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Review Article

Some Methods to Prevent Aging by Protecting the Skin

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Abstract:

To prevent skin aging, adopting a skincare routine with sunscreen, retinol and hydration, ensuring a healthy lifestyle through sufficient rest and adequate water consumption, avoiding smoking and protecting yourself from excessive sun exposure, and a diet rich in antioxidants and Omega-3 fatty acids can contribute to skin elasticity. The active ingredients in nutricosmetics can be classified into two categories: those that replace the key structural elements in maintaining skin health, collagen and hyaluronic acid, and those that prevent tissue destruction through indirect mechanisms such as the antioxidant one, this category can include vitamins, minerals and natural compounds. A balanced diet that provides all categories of macro and micro-nutrients along with protection from UV radiation is the simplest way to slow down the aging process. However, as simple as it may seem, the lifestyle of contemporary man is characterized by speed, so the use of food supplements concentrated in functional ingredients has become a much easier option.

Key words: skin health; collagen; hyaluronic acid; vitamins; minerals; natural compounds

Introduction

The term nutricosmetics was born by combining the concepts of nutrition and cosmetics. A nutrient is a substance that provides energy or allows the growth, repair or proper functioning of the body. Nutrients are divided into different categories, such as minerals, vitamins, proteins, carbohydrates, lipids and water. According to Regulation (EC) No. 1223/2009 of the European Parliament and of the Council of the European Union, "a cosmetic product means any substance or mixture intended to be placed in contact with the external parts of the human body such as the skin, hair, nails, lips and external genitalia, or with the teeth and oral mucosa with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance and/or correcting body odours and/or protecting them or maintaining them in good condition". Awareness of the importance of nutrition for general well-being and the growth of the concept of "beauty from within" have led to the emergence of a new field, namely new product categories: nutricosmetics and nutricosmetics. The term "nutricosmetics" defines natural health products administered orally that improve the function and appearance of human skin, nails and hair. They are agents with a protective or supportive effect used for beautification and/or for beneficial effects of personal hygiene. From the point of view of legislative aspects, nutricosmetics are food supplements, which implies that, in the territory of the European Union, they must be in accordance with Directive 46/2002/EC of the European Parliament and of the Council which establishes that "food supplements" are understood as food products whose purpose is to supplement the diet and which represent concentrated sources of nutrients (vitamins, minerals, amino acids, essential fatty acids, fibers and various plants and plant extracts) or other substances with a nutritional or physiological effect, alone or in combination, marketed in dosage form, respectively in pharmaceutical forms such as: capsules, tablets, lozenges or other similar forms (powder sachets, ampoules, spray bottles). Also, to ensure a high level of consumer protection and to facilitate their choice, products placed on the market must be safe and bear adequate and appropriate labelling [1].

The key factors driving the growth of this market can be considered as follows:

- increasing awareness of the link between nutrition and health, including physical appearance - consumers are becoming more perceptive to the concept of "beauty from within";
- aging of the population in developed areas of the world - they are willing to allocate more financial resources in an effort to maintain a youthful appearance and promote general well-being;
- continued research and development of nutritional active substances for use in nutricosmetics.

The global nutricosmetics market is expected to grow significantly, with a forecast for the period 2020-2025 estimating a compound annual growth rate (CAGR) of 8.63%. The largest share of this market is held by Europe, which is also the continent with the highest average age (42 years), with a significant share also in the Asia-Pacific region, especially Japan. But the North American nutricosmetics market is also growing. Being a relatively new field in the food supplement market, but with great growth potential, competition in developing effective products is fierce. The major research areas that have nutricosmetics as their objective can be divided as follows: identification and development of new ingredients; development of methods to prove the efficacy of ingredients or finished products. Analysis of nutricosmetics products can be done according to the main active ingredients used in the formulation of these products, the most common being: collagen, peptides, proteins, hyaluronic acid, vitamins, minerals, omega-3 fatty acids, as well as plant extracts [2].

