

Clinical Evidence of the Anti-Aging Effects of a Collagen Peptide Nutraceutical Drink on the Skin

ABSTRACT

Nutraceutical supplementation has been shown to have effects on skin. The aim of this article is to establish the acceptability and feasibility of modifying dietary routines to include use of a collagen peptide-based nutraceutical drink (Skinade®, Bottled Science Ltd, London, UK) in order to improve skin quality. Several studies have shown the effects of this nutraceutical drink, which targets the skin as a whole organ by addressing overall skin health through the product's formulation and mechanism of action. Aesthetic professionals have noted improvements in skin appearance and texture, as well as skin healing, after daily intake of the drink, which is derived from ingredients known to improve skin health and ameliorate the effects of skin aging. Maintenance of collagen levels through aesthetic procedures and topical skincare application can produce localized reductions in signs of aging. Dermatologists should be aware of the potential benefits of nutraceuticals used in conjunction with these other aesthetic treatments.

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INTRODUCTION

Dermatologists know that collagen is a building block of healthy skin. Collagen is a structural protein that gives the skin its strength and shape. This building block acts as a “frame” for the skin, while elastin and hyaluronic acid act as “padding” on the frame. The skin specifically needs Types 1 and 3 collagen, which support the skin, muscles, bone health, hair, and nails. Collagen Type 2 comprises the fluids and functions in the cartilage and joints. More than 90% of collagen in the body is comprised of Types 1 and 3 collagen. Over time, the ideal levels of collagen the human body naturally produce begin to decrease. Like most things in the skin, collagen diminishes with age, which is why, after 30 years of age, most individuals start to notice such changes as sagging skin and wrinkles. Genetics, skin type, and exposure to the effects of the sun's ultraviolet rays that can cause damage to the skin are other factors that affect how human skin ages.

Collagen supplementation has been introduced to the market in an attempt to address this situation, but absorption of collagen is a problem. In addition, many supplements introduced to the market contain only Type 1 or Type 2 collagen. A collagen-based nutraceutical drink has been developed (Skinade®, Bottled Science, Ltd, London, UK) that targets the skin as a whole organ by addressing overall skin health through this product's formulation and mechanism of action. This review of the evidence shows how the patented formula of the product promotes hydration and overall skin health and why its mechanism of action is superior to other collagen-based supplements that target the effects of aging on skin health.

KEY FACTORS IN SKIN AGING

Skin health and appearance depend on a sufficient supply of

essential nutrients. The emergence of nutritional supplements (nutraceuticals) for the enhancement of skin quality and for antiaging has become increasingly popular. They are used to boost the human body's health and functioning. Ingredients at the forefront of antiaging strategies include vitamins (eg, vitamins B, and C), omega-3 fatty acids, minerals (eg, copper and zinc), botanicals, and amino acids. Antiaging supplements generally contain nutrients.¹ Among the nutraceuticals that are currently available are ingestible products that boost the skin's hyaluronan, collagen, and elastin production. Collagen peptides are used as a bioactive ingredient in nutraceutical products and have been shown to improve barrier function,² to induce the synthesis of collagen, elastin, and hyaluronic acid, and to promote fibroblast growth activation and proliferation.

Hyaluronan

Hyaluronan is a water-sorbed macromolecule supplied from keratinocytes beneath the stratum corneum layer and is present in the normal stratum corneum.³ Hyaluronic acid is a glycosaminoglycan with the key role of retaining moisture within the skin structure. It is one of the chief components of the extracellular matrix and contributes significantly to cell proliferation and migration. Hyaluronic acid is involved in skin tissue repair and skin healing. The amount of hyaluronic acid in the human skin decreases with age, and this is reflected in the stratum corneum's reduced capacity to retain moisture, leading to dry skin and impairment of the epidermal-barrier function.

