

# Hyaluronic Acid in Cosmeceuticals

Subjects: Biochemistry & Molecular Biology

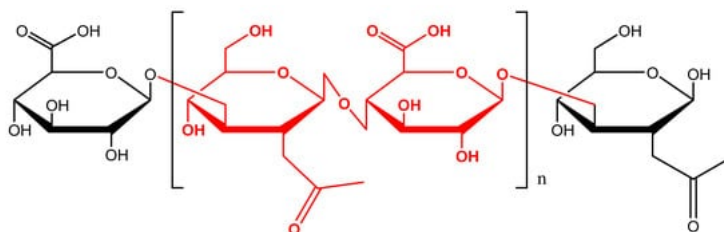
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Hyaluronic acid (HA) is a polysaccharide belonging to the glycosaminoglycans, made up of disaccharide units constituted of N-acetylglucosamine and D-glucuronic acid.

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

## 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][2][3][4][5][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][8][9]. HA has a wide range of molecular weights ranging from  $2 \times 10^5$  to  $10^7$  Da [10][11][12][13]. The HA average molecular weight can influence its physico-chemical properties [3][14].



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

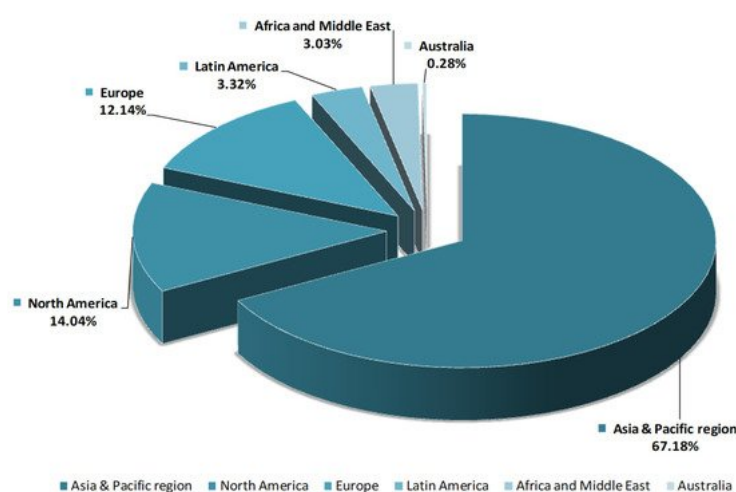
Among the many biological effects, HA is involved in cell differentiation, embryological development, inflammation, wound healing, viscoelasticity, etc. [15]. As it has been observed, the molecular mass and the mode of its synthesis or degradation define the HA biological effects [3][16][17]. By a passive 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].

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 can 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  $\mu\text{m}$  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. 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 [24]. 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 <sup>[16]</sup>.

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 <sup>[10][25][26]</sup>.

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 prevent wrinkles from filling. 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 <sup>[27]</sup>.

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 possesses an occlusive effect. Additionally, HMW-HA, Medium molecular weight (MMW-HA), and LMW-HA hygroscopic properties justify the ability to maintain skin hydration <sup>[27][28]</sup>.

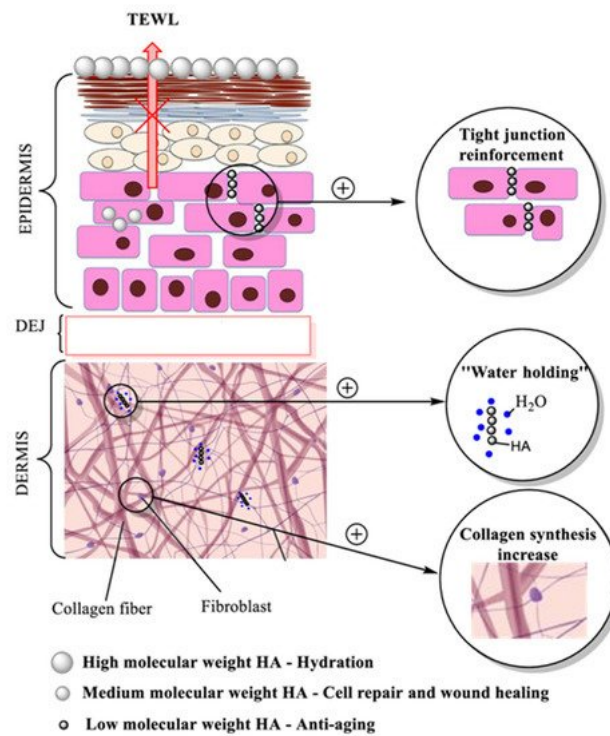
HA is also of particular importance as a delivery system of active ingredients. Currently, there are some commercially available formulations incorporating actives in different concentrations. These products are designated for the topical treatment of actinic keratosis and skin inflammatory diseases. 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.) <sup>[13][29][28]</sup>.