Collagen as an ingredient in nutricosmetics products

Collagen is a protein present in all multicellular animals. To date, 28 types of collagen have been identified and characterized at the molecular level, consisting of 46 unique amino acid chains. Depending on the structure and supramolecular arrangement, there are 4 subfamilies from fibrillar to reticular. Of these, fibrillar collagen is the most abundant form in vertebrates, where it plays a structural role, contributing to the molecular architecture, shape and mechanical properties of tissues, such as the tensile strength of skin and the tensile strength in ligaments. Of the 28 existing types, type I collagen is found in the highest proportion (approximately 90% of the collagen in the body is type I) and is present in almost all connective tissues. It is a component of the interstitial matrix and a major structural protein of bones, skin, tendons, ligaments, sclera, cornea, blood vessels, and is also present in other tissues. Type I collagen comprises approximately 95% of the total collagen content of bone and approximately 80% of the total proteins present in bone, making it the tissue with the highest amount of type I collagen. The main types of collagen in the skin are I and III, but there are also different types of collagen, such as collagen VII, crucial for the integrity of the skin, even though it only constitutes approximately 0.001% of the total collagen in the skin. Collagen is in high demand in the cosmetic and biomedical industries due to its biocompatibility, bioactivity, low immunogenicity, and benefits for the skin. Along with elastin, collagen fibers are responsible for forming the main structural network of the skin, thus contributing to its smooth appearance. Since skin aging is associated with increased degradation of collagen fibers, it is a popular ingredient used as a nutricosmetic product, demonstrating benefits for human skin and connective tissues of cartilage. The aging process is viewed by researchers from two perspectives: intrinsic factors and extrinsic factors. With age, fibroblasts, the cells responsible for collagen synthesis, reduce their activity, so that its level decreases. In addition, the activity of enzymes responsible for collagen degradation is stimulated by UV radiation, which is one of the processes by which “photoaging” occurs. It is easy to understand that the balance is tilted towards the loss of collagen, which explains the lack of firmness, elasticity and structure of the skin of older people. It has been observed that after the age of 20, collagen production in the skin decreases by 1% each year, so the appearance of wrinkles is inevitable, but the speed of appearance can be reduced by protecting against UV radiation and by supplementing the level of collagen in the diet [3].

Types of collagen, sources and method of obtaining. In food supplements, the most common types of collagen are I and II. Type I collagen is extracted from the bones and skin of animals, and type II collagen is found alongside hyaluronic acid and chondroitin sulfate in cartilage (the most important source being those of birds). Although the main source of collagen is represented by products of animal origin such as pigs, cattle or bird bones, skins, tendons and cartilage, researchers are trying to find solutions to the increasing demand and are focusing on different cheaper sources with a lower risk of bovine spongiform encephalopathy (BSE). One such alternative, natural and safe source is marine animals. Bones, skin, fins, scales of freshwater or saltwater fish; starfish, jellyfish, sponges, sea urchins, octopuses, squid, cuttlefish, sea anemones and shrimp are used for this purpose. Advantages of marine collagen:

- lower molecular weight, which leads to better absorption;
- the amounts of biological contaminants and toxins are almost negligible;
- low inflammatory response;
- no risk of BSE transmission;
- high yield.

Disadvantages: low thermal stability, which limits applications. Collagen can also be obtained through systems based on biotechnology that use yeast, bacteria, insect cell cultures or plants, the principle being that of protein recombination. The plant cultures used to obtain recombinant collagen are tobacco, transgenic corn seeds and barley. Another option is the development of 100% artificial fibers that mimic the characteristics of collagen, such as the artificial polymer with the commercial name KOD. This synthetic protein made up of 36 amino acids has proven effective in replacing collagen in various medicinal sponges. These types of collagen can be found in non-hydrolyzed variants, another term being undenatured or hydrolyzed (denatured). Hydrolyzed collagen (HC) is a group of low molecular weight peptides (3-6 kDa) obtained by enzymatic hydrolysis in acidic or alkaline medium at a specific incubation temperature or by hydrolysis based solely on temperature (15). Some properties of HC, such as the molecular weight of the peptide chain, solubility and functional activity, are affected by the type and source of extraction. The enzymatic proteolysis process is faster and uses milder conditions that lead to the obtaining of low molecular weight peptides. Another important aspect in the production of various types of collagen is the qualitative composition of the final products. It has been observed that the amino acids responsible for the health effect are: glycine (Gly), proline (Pro) and hydroxyproline (Hyp); the Pro-Hyp or Hyp-Gly peptides have stimulating effects on skin, joint and bone cells, which leads to increased collagen synthesis [4].

Mechanism of action. The presence of these peptides at the tissue level functions as a false signal of collagen destruction that stimulates fibroblasts and leads to the activation of various biochemical signaling pathways that respond to collagen synthesis. In addition, hyaluronic acid synthesis is also stimulated, which contributes to maintaining the skin's hydration status.