Collagen

A growing body of evidence has demonstrated the efficacy of collagen peptides to improve parameters of skin physiology in pre-clinical studies. Collagen peptides have been shown to

increase hyaluronic-acid production in dermal fibroblasts,^{4,5} and to improve skin-barrier function by increasing the water content of the stratum corneum.^{4,6,7} Furthermore, collagen peptides induce the synthesis of collagen on the mRNA and protein levels^{8,9} and the production of stronger collagen fibrils,¹⁰ promote the growth of skin fibroblasts,¹¹ and induce fibroblast migration.^{12,13}

Collagen compounds for oral supplementation are broken down into peptides through enzyme hydrolyzation, creating particles of lower molecular weight, which are more easily absorbed, appearing in the bloodstream 1 hour after ingestion.¹⁴ Recent randomized controlled trial data has increasingly confirmed that oral intake of hydrolyzed collagen has the effect of improving skin health by affecting skin hydration and inducing collagen synthesis. The evidence also shows increased expression of enzymes key in hyaluronic-acid synthesis, which is associated with increased hydration (Figure 1).

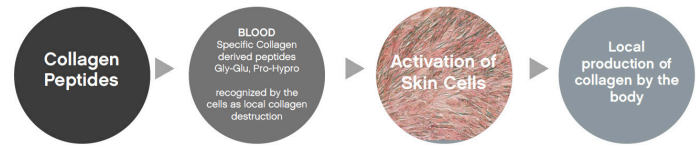
Elastin

Elastin is an important protein in the extracellular matrix that is primarily composed of the amino acids glycine, valine, alanine, and proline. This protein found in elastic connective tissues, enabling those tissues, such as the skin, to return to their original shapes after stretching or contracting. When the skin is manipulated out of shape, such as by poking or pinching, elastin helps the skin resume its original shape and position.¹⁵ Like collagen, elastin is produced by connective tissue fibroblasts, which secrete tropoelastin. The loss of elastic tissue causes the skin to become more fragile and to lose firmness.

Currently, to treat collagen and elastin loss caused by aging, dermatologists recommend topical treatments, such as creams with retinols or growth factors, decrease exposure to the sun to prevent further damage, sunscreens, intense-pulsed light (IPL), skin peels, or more invasive treatments from cosmetic surgeons or laser treatments. Incorporating a nutraceutical daily supplement into other treatment plans could benefit and help prevent disease, and also help to improve the symptoms and outward signs of skin aging.

Oral supplementation for addressing skin aging and age-related skin disorders has an advantage over topical skin-care regimens in that the blood delivers bioactive compounds continuously to the dermis.¹⁶ With the right formulation, nutraceutical supplements can induce better skin health intrinsically with a high level of bioavailability. The Skinade product, which has been the focus of recent research, uses 2kDa patented types 1 and 3 collagen peptides from freshwater fish skin to trigger fibroblast proliferation and increase fibroblast activity in the dermis. Hydrolyzed marine collagen is known to be the most-abundant source of type 1 and 3 collagen that comprise the skin.

FIGURE 1. Mechanism of action of collagen peptides in-vivo.



INGREDIENTS

This supplement consists of high-grade marine collagen peptides from freshwater fish skin that is absorbed well, due to its molecular weight. The supplement contains vitamins to stimulate cell production and help maintain the collagen matrix. Omega 3 and 6 fatty acids, as organic flax seed in the supplement, help balance dry and oily skin. Here are the key ingredients in this nutraceutical product:¹⁷⁻²⁴