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 can vary 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 <sup>[16][30]</sup>.

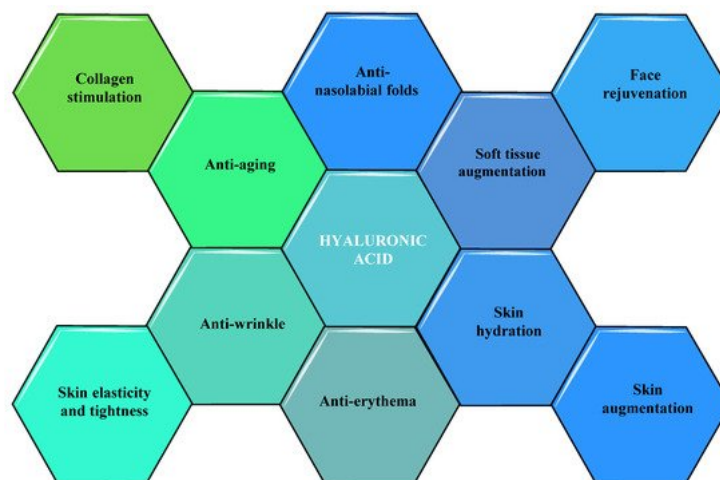
HA is used in cosmetic formulations in concentrations ranging from 0.2 to 1%. The maximum concentration of NaHA in a body lotion is 2%. When a rate of 1 mg/cm<sup>2</sup> of a product is applied, the contribution of hyaluronic acid is 0.02 mg/cm<sup>2</sup> of skin <sup>[20]</sup>.

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 <sup>[27][28]</sup>. 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 face as summarized in **Figure 5** [31].



**Figure 5.** Cosmetic and nutricosmetic effects of HA.

### 2.1. Hydration 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 [32][33][34].

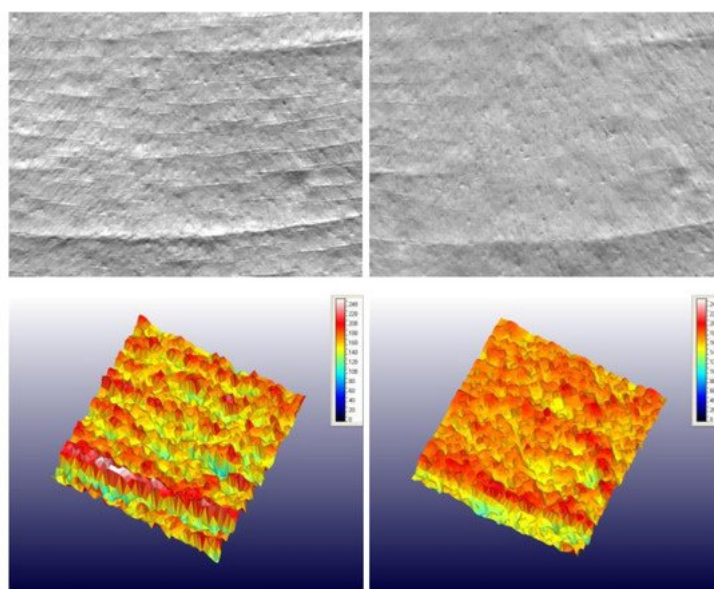
HA, which has the ability to bind water up to 1000 times its volume, has a relevant contribution to cellular growth, adhesion, and membrane receptor function. The major biologic role of HA in the intercellular matrix is to reinforce the intercellular structures and to produce the elastoviscous fluid matrix that firmly envelops collagen and elastin fibers. HA holds moisture, and provides firmness and radiance to the skin as well [35][36]. HA can be used topically to regenerate the skin and support hydration, although its very high molecular weight prevents its penetration through the SC [37][38].

