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Review

Advantages of Hyaluronic Acid and Its Combination with Other Bioactive Ingredients in Cosmeceuticals

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Abstract: This study proposes a review on hyaluronic acid (HA) known as hyaluronan or hyaluronate and its derivates and their application in cosmetic formulations. HA is a glycosaminoglycan constituted from two disaccharides (N-acetylglucosamine and D-glucuronic acid), isolated initially from the vitreous humour of the eye, and subsequently discovered in different tissues or fluids (especially in the articular cartilage and the synovial fluid). It is ubiquitous in vertebrates, including humans, and it is involved in diverse biological processes, such as cell differentiation, embryological development, inflammation, wound healing, etc. HA has many qualities that recommend it over other substances used in skin regeneration, with moisturizing and anti-ageing effects. HA molecular weight influences its penetration into the skin and its biological activity. Considering that, nowadays, hyaluronic acid has a wide use and a multitude of applications (in ophthalmology, arthrology, pneumology, rhinology, aesthetic medicine, oncology, nutrition, and cosmetics), the present study describes the main aspects related to its use in cosmetology. The biological effect of HA on the skin level and its potential adverse effects are discussed. Some available cosmetic products containing HA have been identified from the brand portfolio of most known manufacturers and their composition was evaluated. Further, additional biological effects due to the other active ingredients (plant extracts, vitamins, amino acids, peptides, proteins, saccharides, probiotics, etc.) are presented, as well as a description of their possible toxic effects.

Keywords: hyaluronic acid; cosmeceuticals; biological activity; skin health; moisturising effect; anti-ageing effect; bioactive compounds; molecular weight; hyaluronan derivates

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1. Introduction

Hyaluronic acid (HA) is a polysaccharide belonging to the glycosaminoglycans, made up of disaccharide units constituted of N-acetylglucosamine and D-glucuronic acid (Figure 1). It is a component of the connective, epithelial, and neural tissues and it represents a substantial constituent of the extracellular matrix (ECM) [1–6]. HA was discovered for the first time in the vitreous humour of the eye in 1934, and in 1964 it was synthesized in vitro [7–9]. HA has a wide range of molecular weights ranging from 2×10^5 to 10^7 Da [10–13]. The HA average molecular weight can influence its physico-chemical properties [3,14].

Among the many biological effects, HA is involved in cell differentiation, embryological development, inflammation, wound healing, viscoelasticity, etc. [15]. As it has been observed, the molecular mass and the mode of its synthesis or degradation define

the HA biological effects [3,16,17]. By a passive mechanism, high molecular weight HA (HMW-HA) permits the tissue hydration, contributes to the osmotic balance, and stabilizes the ECM structure. On the other hand, HA interacts with different receptor binding proteins, and its molecular weight can influence the receptor affinity or its uptake by the cells, leading to opposite effects. For example, HMW-HA inhibits the cell growth (angiogenetic activity) and protects the articular cartilage due to its lubrication properties. Low molecular weight HA (LMW-HA) has angiogenetic activity and can induce tumor progression or presents pro-inflammatory activity [15,16]. Thus, the biological activity of HA is due to its binding to different receptors. For example, the binding HA-CD44 transmembrane receptor mediates cell adhesion and migration in many physiological or pathophysiological processes: (a) angiogenesis; (b) ECM structure (linking the HA with cytoskeleton); (c) inflammation (upregulation of the receptors overexpresses the interleukin-1); (d) wound healing; (e) malignant tumors (e.g., pancreatic, breast, lung, etc.). The CD-168 receptor (Receptor for Hyaluronan-Mediated Motility, RHAMM) localized on the cell surface has an important relevance in cell migration. When the receptor is situated intracellularly, it affects the activity of the mitotic spindle. As a result, the HA-RHAMM links can influence the inflammation and tissue repair processes. The HARE (Hyaluronan Receptor for Endocytosis) receptors modulate the glycosaminoglycans clearance. The lymph absorption of HA, implicitly the HA turnover, is controlled by LYVE1 (Lymphatic Vessel Endothelial Hyaluronan receptor-1). As a result, HA-LYVE1 interaction influences the tissue biomechanical properties, including its hydration. Referring to the HA interaction with TLRs (Toll-Like Receptor), it is noticed that LMW-HA has an inflammatory effect, because of its agonist activity on TLR-2 and TLR-4. On the other hand, a high mass of HA decreases the binding capacity to the receptors, forming a dense coat around the cell and covering the receptor surface [15,16,18,19].

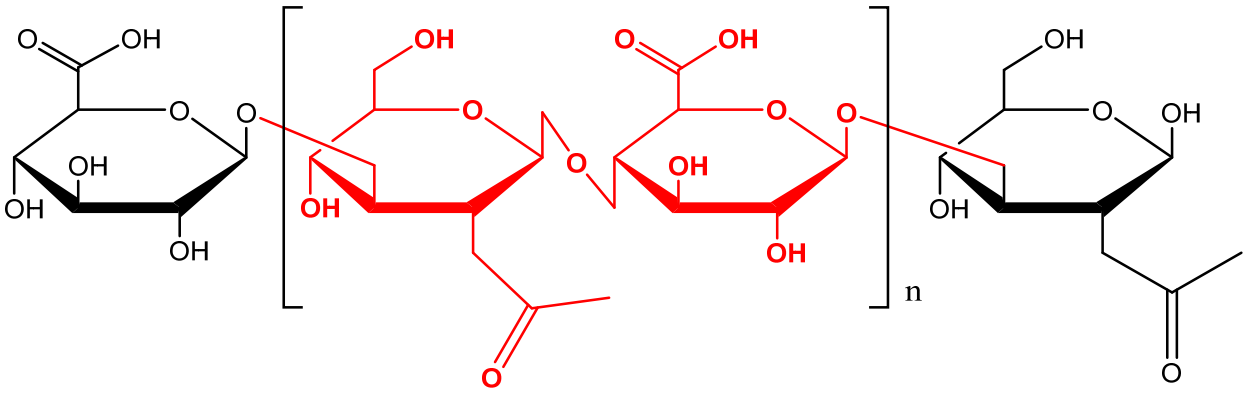

Figure 1. Chemical structure of hyaluronic acid (HA).

Nowadays, there are a lot of studies conducted in order to elucidate the mechanism of action and the biosynthetic pathways of HA, or to optimize its biotechnological production, in order to synthesize derivatives with superior properties and to improve its therapeutic utilization [16].

The list of substances that are restricted or prohibited in the EU for use in cosmetic products does not include hyaluronic acid and sodium hyaluronate (NaHA). As an example, using hyaluronic acid, sodium hyaluronate, or potassium hyaluronate (KHA) in cosmetics is not restricted in Japan [20].

Some studies realized by the Cosmetic Ingredient Review (CIR) experts panel, based on the application of cosmetic HA in various concentrations, showed acute, short-term, or chronic toxicity [20]. Additionally, some side tolerable effects (scaling, erythema, and pruritus) were observed, after the use of a topical product with hyaluronic acid (0.01%), hydroquinone (4%), and glycolic acid (10%) for melasma treatment [4]. Subsequently, HA and NaHA can be nebulized and used in cosmetic products which can be applied as

aerosols (e.g., hair spray) [20]. The nebulized particles cand be stored at different levels of the respiratory system, depending on their size and concentration. Because of this fact, safety assessment of cosmetic aerosols is an important issue. The protective effect of HA on the respiratory system was noticed in some studies [21], however the propellant gas, vapors, and other soluble compounds (e.g., alkanes, alcohols, stabilization polymers, bentonite, aluminium chlorhydrate, perfume oils, cosmetic colorings, complexation agents, lanolin derivates, plant extracts, etc.) associated with hyaluronan in cosmetic aerosols could induce respiratory sensitization effects such as: rhinitis, conjunctivitis, wheeze, dyspnea, or asthma. Moreover, the insoluble particles from aerosols could be responsible for pulmonary overload, leading to chronic toxicity (e.g., chronic inflammation, fibrosis, including lung tumor). These effects are related to their concentration, exposure duration, or particle size. For example, the assessment of the inhalation toxicity of products with insoluble particles with a size below 10 μm is recommended. Regarding these aerosols, an exposure duration of 5 min is indicated, and also it is necessary to avoid the exposure to fine droplets of lipophilic substances, which could produce "acute respiratory syndrome" [22].

Due to various biological activities, HA products are increasingly in demand. Thus, in 2016, the total market of HA (pharmaceuticals, beauty, and personal care) exceeded 141 tones and it is expected to grow more than 30% in 2021 (Figure 2). The most significant increasing of HA market is estimated to be in Europe and Asia [23].

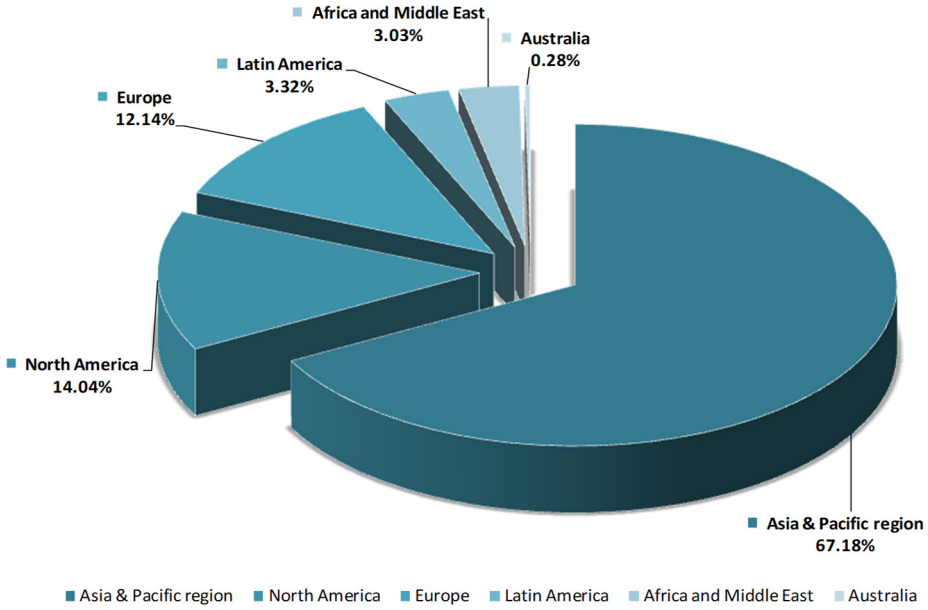

Figure 2. Hyaluronic acid market-regional comparison.