Collagen bioavailability. The absorption rate and bioavailability depend on the form of collagen administered. A blind, randomized, crossover study compared the postprandial absorption of peptides from enzymatically hydrolyzed collagen and those from non-enzymatically hydrolyzed collagen with placebo and determined the impact of exogenous enzymatic hydrolysis on the absorption rate and bioavailability. The results indicated that enzymatic hydrolysis increases

the absorption rate and bioavailability of the amino acids Gly, Pro and Hyp. Not only the method of obtaining influences the bioavailability, but also the composition of the peptides from different types of hydrolyzed collagen. It has been observed that collagen hydrolysates with a higher content of active di- and tri-peptides have a superior effect compared to those with a low content of biopeptides. Therefore, the bioavailability of collagen types can be ordered as follows: products containing biopeptides > enzymatically hydrolyzed collagen > thermally hydrolyzed collagen > pure collagen. It is thus observed that, the lower the molecular mass, the less protein digestion is necessary, the peptides being absorbed at the intestinal level more quickly. As we can see, collagen and its derivatives are widely represented in the field of nutricosmetics due to all the benefits on the skin and also because they are accessible ingredients with a relatively low production cost. The effect of the product is correlated with the content of bioactive peptides, therefore, identifying accessible sources and methods for efficiently obtaining molecules with a high content of bioactive peptides is the main area of research in the case of this ingredient. From this point of view, marine collagen has a composition rich in the three important amino acids. The development of specific bioactive peptides, efficacy and safety are the desires of every nutricosmetics manufacturer [5].

Examples of types of collagen found in nutricosmetic products. The diversity of types of collagen used in cosmetic products is considerable, each product having unique characteristics, and the clinical evidence that reinforces their effect differs from case to case. Below are presented some types of products whose effectiveness has been proven through clinical studies.

Collagen types I and III

1. VERISOL® (GELITA AG, Eberbach, Germany). This is the patented name of specific bioactive peptides of collagen type I and type III with an average molecular weight of 2.0 kDa whose effects on the skin and not only have been proven by placebo-controlled clinical studies. Depending on the raw material used, there are three products: VERISOL® P (porcine raw material), VERISOL® B (bovine raw material) and VERISOL® F (fish raw material). Proven clinical effects:

- improvement of skin elasticity by approximately 30% at a use of 2.5 g/day;
- improvement of wrinkles;
- increase in dermal density;
- reduction of cellulite;
- improvement of nail growth and health;

The doses used in studies for these collagen peptides vary between 4 and 10 g/day to observe effects on the skin.

2. PEPTAN® (Rousselot, France). Active collagen-specific peptides developed for various actions are marketed under the name Peptan®. The products supplied by Rousselot contain collagen type I and III biopeptides with an average molecular weight of 2–5 kDa rich in hydroxyproline, obtained from fish (Peptan® F) and porcine origin (Peptan® P) intended for the production of nutricosmetics. Two double-blind, randomized, placebo-controlled clinical studies were conducted to evaluate the effect of daily oral supplementation with these products on skin hydration, collagen density and collagen fragmentation. They provide clinical evidence of the efficacy of the collagen-specific peptide in improving dermal hydration as a result of increased collagen and glycosaminoglycan synthesis in the skin layers and the prevention and reduction of fragmentation of the dermal collagen network.

3. WELLNEX REPLENWELL™ (Nitta Gelatin Inc., Osaka, Japan). Replenwell™ is an optimized range of bioactive peptides rich in the two dipeptides Pro-Hyp and Hyp-Gly extracted from natural sources (bovine, porcine and marine organisms). The efficacy of the product with a molecular weight of 1 kDa was tested in a double-blind, placebo-controlled study. It was observed that skin hydration and elasticity increased statistically significantly compared to the placebo group, and roughness decreased after 8 weeks of administration of 2.5 g per day. Comparing the efficacy of the product with a low proportion of dipeptides (0.1 g/kg of product) with that of the product with a higher proportion of dipeptides (2 g/kg of product) was the objective of another double-blind, placebo-controlled clinical study. It was observed that, although both products brought improvements in skin hydration and roughness, in the case of the product with a higher dipeptide content there was a marked improvement in elasticity and reduction of wrinkles.

4. GOLD COLLAGEN® (MINERVA Research Labs, London, UK). Two nutricosmetic products containing hydrolyzed type I collagen extracted from fish with a molecular weight between 0.3 and 8 kDa were the subject of double-blind, placebo-controlled clinical studies. Subjects who consumed GOLD COLLAGEN® ACTIVE (4 g CH) or GOLD COLLAGEN® FORTE (5 g CH) for 3 months had a significant overall increase in skin elasticity (+40% in the case of the product with 4 g CH, respectively + 7.5% in the case of the product with 5 g CH), as well as an improvement in skin texture compared to placebo. Histological analysis of skin biopsies revealed positive changes in skin architecture, with a reduction in solar elastosis and an improvement in collagen fiber organization in the group that used the product compared to placebo [6].