### 2.2. 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 [39]. Skin ageing is also associated with a decrease of skin moisture. Hyaluronic acid (hyaluronan) has a unique capacity to link and retain water molecules [40]. 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 [41][42][43][44].

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][45][35][46]. Hyaluronic acid is used in cosmetic preparations for its elasticity effect and for giving shape to the periorbital area after HA cosmetic treatment [47]. 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 [41][48].

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/JSR/Agreement No. 331/30 August 2019 JS. Hamilton Romania S.R.L) [49].



**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) [49].

### 3. 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 [50]. 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 [51]. 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 [50]. 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 [35][44]. 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.

**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 | [52]      |
|                                        | 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, Acetylgarginyltryptophyl 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 | [53]      |
|                                        | DECIEM (Canada) THE ORDINARY Hyaluronic Acid 2% + B5 Serum                 | NaHA          | Panthenol, Ahnfeltia Concinna Extract                                                                                                                                                                                                                                                                                                                                                                                                                            | moisturizing, anti-ageing            | Premium Market | [54]      |
|                                        | 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 | [55]      |
|                                        | FARMEC (Romania) Hyaluronic Acid ampoules 5% Serum                         | NaHA          | Superoxide Dismutase, Lecithin                                                                                                                                                                                                                                                                                                                                                                                                                                   | anti-wrinkle, intensive moisturizing | Mass Market    | [56]      |
|                                        | AVIVA COSMETICS (Romania) INFINITUM Deep Wrinkles Anti-Ageing Serum        | Hydrolyzed HA | Aesculus Hippocastanum Extract                                                                                                                                                                                                                                                                                                                                                                                                                                   | firming, anti-ageing                 | Premium Market | [57]      |
|                                        | 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 | [58]      |

| 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 |
|----------------------------------------|-----------------------------------------------------------------------------------------------|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|----------------|-----------|
|                                        | BALANCE ME (UK)<br>Tinted Wonder Eye Cream<br>Eye cream<br>complexion perfection<br>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    | [59]      |
|                                        | EARTH SCIENCE (USA)<br>Apricot Intensive night cream<br>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    | [60]      |
|                                        | COSMETIC PLANT (Romania)<br>Lift Up—Hyaluronic Acid Day Anti-Ageing Cream<br>Day Cream        | Hydrolyzed HA | Porphyridium Cruentum Extract, Magnolia Liliflora Extract, Tocopherol                                                                                                                                                                                                                                  | anti-ageing                                                 | Mass Market    | [61]      |
|                                        | AVIVA COSMETICS (Romania)<br>INFINITUM Cellular Regenerating Cream                            | Hydrolyzed HA | Aesculus Hippocastanum Extract, Tocopheryl Acetate                                                                                                                                                                                                                                                     | firming, regenerating, rejuvenating                         | Premium Market | [62]      |
|                                        | GEROCOSSEN (Romania)<br>Hyaluron Anti-Age Cream<br>SPF 10 Day Cream                           | NaHA          | Lecithin, Tocopheryl acetate, Retinyl palmitate                                                                                                                                                                                                                                                        | anti-ageing                                                 | Mass Market    | [63]      |
|                                        | AVIVA COSMETICS (Romania)<br>INFINITUM Golden Elixir Anti-Ageing Cream<br>SPF 15 Day Cream    | Hydrolyzed HA | Aesculus Hippocastanum Extract, Gold (CI 777480), Ectoin                                                                                                                                                                                                                                               | firming, anti-ageing, SPF 15                                | Premium Market | [64]      |
|                                        | FARMEC (Romania)<br>Anti-Wrinkle Cream<br>Concentrated with Hyaluronic Acid 3%<br>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    | [65]      |
|                                        | ARBONNE RE9 (USA)<br>Advanced For Men Anti-Aging Moisturizer<br>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 | [66]      |
|                                        | AVIVA COSMETICS (Romania)<br>INFINITUM Anti-Ageing Cleansing Emulsion                         | Hydrolyzed HA | Aesculus Hippocastanum Extract                                                                                                                                                                                                                                                                         | firming, anti-ageing                                        | Premium Market | [67]      |