Some formulations containing HA are already available on the market, with a large experience in their use. At the same time, for other products it is necessary to perform subsequent investigations to confirm their efficacy. HA is a special moisturizing active ingredient, used in cosmetics, particularly formulated as emulsions or serums, claiming hydration and skin elasticity effect. These skin biophysical parameters are closely related to anti-wrinkle effect, but no rigorous scientific evidence does justify this statement completely. Additionally, it should be taken into consideration that the efficacy of hyaluronic acid depends largely on the molecular weight [10].

Hyaluronic acid is one of the most efficient and safe ingredients used frequently in cosmetics. HA properties can be improved by other bioactive ingredients (e.g., plant extracts, vitamins, amino acids, peptides, proteins, minerals, saccharides, probiotics, etc.). Nowadays, there are a multitude of cosmetics containing HA, marketed by different manufacturers. The previously published papers present separately these advantages of HA or bioactive ingredients. In our paper, we present firstly the biological effect of

HA on skin level, after which the portfolio of some popular manufacturers was analyzed, commercially cosmetic brands and products containing HA were identified, and their declared qualitative composition was evaluated. Subsequently, the additional biologic effects and the toxicological potential of the other active ingredients were presented.

2. Applications of Hyaluronic Acid

Taking into account its biological actions, physico-chemical properties, its biocompatibility or safety profile, HA has multiple applications. Figure 3 depicts the utilization of HA and its derivates in: medical (arthrology, cancer therapy, pneumology, odontology, ophthalmology, otolaryngology, rhinology, soft tissue regeneration, urology, wound treatment, etc.), pharmaceutical (e.g., drug delivery systems), nutritional (nutraceuticals, nutricosmeceuticals), or cosmetic field [3,8,9].

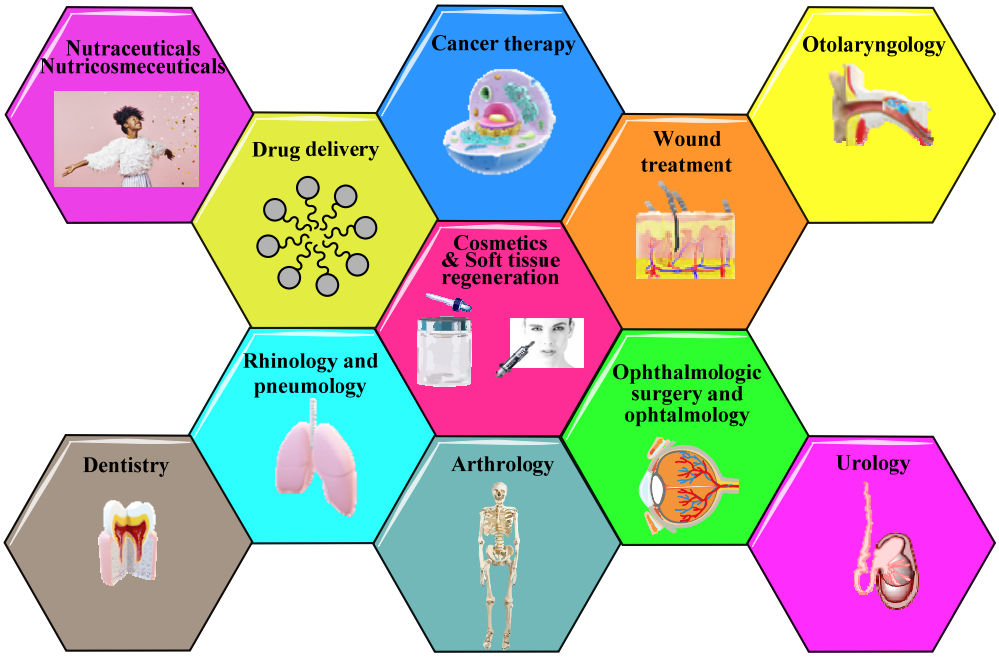

Figure 3. Cosmetic, pharmaceutical, and medical applications of HA and its derivates.

Being an important component of the ECM and due to its available derivatization scenarios, HA is widely used in drug delivery through several routes: cutaneous, ocular (intravitreal, periocular, subretinal), topical, nasal, oral, etc. HA can be conjugated with drug molecules (in the form of prodrugs) or can be incorporated in several molecular architectures (nanoparticles, microparticles, microspheres, gels, polyplexes, polymersomes, liposomes, micelles, implants, etc.). The resulting HA structures possess superior physico-chemical properties and higher therapeutic efficacy. A brief list of HA applications in drug delivery includes: targeting for skin diseases, cancer therapy, and controlled release of proteins, antiseptics, and antibiotics [16,24–30].

Normal body cells have a poor expression of HA receptors while many tumor cells generate overexpressed receptors that bind HA. This fact can lead to several approaches in cancer therapy, involving HA. Firstly, the conjugation of paclitaxel (PXT) and docetaxel (DOX), should be mentioned. PXT alone is not suitable for intravenous injection due to its hydrophobicity and adverse events. The PXT-HA conjugate is hydrophilic enough and seems to overcome limitations. Hydrophobic drug molecules can be loaded in HA micelles in order to achieve target delivery to cancer cells. Both lipophilic and hydrophilic drugs can be loaded in polymersomes. The main advantages of the previously mentioned structure modulations are solubility increase and targeting CD44 receptors on tumor cells. Modifying mesoporous silica nanoparticles with HA leads to an increased uptake in case of CD44 over expressing cells. Other nanomaterials with a potential efficiency in cancer therapy

include dendrimers and liposomes. Additionally, HA coated nanoparticles (NP) are of considerable interest in cancer therapy. Several HA based nanomaterials are used in hyperthermia (an increase in the temperature of the cancer cells at about 42–46°C): NIR-loaded nanoparticles, gold nanoparticles, functionalized graphene, oxide nanoparticles, Prussian Blue nanoparticles, and other particles (related to magnetic hyperthermia treatment). In addition, HA based nanoparticles were used in photodynamic therapy, immunotherapy, and sonodynamic therapy [31–37].

Two major steps in wound healing (in which HA is involved) are inflammation and angiogenesis. Several biomaterials (wound dressings based on HA or combinations of HA with other biopolymers) were synthetized and tested: sponges, films, hydrogels, and electrospun membranes. The main advantages of incorporating HA in these biomaterials are: porosity and swelling improvement, together with exudate absorption. Tissue engineering uses HA for the regeneration and reconstruction of several tissues: cartilage, ocular tissues, skin, vascular tissue, adipose tissue, and peripheral nerve [38–45].

The intended use of HA in dentistry is mainly the regeneration of soft tissues, but also wound healing and regeneration of hard tissues. HA may be used as a co-material (together with other biopolymers) in several procedures related to dentistry: papilla reconstruction, osseointegration of implants, sinus lifting, periodontitis, and stomatitis therapy [46–49].

Orthokeratology is a treatment for correcting patients' refractive error by means of wearing a special lens overnight. Viscous artificial tears (based on HA) proved to be superior (in terms of patients' comfort) in comparison to saline solution, when used for the fitting of the orthokeratology lenses. Nisin was grafted on HA by means of amide bonds. Biocidal capacity of this modified polysaccharide (incorporated in solutions or gels) was tested on Gram positive organisms with promising results. Additionally, HA conjugated with ciprofloxacin and vancomycin were used for the prevention of the infections in ophthalmic surgery. Ophthalmic viscoelastic devices (OVDs) are used during cataract surgery due to their multiple advantages. However, long retention times of OVDs can lead to an increase in intraocular pressure (IOP). The use of two OVDs (Healon GV—1.8% sodium hyaluronate and Healon 5—2.3% sodium hyaluronate) showed a non-significant increase of IOP. The use of artificial tears is the most common therapeutic solution for dry eye syndrome. Tears based on HA and carmellose (carboxymethylcellulose) proved to be superior in terms of stability of the tear film and quality of vision in comparison with normal saline solution [26,50–54].

Physical and physico-chemical properties of HA are highly dependent on its molecular weight (MW). The main benefits of HA use in arthrology are related to the treatment of osteoarthritis, rheumatoid arthritis, and bone cancers. In the case of advanced osteoarthritis, knee joint distraction is a promising procedure for spontaneous cartilage repair, in about 8 weeks. The key factors are HA (in synovial fluid) and mesenchymal stromal cells (MSCs). MSCs are able to adhere to cartilage under the influence of HA (especially the ones with MW > 9 MDa) [55–58].

Interstitial Cystitis/Bladder Pain Syndrome is a chronic inflammatory syndrome and seems to be related to the destruction of bladder mucosa, especially glycosaminoglycan coating, both Chondroitin Sulphate (CS) and non-sulphated–HA [59,60]. A therapeutic approach is the intravesical instillation of CS or a combination of CS and HA while evaluating: Female Sexual Function Index (FSFI), Visual Analog Pain Scale, Interstitial Cystitis Syndrome, and Interstitial Cystitis Problem Index. FSFI was higher for the control group (CS group). The last three parameters were improved in a higher manner when comparing CS/HA and CS groups [60]. No adverse reactions were reported during CS or CS/HA instillations [61,62].

Vesicoureteral Reflux (VUR) affects children and is linked to the patient's Urinary Tract Infection (UTI) history [63]. Surgery is the main therapeutic approach for VUR, but in this case complications may occur. Another approach is endoscopic injection therapy with teflon, polydimethylsiloxane, dextranomer/hyaluronic acid copolymer (Dx/HA), and

polyacrylate polyalcohol copolymer. In the case of Dx/HA combination the short time success rate was high, but more studies are needed regarding long-term success rate [64].

Cystic fibrosis is an inflammatory lung disease linked with high airway levels of neutrophil elastase. Polysulfated GAGs (including polysulfated HA) are currently used for neutrophil elastase inhibition and because of their anti-inflammatory properties [65]. HA is also used in other airway related diseases: chronic sinusitis, asthma, bronchiectasis, and chronic obstructive pulmonary disease [66]. HA was successfully usedin post-operative recovery of nasal mucosa after sinus surgery when administered topically or by means of nebulisation [67,68].

Due to its anti-inflammatory and tissue regeneration properties, HA has been used for gene delivery in otology and there are some promising results in tympanic membrane perforation treatment [68,69].