- *Hydrolyzed marine collagen* Low molecular weight peptides trigger fibroblast proliferation, activation, and hyaluronic-acid production in the target organ.
- *Vitamin C (calcium ascorbate)* supports fibroblast proliferation and maintains stability of collagen during photoaging, via antioxidant activity. The vitamin C also reduces redness. The supplement includes 180 mg of vitamin C in the form of calcium ascorbate, without which the fibroblast proliferation and activation cannot occur.
- *Methylsulfonylmethane (MSM)* provides sulfur for structural proteins required for collagen formation. This ingredient protects the integrity of collagen, which is integral to elastin (improving skin elasticity). MSM also improves skin hydration; serves as an anti-inflammatory, has detoxifying capabilities, and prevents cross-linking of the collagen fibers in the dermis and improves sulphur bridges.
- *B-complex vitamins* have powerful antioxidant properties that are essential for skin health. These vitamins also promote blood flow and, thereby, help oxygenate and supply nutrition to the skin, also contributing to skin radiance and glow.
- *Organic flaxseed*, the botanical, *Linum usitatissimum*, is an excellent source of omega-3 and omega-6 fatty acids in a perfect 4:1 ratio to balance oil production in the sebaceous glands. This botanical has strong anti-inflammatory properties and helps prevent transepidermal water loss to reduce dryness.
- *L-lysine* is an essential amino acid that enhances collagen integrity at the cellular level. This amino acid is an immune-system booster that assists ceramide production when combined with an antioxidant. The amino acid also helps rebuild the collagen matrix.

MSM, L-lysine, and the B vitamins produce a more-clear and uniform complexion. The product does not contain gluten, bovine, or porcine products; nor are there hormones, genetically modified organisms, alcohol, added sugar, artificial flavors or artificial colors.²⁵

CLINICAL STUDIES

A number of clinical studies support the use of this nutraceutical product. These studies are discussed in the sections below.

Collagen Peptides in Daily Oral Supplementation

Two placebo-controlled clinical trials, assessed the effects of daily oral supplementation with collagen peptides used in Skinade on skin hydration by corneometry, on collagen density by high-resolution ultrasound, and on collagen fragmentation by reflectance confocal microscopy. In addition, human skin explants were used to study extracellular matrix components in the presence of collagen peptides *ex vivo*.²

After 4 weeks of supplementation, collagen density in the dermis was increased significantly while fragmentation of the dermal collagen network was decreased significantly. After 8 weeks of intake, skin hydration was increased significantly. Both effects persisted after 12 weeks. The *ex vivo* experiments showed that the collagen peptides induced collagen and glycosaminoglycan production; this could be a mechanistic explanation for the clinical effects that were noted. The researchers concluded that “oral supplementation with collagen peptides is efficacious to improve hallmarks of skin aging.”²

Collagen Peptides Increase Skin Hydration

A double-blinded, placebo-controlled trial in 2008 offered evidence-based results that the collagen peptides used in Skinade increase skin hydration.²⁵ The study was conducted at Souken Laboratories in Tokyo, Japan, to assess the efficacy of night-time oral ingestion of a liquid supplement (Skinade) containing collagen peptides for improving skin condition. The 8-week study included 33 female volunteers, aged 40–59 years, with normal-to-dry skin. The women were divided into 3 groups each of which drank a specially formulated drink at night before bed. One group received a placebo (dextrin) in the drink and the other two groups received 10g of either fish-based or porcine-based collagen peptides in their drinks. The study lasted for 56 consecutive days, during which the subjects ingested the drinks.²⁵

Assessment of facial-skin parameters was performed at baseline and after 4 and 8 weeks of treatment in a controlled environment with a room temperature of 22°C ± 1°C and a relative humidity of 50% ± 10% after 30 minutes of acclimatization. Skin-moisture level was measured by conductance with a Corneometer® device (CK Electronic, Köln, Germany) at 3 different application points per subject. The rate of transepidermal water loss (TEWL) was assessed with a Tewameter® device (CK Electronic, Köln, Germany) on the line between the ear lobe and mouth edge at a 3-cm distance from the earlobe. A self-assessment questionnaire and a product-tolerance evaluation tool were also used in addition to skin imaging systems.²⁵

The tested product increased skin hydration by up to 28% after 8 weeks, with 91% of the volunteers who drank the peptide preparations having an increase in skin hydration ($n = 22$; $n =$ Corneometer skin moisture level measure) as compared with the placebo group, which demonstrated an increase in hydration of $n = 2$. Skin-analysis technology was used to analyze the number of deep wrinkles in the subjects; after 12 weeks, the number of deep wrinkles had increased significantly in the placebo group between baseline and 12 weeks (+30%).²⁵