| 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                         | JONZAC (France)<br>Bébé Bio Dermo-<br>Repair Cream<br>Baby Care                     | Hydrolyzed HA | Malva Sylvestris Extract, Tocopherol, Hydrogenated Lecithin                                                                                                                                                                                                                                          | soothing, regenerating, protecting      | Mass Market    | [68]      |
|                                        | LES MERVEILLEUSES<br>LADUREE (France)<br>Sun Protection<br>Body Cream<br>Body Cream | NaHA          | Rosa Centifolia Extract, Rosa Damascena Extract                                                                                                                                                                                                                                                      | hydrating, SPF 50                       | Premium Market | [69]      |
|                                        | NATURE REPUBLIC (South Korea)<br>Ice Sun, Ice Puff<br>Sun<br>Sun/Sunbed<br>Exposure | NaHA          | Calendula Officinalis Extract                                                                                                                                                                                                                                                                        | anti-wrinkle and skin blefening, SPF 50 | Mass Market    | [70]      |
|                                        | DM ALVERDE<br>NATURKOSMETIK (Germany)<br>Ivital +<br>Hand cream                     | NaHA          | Amaranthus Caudatus Extract, Triticum Aestivum Germ Extract, Punica Granatum Extract, Tocopherol                                                                                                                                                                                                     | smoothes lines and wrinkles             | Mass Market    | [71]      |
|                                        | INNISFREE (South Korea)<br>My Body<br>Tangerine Blossom<br>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    | [72]      |
|                                        | INNISFREE (South Korea)<br>Wine Peeling Jelly<br>Scrub<br>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    | [73]      |
|                                        | TUDE HOUSE (South Korea)<br>Berry AHA! Bleft<br>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, Bífida Ferment Lysate, Lecitin | blefening                               | Mass Market    | [74]      |
| Makeup cosmetics                       | ILLAMASQUA (UK) HYPNOTICA<br>Lipe Lure<br>Colour intense<br>Liquid lipstick         | NaHA          | N                                                                                                                                                                                                                                                                                                    | long-wearing, picture-perfect finish    | Premium Market | [75]      |
|                                        | CLINIQUE (USA)<br>Sun-Kissed Face<br>Gelee<br>Complexion multitasker                | NaHA          | N                                                                                                                                                                                                                                                                                                    | moisturizing                            | Premium Market | [76]      |
|                                        | PAUL& JOE (Japan)<br>Pore<br>SmoothingPrimer<br>Face primer                         | Hydrolyzed HA | Calendula Officianlis Extract, Rosa Canina Fruit Extract, Tocopherol                                                                                                                                                                                                                                 | moisturizing                            | Premium Market | [77]      |



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.