The activity of fibroblasts (in the epidermis) and keratinocytes (in the dermis) seems to slow down together with age and also became less responsive to growth factors [70]. The ageing process consists of both intrinsic and extrinsic ageing which leads to a reduction of HA in the skin [71]. Because of the great number of polar groups present in its molecule, hyaluronic acid is a hydrophilic macromolecule with anti-ageing and hydrating claims. In aqueous solutions it can form viscoelastic gels, and when it is applied to the skin it ensures moisturizing, firming, rejuvenation, and has improved wound healing effects [10,12]. In contact with water, HA has the capacity to augment its volume, having the effect of softening the wrinkles by filling the spaces between the cells of the skin forming a viscid gel matrix. The half-life of HA in the tissues, in its natural form, is of just 12–24 h. As a result, crosslinked forms of HA are used in topical and cosmetic preparations [72–74]. Nevertheless, the high molecular weight of HA does not allow it to penetrate the deeper layers of the skin which restricts its benefits to topical effects [75]. Many studies showed the exogenous HA significant role in the epidermis and especially in the dermis, and its involvement in remodelling, tissue repair, and healing [2,76–80]. In a randomized, placebo-controlled, single-blind trial (daily oral intake, for 60 days, of 200 mg of hyaluronic acid, 500 mg of L-carnosine, and 400 mg of methylsulfonyl methane) it was proven that skin hydration and elasticity were improved and glabellar sebaceous secretion decreased [81]. Ingestion of HA/hyaluronans can improve skin moisture content and reduce ageing symptoms and signs [82,83].

3. Use of Hyaluronic Acid in Cosmetology

Nowadays, HA is one of the most widely used active ingredients in cosmetic formulations. General perception about skin regeneration is of constant interest for both industry professionals and consumers. It is evident that the skin is an indicator of individuals' health and HA is one of the main factors for healthy skin [84]. As shown above, hyaluronic acid is a biopolymer considered of primary interest from a scientific point of view, due to its multitude of applications in cosmetic and biomedical fields. Such being the case, exploration on this ingredient is increasing in many interdisciplinary domains targeting, on the one hand, the improvement of production processes in terms of biotechnology and on the other hand the development of new formulations incorporating hyaluronan or HA-based innovative ingredients. Scientific efforts are moving nowadays towards the production of appropriate molecular weight biopolymers. This specific aspect relies precisely to the biological function, as indicated by bibliographic studies. Although HA was synthesized a very long time ago, it is still needed to investigate this active ingredient in terms of physico-chemical and biological properties [16].

HA has a multitude of applications based on specific properties such as: (1) high hygroscopicity; (2) viscoelastic nature; (3) biocompatibility; (4) non-immunogenicity. Nevertheless, the HA skin penetration mechanism is still barely understood. A multitude of factors are studied, including the existence of HA receptors for an active transport and a particular structure of the hydrated HA. The general hydration effect of the skin may also optimize dermal absorption of active ingredients and can assist their retention within

the moisturized epidermal layers. HA is appropriate for biomacromolecules because it ensures protein stabilizing properties. However, the precise mechanism for the transdermal transport of HA remains to be elucidated [10,85,86].

In wound regeneration, HA has mainly cosmetic applications. In skin care formulations, it can be used as a moisturizing component, because of its hydrophilic nature. Using cosmetic products such as creams or lotions that contain HA helps to moisturize the skin and to improve elasticity, thereby decreasing the depth of wrinkles. It is assumed that, when applied onto the surface of the skin, HA solutions form an occlusive layer, absorb moisture, thereby hydrating the skin, and default wrinkles filling occurs. HA is assumed to stimulate the migration of epidermal cells. Additionally, the occlusive properties given by HA may allow the biologically active substances incorporated in cosmetics to persist in the skin layers and possibly make it easier for them to penetrate the epidermis. According to previous studies, some cosmetic HA products have been proven efficient in protecting the skin from UV irradiation. At the same time, sunscreen products containing hyaluronic acid help to maintain a firmer skin, protecting it from the injurious impact of UV radiation, due to the potential antioxidant effect of HA [87].

In cosmetic formulations, hyaluronic acid has the function of a viscosity modifier and/or a skin conditioning agent. HA is mainly used in anti-ageing cosmetic products. LMW-HA has the ability to enhance the level of moisture of the skin and expedite regeneration. HMW-HA forms a viscoelastic film when applied onto the skin and has a moisturizing effect. The main action of the HMW-HA polymer is film forming and it reduces evaporation of water from the skin and thus possessesan occlusive effect. Additionally, HMW-HA, Medium molecular weight (MMW-HA), and LMW-HA hygroscopic properties justify the ability to maintain skin hydration [87,88].

HA is also of particular importance as a delivery system of active ingredients. Currently, there are some commercially available formulations incorporating actives in different concentrations. These products are designated for the topical treatment of actinic keratosis and skin inflammatory diseases. In fact, it has been proven that HA enhances the penetration of the active ingredient through the stratum corneum (SC), which behaves as a barrier to the entry of the molecule into the deeper layers of the skin, and the holding and locating the active ingredient in the epidermis. Topical preparations containing HA in formulation are used for their healing properties, decreasing the skin irritation. A topical preparation that contains HA (0.2% w/w sodium hyaluronate (NaHA)) as a main component is currently available for the amelioration of acute and chronic wounds (areas of grafted skin, post-surgical incisions, etc.) [13,77,88].

A significant number of in vitro and in vivo studies have shown the effectiveness of HA treatment as: anti-inflammatory, skin regeneration and chondro-protective effect, anti-ageing and immunosuppressive effects, etc.

Although hyaluronan has various applications, subsequent research and technological development are needed, because there are currently certain issues to be elucidated. Firstly, further consideration of aspects regarding HA metabolism and receptor clustering analysis is necessary in order to explain the various biological actions and to foresee the effects that canvary with the molecular weight of HA. Some pharmaceuticals and/or cosmetics can incorporate HA with different molecular weight. Thus, studies are necessary for assessing the implications of molecular weight in the HA effects. Next-generation products with derivatives of crosslinked HA-conjugated polymer-delivery systems and drug substances should be developed, granting a high level of biocompatibility, prolonged half-life, and permanent in situ performance. Therefore, clinical exploration is imperative to fully characterize the safety and efficacy profile of these substances. So far, recent in vitro studies have shown promising results regarding the safety and efficacy of these promising and novel compounds: for example, HA-CL (urea-crosslinked hyaluronic acid) showed a significant biocompatibility with human corneal epithelial cell, having antioxidant, anti-inflammatory, and skin regeneration properties [16,24].

HA is used in cosmetic formulations in concentrations ranging from 0.2 to 1%. The maximum concentration of NaHA in a body lotion is 2%. When a rate of 1 mg/cm^2 of a product is applied, the contribution of hyaluronic acid is 0.02 mg/cm^2 of skin [20].

Interest in using hyaluronic acid as a cosmetic ingredient in skin care products occurred with the discovery that the amount of HA found in natural skin diminishes with age, and when reintroduced into the skin care products, it keeps skin hydrated, attenuates the appearance of wrinkles, and smooths the skin. HA has many qualities that make it superior to other substances used in skin regeneration, with pronounced moisturizing and anti-ageing effects [87,88]. Biological activity and HA penetration into the skin depends on the molecular weight of this substance showing different effects on the skin, as presented in Figure 4.

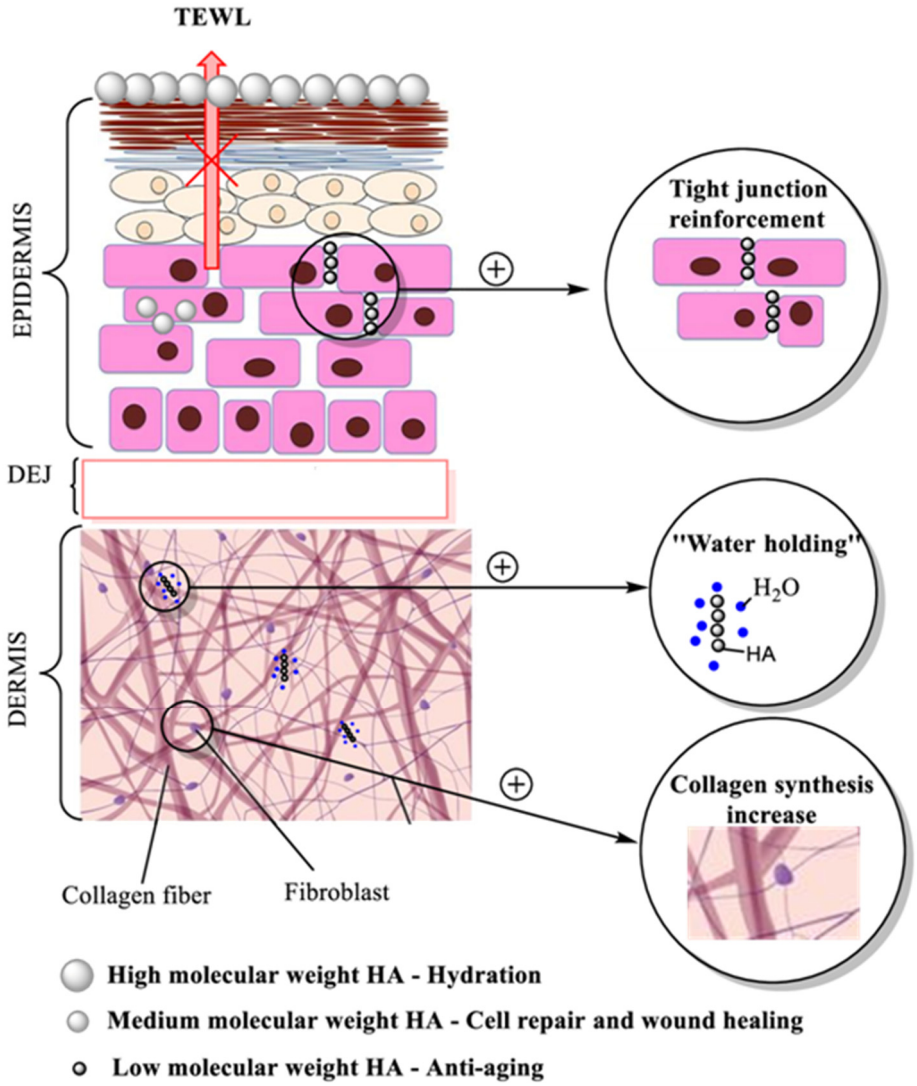

Figure 4. Hyaluronic acid activity, molecular weight dependence and claimed effect of HA. (TEWL—Transepidermal Water Loss; DEJ—Dermoepidermal junction).

It has been demonstrated by some researchers, that HA has extraordinary cosmetic and nutricosmetic efficacy in improving diverse skin imperfections such as wrinkles, periorbital and nasolabial folds, and skin ageing. These types of effects of HA have been correlated with their capacity to induce the augmentation of soft tissue, to hydrate the skin, stimulate collagen, and rejuvenate the faceas summarized in Figure 5 [89].

