cosmetics

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Review

Biotechnology Applied to Cosmetics and Aesthetic Medicines

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Abstract: Biotechnology uses microorganisms and/or enzymes to obtain specific products through fermentative processes and/or genetic engineering techniques. Examples of these products are active ingredients, such as hyaluronic acid, kojic acid, resveratrol, and some enzymes, which are used in skin anti-aging products. In addition, certain growth factors, algae, stem cells, and peptides have been included in cosmetics and aesthetic medicines. Thus, biotechnology, cosmetics and aesthetic medicines are now closely linked, through the production of high-quality active ingredients, which are more effective and safer. This work describes the most used active ingredients that are produced from biotechnological processes. Although there are a vast number of active ingredients, the number of biotechnological active ingredients reported in the literature is not significantly high.

Keywords: biotechnology; cosmetics; cosmetic ingredients; skin care; genetic engineering

1. Introduction

Biotechnology is defined as the application of knowledge in life sciences to create products or services that are beneficial to humans, being used to improve the quality and efficiency of food production, or even the production of cosmetic active ingredients, drugs, and vaccines [1].

In prehistory, a primitive form of biotechnology was practiced by farmers who established species of plants and animals of better quality by methods of cross-pollination or cross-breading. The selective breeding of animals; the cultivation of crops; and the use of microorganisms to produce products such as cheese, yogurt, bread, beer, and wine are considered previous forms of biotechnology. Currently, biotechnology places more emphasis on the development of hybrid genes, followed by their transfer to different organisms [2].

This area has important applications, for example, in agriculture for the development of transgenic plants, in health through the production of biopharmaceuticals, in preserving the environment by creating sustainable solutions that help to protect the natural environment, and in industry for the production of ethanol and biogas [3]. It also encompasses many disciplines, such as biochemistry, biology, and engineering, among others [2].

The applications of biotechnology are so extensive that, currently, almost all industries can use this technology. This means that these industries can produce new or better products faster and more efficiently. Technological advances will provide a better understanding of the relationship between genetics and biological function, unravel the underlying causes of certain diseases, explore the association between genomic variation and response to drugs,

improve pharmaceutical research, and stimulate discovery and development of new biopharmaceuticals, for example [2]. Modern biotechnology can provide the means to combat rare and disabling diseases, reduce environmental impacts, and achieve more efficient manufacturing processes [4].

Since biotechnology became a growing area, there are currently more than 250 products obtained by biotechnological processes, including therapeutic proteins and monoclonal antibodies [4].

Biotechnology has had an impact on cosmetics in several ways. Cosmetics companies use biotechnology to discover, develop, and produce components of cosmetic formulations and to evaluate the activity of these components on the skin, in particular, how they can affect the changes associated with aging. Thus, biotechnology represents a good alternative tool for developing active ingredients that are able to slow down the aging process [5]. In this review, we focus on the description of all the active ingredients obtained through biotechnological processes, found in the available literature.

2. Fermentation Processes

Classical biotechnology is related to fermentation processes, which are defined as operations where microorganisms such as bacteria, fungi, yeast, and some enzymes are used to obtain biotechnological products [6]. Microorganisms have proved to be particularly useful owing to their ease of mass cultivation, speed of growth, use of cheap substrates, and the diversity of products they can originate [7].

In most industrial fermentation processes, there are several stages. These can include several stages of propagation of the inoculum (starter culture), pilot scale fermentations, and the main production fermentation [7]. Traditionally, these processes have used the general property of microorganisms to convert substrates (e.g., glucose and oxygen) into products such as ethanol, organic acids (citric, lactic), aminoacids (lysine, glutamic acid), and antibiotics (penicillins, cephalosporins) [6]. In 1978, Boyer inserted the human insulin gene in *Escherichia coli*, to produce human insulin, through fermentation processes [2]. These microorganisms can ferment various substrates and the final products depend on the specific microorganism, the substrate, and the enzymes that are present and active [8].

The containers used to carry out fermentation processes at the industrial level are called bioreactors. The main function of a bioreactor is to provide a suitable environment (e.g., optimal temperature and pH), where an organism can efficiently produce products (e.g., cell biomass, metabolites, or bioconversion products) from substrates that are supplied to the bioreactor medium [7].