### 3.1. 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**.

**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                                                                               |
|---------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|
| <i>Acer saccharum</i>                       | phenolic compounds (maplexins, ginnalins) <sup>[78][79]</sup>                                                                                                                                                                   | increases the intracellular ceramide level<br>stimulates the proliferation and differentiation of keratinocytes<br>maintains the homeostasis of the epidermis<br>antioxidant capacity <sup>[78][80][81]</sup>                                                                                                                                    | * N                                                                                                        |
| <i>Ahnfeltia concinna</i> (red algae)       | polysaccharides (carrageenan, agar), amino acids, minerals, vitamins, trace elements <sup>[82][83][84]</sup>                                                                                                                    | antioxidant capacity, anti-wrinkle, skin-whitening (suppresses the melanin production), skin moisturizing <sup>[83][84][85][86]</sup>                                                                                                                                                                                                            | not toxic in topical applications<br>possible irritation, sensitization, or photoreactions <sup>[86]</sup> |
| <i>Alaria esculenta</i> (brown algae)       | polyphenols, diterpenoids, fatty acids, polysaccharides, fucosterol, fucoxanthin (e.g., retinoic acid), amino acids, minerals, vitamins, trace elements <sup>[87][88][89]</sup>                                                 | hyperpigmentation amelioration<br>increases skin firmness and elasticity<br>stimulates collagen and keratin synthesis, reducing the progerin production (increased in aged skin) of 'aged' fibroblasts<br>skin-whitening, antioxidant capacity <sup>[86][87][90][91]</sup><br>anti-cellulite and anti-edema activity <sup>[86][92][93][94]</sup> | possible local irritation, sensitization, or photoreactions <sup>[86]</sup>                                |
| <i>Aloe sp.</i> ( <i>Aloe barbadensis</i> ) | anthraquinones, polysaccharides, phenolic compounds, organic acids <sup>[95][96][97][98]</sup>                                                                                                                                  | antimicrobial activity <sup>[99][100]</sup><br>antioxidant capacity, anti-inflammatory, anti-pyrotic <sup>[100][101][102]</sup><br>improves skin moisture and water retention in the SC <sup>[97][100][101][103][104]</sup>                                                                                                                      | phototoxicity, eczema, contact dermatitis <sup>[95][96]</sup>                                              |
| <i>Amaranthus caudatus</i>                  | amino-acids, proteins, amylopectin, minerals, vitamins (vitamin A, E, K), fibers, essential fatty acids, triterpenes (squalene) <sup>[105][106]</sup>                                                                           | antioxidant capacity, moisturizing, skin hydration, suppressing the pigmentation <sup>[106][107][108]</sup>                                                                                                                                                                                                                                      | * N                                                                                                        |
| <i>Angelica keiskei</i>                     | coumarins, terpenes, phenolic compounds <sup>[109][110][111][112]</sup>                                                                                                                                                         | antioxidant capacity, astringent, emollient, skin conditioning and protecting, skin whitening and lightening, sunlight protection <sup>[109]</sup>                                                                                                                                                                                               | * N                                                                                                        |
| <i>Arnica montana</i>                       | fatty acids (palmitic, linoleic, myristic), essential oil, triterpenic alcohols, sugars, phytosterols, phenol acids, tannins, choline, inulin, flavonoids, carotenoids, coumarins, sesquiterpene lactones <sup>[113][114]</sup> | anti-inflammatory effect <sup>[102][115]</sup><br>reduces the ecchymosis and oedema <sup>[102]</sup>                                                                                                                                                                                                                                             | contact dermatitis <sup>[113][116]</sup><br>rarely ocular irritation <sup>[114]</sup>                      |

