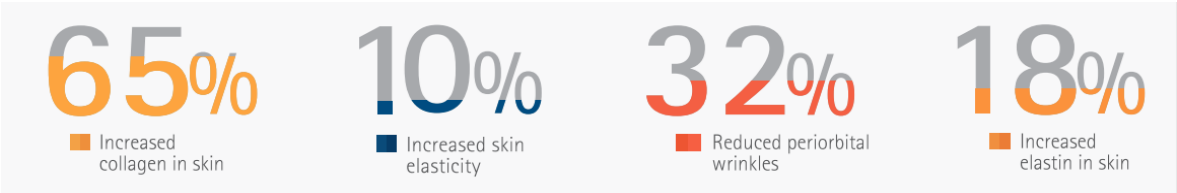
In fact, in the pharmaceutical industry, for example, the new generation of “Cell-Penetrating Peptides” – called the ‘triple helical’ CPPs – are mimicking the native collagen folding in their structure for improved stability against

enzymatic breakdown and for a safer and more efficient route for delivery of active substances across the intestinal barrier (16).

1.2 CLINICAL EFFICACY

Collagen as an oral ingredient has been scrutinized by the scientific community. Largely this has been the case since little standardization has been seen between the studies and individual peptides were not tested (with except of herein mentioned VERISOL peptides). Additionally different peptides with different molecular weights and compositions have been used.

At HealFast, we decided to focus on a single peptide, VERISOL, since it has the most scientific merit out of all collagen peptides studied. **Please note:** the results included herein may not apply to all collagen peptides, they are specific to VERISOL Bioactive Collagen Peptides®, administered at 2.5g per day, for a minimum of 4 weeks.



In a first study, a 114 women aged 45–65 years were randomized to receive 2.5 g of BCP or placebo, once daily for 8 weeks, with 57 subjects being allocated to each treatment group. Skin wrinkles were objectively measured in all subjects, before starting the treatment, after 4 and 8 weeks as well as 4 weeks after the last intake (4-week regression phase). (20)

The ingestion of the specific BCP used in this study promoted a statistically significant reduction of eye wrinkle volume ($p < 0.05$) in comparison to the placebo group after 4 and 8 weeks. Moreover a positive long-lasting effect was observed 4 weeks after the last BCP administration ($p < 0.05$).

Additionally, after 8 weeks of intake a statistically significantly higher content of procollagen type I (65%) and elastin (18%) in the BCP-treated volunteers compared to the placebo-treated patients was detected.

In another study, double-blind, placebo-controlled trial, 69 women aged 35–55 years were randomized to receive 2.5 g or 5.0 g of CH or placebo once daily for 8 weeks, with 23 subjects being allocated to each treatment group found skin elasticity in both dosage groups showed a statistically significant improvement in comparison to placebo. After 4 weeks of follow-up treatment, a statistically significantly higher skin elasticity level was depicted. (21)

Further BCP have been shown to reduce cellulite. A double-blind, placebo-controlled clinical study, 105 women aged 24–50 years with moderate cellulite were randomized to orally receive a daily dosage of 2.5 g BCP or a placebo over 6 months. In addition, skin waviness, dermal density, and the length of subcutaneous borderline were assessed. BCP treatment led to a statistically significant decrease in the degree of cellulite and a reduced skin waviness on thighs ($P < 0.05$). Moreover, dermal density was significantly improved ($P < 0.05$) compared to placebo. (22)