Bioreactors can also be widely used to culture plant cells for the large-scale production of recombinant proteins, secondary metabolites, and cosmetic ingredients [2]. Bioreactor-based cell culture systems, which can be rapidly scaled-up and are free of mammalian pathogens, have been adopted by traditional fermentation-based companies [9]. For industrial fermentation processes, the bioreactors used are very large, storing around 500,000 L of medium [8].

The operation of a bioreactor generally consists of introducing air through a diffuser at the base (which interrupts the air flow received to maximize aeration), and a series of impeller blades and the deflector wall that prevent the passage of fluids and maintain the suspension under agitation [8]. Bioreactor operations are critical for the successful development of large-scale production processes. Thus, fermentation systems must be efficiently controlled to optimize productivity and product yield [7].

3. Recombinant DNA Technology

Recombinant DNA technology involves the manipulation of genetic material (i.e., DNA) outside the native organism to obtain a new genetic combination that allows the production of compounds with improved characteristics, on a large-scale [10].

A vector is a DNA molecule that carries exogenous DNA into a cell. Exogenous DNA is inserted into the vector in vitro. The DNA molecule chosen as a vector must be self-replicating, like a plasmid or a viral genome. This recombinant DNA vector is introduced into a cell, where it can multiply. The cell containing the recombinant vector is then multiplied in culture to form a clone of many genetically

identical cells, each carrying a copy of the vector and, therefore, many copies of the gene of interest [8]. The DNA sequences that are used in the construction of recombinant DNA molecules can be originated from any species. In addition, small DNA sequences that do not occur in nature can be created by chemical synthesis of DNA and incorporated into recombinant molecules [11].

This field combines elements from two other areas of study, including microbial genetics, which studies the mechanisms by which microorganisms inherit characteristics, and molecular biology, which studies how genetic information is transported in DNA molecules and how DNA directs protein synthesis [8].

Applications of recombinant DNA technology are increasing every year. The discovery of this technique offered new opportunities for the development of a wide range of biopharmaceuticals, modifying microorganisms, animal cells, and plants, to produce useful substances for medical use [12].

Most biopharmaceuticals obtained by biotechnological processes are recombinant and play a key role against human lethal diseases. So, this technology plays a vital role in improving health conditions by developing new vaccines, biopharmaceuticals, and other ingredients [13]. Human insulin produced by genetically modified *E. coli* was the first marketed biopharmaceutical derived from recombinant DNA technology [14].

4. Active Ingredients Obtained by Biotechnological Processes

According to European Commission Regulation No 1223/2009, a cosmetic product means any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips, and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly of cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition, or correcting body odours [15].

There are several chemical compounds that have been used in cosmetics and that may have potential adverse effects on their users. Because of these effects and the environmental impact of chemical compounds, herbal extract cosmetics have attracted consumer's interest and have become very important in the cosmetics industry since the early 1990s. Currently, some certain compounds resulting from biotechnological processes have shown interesting skin care properties and may come to be considered effective ingredients [16].

4.1. Kojic Acid

Kojic acid (KA) (5-hydroxy-2-hydroxymethyl-pyran-4-one) is widely used in food, pharmaceuticals, and the cosmetics industry [17,18].

KA can be used as a fungistatic agent against the pathogenic yeast, *Cryptococcus neoformans*, inhibiting the production of melanin necessary for this fungal infection. It can also be used as a skin lightener or depigmentant in cosmetics [19,20].

It is a natural pyrone produced by certain filamentous fungi, mainly by species of *Aspergillus* and *Penicillium* [19]. *Aspergillus oryzae* is a microorganism that produces large amounts of compounds, including proteins. Its genetic modification processes are well known, and KA is one of the major secondary metabolites of this microorganism [21]. This compound is obtained from soybean and rice fermentation by *Aspergillus oryzae*, thus being widely used in cosmetics as a depigmenting agent [22,23].

Abnormal melanin production is the cause of hyperpigmentation, post inflammatory pigmentation, melasma, and the aging process of the skin [24,25]. Kojic acid is a well-known inhibitor of the tyrosinase enzyme, used in the treatment of hyperpigmentation, melasma, and wrinkles [26–28]. The properties of KA esters are important for inhibiting melanin synthesis. These molecules must penetrate the cell membrane to inhibit the synthesis of cellular tyrosinase and, consequently, the synthesis of melanin, which is one of the products of the action of this enzyme [29].