| Active Ingredient/Plant Species                                                                                           | Bioactive Components                                                                                                                                                                                            | Biological Role and Benefits for Skin                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Toxicity of Topical Products                                                                                                                                                                      |
|---------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Artemia salina</i>                                                                                                     | diguanosine-tetraphosphate, D-myo-inosite-1,4,5-triphosphate, proteins, glucan <sup>[117]</sup>                                                                                                                 | 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 <sup>[117]</sup>                                                                                                                                                                                                                                                                                                 | * N                                                                                                                                                                                               |
| <i>Bambusa arundinacea</i>                                                                                                | flavonoids, phenolic compounds, chlorogenic acid, caffeic acid, ferulic acid, 8-C-glucosyl apigenin, luteolin derivatives <sup>[118]</sup>                                                                      | antioxidant capacity, anti-ageing, photo-protection, skin pigmentation modulating effect, anti-allergic effect (inhibiting the production of IgE and lymphocytes) <sup>[118]</sup>                                                                                                                                                                                                                                                                                                                                                              | * N                                                                                                                                                                                               |
| <i>Calendula officinalis</i>                                                                                              | triterpenes, polyphenolic compounds, polysaccharides, vitamin C, tocopherols, quinones, carotenoids saponins, sterols <sup>[119][120][121][122]</sup>                                                           | anti-inflammatory effect <sup>[119][123]</sup><br>cell rejuvenation effect <sup>[123][124]</sup><br>skin smoothing and softening effect <sup>[123]</sup><br>prevents skin alteration and early ageing (improving the skin elasticity) <sup>[120][124][125]</sup><br>anti-irritant, anti-psoriatic and callus treating <sup>[102]</sup><br>stimulates the regeneration and epithelisation of wounded skin <sup>[119][123][124][125]</sup><br>antioxidant capacity <sup>[119][120][123][124]</sup><br>antimicrobial activity <sup>[99][123]</sup> | rare sensitization or allergic contact reactions <sup>[113][119][126]</sup>                                                                                                                       |
| <i>Camelia</i> sp.<br>( <i>C. sinensis</i> ,<br><i>C. japonica</i> )                                                      | polyphenols, catechins <sup>[120]</sup>                                                                                                                                                                         | antioxidant capacity, reduces the sebum production, improves skin hydration, skin smoothing and softening, photoprotective, and anti-inflammatory effect <sup>[120][127][128][129][130][131]</sup>                                                                                                                                                                                                                                                                                                                                              | contact dermatitis <sup>[116]</sup>                                                                                                                                                               |
| <i>Chamomila recutita</i>                                                                                                 | polysaccharides, flavonoids ( $\alpha$ -bisabolol, apigenin), sesquiterpene lactones <sup>[113][120]</sup>                                                                                                      | anti-inflammatory effect, antioxidant capacity <sup>[132]</sup><br>repairs the SC, wound healing, anti-ageing activity<br>skin smoothing and softening, also being used in the treatment of eczema <sup>[120][132][133]</sup>                                                                                                                                                                                                                                                                                                                   | skin sensitization, contact dermatitis <sup>[113][133][134]</sup>                                                                                                                                 |
| <i>Centella asiatica</i>                                                                                                  | saponins, flavonoids (quercetin, kaempferol, apigenil, naringenin, phenolic acids (chlorogenic acid), triterpenic steroids, amino acids, sugars <sup>[135][136]</sup>                                           | antioxidant capacity, anti-inflammatory, anti-ageing effect<br>stimulates the fibroblast proliferation, increasing the collagen synthesis<br>increases the SC hydration and the epidermal barrier function<br>anti-cellulite effect <sup>[135][136]</sup>                                                                                                                                                                                                                                                                                       | local allergic reactions, burning, eczemas, vesicles, pruritus <sup>[136]</sup>                                                                                                                   |
| <i>Ceratonia siliqua</i>                                                                                                  | flavonoids, phytosterols, acids, esters, terpenoids, fenolic compounds <sup>[137][138][139]</sup>                                                                                                               | anti-cellulite effect (increasing the aquaglyceroporines activity, stimulating lipolysis, reducing the localized fat overload), antioxidant capacity, depigmentation effect (anti-tyrosinase activity), skin lightening effect <sup>[137][138][140]</sup>                                                                                                                                                                                                                                                                                       | non-irritation potential <sup>[137]</sup>                                                                                                                                                         |
| <i>Citrus</i> sp.<br>( <i>C. aurantium dulcis</i> ,<br><i>C. grandis</i> ,<br><i>C. limon</i> ,<br><i>C. unshiu</i> peel) | bergapten, bergamotin, isopimpinellin, coumarins, psoralenes, angelical, volatile oil (limonene, linalool, linalyl acetate, terpineol, terpinene, terpinolene, ocimene, pinene etc.) <sup>[141][142][143]</sup> | antioxidant capacity, anti-inflammatory, antiseptic and anti-verrucous effect, used in acne treatment, wound healing properties, used as fragrance <sup>[102][141][142][143]</sup>                                                                                                                                                                                                                                                                                                                                                              | possible irritation, skin sensitization, hyperpigmentation, redness, oedema, photo-toxicity <sup>[141][142][143][144]</sup>                                                                       |
| <i>Cucumis sativus</i>                                                                                                    | flavonoids, saponins, sterols, carbohydrates, triterpenes, vitamins (C, B), fatty acid, proteins <sup>[145][146]</sup>                                                                                          | used in the treatment of periorbital edema, soothing emollient, anti-wrinkle, anti-ageing, anti-itching effects<br>depigmentant and antioxidant capacity, anti-hyaluronidase and anti-elastase actions <sup>[145]</sup>                                                                                                                                                                                                                                                                                                                         | erythema after semi occlusive patch testing and conjunctival hyperemia/ocular irritation after a using of an eye lotion containing 1% <i>C. sativus</i> (cucumber) fruit extract <sup>[146]</sup> |