Type II Collagen

Generally, type II collagen is used in dietary supplements for joint conditions, for example, the manufacturer Rousselot, whose product Peptan IIm® contains bioactive peptides and glycosaminoglycans, a composition that mimics that of human cartilage tissue and is promoted for maintaining good joint condition. However, there are clinical studies that have shown beneficial effects on the skin in the case of type II collagen as well. BioCell Collagen® (BioCell Technology, LLC) contains a hydrolyzed type II collagen extracted from chicken sternal cartilage. Along with collagen peptides with an average molecular weight of 1-2.5 kDa, it also contains low molecular weight hyaluronic acid and chondroitin sulfate. The product was first studied in an open pilot study on 26 healthy women who showed visible signs of aging on the face. Daily supplementation with 1 g of BioCell Collagen for 12 weeks was observed to result in a significant reduction in skin dryness/flaking (76%) and global lines/wrinkles (13.2%). The effects observed after 6 weeks of use were significant increases in hemoglobin and collagen content (6.3%) in the dermis. The results were validated in a 12-week, double-blind, placebo-controlled study [7].

Types of Collagen Formulations

Different types of hydrolyzed collagen are used in various skin and hair preparations due to their characteristics and properties, such as very low viscosity in aqueous solution, neutral odor, colorless, transparent, role as an emulsifier and stabilizer, wettability, solubility, dispersibility, compressibility (in the case of solid forms) and low allergenicity. Due to its low viscosity and high solubility in water, hydrolyzed collagen can be

added to beverages to improve their nutritional and functional properties without causing technological problems in production. The versatility of different types of hydrolyzed collagen leads to easy formulation of tablets, capsules, powders for oral dispersions, drinkable solutions and other types of pharmaceutical forms. The formulator must consider ensuring the bioavailability of the ingredients and reproducibility. The organoleptic properties of the product can influence compliance, which is a key factor in sales strategies, therefore, the use of tasteless and odorless peptides is desirable in the formulation of nutricosmetics. They allow the association of dyes and flavorings that lead to the obtaining of formulations with increased acceptability.

Adverse effects. Due to the sources of origin, collagen is a safe ingredient, for which adverse effects are very rare. However, depending on individual sensitivity, digestive adverse effects of low intensity may occur. To attribute the adverse effect to collagen, the formula of the administered product must be analyzed, as various excipients, such as polyols used as sweeteners, may also have digestive adverse effects. Products derived from fish or shellfish may cause allergic reactions, if there is a sensitivity to these sources. Producers of collagen from bovine sources are required to use raw materials only from healthy animals, without the risk of contamination with prions responsible for the production of BSE. The safety of using products containing collagen by pregnant women, breastfeeding women or children has not been proven by controlled studies, therefore caution is recommended in administration [8].