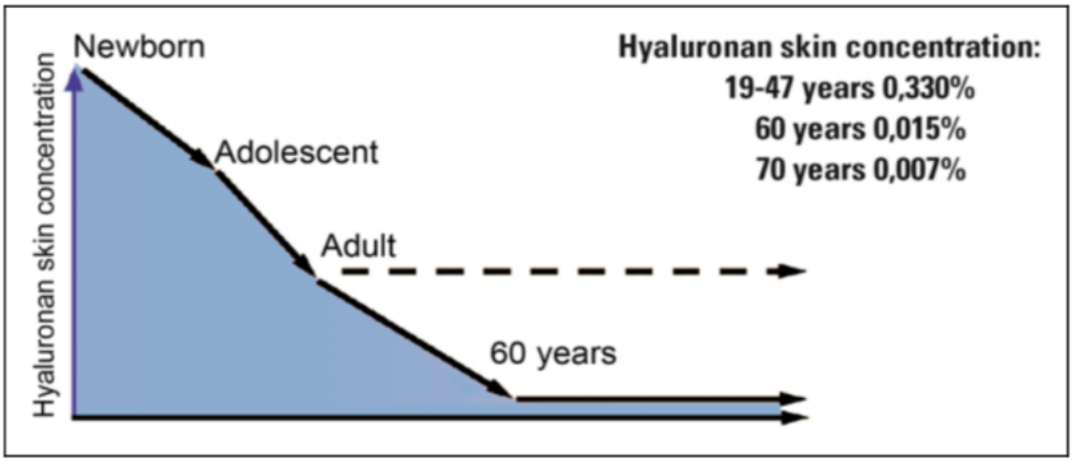
The Bioactive Collagen Peptides of VERISOL® has also been shown to improve growth and health of fingernails, which showed a decrease in cracked and/or chipped nails after 2 months of treatment, reaching a decrease of 42% after 6 months. Compared to the control group, the nail growth speed is increased, and at the same time, there was a notable improvement in nail peeling and a clearly decreased nail edge irregularity. 80% of the patients were completely satisfied and satisfied with VERISOL® treatment. 75% of the women perceive their nails as longer, 71% said their nails grew faster and became longer.

2. HYALURONIC ACID

Hyaluronic acid (HA) is a high-molecular-weight polysaccharide composed of repeated polymeric disaccharides of D-glucuronic acid and N-acetyl-D-glucosamine.(23) HA is a major component of the extracellular matrix of the skin and plays a key role in the metabolism of the dermis. It is one of the most hydrophilic molecules in nature and has been described as nature´s moisturizer. (23, 24)

2.1 CLINICAL EFFICACY

With aging, the epidermal HA content decreases from 0.03% in women aged 19 to 47 years down to 0.015% in women aged 60 years and halves to 0.007% in women aged 70 years. (25)



One trial tested HAs with 2 different molecular weights improved the skin condition by increasing the moisture content in Japanese women aged 35 to 60 years, who complained about dry and sagging skin or wrinkles around the outer canthus. (26)

Another study, tested twenty female subjects with healthy skin in the age group of 45 to 60 years who took the product once daily for 40 days and found that intake of the HA solution led to a significant increase in skin elasticity, skin hydration, and to a significant decrease in skin roughness and wrinkle depths. (27) increase in skin hydration was up to 37%, elasticity gained was up to 26%, skin roughness decreased by up to 30%, reduction of wrinkle depths was up to 37%. Participants also noted stronger hair and nails as a part of the study and 70% of patients would recommend the HA supplementation.

These findings have been echoed by multiple other studies depicted in the table below:

Test method	Test design	Substance	Subjects	Results	References
Oral consumption of HA at 240 mg daily for 6 weeks	Randomized, double-blind, placebo-controlled trial	HA (M.W.: 80 K)	22 patients with dry skin (in Japan)	Improved dry skin on the face and whole body Significant increase of skin moisture	Kajimoto, O. *et al.* (2001) [15]
Oral consumption of HA at 120 mg daily for 4 weeks	Randomized, double-blind, placebo-controlled trial	HA (M.W.: 80 K)	35 patients with dry skin (in Japan)	Significant increase of skin moisture	Sato, T. *et al.* (2002) [16]
Oral consumption of HA at 120 mg daily for 6 weeks	Randomized, double-blind, placebo-controlled trial	HA (M.W.: 80 K)	39 female patients with dry skin (in Japan)	Significant increase of skin moisture	Sato, T. *et al.* (2007) [17]
Oral consumption of HA at 120 mg daily for 6 weeks	Randomized, double-blind, placebo-controlled trial	HA (M.W.: 30 K)	42 female patients with dry skin (in Japan)	Significant increase of skin moisture	Yoshida, T. *et al.* (2009) [18]
Oral consumption of HA at 37.52 mg daily for 30 days	Randomized, single-blind, placebo-controlled trial	Mixture containing HA (M.W. of HA: 2,500)	107 healthy subjects (in China)	Significant increase in skin moisture Significant increase in skin pH	Terashita, T. *et al.* (2011) [19]
Oral consumption of HA at 100 mg daily for 12 weeks	Prospective open-label trial	Mixture containing HA(M.W.: unknown)	26 healthy female subjects (Caucasian, African-American, Hispanic, and others)	Improved aging symptoms on the face	Schwartz, S. R. *et al.* (2012) [20]