Nanodelivery systems, such as polymeric nanoparticles and liposomes, have been studied to transport KA through the skin in order to inhibit the synthesis of melanin. There are already some commercial cosmetic products containing KA, including lotions, creams, and soaps [20].

4.2. Hyaluronic Acid

Hyaluronic acid (HA) is a nonsulfated glycosaminoglycan composed of repeated disaccharide units of D-glucuronic acid and *N*-acetyl-D-glucosamine [30]. This natural biopolymer is particularly concentrated in the extracellular matrix of smooth connective tissue, skin dermis, eye vitreous fluid, hyaline cartilage, synovial joint fluid, intervertebral disc, and umbilical cord [31].

The HA molecule has interesting properties, such as versatility, biocompatibility, biodegradability, and mucoadhesiveness [32,33], which allow its use in different medical, pharmaceutical, and cosmetic applications [32]. When HA networks are strengthened, owing to increased molecular weight and concentration, HA solutions increase viscosity and viscoelasticity. These properties allow the HA molecules to be used in cosmetics to restore hydration and elasticity, while improving the skin's appearance [34].

HA is found in the extracellular matrix and interfaces of collagen and elastin fibers. In aged skin, these connections are particularly absent, which may contribute to the disorganization of collagen and elastin fibers, and thus lead to skin aging [35]. Even though the mechanism of skin aging is not fully understood, it is evident that, during this process, the dermis loses HA, thus resulting in dehydration of the skin and the appearance of wrinkles [36]. Bukhari et al. concluded that HA had a high cosmetic efficiency, for example, in reducing wrinkles and aging. Besides, these authors proved that nanodelivery systems containing HA enhanced its penetrability across the biological membranes [35].

HA is a moisturizing active ingredient widely used in cosmetic formulations (gels, emulsions, or serums) to restore the appearance of the skin.

Nowadays, commercial HA is mainly obtained through microbial fermentation [37]. The most frequently used bacteria in the industrial production of this compound are *Streptococcus*. However, this genus is known to have several human pathogens and, therefore, the costs of HA purification using these bacteria are high [38].

Therefore, genetically modified microorganisms were considered for HA production [37]. One of such microorganisms is *Bacillus subtilis*, which is one of the most widely used models in genetic engineering, which guarantees products free from any endotoxin [39].

4.3. Resveratrol

Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) is a polyphenol produced by plants under microbial attack, possesses a wide range of biological activities, and can be used as antioxidant and anti-inflammatory [16]. Furthermore, resveratrol is also widely used as a dietary supplement [40].

A cosmetic formulation based on resveratrol showed an antioxidant potential 17 times greater than idebenone, and its topical application resulted in protection against photoaging [41]. Resveratrol has been shown to be effective in neutralizing the formation of reactive oxygen species under in vitro conditions [42].

However, the beneficial effects of resveratrol are limited owing to its instability when the molecule is exposed to light and oxygen, or also in environments with severe pH conditions. These stimuli can cause isomerization or oxidation, which lead to a reduction in the bioavailability and bioactivity of the compound. For this reason, it is important to develop resveratrol derivatives like *trans*-resveratrol with enhanced stability [43].

The polyphenol *trans*-resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) is one of the best-known plant secondary metabolites. *Trans*-resveratrol, one of the isomeric forms of resveratrol, has powerful antioxidant properties and can play an important role in skin anti-aging [44].

For industrial purposes, resveratrol is generally obtained by biotechnological processes, using yeasts *Saccharomyces cerevisiae* or *Pichia pastoris* [42]. As *trans*-resveratrol is an interesting molecule for human health, it was important to develop an effective method to obtain it commercially [44]. Genetic modification of yeast and bacteria with genes encoding enzymes of the *trans*-resveratrol production pathway may lead to increased bioproduction of this compound. For example, Transderma (Sweden) created a serum containing *trans*-resveratrol that delivers antioxidant benefits to the skin [45].

4.4. Growth Factors

A growth factor is defined as a biologically active molecule that is secreted and can affect cell growth. Growth factors may act on specific cell surface receptors that subsequently transmit these cell signals to other intracellular components [46]. The ability of growth factors to promote growth, differentiation, and/or cell division has attracted the attention of not only the pharmaceutical industry, but also the cosmetics industry [47].