Hyaluronic acid

Hyaluronic acid (HA), also known as hyaluronan, is an anionic, non-sulfated glycosaminoglycan, well represented in connective and epithelial tissues, being an important component of the extracellular matrix of the skin with a role in the metabolism of the dermis, the main role being to maintain skin hydration due to its ability to retain water (hygroscopicity). This molecule is made up of an energetically stable oligosaccharide composed of D-glucuronic acid and N-acetyl-glucosamine groups joined by alternating β-1,4 and β-1,3 glycosidic bonds. These individual disaccharides are linked and arranged in different shapes ranging from a loop to a coil. The chain structure can have varying lengths and a relative molecular mass ranging from 10 to 1000 kDa. With such a wide range in its molecular weight, HA has acquired different elastic properties that can be used for different medicinal uses. Although it is present in all tissues, more than 50% of hyaluronic acid in the body is present in the skin and is an essential part of the wound healing and tissue scarring process due to its ability to maintain a moist environment, favorable to the stimulation of growth factors, cellular constituents and the migration of various cells essential for healing. Due to the roles that HA performs, the pharmacological uses are: anti-inflammatory, immunomodulatory, antiproliferative, antidiabetic, cicatrizing, and for cosmetic purposes it is used due to its regenerative, tissue repair and anti-aging effects. For cosmetic purposes, HA is used in topical delivery systems with a local effect on the skin, such as creams, gels, serums or transdermal formulations that deliver active compounds through the skin into the bloodstream. In topical formulations, HA is able to hydrate both the stratum corneum and the dermis due to its exceptionally strong water-absorbing property. It was observed that low molecular weight HA (5 kDa) exhibited a higher ability to hydrate the stratum corneum compared to medium (100 kDa) and high molecular weight (1 MDa). This is because high molecular weight HA increases the viscosity of the formulations, ensuring a lower diffusion rate of drugs from the formulation to the skin surface, which ultimately leads to delayed permeability. As a biocompatible, biodegradable and non-immunogenic biomaterial, HA can be easily administered by minimally invasive injections in aesthetic procedures, which is the main form in which HA is used for cosmetic purposes. Although injectable HA formulations may appear equivalent, in fact several factors such as HA concentration, degree of crosslinking, particle size, extrusion force and elastic modulus influence product selection and indications. Numerous clinical studies have aimed to study the effects of injectable HA for the correction of nasolabial and facial wrinkles or for lip augmentation, with the results always being positive. Although in most cases this method is well tolerated, it is not without adverse effects such as the appearance of nodules, granulomas, persistent edema, infections that can worsen, tissue necrosis, and injection into the eye area even leading to ischemic complications that have consequences on vision. To avoid all this, it is very important to correlate the type of product with the area where it is administered, the type of wrinkle and the depth of the injection. Another factor that indirectly influences the result obtained is the experience of the person performing the procedure, which is why these products are only sold in specialized clinics. As in the case of collagen, the level of hyaluronic acid in the skin decreases throughout life, so oral supplementation could be beneficial. Studies conducted up to 2022 that aimed to assess the effects of oral HA consumption on the skin were analyzed and concluded that daily consumption of 35 to 240 mg of HA for at least one month significantly increases skin hydration [9].

Bioavailability of hyaluronic acid. In vitro studies have shown that the physiological activities of hyaluronic acid differ depending on the molecular weight of the product, so the need for clinical studies arose. Kewpie Corporation (Tokyo, Japan) is a manufacturer of various grades of hyaluronic acid intended for use in dietary supplements. Some grades have been studied in double-blind, placebo-controlled clinical studies. The first study compared the effects of HA with a molecular weight (MW) of 800 kDa (Hyaluronsan HA-F) with those of HA with a molecular weight of 300 kDa (Hyabest® (S) LF-P). The study confirmed that daily ingestion of 120 mg of HA (800 kDa and 300 kDa) for 6 weeks increased skin hydration and improved symptoms of facial aging, such as radiance and suppleness, in subjects with dry skin. There were no statistically significant differences between the effects produced by the two HA variants, both improving signs of skin aging. In the second, Hyabest® (A) (2 kDa) and Hyabest® (S) LF-P (300 kDa) were studied. The dose used was 120 mg HA per day for 12 weeks. In both the group that consumed HA 300 kDa and the group that consumed HA 2 kDa, a reduction in wrinkles was observed compared to the placebo group. The two studies confirm the oral effects of hyaluronic acid previously observed and, in addition, represent evidence that the efficacy of HA administered orally is not influenced by the molecular weight of the product, an explanation could be the digestion stage, with HA being hydrolyzed at the digestive and intestinal levels and then absorbed.

Types of hyaluronic acid formulations. Unlike collagen, which is frequently found as a single ingredient in nutricosmetic products, hyaluronic acid is often found in combinations with other active ingredients, such as vitamins, minerals, various amino acids. The relatively low effective dose makes it possible to associate it with other ingredients, thus obtaining products with superior efficiency. High-purity hyaluronic acid is presented in the form of a tasteless and odorless powder soluble in water, being easy to formulate, however, the hygroscopicity of the molecule can be a problem in the case of solid product formulations (tablets, capsules), and the variation of viscosity depending on pH must

be a factor to be considered in the case of liquid formulations. Oral administration of hyaluronic acid is safe, the possible adverse effects being allergic reactions [10].

Vitamins

Vitamins are almost ubiquitous ingredients in nutricosmetic formulations, the most common being vitamins C, D and E, but also biotin, which has gained popularity in hair and nail care products.