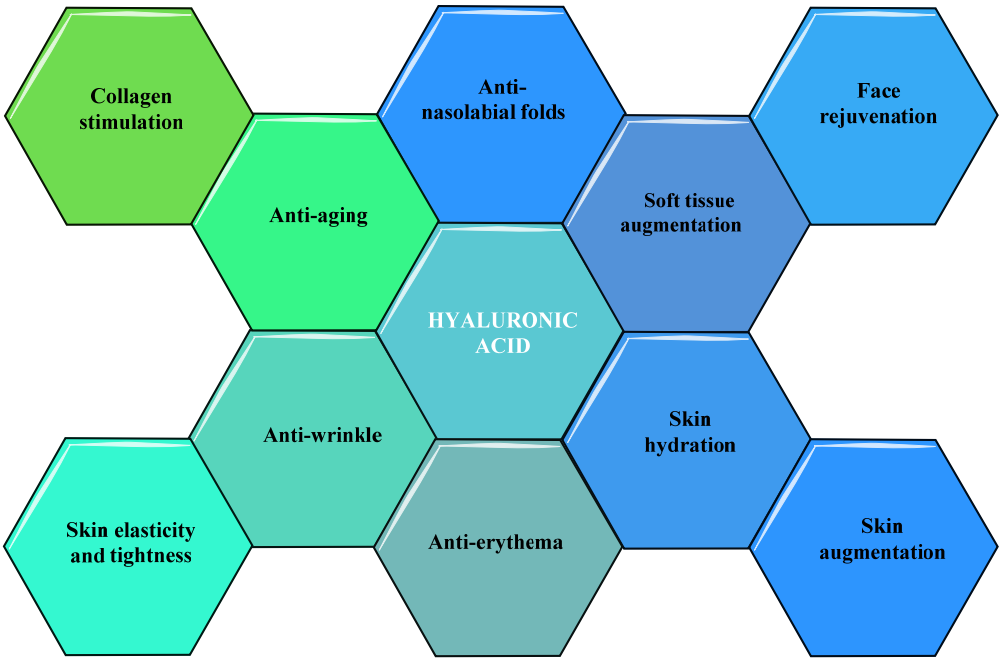

Figure 5. Cosmetic and nutricosmetic effects of HA.

3.1. Hydratation Effect of HA in Cosmetic Formulations

The amount of hyaluronic acid synthesized is more substantial in the epidermis than in the dermis. Since the dermis is much thicker than the epidermis, it comprises four to nine times more HA, but it was demonstrated that for equivalent tissue quantities, the epidermis synthesizes four times more hyaluronic acid than the dermis. In the epidermis, HA is located in the intercellular matrix of the basal and spinous layers. Similarly as in the dermis, the hygroscopic properties of the hyaluronic acid are of substantial relevance in hydrating the deep layers of the epidermis, but its contribution goes further than conventional hydration [90–92].

HA, which has the ability to bind water up to 1000 times its volume, has a relevant contribution to cellular growth, adhesion, and membrane receptor function. The major biologic role of HA in the intercellular matrix is to reinforce the intercellular structures and to produce the elastoviscous fluid matrix that firmly envelops collagen and elastin fibers. HA holds moisture, and provides firmness and radiance to the skin as well [93,94]. HA can be used topically to regenerate the skin and support hydration, although its very high molecular weight prevents its penetration through the SC [95,96].

3.2. Anti-Ageing Effect of HA in Cosmetic Formulations

HA also has an important role regarding skin ageing. Cells lose their ability to produce HA with ageing. The skin becomes drier, thinner, and looser, leading to wrinkling, among other significant changes [97]. Skin ageing is also associated with a decrease of skin moisture. Hyaluronic acid (hyaluronan) has a unique capacity to link and retain water molecules [98]. As it was shown, hyaluronic acid is a natural component that is present in the whole body. In a 70 kg individual there are 15 g of hyaluronic acid, 5 g of which are replaced daily. HA is naturally and constantly renewed because of its rapid degradation, but its renewal tends to slow with age and external aggressions. Therefore it is necessary to act very early, sustaining an optimal hyaluronic acid turnover, similar to that of young skin, in order to prevent the signs of ageing [76,99–101].

In relation to its biological effects at skin level, it is known that hyaluronic acid is actively involved in skin cell signaling (by binding the CD44 and LYVE-1 receptors) and thus influences the ECM stability. It has been noticed that HA has an impact on the growth of keratinocytes which protect the epidermis from ageing [10,16,79,93,102]. Hyaluronic

acid is used in cosmetic preparations for its elasticity effect and for giving shape to the periorbital area after HA cosmetic treatment [103]. Additionally, the chemical double binding structure of the D-glucuronic acid unit confers antioxidant properties to hyaluronic acid. Furthermore, HA restrains the proliferation of the skin cells via the CD44 receptor and HA also has anti-inflammatory properties on the skin [76,104].

Hyaluronic acid is applied in a multitude of anti-ageing products. For example, Figure 6 presents the effect of an anti-ageing cream incorporating 0.5% (*w*/*w*) LMW-HA (20–50 KDa) and 3% (*w*/*w*) encapsulated HMW-HA (1–1.4 MDa) on periorbital wrinkles before treatment and after 28 days of treatment (Protocol Report No. 300924/19/JSHR/ Agreement No. 331/30 August 2019 JS. Hamilton Romania S.R.L) [105].

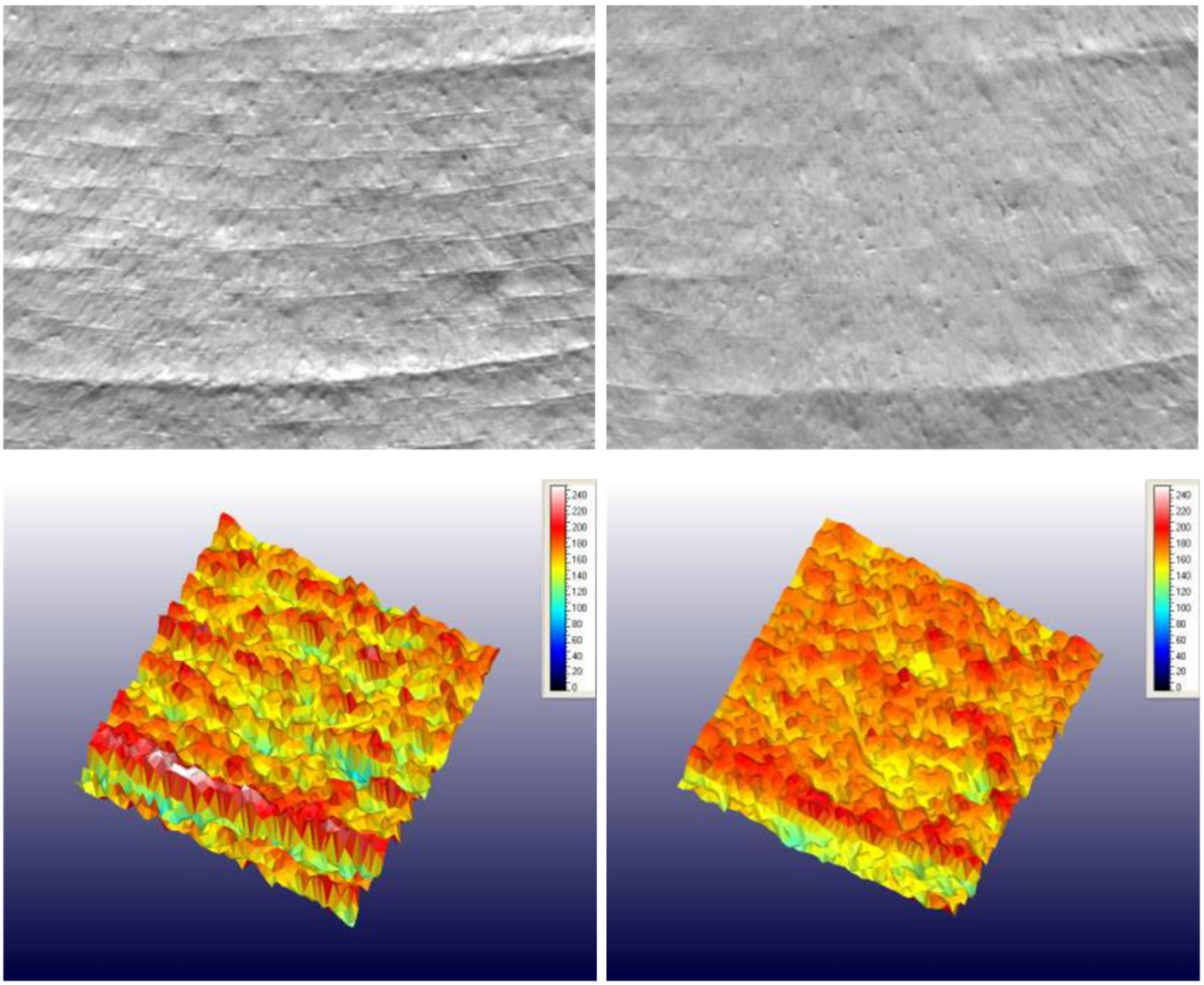

Figure 6. The images of skin texture before product application (D0) and after 28 days (D28) of regular application of an anti-ageing cream incorporating 0.5% (*w*/*w*) LMW-HA (20–50 KDa) and 3% (*w*/*w*) encapsulated HMW-HA (1–1.4 MDa) [105].

4. Cosmetic Products with HA and Its Derivates Available on the Market

The cosmetic industry has been using HA for over 20 years for its great skin moisturizing properties. In 2016, over 5900 end products launched on the market contained either HA or hydrolyzed HA, with more than 70% of these products now dedicated to the mass market and masstige market [106]. According to the price, cosmetic companies can position their products on the market as: (1) premium products; (2) mass-premium products; (3) mass-market products [107]. For marketing, it is known that the price plays a psychological role in a collective imagination, for a product with a high price, consumers attribute a high value. Premium cosmetics include products with a higher purchasing price, while mass-market products have, in general, a lower price.

HA and its sodium and potassium salts are important cosmetic ingredients that are incorporated in moisturizing and anti-ageing products. Additionally, products that contain HA represent only 5%, while more than 95% of the total products contain sodium hyaluronate [106]. Hyaluronic acid and its derivates are incorporated in a multitude of cosmetic products for eye contour, lips, facial, and neck care, anti-cellulite body care, or cosmetic color conditioning in different cosmetic categories: creams, lotions, serums, masks [93,101]. A significant number of cosmetics based on hyaluronan have been launched on the market in the last years. Some examples of last products launched in the period 2015–2020 are listed in Table 1, depending on product category or proposed use, trade name and producer, and the incorporated HA forms in the cosmetic formulation. Additionally, the market segment of HA cosmetic products is indicated.