Human growth factors are considered extraordinary molecules in the cosmetics industry, thanks to their important role in skin care [16]. The use of these molecules for skin rejuvenation is thought to be an emerging and promising strategy. Advances in knowledge of the role of growth factors in wound healing and regeneration have aroused great interest in the role that these molecules may play in the repair of skin structures [48]. As the endogenous functionalities of the growth factors decrease as a result of the smaller reduction of skin cells during skin death, an exogenous supplementation of growth factors can promote the repair of aging skin and revitalize it. A combination of growth factors together with antioxidants, matrix building agents, and skin conditioning agents can be effective in treating skin anti-aging [16]. A cosmetic formulation based on this combination of ingredients was launched on the market, called TNS (Tissue Nutrient Solution) Recovery Complex System with NouriCel-MD^{TM} (USA). This product promoted the disappearance of wrinkles and pigmentation and, at the same time, improved skin firmness [49].

Growth factors can be applied topically or injected. Several clinical studies have shown that topical application of animal growth factors, or the injection of autologous growth factors, can also increase collagen synthesis in the dermis. The purpose of administering topical or injectable growth factors is to increase the activity of the cells responsible for the remodeling of the dermis, in order to delay or reverse the aging of the skin [50]. The clinical applications of topical and injectable growth factors are promising and still need to be studied in terms of their safety, efficacy, tolerability, and stability.

Human epidermal growth factor (hEGF) can speed up the healing process and was also found to be effective in the treatments of wrinkles, age spots, and freckles [51,52]. Pure hEGF can potentially be produced on a large scale through genetic engineering. HEGF had been produced in several hosted systems, including *E. coli* [53] and *S. cerevisiae.* When *E. coli* is used as host, the yield is not appropriate for industrial requirements, as the hEGF cytoplasm tends to form inclusion bodies, which can be rapidly degraded by proteases. Thus, the total production cost ends up increasing owing to the additional production steps required to release hEGF from inclusion bodies. In addition, the hEGF produced by prokaryotic systems is lower compared with that produced by eukaryotic systems. Therefore, the use of eukaryotic systems, such as *P. pastoris*, can produce the growth factor on a large scale [51]. Skin Actives (USA) markets heterologously expressed EGF in *E. coli* to use as a skin conditioning agent [16].

4.5. Enzymes

Enzymes are proteins that are present in living organisms and catalyze several biochemical reactions that are necessary for life [54].

Isolated microorganisms from various environments represent a source of enzymes that can be used in industrial processes. Using recombinant DNA technology, it is possible to clone the genes encoding these enzymes, and thus express them heterologously in strains commonly used in the pharmaceutical and cosmetics industries [16].

In the cosmetics industry, various types of enzymes are used to develop formulations that facilitate the course of biochemical skin reactions, protecting the skin from aging. These enzymes are also responsible for protecting the skin against some external agents (such as UV radiation) and against free radicals [55].

The use of enzymes in cosmetics provides a specific biochemical pathway that is more beneficial and leads to a better performance of the skin. One of such enzymes is the superoxide dismutase (SOD), which through its mechanism of action, prevents damage caused by free radicals and other harmful pollutants [16]. SOD enzymes control the levels of a variety of reactive oxygen species (ROS) and reactive nitrogen species (formed through UV exposure and other radiation, as well as from normal cellular metabolism), limiting the potential toxicity of these molecules and controlling cellular aspects that are regulated by their signaling functions [56]. ROS produced in the metabolic pathways have been shown to lead to skin deterioration and, therefore, SOD is considered an anti-aging enzyme as it helps to remove these ROS in humans. In addition, SOD maintains the integral keratin structure, promotes skin elasticity, and provides a smooth feeling to the skin [57]. SOD can be obtained through genetic modification of *S. cerevisiae* [58].