Vitamin C; Ascorbic-acid or IUPAC Name: (4R,5R)-5-[(1S)-1,2-dihydroxyethyl]-4-hydroxyoxolane-2,3-dione [$C_6H_8O_6$]. Scurvy, a disease characterized by a lack of vitamin C, is characterized by symptoms such as skin spots, skin fragility, gingivitis and bleeding in the mucous membranes. Thus, vitamin C is an essential component in maintaining skin integrity, being present in the dermis and epidermis, both in the reduced and oxidized form. Among its roles, we can mention: promoting fibroblast proliferation, favoring keratinocyte differentiation and improving cohesion between the dermis and epidermis. Vitamin C also plays an important role in the synthesis and release of type IV collagen and has the ability to neutralize oxidative stress through a process of electron donation or transfer, thus contributing to the regeneration of endogenous antioxidants. These activities are necessary to maintain the skin's youthful appearance, therefore, it is a frequent ingredient in nutricosmetic formulations.

The challenges regarding formulations containing vitamin C relate to maintaining its stability. It is easily degraded in aqueous medium, at high pH, in the presence of metal ions and oxygen. Some strategies used to prevent these processes are: controlling the presence of oxygen during formulation and storage, adjusting the pH in the acidic range, choosing water-free formulations, combining antioxidants (ferulic acid, sodium metabisulfite), using more stable vitamin C derivatives and developing liposomal systems. Currently, a diversified diet rich in vegetables and fruits provides the daily requirement of vitamin C, scurvy being a forgotten disease. The recommended daily allowance (RDA) is 90 mg per day for men and 75 mg/day for women. Since it is a water-soluble vitamin and easily eliminated through urine, it is considered safe, however, digestive effects, diarrhea, nausea, abdominal cramps, have been reported at doses above 2-6 g/day [11].

Vitamin E; 5,7,8-Trimethyltocol or IUPAC Name: 2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-3,4-dihydrochromen-6-ol [$C_{29}H_{50}O_2$]. A group of 8 lipophilic molecules (tocopherols and tocotrienols) are known as vitamin E. The main sources of vitamin E are oilseeds and vegetable oils. Vitamin E works synergistically with vitamin C, which is an endogenous fat-soluble antioxidant.

Topical vitamin E has shown photoprotective effects when applied before exposure to UVA and UVB, and oral supplementation combined with topical application may enhance the beneficial effects in dry skin conditions, such as atopic dermatitis. The RDA for vitamin E is 15 mg for adults, and the maximum permissible dose is 1000 mg. In high doses, vitamin E can cause bleeding, with in vitro studies suggesting that the mechanism of action is inhibition of platelet aggregation. For this reason, caution is recommended when combining vitamin E, especially in high doses and prolonged treatment, with anticoagulants and platelet antiaggregants [12].

Vitamin D or IUPAC Name: 5-[(3aS,4S,6aR)-2-oxo-1,3,3a,4,6,6a-hexahydrothieno[3,4-d]imidazol-4-yl]pentanoic acid [$C_{10}H_{16}N_2O_3S$]. Vitamin D is a fat-soluble vitamin that occurs in 2 main forms: ergocalciferol (vitamin D2), of plant origin, and cholecalciferol (vitamin D3), derived from animal foods. The human body has the ability to synthesize vitamin D in the skin in the presence of UV radiation, which is the main source. The roles of vitamin D are multiple, the best known being its implications in the metabolism of calcium and phosphorus, and the regulation of parathyroid hormones. However, the relationship between vitamin D and skin diseases is being reviewed by some researchers, the diseases in which vitamin D seems to play a role are: psoriasis, atopic dermatitis, congenital ichthyosis, acne, hidradenitis suppurativa, vitiligo, systemic lupus erythematosus, mild polymorphic eruption, alopecia, melanoma and non-melanoma skin cancer. Vitamin D is used in various skin conditions due to its antiproliferative, antiapoptotic and immunomodulatory effects. To date, clinically proven beneficial effects exist for psoriasis and atopic dermatitis. Since the implications of vitamin D in maintaining skin health are clinically proven and in most cases sun exposure and dietary intake are insufficient to maintain an optimal vitamin D status, the use of vitamin D supplements is necessary. Currently, there is no international consensus on optimal doses, with recommendations varying from country to country between 400 and 2000 IU daily. Significant variations are also found regarding maximum safe doses, with the Endocrine Society establishing an upper daily limit of 10000 IU, and the European Food Safety Authority and the US Institute of Medicine recommending that the daily intake be below 4000 IU. The maximum permissible dose, in most countries, is 2000 IU (50 µg)/day. Being a fat-soluble vitamin, it tends to accumulate in the body, so administration is strictly done with breaks. Signs and symptoms of hypervitaminosis D are: hypercalcemia with arrhythmia, headache, nausea, weakness, hypertension, calcium lithiasis, renal failure. For this reason, caution is recommended in patients suffering from: hypercalcemia, hypercalciuria, calcium lithiasis [13].