2.2 ABSORPTION

In regards to HA absorption: In the oral administration test of radioactively labeled, high MW HA (MW: 1 × 106), approximately 90% of ingested HA was absorbed and used by the body (rodent study).

It is noted that this radioactively labeled, high- and low-MW HA (MW: 1 × 106 and 1 × 105, respectively) accumulated preferentially in skin tissues. (28,29)

2.3 MECHANISM OF ACTION

HA oligosaccharides (MW: 1–2 × 103) increased HA production in human fibroblasts by displacing endogenous HA from the receptors and promoting a stimulatory effect on further HA production (30). It has been shown that low MW HA are used as primers when high-molecular-weight HA is synthesized in cells (31).

Another study shows that High MW HA (MW: 1.1 × 106) promotes cell proliferation of human fibroblasts and increased population of collagen lattices (33). HA stimulates an increase in the number of HA producing cells and hence increase of the cell number suppresses the skin's water loss by filling the gaps of the skin cells as well as increasing the amount of HA synthesis in the skin.

The aforementioned reports suggest that both low- and high-MW HA transfer to the skin and affect the fibroblast cells to promote HA synthesis and cell proliferation, both of which contribute to skin moisture and collagen production.

3.0 KERATIN - CYNATINE HNS

Cynatine HNS is a compound that contains a protein called keratin, in a peptide form obtained by proprietary processing of New Zealand sheep wool. Keratin protein is noted to be one of nature's richest sources of Cysteine.

Cynatine HNS has several proposed mechanisms of action, and may act synergistically with the cells' own antioxidant defence, boosting glutathione and other sulphur-rich proteins and peptides.

Keratin is found in many different layers of the skin. Outer skin cells are filled with keratin, helping the skin to retain moisture and delivering the skin's elasticity and smoothness. The outer keratin layer also protects the underlying layers of skin.

In vitro studies have shown that Cynatine HNS is highly bioavailable, making it capable of delivering keratin peptides to the body, particularly to the skin.

In one study, a total of 50 females were included and randomized into two groups. The active group (n = 25) received two capsules totalling of Cynatine HNS, comprised of Cynatine" brand keratin (500 mg).

Overall, there were noted improvement skin roughness, skin elasticity, skin wrinkles, and skin appearance. 95.8% of the subjects in the active group showed an improvement in skin cohesivity. Skin has appeared to be clinically improved as determined by a dermatologist in the clinical assessment with a total improvement of 54-58% improvement compared with placebo. (34)

Overall, Studies Have Shown the Cynatine HSN

1. **Cynatine reduces fine lines and wrinkles**
   Through its zinc and copper complexes bound to proteins

2. **Cynatine Promotes firmness and Elasticity in Skin**
   By improving the protein structure and improving moisture retention

3. **Cynatine Reduces Redness from Inflammation or Sensitive Skin**

By blocking PGE2 production

4. **Cynatine improves the brightness and radiance of skin**
   Through its natural antioxidant properties and its ability to promote SOD and glutathione production

Further, Keratin is the protein from which the majority of hair and nails are made.

In a randomized, parallel group, double-blind, placebo-controlled 90-day intervention study in 50 subjects with signs of damaged hair and nails conducted at a single site in Italy. The study found up to 34% decreased hair loss, 5.9% improved hair strength, and clinical evaluation by the physician concluded that hair shininess and brightness had improved in the Cynatine HNS group in 87.5% of the subjects compared to only 16.7% in the placebo group.