Some manufacturers launched cosmetic products on the market, containing HA or hyaluronates in combination with other active ingredients, like botanical extracts, vitamins, probiotics, amino acids, peptides, proteins, etc. These compounds improve the cosmetic formulation qualities and benefits, awarding additional claims.

4.1. Bioactive Compounds in Cosmetics with HA and HA Derivates

Different vegetal extracts incorporated in HA available cosmetics can claim different additional effects such as antioxidant, anti-inflammatory, skin conditioning, hydrating, anti-wrinkle, skin whitening, or photoprotective properties. From the cosmetovigilance point of view, vegetal extracts are mostly considered as safe for cosmetic use, but some minor adverse effects (e.g., irritation, sensitization, allergic contact reactions) have been reported.

Literature data contains a wealth of information describing the aspects regarding composition, effects, and also adverse reactions of diverse bioactive ingredients incorporated into commercially available HA or HA derivates cosmetics. Some examples are mentioned below, describing their bioactive components, cosmetic claims, and benefits, as well as reported adverse effects as indicated in Table 2.

4.2. Other Active Ingredients in Commercialy Available HA and HA Derivates Cosmetics

Besides plant extracts, commercially available cosmetics containing HA or NaHA incorporate different categories of active ingredients (e.g., probiotics, amino acids, peptides, proteins, vitamins, saccharides, or other active compounds like allantoin, lactic acid, lecithin, urea, Superoxide Dismutase (SOD), gold, malachite extract) claiming additional effects, such as moisturizing, anti-ageing, antioxidant, keratolytic, skin lightening, depigmenting, etc. These active ingredients are considered safe when used in cosmetic products and show good skin compatibility. Minor adverse reactions like contact dermatitis were reported.

More data indicating the category of other active ingredients, the cosmetic claims, skin benefits, and reported adverse effects in commercially available hyaluronan cosmetics are presented in Table 3.

Table 1. Commercially available cosmetics incorporating HA and HA derivatives.

Cosmetic Product Category/Proposed Use	Producer (Country of Origin)/Cosmetic Product Trade Name	HA Form	Other Active Ingredients Incorporated in the Cosmetic Formulation (INCI—International Nomenclature of Cosmetic Ingredients Denomination)	Cosmetic Claim	Market Segment	Reference
Skin care cosmetics	FRESH (USA) Deep Hydration Face Serum Serum	NaHA	Porphyridium Cruentum Extract, Pyrus Cydonia Seed Extract, Angelica Keiskei Extract, Voandzeia Subterra Nea Seed Extract, Cucumis Sativus (Cucumber) Fruit Extract, Tocopheryl Acetate	24-h moisture	Premium Market	[108]
	DECIEM (Canada) The ORDINARY "Buffet" Multi-Technology Peptide Serum Serum	NaHA	Lactococcus Ferment Lysate, Acetyl Hexapeptide-8, Pentapeptide-18, Palmitoyl Tripeptide-1, Palmitoyl Tetrapeptide-7, Palmitoyl Tripeptide-38, Dipeptide Diaminobutyroyl BenzylamideDiacetate, Acetylarginyltryptophyl Diphenylglycine, Allantoin, Glycine, Alanine, Serine, Valine, Isoleucine, Proline, Threonine, Histidine, Phenylalanin, Arginine, Aspartic, Acid, Trehalose, Fructose, Glucose, Maltose, Urea, Sodium PCA, PCA, Hydroxypropyl Cyclodextrin	anti-ageing	Premium Market	[109]
	DECIEM (Canada) THE ORDINARY Hyaluronic Acid 2% + B5 Serum	NaHA	Panthenol, Ahnfeltia Concinna Extract	moisturizing, anti-ageing	Premium Market	[110]
	APIVITA (Greece) 5-action Eye Serum Advanced eye care Serum	Hydrolyzed HA	Lilium Candidum Extract, PfaffiaPaniculata Extract, PtychopetalumOlacoides Extract, CopperLysinate/Prolinate, Propolis Extract, Mel Extract, Methylglucoside Phosphate, Euphrasia Officinalis Extract, Lecithin, Hydroxypropyl Cyclodextrin, Ascorbyl Tetraisopalmitate, Panthenol, SideritisPerfoliata Extract, Aloe Barbadensis Extract, SideritisScardica Extract, SideritisRaeseri Extract, Bisabolol	anti-ageing, moisturizing	Premium Market	[111]

Table 1. *Cont.*

Cosmetic Product Category/Proposed Use	Producer (Country of Origin)/Cosmetic Product Trade Name	HA Form	Other Active Ingredients Incorporated in the Cosmetic Formulation (INCI—International Nomenclature of Cosmetic Ingredients Denomination)	Cosmetic Claim	Market Segment	Reference
	FARMEC (Romania) Hyaluronic Acid ampoules 5% Serum	NaHA	Superoxide Dismutase, Lecithin	anti-wrinkle, intensive moisturizing	Mass Market	[112]
	AVIVA COSMETICS (Romania) INFINITUM Deep Wrinkles Anti-Ageing Serum	Hydrolyzed HA	Aesculus Hippocastanum Extract	firming, anti-ageing	Premium Market	[113]
	GARANCIA (France) MYSTÉRIEUX MILLE ET UN JOURS Anti-Ageing Day Emulsion	Hydrolyzed HA	Alaria Esculenta Extract, Cyathea Cumingii Extract, Dipeptide Diaminobutyroyl Benzylamide Diacetate, Hydroxypropyl Cyclodextrin, Palmitoyl Tripeptide-38	relax expression lines	Premium Market	[114]
	BALANCE ME (UK) Tinted Wonder Eye Cream Eye cream complexion perfection Day Cream	Hydrolyzed HA	Picea Abies Extract, Rubus Chamaemorus Seed Extract, Aloe Barbadensis Extract, Styrax Benzoin Extract, Rosmarinus Officinalis Extract, Vitis Vinifera Seed Extract, Tocopherol	soothing, anti-ageing	Mass Market	[115]
	EARTH SCIENCE (USA) Apricot Intensive night cream Night Cream	NaHA	Pyrus Malus Extract, Glycyrrhiza Glabra Extract, Glycine Soja Seed Extract, Tocopherol, Citrus Grandis Seed Extract, Calendula Officinalis Extract, Bambusa Arundinacea Extract, Sambucus Nigra Extract, Cucumis Sativus Extract, Arnica Montana Extract, Hedera Helix Extract, Lactic acid, Allantoin	reduces the appearance of fine lines and wrinkles	Mass Market	[116]

Table 1. *Cont.*

Cosmetic Product Category/Proposed Use	Producer (Country of Origin)/Cosmetic Product Trade Name	HA Form	Other Active Ingredients Incorporated in the Cosmetic Formulation (INCI—International Nomenclature of Cosmetic Ingredients Denomination)	Cosmetic Claim	Market Segment	Reference
	COSMETIC PLANT (Romania) Lift Up—Hyaluronic Acid Day Anti-Ageing Cream Day Cream	Hydrolyzed HA	Porphyridium Cruentum Extract, Magnolia Liliflora Extract, Tocopherol	anti-ageing	Mass Market	[117]
	AVIVA COSMETICS (Romania) INFINITUM Cellular Regenerating Cream	Hydrolyzed HA	Aesculus Hippocastanum Extract, Tocopheryl Acetate	firming, regenerating, rejuvenating	Premium Market	[118]
	GEROCOSSEN (Romania) Hyaluron Anti-Age CreamSPF 10 Day Cream	NaHA	Lecithin, Tocopheryl acetate, Retinyl palmitate	anti-ageing	Mass Market	[119]
	AVIVA COSMETICS (Romania) INFINITUM Golden Elixir Anti-Ageing Cream SPF 15 Day Cream	Hydrolyzed HA	Aesculus Hippocastanum Extract, Gold (CI 777480), Ectoin	firming, anti-ageing, SPF 15	Premium Market	[120]
	FARMEC (Romania) Anti-Wrinkle Cream Concentrated with Hyaluronic Acid 3% Day Cream	NaHA	Pseudoalteromonas Ferment Extract, Hydrolyzed Wheat Protein, Hydrolyzed Soy Protein, Tripeptide-10 Citrulline, Tripeptide-1, Lecithin, Artemia Salina Extract, Superoxide Dismutase	anti-wrinkle, line filling and smoothing, intense hydration	Mass Market	[121]
	ARBONNE RE9 (USA) Advanced For Men Anti-Aging Moisturizer Broad Spectrum Men Care	NaHA	Aloe Barbadensis Gel, Ceratonia Siliqua Extract, Laminaria Digitata Extract, Malachite Extract, Chamomilla Recutita Extract, Sophora Japonica Flower Extract, Tripleurospermum Maritimum Extract	moisturizing, SPF 15	Premium Market	[122]

Table 1. *Cont.*

Cosmetic Product Category/Proposed Use	Producer (Country of Origin)/Cosmetic Product Trade Name	HA Form	Other Active Ingredients Incorporated in the Cosmetic Formulation (INCI—International Nomenclature of Cosmetic Ingredients Denomination)	Cosmetic Claim	Market Segment	Reference
Body cosmetics	AVIVA COSMETICS (Romania) INFINITUM Anti-Ageing Cleansing Emulsion	Hydrolyzed HA	Aesculus Hippocastanum Extract	firming, anti-ageing	Premium Market	[123]
	JONZAC (France) Bébé Bio Dermo-Repair Cream Baby Care	Hydrolyzed HA	Malva Sylvestris Extract, Tocopherol, Hydrogenated Lecithin	soothing, regenerating, protecting	Mass Market	[124]
	LES MERVEILLEUSES LADUREE (France) Sun Protection Body Cream Body Cream	NaHA	Rosa Centifolia Extract, Rosa Damascena Extract	hydrating, SPF 50	Premium Market	[125]
	NATURE REPUBLIC (South Korea) Ice Sun, Ice Puff Sun Sun/Sunbed Exposure	NaHA	Calendula Officinalis Extract	anti-wrinkle and skin bleftening, SPF 50	Mass Market	[126]
	DM ALVERDE NATURKOSMETIK (Germany) Ivital + Hand cream	NaHA	Amaranthus Caudatus Extract, Triticum Aestivum Germ Extract, Punica Granatum Extract, Tocopherol	smoothes lines and wrinkles	Mass Market	[127]
	INNISFREE (South Korea) My Body Tangerine Blossom Body lotion	Hydrolyzed HA	Citrus Unshiu Peel Extract, Algae Extract, Eclipta Prostrata Extract, Orhid Extract, Camelia Sinensis Extract, Camelia Japonica Extract, Opuntia Coccinellifera Extract, Tocopherys Acetate	moisturizing	Mass Market	[128]