Biotin or IUPAC Name: 5-[(3aS,4S,6aR)-2-oxo-1,3,3a,4,6,6a-hexahydrothieno[3,4-d]imidazol-4-yl]pentanoic acid [$C_{10}H_{16}N_2O_3S$]. Biotin is a water-soluble B vitamin, also known as vitamin B7 or vitamin H. It is an essential nutrient found naturally in foods such as meat, fish, eggs, nuts, and grains. It functions as a cofactor for five carboxylases involved in the metabolism of fatty acids, glucose, and amino acids. Symptoms of biotin deficiency include skin rashes, hair loss, and brittle nails, and biotin supplements are often promoted for hair, skin, and nail health.

However, clinical evidence for the effectiveness of biotin in improving brittle nails and hair loss is relatively limited, with most of the evidence being case reports or uncontrolled placebo-controlled studies. Research on the recommended daily intake or maximum tolerated dose is also limited, and toxic effects at high intake are still unknown [14].

Minerals

Copper. Oral administration of copper contributes to skin rejuvenation because this mineral promotes the proliferation of keratinocytes and fibroblasts, is an important cofactor in the enzymatic reactions necessary for the binding of collagen to elastin by lysyl oxidase, regulates the production of collagen (types I, II and V) and components of elastin fibers produced by fibroblasts (elastin, fibrillin), is a cofactor for superoxide dismutase, inhibits oxidative cellular effects such as membrane damage or lipid peroxidation and is a cofactor for tyrosinase, an enzyme essential for the biosynthesis of melanin which is responsible for skin and hair pigmentation. The RDA of copper for an adult is 900 mcg, dietary intake

is usually sufficient, a dose of 10 mg being the maximum tolerated dose. Foods rich in copper include shellfish, seeds and nuts, organ meats, whole grain products and chocolate. Chronic exposure to high doses of copper leads to liver damage and gastrointestinal symptoms (abdominal pain, cramps, nausea, diarrhea, and vomiting). Copper poisoning is rare in healthy people but can occur from drinking water with a high copper content (water distribution systems and household plumbing that allow copper to leach into the water) and in people with Wilson's disease, a rare, autosomal recessive disease [15].

Selenium. Selenium is an essential trace element in the human body, being a constituent of some enzymes with an antioxidant role, such as glutathione peroxidase, thioredoxin reductase, methionine sulfoxide reductase. Selenium is frequently found in nutricosmetic products because in the aging process, oxidative stress has significant implications, and selenium contributes to the improvement of inflammation caused by reactive oxygen species (ROS) and reduces the process of DNA damage. Numerous clinical studies have shown that the mechanisms by which selenium combats aging are related to its cellular activity. It has been observed that selenium supplementation, in vivo, significantly reduces malondialdehyde concentrations (a biomarker of oxidative stress) and improves the activity of superoxide dismutase, glutathione peroxidase and the antioxidant capacity to antagonize aging induced by D-galactose. Following clinical studies on selenium and its action on the aging process, it has been clarified that selenium supplementation has anti-inflammatory and anti-aging roles.

Although it is known that the RDA of selenium for adults is 55 mcg, more studies are needed to determine the ideal daily dose of selenium to obtain maximum skin benefit. The maximum tolerated dose is 400 mcg. Excessive selenium intake produces a garlic odor on the breath and a metallic taste in the mouth. The most common clinical signs of chronic selenium consumption are hair loss and brittleness to loss of nails. Other symptoms include skin and nervous system lesions, nausea, diarrhea, rashes, stained teeth, fatigue, irritability, and nervous system abnormalities [16].

Zinc. Zinc is an important cofactor for cellular activity and defense. It protects against lipid peroxidation, UV-induced cytotoxicity and ROS-induced oxidative stress. It plays a major role in wound healing and keratinocyte cell survival and also has an anti-inflammatory effect by inhibiting intercellular adhesion molecule 1, a pro-inflammatory marker of keratinocytes and decreasing nitric oxide production. Evidence of the importance of zinc in skin diseases is the very symptomatology of zinc deficiency in which skin lesions, delayed wound healing, hair loss, as well as other symptoms such as diarrhea, loss of appetite, growth retardation can be observed. The RDA for zinc is 11 mg for men and 8 mg for women, the main sources being oysters, seafood, red meat, nuts and cereals. The maximum tolerated dose is 40 mg. Adverse effects in case of acute zinc poisoning include nausea, vomiting, loss of appetite, abdominal cramps, diarrhea and headaches. Chronically high zinc intake can lead to mineral imbalances, such as decreased copper and iron levels, which can lead to decreased immune function. As with all over-the-counter products, vitamin and mineral dosages in nutricosmetics should be within the recommended daily allowances. Particular care should be taken in individuals who use multiple types of dietary supplements, which may contain some common ingredients, thus risking an intake that exceeds the maximum permissible doses [17].