Proteases are enzymes that break down proteins into peptides and later into amino acids [7]. In cosmetics, proteases are primarily aimed at promoting skin exfoliation, which corresponds to the scaling of the keratinized superficial corneal layer, and to increase the absorption of water and other ingredients present in cosmetics. By promoting exfoliation, these proteases will improve the appearance of the skin. Bromelain, papain, and chymotrypsin are the examples of herbal proteases used in cosmetics, but cannot be used by most individuals, owing to the risk of allergy [16]. Seki et al. reported that subtilisin, a serine protease produced by *Bacillus licheniformis*, is an effective skin exfoliator [59]. Commercial proteases for cosmetic use can be obtained by the recombinant DNA technology [16].

Another type of enzyme that has gained interest is DNA repair enzymes such as photolyases. When DNA repair is deficient and the melanin present in the skin cannot protect the skin from the damage caused by solar radiation, the risk of accumulation of cancer-induced mutations induced by UV radiation may increase. DNA photolyases can reverse these lesions by eliminating thymine dimers that are formed and play a critical functional role in DNA repair [60]. Navarrete-Dechent and Molgó performed a clinical study to evaluate the usefulness of a new topical sunscreen containing DNA photolyase for the treatment of actinic keratoses. The cream used was applied twice a day for three months. They concluded that DNA photolyase decreased the number of lesions, supporting a role for photolyase as a treatment to reverse UV damage. These results have encouraged the research for new highly active photolyases and the development of photolyase-containing products [61]. Marizcurrena et al. produced a bacterial recombinant photolyase from *Hymenobacter* sp. UV11, and did the characterization of its DNA repair ability. So, an enzyme was easily produced in a host cell and showed potential UV-damaged DNA repair activity in vitro. This work showed that the results obtained could contribute to the development of cosmetic products containing photolyases [62].

4.6. Algae

Billions of years ago, algae adapted to adverse and competitive environments, producing compounds and secondary metabolites for their protection, and being able to live in a wide range of ecological niches. Algae size ranges from microscopic individual microalgae cells to much larger organisms, macroalgae, which may reach above 30 m [63].

Microalgae are a rich source of various bioactive molecules, such as carotenoids, lipids, fatty acids, proteins, and amino acids, among others [63]. Significant advances have been made in microalgae biotechnology, with microalgae suspensions cultures being used to produce recombinant proteins and other valuable ingredients that can be used in cosmetics [64].

One of these microalgae is *Spirulina*, which has been used in cosmetics [65]. Maia Campos et al. developed some preliminary studies and showed antioxidant potential, skin compatibility,

and immediate effects on the skin hydration with formulations containing *Spirulina* extract obtained by biotechnological processes [66]. This alga produces a bioactive compound, phycocyanin, which has antioxidant properties and repairs the signs of premature aging [67]. The use of *Spirulina* extracts in dermocosmetic formulations allows the development of more stable and safe formulations, and at a lower cost. However, long-term studies are needed to prove its anti-aging effectiveness [65].

In addition to *Spirulina* extracts, *Chlorella* extracts are also used in skin care to repair the signs of premature aging, stimulate collagen synthesis, prevent stretch marks, and reduce wrinkles [68]. Many *Chlorella* strains can grow rapidly and achieve high cell density under controlled conditions, and are thus considered promising protein sources. These microalgae can serve as hosts to produce various components through genetic engineering [69].

Another well-known microalga is *Dunaliella salina*, which is rich in carotenoids, mainly β-carotene, which has anti-aging properties [70]. For cosmetic applications, it is important that no toxic organic solvents are used in the separation process of β-carotene [16].

Macroalgae produce bioactive compounds including proteins, polyphenols, and some pigments. The cosmetic industry is also interested in using macroalgae as a source of biosustainable ingredients as they are extremely rich in biologically active compounds [71].

4.7. Stem Cells

A stem cell is an undifferentiated cell that can self-renew to replicate or can originate several specialized cell types [72]. For example, hematopoietic stem cells can differentiate into red blood cells, white blood cells, and platelets [73].

Owing to the limited life cycle of most somatic cells, the ability of stem cells to replace damaged somatic cells is crucial for the tissue homeostasis of many organisms. Therefore, there is a tremendous interest in understanding the mechanisms of stem cells' self-renewal and differentiation, given their potential applications in regenerative medicine and aging studies [74].

With aging, the functional capacities of stem cells diminish, resulting in reduced organ function and delayed tissue regeneration. Thus, the decrease in stem cell function results in changes in the physiology of the tissue itself, which may affect the organism's health and viability [75].