While there was no change in the placebo group, the oral intake of fish peptides over 8 weeks led to a significant increase of skin moisture level by 12%. Porcine-based peptides significantly increased skin-moisture level by 16% after 4 weeks of treatment and as much as 28% after 8 weeks of treatment ($P = 0.003$ versus placebo at 8 weeks). TEWL was not different between both active groups and the placebo. Thus, the researchers opined that oral intake of peptides seems to improve skin hydration effectively without affecting TEWL.²⁵

Effect of Collagen Peptides on Cutaneous Properties

A double-blinded clinical study, in 2008, by DermScan, in Lyon, France, was conducted to evaluate the effects of oral intake of collagen peptides on cutaneous properties versus the effects of a placebo. The study assessed the efficacy of peptides after 6 and 12 weeks during winter including the supplement's antiwrinkle effect and biomechanical properties. Self-assessment was obtained from 47 female volunteers, aged 35–55 years, with normal-to-dry skin. These participants were given 10g of collagen peptides per day (2 x 5g) or placebo (dextrins) for 12 weeks (October–January). Investigations were focused on the dermophysiologic measures taken in a temperature and humidity conditioned room; skin moisture level (measured by Corneometer® CM 825, CK Electronic, Köln, Germany), elasticity of skin (measured by Cutometer® MPA 580, CCK Electronic, Köln, Germany); and deep-wrinkle formation measured by skin replica imaging and analysis (3D Roughness Analyzer ASA-03R; Asahi Biomed Co., Yokohama, Japan, and Quantirides® SIA). Acceptability was measured by a self-assessment questionnaire and a product-tolerance evaluation.²⁶

The results showed increased skin hydration after 8 weeks. The Corneometer measurements showed an increase in hydration ($n = 22$) by 28% after 8 weeks, compared with placebo. Among the volunteers who drank the collagen peptides, 91% had increased hydration levels after 8 weeks. The study also showed that peptides prevented deep-wrinkle formation. The number of deep wrinkles significantly increased (+30%) in the placebo group between baseline and 12 weeks.²⁶

In Vivo Effects of Oral Ingestion of Fish Collagen Peptides

A double-blinded clinical study conducted by COSderma

(Bordeaux, France)²⁷ investigated the effect of oral ingestion of fish collagen peptides versus placebo on skin properties in vivo. Effects on the skin's collagen structure were measured by visual and laser scanning technology. Volunteers included 106 Caucasian females ages 40–65, who were given a 10 g daily dose of a powdered drink, fish collagen peptides, or placebo (maltodextrins) for the study duration of 84 days.²⁷

The investigators used the latest skin analysis technology, including VivaScope® 3000 (Caliber I.D., Rochester, NY) confocal laser technology, using a laser ray of 830 nm to take capture images at different layer depths. Collagen fragmentation was analyzed at 2 depths: "S" at the surface of the superficial dermis papillary and "D" at 25 µm deeper than S. Dermcup® echography (Atys Medical, Soucieu en Jarrest, France) with a 25 MHz probe was used to quantify collagen density.²⁷

Collagen fragmentation decreased significantly in the deep layers of the skin with peptides. No change in collagen fragmentation was observed in the placebo group. Density of collagen network significantly increased in just 28 days in the active group, with no change in the placebo group. The researchers concluded that, after 8 weeks of ingesting collagen peptide supplementation, the volunteers' skin hydration was increased significantly.²⁷

Another take-away from the COSderma study is that hydrolyzed marine collagen is known to be the most abundant source of Types 1 and 3 collagen, the same collagen types that comprise the skin. The supplement thus provides the ability to not only reach the target organ (the dermis), but also trigger HAS2 receptors' natural hyaluronic-acid production. This increases hydration and skin elasticity, reduces fine lines and deep wrinkle formation, and benefits photodamaged skin.²⁷