Natural compounds

As part of the diet, plants represent an important source of nutrients, not only vitamins and minerals, but also various compounds with a significant role in human health. The effects of natural compounds on health have been known since ancient times, with plants representing important sources in the traditional medicine of each people. The multiple beneficial effects of natural compounds, but also economic considerations such as the availability of raw materials or the sustainability of sources are reasons why these substances are very often used in the food supplement industry. The implications of oxidative stress in the aging process are clinically proven; ROS are responsible for most pathological changes in human skin, such as: DNA damage, inflammatory response, reduced antioxidant production and activation / inhibition of various signaling factors that lead to collagen and elastin degradation. Wrinkles, age spots and loss of skin tone are some of the visual changes that reflect the aging process. Natural compounds used in nutricosmetic products are predominantly substances with antioxidant effects such as polyphenols or carotenoids [18].

Polyphenols. Polyphenols are a very diverse group of natural compounds consisting of three main categories: phenolic acids, flavonoids and nonflavonoids. These compounds are highly studied as anti-aging agents due to their antioxidant activity. A specific study on the potential uses of polyphenolic compounds in nutricosmetics was carried out by some researchers who analyzed polyphenol-rich extracts obtained from various species of maple, birch and pine. Their results showed that the extracts have ROS-inhibiting potential and the ability to inhibit enzymes involved in the loss of skin elasticity and hyperpigmentation and could act as anti-aging agents. The main polyphenolic compounds found in nutricosmetics are resveratrol, quercetin (synonym quercetin), curcumin and catechins / epigallocatechin 3-O-gallate (EGCG). Numerous studies have established that the benefits of these compounds are based on antioxidant and anti-inflammatory mechanisms. The inclusion of polyphenols in nutricosmetic products can raise formulation issues regarding their stability and bioavailability. The polyphenol content of a product is very easily influenced by a series of reactions caused by acidity, heat, light and the presence of certain enzymes that can occur during the processing of fresh fruits and vegetables. The relatively low solubility in water is a disadvantage that influences bioavailability. Therefore, the formulation of polyphenols requires some methods to protect them such as inclusion in liposomal forms or the formation of complexes with higher solubility [19].

Carotenoids. Carotenoids are isoprenoid metabolites synthesized by all organisms capable of photosynthesis, and for humans they are essential nutrients, the exogenous intake being necessary for the production of retinoids such as vitamin A. These compounds represent the most efficient singlet oxygen ($^1O_2$) neutralizing agents in biological systems with a protective role against oxidative damage caused by UV light in the tissues in which they accumulate: β-carotene in the skin and lutein and zeaxanthin in the macula lutea. Several studies have demonstrated that carotenoid supplements protect the skin from UV-induced erythema. In addition to the photoprotective effect, they have also proven beneficial effects in preventing and improving skin aging (improved skin elasticity and hydration, skin texture, wrinkles and age spots). Therefore, the inclusion of carotenoids as antioxidant ingredients in nutricosmetics is justified by their effects and their accumulation in the target tissue, the skin [20].

Conclusions

The aging process and, implicitly, the general state of health are influenced by three main factors: genetics and family history; lifestyle and physical exercise and, last but not least, diet and nutrition. Nutrition is probably the most accessible solution in preventing aging and its associated morbidity, and the multitude of nutricosmetic products is proof of this. Collagen is the main structural element of the skin that undergoes changes throughout life, determining the general appearance of aging skin. Maintaining collagen levels from youth to old age is a challenge because interventions can only be carried out on extrinsic factors. This is also the reason why collagen is the main ingredient in nutricosmetic products, with research focusing both on finding sustainable and efficient sources and on optimizing extraction methods and discovering the perfect qualitative and quantitative composition. Supplementing the diet with collagen peptides has been shown to be effective in slowing down the aging process, thus contributing to an increase in the quality of life. As has been observed, not all products containing collagen are equivalent, on the contrary, the differences between them being very large. Choosing a product that contains a clinically tested form of collagen is always an advantage. Even though hyaluronic acid produces rapid effects when administered by an invasive method, oral intake has shown that it can be a promising ingredient in nutricosmetics.

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