Table 1. *Cont.*

Cosmetic Product Category/Proposed Use	Producer (Country of Origin)/Cosmetic Product Trade Name	HA Form	Other Active Ingredients Incorporated in the Cosmetic Formulation (INCI—International Nomenclature of Cosmetic Ingredients Denomination)	Cosmetic Claim	Market Segment	Reference
	INNISFREE (South Korea) Wine Peeling Jelly Scrub Peeling Scrub	NaHA	Vitis ViniferaExtract, Ulmus Davidiana Root Extract, Amaranthus Caudatus Extract, Centella Asiatica Extract, Ficus Carica Extract, Citrus Unshiu Extract, Orchis Extract, Camelia Sinensis Extract, Camelia Japonica Extract, Opuntia Coccinellifera Extract, Niacinamide, Allantoin, Ceramide 3	moisturizing	Mass Market	[129]
	TUDE HOUSE (South Korea) Berry AHA! Bleft Peel Bubble Wash	Hydrolyzed HA	Algae Extract, Eclipta Prostrata Extract, Vaccinium Myrtillus Extract, Saccharum Officinarum Extract, Citrus Limonum Extract, Citrus Aurantium Dulcis Extract, Ulmus Davidiana Extract, Amaranthus Caudatus Extract, Acer Saccharinum Extract, Nymphaea Alba Extract, Bifida Ferment Lysate, Lecitin	bleftening	Mass Market	[130]
Makeup cosmetics	ILLAMASQUA (UK) HYPNOTICA Lipe Lure Colour intense Liquid lipstick	NaHA	N	long-wearing, picture-perfect finish	Premium Market	[131]
	CLINIQUE (USA) Sun-Kissed Face Gelee Complexion multitasker	NaHA	N	moisturizing	Premium Market	[132]
	PAUL& JOE (Japan) Pore SmoothingPrimer Face primer	Hydrolyzed HA	Calendula Officianlis Extract, Rosa Canina Fruit Extract, Tocopherol	moisturizing	Premium Market	[133]

NaHA—Sodium Hyaluronate; Hydrolized HA—Hydrolized Hyaluronic Acid; N—Not known.

Table 2. The benefits and potential adverse effects of botanical extracts used in cosmetic products associated with hyaluronic acid and HA derivates.

Active Ingredient/Plant Species	Bioactive Components	Biological Role and Benefits for Skin	Toxicity of Topical Products
Acer saccharum	phenolic compounds (maplexins, ginnalins) [134,135]	increases the intracellular ceramide level stimulates the proliferation and differentiation of keratinocytes maintains thehomeostasis of the epidermis antioxidant capacity [134,136,137]	* N
Ahnfeltia concinna (*red algae*)	polysaccharides (carrageenan, agar), amino acids, minerals, vitamins, trace elements [138–140]	antioxidant capacity, anti-wrinkle, skin-whitening (suppresses the melanin production), skin moisturizing [139–142]	not toxic in topical applications possible irritation, sensitization, or photoreactions [142]
Alaria esculenta (*brown algae*)	polyphenols, diterpenoids, fatty acids, polysaccharides, fucosterol, fucoxhantin (e.g., retinoic acid), amino acids, minerals, vitamins, trace elements [143–145]	hyperpigmentation amelioration increases skin firmness and elasticity stimulates collagen and keratin synthesis, reducing the progerin production (increased in aged skin) of 'aged' fibroblasts skin-whitening, antioxidant capacity [142,143,146,147] anti-cellulite and antiedema activity [142,148–150]	possible local irritation, sensitization, or photoreactions [142]
Aloe sp. *(Aloe barbadensis)*	antraquinones, polysaccharides, phenolic compounds, organic acids [151–154]	antimicrobial activity [155,156] antioxidant capacity, anti-inflammatory, anti-pyrotic [156–158] improves skin moisture and water retention in the SC [153,156,157,159,160]	phototoxicity, eczema, contact dermatitis [151,152]
Amaranthus caudatus	amino-acids, proteins, amylopectin, minerals, vitamins (vitamin A, E, K), fibers, essential fatty acids, triterpenes (squalene) [161,162]	antioxidant capacity, moisturizing, skin hydration, suppressing the pigmentation [162–164]	* N
Angelica keiskei	coumarins, terpens, phenolic compounds [165–168]	antioxidant capacity, astringent, emollient, skin conditioning and protecting, skin whitening and lightening, sunlight protection [165]	* N
Arnica montana	fatty acids (palmitic, linoleic, myristic), essential oil, triterpenic alcohols, sugars, phytosterols, phenol acids, tannins, choline, inulin, flavonoids, carotenoids, coumarins, sesquiterpene lactones [169,170]	anti-inflammatory effect [158,171] reduces the ecchymosis and oedema [158]	contact dermatitis [169,172] rarely ocular irritation [170]

Table 2. *Cont.*

Active Ingredient/Plant Species	Bioactive Components	Biological Role and Benefits for Skin	Toxicity of Topical Products
Artemia salina	diguanosine-tetraphosphate, D-myo-inosite-1,4,5-triphosphate, proteins, glucan [173]	stimulates skin regeneration, strengthens the immune system of the skin, sustains epidermal cell proliferation, anti-ageing (inhibiting the cells senescence, stimulating the collagen expression) and photo-protection effect [173]	* N
Bambusa arundinacea	flavonoids, phenolic compounds, chlorogenic acid, caffeic acid, ferulic acid, 8-C-glucosyl apigenin, luteolin derivatives [174]	antioxidant capacity, anti-ageing, photo-protection, skin pigmentation modulating effect, anti-allergic effect (inhibiting the production of IgE and lymphocytes) [174]	* N
Calendula officinalis	triterpenes, polyphenolic compounds, polysaccharides, vitamin C, tocopherols, quinones, carotenoids saponins, sterols [175–178]	anti-inflammatory effect [175,179] cell rejuvenation effect [179,180] skin smoothing and softening effect [179] prevents skin alteration and early ageing (improving the skin elasticity) [176,180,181] anti-irritant, anti-psoriatic and callus treating [158] stimulates the regeneration and epithelisation of wounded skin [175,179–181] antioxidant capacity [175,176,179,180] antimicrobial activity [155,179]	rare sensitization or allergic contact reactions [169,175,182]
Camelia sp. (*C. sinensis*, *C. japonica*)	polyphenols, catechins [176]	antioxidant capacity, reduces the sebum production, improves skin hydration, skin smoothing and softening, photoprotective, and anti-inflammatory effect [176,183–187]	contact dermatitis [172]
Chamomila recutita	polysaccharides, flavonoids (α-bisabolol, apigenin), sesquiterpene lactones [169,176]	anti-inflammatory effect, antioxidant capacity [188] repairs the SC, wound healing, anti-ageing activity skin smoothing and softening, also being used in the treatment of eczema [176,188,189]	skin sensitization, contact dermatitis [169,189,190]

Table 2. *Cont.*

Active Ingredient/Plant Species	Bioactive Components	Biological Role and Benefits for Skin	Toxicity of Topical Products
Centella asiatica	saponins, flavonoids (quercetin, kaempferol, apigenil, naringenin, phenolic acids (chlorogenic acid), triterpenic steroids, amino acids, sugars [191,192]	antioxidant capacity, anti-inflammatory, anti-ageing effect stimulates the fibroblast proliferation, increasing the collagen synthesis increases the *SC* hydration and the epidermal barrier function anti-cellulite effect [191,192]	local allergic reactions, burning, eczemas, vesicles, pruritus [192]
Ceratonia siliqua	flavonoids, phytosterols, acids, esters, terpenoids, fenolic compounds [193–195]	anti-cellulite effect (increasing the aquaglyceroporines activity, stimulating lipolysis, reducing the localized fat overload), antioxidant capacity, depigmentation effect (anti-tyrosinase activity), skin lightening effect [193,194,196]	non-irritation potential [193]
Citrus sp. (*C. aurantium dulcis*, *C. grandis*, *C. limon*, *C. unshiu* peel)	bergapten, bergamotin, isopimpinellin, coumarins, psoralenes, angelical, volatile oil (limonene, linalool, linalyl acetate, terpineol, terpinene, terpinolene, ocimene, pinene etc.) [197–199]	antioxidant capacity, anti-inflammatory, antiseptic and anti-verrucous effect, used in acne treatment, wound healing properties, used as fragrance [158,197–199]	possible irritation, skin sensitization, hyperpigmentation, redness, oedema, photo-toxicity [197–200]
Cucumis sativus	flavonoids, saponins, sterols, carbohydrates, triterpenes, vitamins (C, B), fatty acid, proteins [201,202]	used in the treatment of periorbital edema, soothing emollient, anti-wrinkle, anti-ageing, anti-itching effects depigmentant and antioxidant capacity, anti-hyaluronidase and anti-elastase actions [201]	erythema after semi occlusive patch testing and conjunctival hyperemia/ocular irritation after a using of an eye lotion containing 1% *C. sativus* (cucumber) fruit extract [202]
Cydonia oblonga seed	cellulose, polysaccharides, polyphenols [203,204]	stimulates fibroblasts proliferation, wound, and burns healing maintains skin barrier function anti-inflammatory, anti-allergic and protective effects antioxidant capacity [203–208]	* N
Eclipta prostrata	flavonoids (luteolin, apigenin), wedelolactone, terpenoids, sterols, alkaloids, volatile oils [209–213]	depigmentant effect (anti-tyrosinase activity) hair revitalizing, dye in cosmetic products antioxidant and photoprotective capacity [209–212]	* N