Global Skin Rejuvenation of the Face

In a placebo-controlled, double-blinded, clinical case study carried out by Santi Labs (London, UK), the impact of a 90-day supply of Skinade on global skin rejuvenation of the face was assessed.²⁸ A total of 20 participants, including 15 participants who took the supplement and 5 control subjects, were monitored every 15 days and measured every 30 days throughout the course of the study. Cortex Technology measured a number of skin parameters including collagen-structure imagery, hydration, elasticity, TEWL, skin color, photomicroscopy, and skin pH. After a 90-day course of Skinade, collagen density increased 25.5%, skin elasticity increased 28%, and skin hydration increased 34% in the treated subjects compared with the subjects in the placebo group. Changes in collagen structure were immediately noticeable in the cortex images of a 58-year-old female subject who had a 58% increase in collagen density at day 90 (Figure 2) and in a 58-old female subject who had a 73% collagen density increase

FIGURE 2. Changes in collagen structure were immediately noticeable in the cortex images of a 58-year-old female subject who had a 58% increase in collagen density at day 90. (Left) baseline; (Right) day 90.

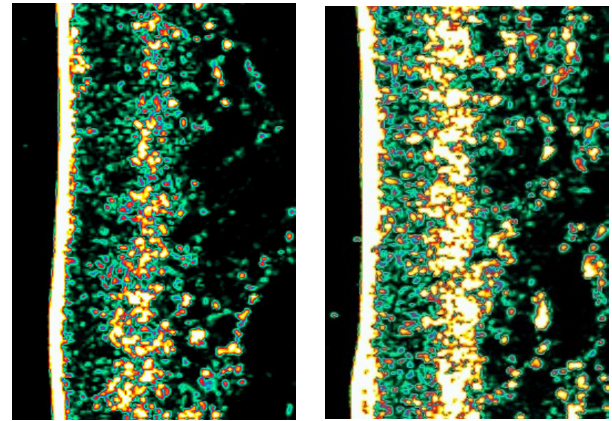
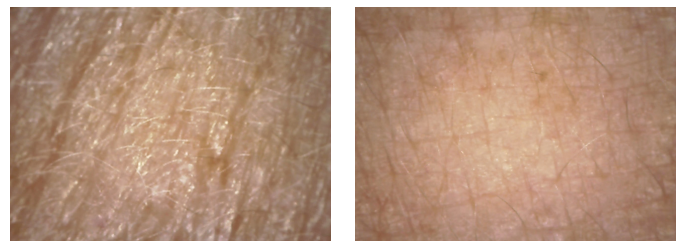


FIGURE 3. Photomicroscopy of 58-old female subject who had a 73% collagen density increase at day 90. (Left) baseline; (Right) day 90.



at day 90. Photomicroscopy indicated significant improvements in skin texture and pigmentation by day 90 (Figure 3).²⁸

Clinical Observations

Dermatologist empirical observations after treatments have indicated a decrease in bruising when the oral nutraceutical was taken daily for a duration of 4 weeks. While under this treatment, patients reported a decrease in bruising, a common phenomenon that can be detrimental to patients' self-esteem. Within a period of three 3 months, during follow-up visits, patients were able to perceive a difference in the texture and tone of their skin.

Absorption and Persistence of Collagen Hydrolysate

Optimization of the bioavailability of the active ingredients in Skinade gives the nutraceutical an advantage over other collagen supplements. By developing an isotonic solution of low molecular weight marine collagen, vitamins, methylsulfonylmethane, fatty acids, and amino acids, the formulation has a 90-95% absorption rate that ensures the nutrients are available in the dermis. Researchers investigated the absorption mechanism of low-molecular-weight collagen hydrolysate (LMW-CH) and its effects on osteoporosis in rats.²⁹