Unlike human cells, plant cells are not only capable of regenerating tissues, but can also originate a new plant [76]. For cosmetics, plant stem cells are reproduced in cell culture by a micropropagation method, which is involved in vitro cell culture. Many companies scaled up the production of stem cells from in vitro cultures to bioreactors that are used on a large scale. Plant stem cell extracts are sources of many active ingredients that are safe for the human body [77].

Plant stem cells are responsible for several effects, such as the following [78,79]:

- Prolongation of fibroblasts life;
- Increased epidermis flexibility;
- Regulation of cell division;
- Reconstruction of damaged epidermis;
- Activation of cell DNA repair;
- Protection against UV radiation.

The pioneer company in the production of plant stem cells for the cosmetic industry is Mibelle AG Biochemistry (Switzerland), which produced liposomes containing apple stem cells from *Uttwiler Spätlauber*, a rare variety of Swiss apple (PhytoCellTec™ *Malus domestica*), in 2008. The clinical study that was conducted confirmed the efficacy of these stem cell extracts in reducing wrinkles after 28 days [80]. This company has also introduced plant stem cell extracts from *Vitis vinifera* (PhytoCellTec™ Solar Vitis, Switzerland), *Saponaria pumila* (PhytoCellTec™ nunatak®, Buchs, Switzerland), and *Argania spinosa* (PhytoCellTec™ Argan, Switzerland) in the cosmetics market. These extracts are presented in the form of a suspension and also show great effects in the treatment of wrinkles and improve the activity of epidermal stem cells [81].

Stem cells from other plants have also been tested. For example, *Syringa vulgaris* contains verbascosides with skin anti-inflammatory and anti-aging effects [77]; *Lycopersicon esculentun* from tomato has antioxidant properties, protecting skin cells from oxidative stress [81]; *Coffea bengalensis* and *Nicotiana sylvestris* stimulate fibroblasts collagen production, promoting skin regeneration [81,82]; orange stem cells (Citrustem^{TM}) improve skin elasticity and smoothness [77,83]; and stem cells from ginger leaves (*Zingiber officinale*) reduce skin pores and sebum production, which leads to a smooth texture [81,84].

According to some studies, one of the strongest inhibitors of the human cell aging process is kinetin, which is a cytokinin found in high concentrations in stem cells of, for example, citrus fruits and raspberries [85]. Kinetin is a natural antioxidant that protects proteins and nucleic acids from oxidation processes and other types of damage [86,87]. This compound allows cells to remove the excess of free radicals to protect them from oxidative stress and can be responsible for reducing the protein glycation. This cytokinin has been found to contribute to the prevention of skin aging [77,88]. Kinetin, which can be designated as a natural growth hormone, is important for stimulating skin stem cells as it improves the epidermis barrier function, stimulates keratinocytes production, reduces trans-epidermal water loss, and reduces superficial wrinkles [88,89]. According to the literature, kinetin has little or no photoprotection effect compared with other compounds and, therefore, should not be used in sunscreens [90].

4.8. Peptides

Naturally occurring peptides are known to play diverse biological roles, primarily as signaling molecules in a wide variety of physiological processes, including immunity, stress, growth, homeostasis, and reproduction [91].

The signaling function is the result of matricins, which are small peptides originating from the extracellular matrix that result from the breakdown of dermal proteins. These peptides can increase the production of collagen and other extracellular matrix molecules, promoting skin rejuvenation, mainly at the papillary dermis [92].

The pharmaceutical and cosmetics industries, through biotechnological processes, have been developing many peptides that play an important role in extracellular matrix synthesis, pigmentation, innate immunity, and inflammation [93]. The main barrier for topical products is the stratum corneum, the outermost layer of the epidermis, and, for example, chemical penetration enhancers can be useful for dermal delivery of peptides [94]. During aging, the extracellular matrix components undergo progressive loss and fragmentation, leading to thin and structurally weakened skin. Several studies have shown that high molecular weight molecules, such as peptides (more than 500 Da), can cross the skin barrier, especially in the case of dry and aged skin [95,96].