Table 2. *Cont.*

Active Ingredient/Plant Species	Bioactive Components	Biological Role and Benefits for Skin	Toxicity of Topical Products
Euphrasia officinalis	iridoids, flavonoids, polyphenols, saponins, alkaloids, tannins, etheric oils [214,215]	anti-inflammatory and astringent effect antioxidant capacity photo-protection, protective effect against photo-ageing, stimulates collagen synthesis [214,216,217]	* N
Ficus carica	phytosterols, anthocyanins, amino acids, atty acids, phenolic acids, flavonoids, volatile components [218,219]	antioxidant capacity, anti-warts and anti-verrucous activity used in the treatment of dry skin, eczema, acne anti-inflammatory, anti-ageing, anti-wrinkle and skin protection effects [158,218–220]	no side effects observed [220]
Glycyrrhiza glabra	saponins (glycyrrhizin), flavonoids (liquiritigenin, liquiritin), glycosides, isoflavons (glabridin, coumarins, stilbenoids) [221,222]	anti-inflammatory effect, antioxidant capacity, photo-protection effect reduces erythema and hyperpigmentation improves epidermal hydration and transepidermal water loss antibacterial and antifungal effect anti-dandruff effect [221–224]	eye sensitivity (burning, itch, redness), scalp pruritus (itch, dandruff) [221]
Glycine max	phenolic acids (ferulic, syringic, sinapic, flavonoids (isoflavons), soy proteins (β-conglycinin, glycinin), lipids, vitamin E [225–227]	anti-inflammatory effect, antioxidant capacity skin lightening and depigmentant protective effect against photo-ageing stimulates collagen and elastin synthesis, increasing the hyaluronic acid levels in aged skin skin regeneration effect, providing nutrients for cell renewal [225–231]	none allergic reactions to human skin toxicity evaluation [226,232] itching eczema after several months of exposure to a soy-based ingredients in cosmetic lotions [233]
Hedera helix	saponins (hederin, hederagenin, hederacosides, hederacolchisides etc.), flavonoids, anthocyanins, coumarins and phenolic acids, steroids, vitamins, volatile and fixed oils [234]	antiseptic, anti-elastase and anti-hyaluronidase effect indicated in cellulitis, cicatrisation, and wound healing [158,234,235]	contact dermatitis [234]
Lilium candidum	saponins, flavonoids, glycosides, nitrogenous compounds [236,237]	amelioration of skin redness, burn healing, hyperpigmentation, edema/skin inflammation anti-irritant, anti-inflammatory, antioxidant effect, and also emollient and sebostatic effect capacity of reducing ecchymosis, providing keratinocytes proliferation [158,236,238,239]	no irritations in vitro dermal or ocular irritation model [240]

Table 2. *Cont.*

Active Ingredient/Plant Species	Bioactive Components	Biological Role and Benefits for Skin	Toxicity of Topical Products
Magnolia liliflora	terpenes, flavonoids, chlorogenic acid, rutin, quercetin, kaempferol, volatile oil (phenyethyl alcohol, levoxine, pinene, caryophyllene oxide, caryophyllene, bourbonene, farnesene, aerpineol, humulene) [241–243]	antioxidant capacity, anti-dermatophytes action, anti-inflammatory effect [241–243]	* N
Malus domestica/sylvestris	polyphenols (phloridizin, phloretin, quercetin, glycosides, rutin), acids (citric, malic, lactic, pyruvic, ascorbic etc.) [244–246]	confers cell protection, anti-ageing and photoprotective effect, antioxidant capacity increases moisture, reduces tyrosinase activity (depigmentation effect) [245–248]	absence of skin irritation of a cosmetic product containing 6% *Malus sylvestris* fruit extract under 24 h occlusive patch testing [245]
Malva sylvestris	mucilaginous polysaccharides, tannins, polyphenols, vitamin C, vitamin E, β-carotene, anthocyanidines, terpenes, naphthoquinones, flavonoids, fatty acids (e.g., α-linolenic acid) and minerals [158,249–255]	anti-pruritus, anti-psoriatic and antiseptic effect emollient, anti-inflammatory and antimicrobial capacity wound healing (stimulates the formation of free granulation tissue and reepithelization) [158,249–253,255]	low toxicity of *Malva sylvestris* hydro-alcoholic extract on topical application [256]
Nymphaea alba	polyphenols, flavonoids, essential oil, vitamin E, ellagitannins, sterols, fatty acids [257–259]	stimulates the autophagy (reduces the accumulation of advanced glycation end products which determine inflammatory response, destroys the protein structureand colors the skin in yellow or brown) antioxidant and photo-protection capacity reduces the hyperpigmentation [258,260]	* N
Opuntia cochenillifera	flavonoids, terpenes, cellulose, hemicellulose, lignins, pectines, malic acid, citric acid, ascorbic acid, oligosaccharides (fructose, glucose, sucrose, maltose etc.), amino-acids, fatty-acids [261–264]	antioxidant capacity, immunomodulation, hydration and cooling effects, wound healing [262,263]	* N
Orchid sp.	flavonoids, anthocyanins, fatty acids, organic acids, sterols, stilbenoids (resveratrol), amino-acids [265–267]	anti-inflammatory effect, antioxidant capacity, anti-tyrosinase activity, inhibits collagenase and elastase photo-protection, wound healing capacity cooling agent astringent, anti-ageing, emollient, skin moisturizing and whitening effect [265,266,268,269]	allergic contact dermatitis [270]

Table 2. *Cont.*

Active Ingredient/Plant Species	Bioactive Components	Biological Role and Benefits for Skin	Toxicity of Topical Products
Pfaffia paniculata	saponins (pfaffosides), pfaffic acid, sterols, allantoin [236,271]	anti-inflammatory and anti-cellulite effect, antioxidant capacity, protective effect against photo-ageing [236,271]	* N
Picea abies	diterpene, stilbene glycosides (E-astringin, E-isorhapontin, flavonoids (catechin, taxifolin, taxifolin-3′-O-glucoside), lignin (pinoresinol) phenolic acid derivates, saccharose [272,273]	antioxidant capacity, antibacterial activity inhibits collagenase (anti-ageing activity), elastase (anti-ageing, anti-inflammatory and anti-psoriatic effect) and tyrosinase (whitening activity) wound healing and skin regeneration properties (cellular regeneration and epithelialization) [272–276]	possible allergic skin reactions (e.g., contact dermatitis) [276]
Porphyridium cruentum	exopolysaccharide, phycoerythrins, phycoerythrocyanins, phycocyanins, sterols, superoxide dismutase, polyunsaturated fatty acids [277–279]	antioxidant capacity, anti-inflammatory, anti-redness effect restores skin barrier permeability, photo-protection, regenerative and anti-wrinkles effect natural dye for cosmetics (creams, powders, lipsticks, make-up, eye shadows) [278–282]	* N
Ptychopetalum olacoides	fatty acids, saponins, flavonoids (rutin), sterols, aromatic oil, alkaloids, lupeol [236,283]	antioxidant capacity, anti-cellulite effect [236]	* N
Punica granatum	anthocyanins, ellagic acid, tannins [176]	improves viscoelasticity, anti-ageing effect, anti-inflammatory and antioxidant capacity antimicrobial activity [176,284,285]	no adverse effects [286]
Rosa sp. (*R. damascena*, *R. canina*, *R. centifolia*, *R. davurica*, *R. mosqueta*, *R. rugosa*)	carotenoids, sterols, anthocyanins, catechins, polyphenolic compounds (tocopherol), vitamin C, fatty acids (trans-retinoic acid, arachidonic acid, and unsaturated fatty acids, such as oleic, linoleic and linolenic acids) [287,288]	anti-inflammatory effect (suppressing proinflammatory cytokines) [289–292] antibacterial against skin bacteria (*Propionibacterium acnes*) [289–293] antioxidant capacity [290,292,294] antiproliferative and chemopreventive effects [290] fragrance in the perfumery industry [295]	well tolerate [296] no toxicity on human keratinocyte HaCaT cells [289] contact dermatitis to Rosa mosqueta oil applied for 3 days [288]
Rosmarinus officinalis	triterpes (rosmarinic acid, oleanolic acid, ursolic acid) [172,297]	antioxidant capacity, photoprotective effect, anti-aging, wound healing, anti-inflammatory, increases skin elasticity, wrinkles reducing effect [157,297,298]	eczema, contact dermatitis [172,299]

Table 2. *Cont.*

Active Ingredient/Plant Species	Bioactive Components	Biological Role and Benefits for Skin	Toxicity of Topical Products
Rubus chamaemorus	ellagitannins, proanthocyanidins, fenolic acids, flavonoids, lignans, vitamin C, fatty acids (oleic, linoleic, linolenic etc.) [300]	antioxidant capacity antimicrobial effect (Staphylococcus aureus skin infections) reduces periorbital inflammations and ameliorates pruritus [300,301]	no irritation after an 48 h occlusive patch testin of a cosmetic product incorporating 2.5% *Rubus chamaemorus* Seed Oil (25 µL testing product quantity) [302]
Saccharum officinarum	fatty acids, fatty alcohols, acids, esters, aldehydes, ketones, sterols, terpoides, phenolic acids, flavonoids (flavones glycosides) [303–305]	antioxidant capacity, anti-tyrosinase activity photo-protection effect [304,305]	low toxicity after in vitro cytotoxicity assay [304]
Sambucus nigra	phenolic acids (caffeic, chlorogenic, ferulic, rosmarinic), flavonoids (quercetin, rutin, kaempferol), anthocyanins, tannins, triterpenes, organic acids [306–308]	antioxidant capacity, reduces tyrosinase activity antiseptic, anti-inflammatory, anti-psoriatic, photoprotective effects [306–312]	* N
Sideritis sp. (*S. perfoliata*, *S. raeseri*)	terpenes, phenolic compounds (flavonoids, phenylpropanid glycosides), tannins [313–317]	antioxidant capacity, anti-elastase, anti-melanin and anti-tyrosinase activity (anti-wrinkle and depigmentation effect) anti-inflammatory and antibacterial capacity photo-protection effect [313,314,316,317]	* N
Sophora japonica	flavonoids (rutin, quercetin etc.), tripterpenoids, alkaloids, saponins, polysaccharides [318–320]	antioxidant capacity, photo-protection, anti-melanin and anti-tyrosinase activity (skin-whitening) [318–321]	* N
Triticum aestivum	oligosaccharides [322]	stimulates hyaluronan synthase, fibronectin synthesys, restores the skin barrier integrity (wound healing: decubitus ulcers, skin lesions and burns), anti-inflammatory effect, antioxidant capacity [322–325]	possible hypersensitivity reactions [326]
Ulmus davidiana	saccharides (galactose, rhamnose, glucose), succinic acid, terpenoids (epifriedenalol), lignans, flavonoids (catechin) [327–329]	moisturizing, photoprotective, anti-ageing, anti-allergic and anti-inflammatory effect [327,328]	* N
Vaccinium myrtillus	anthocyanins (cyanidin, delphinidin, malvidin, peonidin, petunidin), flavonoids, phenolic acids [330]	antioxidant capacity, photoprotective and anti-inflammatory effect (anti-psoriatic, anti-erythematous), astringent properties, wound healing, restores and protects the skin barrier function [330–335]	* N

Table 2. *Cont.*

Active Ingredient/Plant Species	Bioactive Components	Biological Role and Benefits for Skin	Toxicity of Topical Products
Vitis vinifera	polyphenols (resveratrol, anthocyanins), coumarn, carotenoids, flavonoids, tartaric acid, tannins, terpene alcohols [336–338]	anti-ageing effect, antioxidant capacity, anti-melanogenic activities, sunscreen protection [157,176,338,339]	allergic dermatitis [336,340]
Voandzeia subterranean	alkaloids, flavonoids, glycosides, saponins, steroids, triterpenoids, phenols, anthocyanins, carotenoids proteins, crude fiber, carbohydrates [341,342]	anti-wrinkle effects, photoprotective, anti-irritant, anti-pollution, hydrating effects, antioxidant capacity, anti-ageing activity, inhibits proteases, elastases, collagenases and catalase [343]	* N

* N—No article reported.