When administered to Wistar rats with either [^{14}C]proline (Pro group) or glycyl-[^{14}C]prolyl-hydroxyproline (CTp group), LMW-CH rapidly increased plasma radioactivity. The LMW-CH was absorbed into the blood of Wistar rats in the peptide form. CTp tripeptide remained in the plasma of the rats and accumulated in their kidneys. In both groups, radioactivity was retained at a high level in the skin until 14 days after administration.²⁹

DISCUSSION

Human skin specifically needs Types 1 and 3 collagen. Types 1 and 3 support skin, muscles, bone health, and hair and nail maintenance. Collagen Type 2 comprises the fluids and functions in the cartilage and joints; thus this type of collagen will not act as a specifically a skin supplement. More than 90% of collagen in the body is comprised of Type 1 and 3 collagen. Over time, as noted previously, the ideal levels of collagen that the human body naturally produces begin to decrease. Collagen fibers break down or no longer regenerate; this leads to a “deflation” effect on the surface of the skin.

By the age of 40, the body’s ability to produce collagen decreases by ~25% and, by age 60, collagen has decreased to ~50%. Given that the body can no longer keep up with the demand for naturally occurring collagen to maintain youthful skin, if one desires this, one needs to think about supplementation and corresponding levels of collagen depletion.

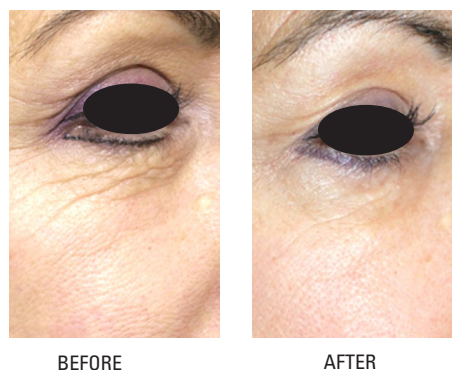
In addition, many patients are overwhelmed by the choice of beauty products available on the market and welcome a tailored approach to their skin care. Given that daily intake of an oral nutraceutical supplement drink has been shown to increase collagen density, Skinade is recommended for patients who are undergoing treatment in which the aim is collagen stimulation (e.g., poly-L-lactic acid, medical microneedling, polydioxanone thread lifting, and radiofrequency). Ideally, a patient will begin drinking the product 1 month before treatment to ensure that the skin is in optimal condition at the time of the procedure. Continued use of the supplement for 2–3 months postprocedure and beyond the treatment phase may help enhance treatment outcomes (See Figures 4 and 5).

Maintenance of collagen levels through aesthetic procedures and topical skin-care application can help reduce signs of aging. Although aesthetic practitioners already offer a myriad of localized topical, injectable, and laser treatments at their clinics, these procedures only address patients’ concerns from the outside, when so many of the factors that contribute to global skin health and aging are influenced by what is happening inside the body (ie, inflammation, glycation, and oxidation).²⁹ It therefore makes sense to combine these treatments with products that work from the inside out to maximize all opportunities for skin-health improvement.

FIGURE 4. Before and after images of neck following 90-day course of Skinade oral supplement.



FIGURE 5. Before and after images of face following 30-day Skinade regimen. The 'BEFORE' image shows a close-up of a person's eye area with visible wrinkles and skin laxity. The 'AFTER' image shows the same area after 30 days of treatment, with smoother skin and reduced wrinkles.



Limitations

For most people, a fish-based supplement is preferable; however, Skinade does contain marine collagen, which could affect individuals with fish allergies adversely and is not suitable for patients with vegetarian or vegan diet restrictions. It is also important to note that there have been no studies relating to the safety of the product during pregnancy.

CONCLUSIONS

In the recent past, the approach to skin rejuvenation traditionally has been topical—from the outside in—but there is growing interest in nutraceuticals to support skin function and skin health. Aesthetic practitioners already offer patients a vast array of topical, injectable, and laser treatments at their clinics; these approaches all address patients’ concerns from the outside. However, when so many of the factors that contribute to skin health and aging are influenced by what is happening inside the body, it makes sense to combine these treatments with nutraceutical products that work from the inside out to maximize all opportunities for skin care.

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