Peptides can be divided into three groups: signal peptides, carrier peptides, and neurotransmitter-inhibiting peptides [48]. Signal peptides or matricins act as messengers that trigger the synthesis of collagen by fibroblasts. This increase in collagen synthesis will lead to firmer and more youthful-looking skin [48,93]. Carrier peptides use or stabilize trace elements such as copper and manganese, necessary for wound healing and enzymatic progress. The expected effect is a better texture and appearance of the skin owing to the production of collagen [48,97]. Neurotransmitter-inhibiting peptides were developed to mimic botulinum toxin, blocking acetylcholine release at the neuromuscular junction. These peptides penetrate the skin and relax muscles, causing the reduction and softening of wrinkles and fine lines [48]. Table 1 summarizes some peptides that can be used in cosmetics and that have been shown to be effective on human skin.

Table 1. Topically used peptides.

Peptide Type	Peptide Name
Signal peptides or matricins	Palmitoyl Tripeptide-1 Palmitoyl Tetrapeptide-7 Palmitoyl Pentapeptide-3 Palmitoyl Oligopeptide
Carrier peptides	Copper tripeptide
Peptides mimetics or neurotransmitter-inhibiting peptides	Pentapeptide-3 Acetylhexapeptide-3

The development of active peptides has opened a new field in cosmetical skin care in the last decade. The two types of signal peptides most used in cosmetics are Palmitoyl oligopeptide and Palmitoyl tetrapeptide-7. Palmitoyl oligopeptide will stimulate dermic cells into producing more collagen. When used twice a day for at least six months, many users have experienced firmer and tighter skin; Palmitoyl tetrapeptide-7 is used to reduce inflammation in the skin, in situations of sun damage, internal stress, or even pollution. Thus, this peptide prevents premature wrinkles and skin damage, which are a consequence of this inflammation; Maytrixyl®-3000 is relatively new on the cosmetic market. This peptide combines Palmitoyl oligopeptide and Palmitoyl tetrapeptide-7 and stimulates the human fibroblasts that control collagen production in the skin [98]; Palmitoyl tripeptide-1 is used in cosmetics in anti-wrinkle skincare. In a study with 15 women, a cream containing Palmitoyl tripeptide-1 was applied twice daily for four weeks, leading to statistically significant reductions in wrinkles [93]. It has been proven that Palmitoyl pentapeptide-3, one of the most researched forms of peptide, stimulates the production of collagen and fibronectin in the body, which plays an important role in skin health [98].

Copper tripeptide is used in anti-aging, anti-wrinkle, after-sun, skin renewal, skin moisturizer, and hair growth stimulating products [93]. One study compared the skin's production of collagen after applying creams containing copper tripeptide, vitamin C, or retinoic acid to thighs daily for one month, in 20 women. One month later, copper tripeptide increased collagen in 70% of the women, versus 50% treated with vitamin C, and 40% treated with retinoic acid [99].

Pentapeptide-3 is an antagonist of the acetylcholine receptor, and blocks nerves at the post-synaptic membrane, leading to muscle relaxation. Most clinical studies demonstrated a reduction of wrinkles and lesser skin roughness, after a treatment of 28 days [93]; Acetyl hexapeptide-3 had promising results. The depth of wrinkles was reduced more than 30% versus 10% for the placebo after 30 days [98].

Many of the peptides that are marketed aim to slow or even reverse the aging process of the skin and are used for collagen stimulation, wound healing, "Botox-like" wrinkle smoothing, as well as antioxidative and antimicrobial effects. In addition, substance mixtures are on the market and are tested in cosmetic formulations, in case the actual effect of individual peptides on the skin remains unclear [93].

5. Conclusions and Outlook

Currently, the cosmetics market has gained interest worldwide, owing to a more active and consistent participation of consumers, who started to use these products more frequently.

The cosmetics industry, through biotechnological processes, has contributed to obtaining a wide variety of cosmetic active ingredients. Through these processes, it is possible to produce active ingredients at large-scale, with lower costs, and free of contaminants. For example, kojic acid, hyaluronic acid, and resveratrol, among other biotechnological active ingredients, have been found in various types of cosmetic products, especially for skin care. Thus, biotechnology, cosmetics and aesthetic medicines have been closely intertwined, allowing for new effective and safe formulations of active ingredients. Despite that this is a very promising area, currently, the number of biotechnological

cosmetic products is small, although its increase is expected soon. For example, producing active ingredients with different cosmetic applications.

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