| Active Ingredient/Plant Species | Bioactive Components                                                                                                                                                                         | Biological Role and Benefits for Skin                                                                                                                                                                                                                                                                                                          | Toxicity of Topical Products                                                                                                                                                                       |
|---------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Cydonia oblonga</i> seed     | cellulose, polysaccharides, polyphenols <sup>[147][148]</sup>                                                                                                                                | stimulates fibroblasts proliferation, wound, and burns healing<br>maintains skin barrier function<br>anti-inflammatory, anti-allergic and protective effects<br>antioxidant capacity <sup>[147][148][149][150][151][152]</sup>                                                                                                                 | * N                                                                                                                                                                                                |
| <i>Eclipta prostrata</i>        | flavonoids (luteolin, apigenin), wedelolactone, terpenoids, sterols, alkaloids, volatile oils <sup>[153][154][155][156][157]</sup>                                                           | depigmentant effect (anti-tyrosinase activity)<br>hair revitalizing, dye in cosmetic products<br>antioxidant and photoprotective capacity <sup>[153][154][155][156]</sup>                                                                                                                                                                      | * N                                                                                                                                                                                                |
| <i>Euphrasia officinalis</i>    | iridoids, flavonoids, polyphenols, saponins, alkaloids, tannins, etheric oils <sup>[158][159]</sup>                                                                                          | anti-inflammatory and astringent effect<br>antioxidant capacity<br>photo-protection, protective effect against photo-ageing, stimulates collagen synthesis <sup>[158][160][161]</sup>                                                                                                                                                          | * N                                                                                                                                                                                                |
| <i>Ficus carica</i>             | phytosterols, anthocyanins, amino acids, atty acids, phenolic acids, flavonoids, volatile components <sup>[162][163]</sup>                                                                   | antioxidant capacity, anti-warts and anti-verrucous activity used in the treatment of dry skin, eczema, acne<br>anti-inflammatory, anti-ageing, anti-wrinkle and skin protection effects <sup>[102][162][163][164]</sup>                                                                                                                       | no side effects observed <sup>[164]</sup>                                                                                                                                                          |
| <i>Glycyrrhiza glabra</i>       | saponins (glycyrrhizin), flavonoids (liquiritigenin, liquiritin), glycosides, isoflavons (glabridin, coumarins, stilbenoids) <sup>[165][166]</sup>                                           | anti-inflammatory effect, antioxidant capacity, photo-protection effect<br>reduces erythema and hyperpigmentation<br>improves epidermal hydration and transepidermal water loss<br>antibacterial and antifungal effect<br>anti-dandruff effect <sup>[165][166][167][168]</sup>                                                                 | eye sensitivity (burning, itch, redness), scalp pruritus (itch, dandruff) <sup>[165]</sup>                                                                                                         |
| <i>Glycine max</i>              | phenolic acids (ferulic, syringic, sinapic, flavonoids (isoflavons), soy proteins ( $\beta$ -conglycinin, glycinin), lipids, vitamin E <sup>[169][170][171]</sup>                            | anti-inflammatory effect, antioxidant capacity<br>skin lightening and depigmentant<br>protective effect against photo-ageing<br>stimulates collagen and elastin synthesis, increasing the hyaluronic acid levels in aged skin<br>skin regeneration effect, providing nutrients for cell renewal <sup>[169][170][171][172][173][174][175]</sup> | none allergic reactions to human skin toxicity evaluation <sup>[170][176]</sup><br>itching eczema after several months of exposure to a soy-based ingredients in cosmetic lotions <sup>[177]</sup> |
| <i>Hedera helix</i>             | saponins (hederin, hederagenin, hederacosides, hederacolchisides etc.), flavonoids, anthocyanins, coumarins and phenolic acids, steroids, vitamins, volatile and fixed oils <sup>[178]</sup> | antiseptic, anti-elastase and anti-hyaluronidase effect indicated in cellulitis, cicatrisation, and wound healing <sup>[102][178][179]</sup>                                                                                                                                                                                                   | contact dermatitis <sup>[178]</sup>                                                                                                                                                                |
| <i>Lilium candidum</i>          | saponins, flavonoids, glycosides, nitrogenous compounds <sup>[180][181]</sup>                                                                                                                | amelioration of skin redness, burn healing, hyperpigmentation, edema/skin inflammation<br>anti-irritant, anti-inflammatory, antioxidant effect, and also emollient and sebostatic effect<br>capacity of reducing ecchymosis, providing keratinocytes proliferation <sup>[102][180][182][183]</sup>                                             | no irritations in vitro dermal or ocular irritation model <sup>[184]</sup>                                                                                                                         |