An overall assessment of hair brightness showed a 64.7% change compared to only 17.6% in placebo. This is more than a 3x improvement in hair brightness at the end of the test period.

Hardness of nails improved from 37.5% of subjects reporting hard nails to 87.5% at the end of 90 days.

That goes hand in hand with the improvement in resistance and none broken nails. The clinical evaluation by a physician also went along the same lines and an improvement in tendency to break was seen in 87.5% of subjects as compared to only 28.6% in the placebo group. (35)

4. ANTIOXIDANTS, VITAMINS, AND MINERALS

Here we address the cofactors that are needed to keep skin healthy. Collagen, HA, and keratin require several vitamins and minerals for proper synthetic function and maintenance. Even a slight deficiency in these factors can adversely impact skin health. Since skin undergoes turnover every 27 days, it is particularly imperative to maintain repletion these co-factors.

4.1 VITAMIN C

Vitamin C (ascorbic acid) is a strong antioxidant has a crucial role in collagen synthesis. Dietary vitamin C has been shown to help prevent and treat ultraviolet (UV)-induced photodamage, dry skin, and prevent formation of new wrinkles and pigmentation.

Vitamin C normally found in high levels in skin, in both the dermis and epidermis (36,37). Aging, however, causes a decline in vitamin C content in both the epidermis and dermis (37). Excessive exposure to UV light or pollutants (e.g., cigarette smoke and ozone) may also lower vitamin C content, primarily in the epidermis (38-40).

As an antioxidant activity of vitamin C protects against UV-induced damage caused by free radicals (41) UV light decreases vitamin C content of skin, an effect that is dependent on the intensity and duration of UV exposure (38-40)

The accumulation of oxidative damage to proteins is a distinguishing feature of both photodamage and intrinsic aging. This oxidative damage can lead to changes in skin structure.

In addition to its antioxidant functions, vitamin C regulates the synthesis of the structural protein collagen. The role of vitamin C in the hydroxylation of collagen molecules is well characterized (42). Hydroxylation of collagen is necessary for its extracellular stability and support of the epidermis. Vitamin C also increases the proliferation rate of fibroblasts and stimulates DNA repair in cultured fibroblasts (43)

Two observational studies found that higher intakes of vitamin C from the diet were associated with better skin appearance, with notable decreases in skin wrinkling (44-45). Vitamin C may have additional roles in wound healing, for example, by promoting keratinocyte differentiation (46, 47), stimulating the formation of the epidermal barrier (46), and re-establishing the stratum corneum (48). Additionally, higher intakes of dietary vitamin C has been correlated with a decreased risk of dry skin (49)

B-VITAMINS AND MINERALS

B-Vitamins are responsible an incredibly diverse functions in human physiology, some of which involve skin physiology. There have been several small studies to suggest that they may be individually involved in skin health. However, it is duly noted that B-vitamins are integral to collagen and extracellular matrix synthesis as well as structure and function, and metabolism in the skin. Most notable vitamins that have scientific evidence is Biotin, Niacin, and B-6.

Additionally, two important minerals are required for extracellular matrix regeneration and have shown effects in skin regeneration and wound healing. These include Zinc and Copper. They are required only in small amounts, but deficiency in either drastically reduces healing and regeneration rates. Resultantly, due to rapid skin turnover and continued synthesis, it remains important to continually maintain adequate levels of these important cofactors.

CONCLUSION

To review, the skin is a complex organ that maintains physiological homeostasis and acts as a barrier from the outside environment.

Skin health is often a reflection of the overall bodily health.

Although topical skincare products intervention can be considered, many agents are not able to cross the skin barrier and often do not support skin metabolism effectively.

Novel scientific advances have suggested several agents and mechanism of stimulating regenerative processes in the skin when taken orally.

Due to the weight of science behind them, they are worth consideration for maintaining skin health and regenerating skin tissue.

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