Table 3. Benefits, cosmetic claim, and toxicity of some active ingredients used in cosmetics together with hyaluronic acid and HA derivates.

Active Ingredient	Cosmetic Claim and Skin Benefits	Toxicity of Topical Products
Probiotics	prevention and improvement of skin conditions (e.g., external signs of ageing, acne, rosacea, yeast and bacterial infections, psoriasis, dermatitis) [344–350]	no side effects [344,350]
Bifida Ferment Lysate	improves the skin's epidermal renewal process [351] diminishes clinical signs and symptoms of atopic eczema [352–354] regulates skin reactivity and dryness [355]	non-sensitizing [356]
Lactococcus Ferment Lysate	stimulates the skin's self-renewal [357] significant improvement of atopic dermatitis (AD) [354]	non-irritant, no allergenic potential [358]
Pseudoalteromonas Ferment Extract	reduces skin shininess, pores, spots, and sebum [359,360]	non-sensitizing, non-irritating [361]
Amino acids, *Peptides*, *Proteins*	common ingredients in cosmetics, as they function as natural moisturizing factors which act as water-binding molecules stimulating collagen and elastin synthesis in skin and improving surface healing anti-ageing effect, increase hydration of the skin which helps to reduce wrinkles and improves the functions of the skin barrier [362]	safe in cosmetics [362]
Alanine	natural moisturizing factor which acts as a water binding molecule [362]	safe for cosmetic use no dermal irritation or sensitization [363]

Table 3. *Cont.*

Active Ingredient	Cosmetic Claim and Skin Benefits	Toxicity of Topical Products
Arginine	moisturizing effect increases skin hydration and alleviates the condition of skin dryness [364]	no dermal irritation or sensitization [363]
Isoleucine	an essential amino acid known for its ability to support tissue repair effective in the treatment of mild to moderate chronic lesion of atopic eczema of the face [365]	safe for cosmetic use [363]
Acetyl Hexapeptide-8	cosmetic application for wrinkles, working by relaxing of superficial dermal muscles [366] decreases hyperkinetic facial lines or expression wrinkles, effective in reducing skin roughness [367] neurotransmitter inhibitor peptide, used in anti-wrinkle formulations applied to the periorbital area [368]	well tolerated, with lack of burning and discomfort to the patient safe for topical application [369]
Acetylarginyltryptophyl Diphenylglycine	enhances skin elasticity and tightness, increases type I collagen synthesis [370]	* N
Pentapeptide-18	neurotransmitter-inhibiting peptide that decreases neuronal activity and catecholamine release, giving it Botox-like effects in reducing fine lines and wrinkles, and improving skin firmness [371]	safe for cosmetic use [372]
Dipeptide Diaminobutyroyl Benzylamide Diacetate	a small tripetide with anti-ageing and mattifying effect, stimulates PLOD 3 (procollagen-lysine, oxoglutarate 5-dioxygenase 3), enzyme which is known to be of importance for the intermolecular collagen crosslink stability, increasing the stability of collagen, especially in mature skin [373]	* N
Palmitoyl Tripeptide	improvement of facial wrinkles, elasticity, dermal density and skin tone [374]	safe in cosmetic products [375]
Vitamins	useful role in the treatment of skin ageing and protection of human skin against UV induced ageing [376]	
Ascorbyl Tetraisopalmitate	antioxidant and anti-inflammatory properties, increases skin hydration and smoothness [377]	contact dermatitis [378,379]
Niacinamide	antipruritic, antimicrobial, vasoactive, photoprotective, sebostatic capacity, lightening effect depending on its concentration [380]	safe for cosmetic use [381]
Panthenol	hydrating and softening potential, significantly accelerating epidermal regeneration [382]	allergic contact dermatitis [383,384]

Table 3. *Cont.*

Active Ingredient	Cosmetic Claim and Skin Benefits	Toxicity of Topical Products
Retinoids	antioxidant capacity, anti-wrinkle, depigmentation, anti-roughness, keratolytic effects, improve skin texture and laxity, protective effect against photo-ageing [385,386]	photosensitization, irritation, erythema, dermatitis, pruritus, burning sensation [386]
Tocopherol Tocotrienols	antioxidant capacity, anti-wrinkle effect, improving skin moisture [157,385,387]	erythema, oedema, local irritation [387]
Saccharides		
Trehalose	moisture retaining agent in several cosmetic creams and lotions [388,389]	safe for use in cosmetic products [388]
Bee products (Honey, Propolis)		
Honey Extract Propolis Extract	antimicrobial and immunomodulatory effect, antioxidant capacity, wound healing (stimulates angiogenesis, granulation, epithelialization, TNF-α (tumor necrosis factor-α) production, increasing collagen and fibroblasts synthesis), emollient, humectant, moisturizing, nourishing and protective effects against photo-ageing, restoration capacity of skin barrier function [390–397]	contact dermatitis, acute sensitization [391,396,397]
Other Chemical Compounds		
Allantoin (5-ureidohydantoin)	anti-inflammatory effect and anti-irritation, wound healing and keratolytic properties, hydration effect, tissue regeneration and cell proliferation capacity [398,399]	no adverse effects [399]
Ceramide 3	increases SC hydration, enhances the barrier function and reduces inflammation [400,401]	safe for use in cosmetic products [402]
Gold	anti-inflammatory and antioxidant effect, tissue regeneration capacity, restores skin elasticity, reduces signs of stress and ageing [403–405]	particles larger than 30 nm can be considered as safe but there is a need to comprehensively study the effects of gold nanoparticles on the basis of their size distribution for their safe application in cosmetics [404]
Lactic acid	primarily used as moisturizer and pH regulator in cosmetics, antimicrobial activity, skin lightening effect, keratolytic properties, possesses high water-binding capacity, antibacterial effect [406,407] peeling agent used in the amelioration of acne vulgaris and in the treatment of melasma [408]	good skin compatibility, showing only minor reactions [407]

Table 3. *Cont.*

Active Ingredient	Cosmetic Claim and Skin Benefits	Toxicity of Topical Products
Lecithin	antioxidant effect, dispersing agent for pigments [409]	safe as used in rinse-off products safe for use in leave-on products at concentrations of 15% insufficient data to determine the safety for use in cosmetic products where Lecithin or Hydrogenated Lecithin are likely to be inhaled [409]
Malachite Extract	a copper complex extracted from the malachite stone, being a powerful free radical scavenger, boosting cellular defenses, offering protection and detoxifying benefits [410]	* N
Sodium Pyrrolidone Carboxylate	skin moisturizing effect [411]	safe in cosmetics non-irritating in a reconstructed human epidermis model test using the EpiSkin model [412]
Superoxide Dismutase (SOD)	reduces UV-induced erythema, free radical scavenger, anti-irritant effect, anti-ageing capacity [413]	non-irritating and non-sensitizing [413]
Urea	humectant, decreases TEWL in normal skin and especially in xerotic skin disorders (AD patients) [414] moisturizing effect, desquamating actions (urea dissolves the intercellular cementing substance in the SC), antimicrobial action [415–417]	safe as used in cosmetic products [415].

* N—No article reported. We used background color for cosmetic ingredients classes which represent examples of ingredients from the class presented above.

5. Conclusions

Presently, the cosmetic industry is increasingly focusing on the development and formulation of active cosmetic products and cosmeceuticals. Although HA and its derivates have a large applicability in the cosmetic practice, with a multitude of useful and interesting applications, further exploration and technological development are imperative. As shown, the efficacy of hyaluronic acid depends largely on the molecular weight, claiming different effects like hydrating, regenerating, and anti-ageing. Further consideration of aspects regarding HA metabolism and receptor clustering analysis and explanations regarding various biological changes and foreseeable effects related to the molecular weight of HA are needed.

Lately, there have been a multitude of commercially available cosmetic formulations which incorporate HA or HA derivates. Categorized from mass-market to prestige or luxury products, it is important to mention that finished products containing HA represent only a small percentage, and the majority of the total products contain sodium hyaluronate.

Cosmetics incorporating HA or NaHA also contain in their formulation different plant extracts, vitamins, amino acids, peptides, proteins, saccharides, probiotics, and even gold or malachite extract. Although these additional active ingredients can cause some minor side effects, they can raise the market price, and sustain additional claims of the cosmetic product containing HA or HA derivates.

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Abbreviations

AD	Atopic dermatitis
CIR	Cosmetic Ingredient Review
CS	Chondroitin sulphate
DEJ	Dermoepidermal junction
DOX	Docetaxel
Dx/HA	Dextranomer/hyaluronic acid copolymer
ECM	Extracellular matrix
FSFI	Female sexual function index
HA	Hyaluronic acid
HARE	Hyaluronan receptor for endocytosis
HMW-HA	High molecular weight hyaluronic acid
IOP	Intraocular pressure
KHA	Potassium hyaluronate
LMW-HA	Low molecular weight hyaluronic acid
LYVE1	Lymphatic vessel endothelial hyaluronan receptor-1
MMW-HA	Medium molecular weight hyaluronic acid
MSCs	Mesenchymal stronal cells
NaHA	Sodium hyaluronate
NP	Nanoparticles

OVD	Ophthalmic viscoelastic device
PLOD 3	Procollagen-lysine, oxoglutarate 5-dioxygenase 3
PTX	Paclitaxel
RHAMM	Receptor for hyaluronan-mediated motility
SC	Stratum corneum
SOD	Superoxide dismutase
TEWL	Transepidermal water loss
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor-α
UTI	Urinary tract infection
VUR	Vesicoureteral reflux

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