| Active Ingredient/Plant Species   | Bioactive Components                                                                                                                                                                                                                                               | Biological Role and Benefits for Skin                                                                                                                                                                                                                                                                                               | Toxicity of Topical Products                                                                                                                             |
|-----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Magnolia liliflora</i>         | terpenes, flavonoids, chlorogenic acid, rutin, quercetin, kaempferol, volatile oil (phenylethyl alcohol, levoxine, pinene, caryophyllene oxide, caryophyllene, bourbonene, farnesene, aerpineol, humulene) <sup>[185][186][187]</sup>                              | antioxidant capacity, anti-dermatophytes action, anti-inflammatory effect <sup>[185][186][187]</sup>                                                                                                                                                                                                                                | * N                                                                                                                                                      |
| <i>Malus domestica/sylvestris</i> | polyphenols (phloridizin, phloretin, quercetin, glycosides, rutin), acids (citric, malic, lactic, pyruvic, ascorbic etc.) <sup>[188][189][190]</sup>                                                                                                               | confers cell protection, anti-ageing and photoprotective effect, antioxidant capacity increases moisture, reduces tyrosinase activity (depigmentation effect) <sup>[189][190][191][192]</sup>                                                                                                                                       | absence of skin irritation of a cosmetic product containing 6% <i>Malus sylvestris</i> fruit extract under 24 h occlusive patch testing <sup>[189]</sup> |
| <i>Malva sylvestris</i>           | mucilaginous polysaccharides, tannins, polyphenols, vitamin C, vitamin E, $\beta$ -carotene, anthocyanidines, terpenes, naphthoquinones, flavonoids, fatty acids (e.g., $\alpha$ -linolenic acid) and minerals <sup>[102][193][194][195][196][197][198][199]</sup> | anti-pruritus, anti-psoriatic and antiseptic effect emollient, anti-inflammatory and antimicrobial capacity wound healing (stimulates the formation of free granulation tissue and reepithelization) <sup>[102][193][194][195][196][197][199]</sup>                                                                                 | low toxicity of <i>Malva sylvestris</i> hydro-alcoholic extract on topical application <sup>[200]</sup>                                                  |
| <i>Nymphaea alba</i>              | polyphenols, flavonoids, essential oil, vitamin E, ellagitannins, sterols, fatty acids <sup>[201][202][203]</sup>                                                                                                                                                  | stimulates the autophagy (reduces the accumulation of advanced glycation end products which determine inflammatory response, destroys the protein structure and colors the skin in yellow or brown) antioxidant and photo-protection capacity reduces the hyperpigmentation <sup>[202][204]</sup>                                   | * N                                                                                                                                                      |
| <i>Opuntia cochenillifera</i>     | flavonoids, terpenes, cellulose, hemicellulose, lignins, pectines, malic acid, citric acid, ascorbic acid, oligosaccharides (fructose, glucose, sucrose, maltose etc.), amino-acids, fatty-acids <sup>[205][206][207][208]</sup>                                   | antioxidant capacity, immunomodulation, hydration and cooling effects, wound healing <sup>[206][207]</sup>                                                                                                                                                                                                                          | * N                                                                                                                                                      |
| <i>Orchid</i> sp.                 | flavonoids, anthocyanins, fatty acids, organic acids, sterols, stilbenoids (resveratrol), amino-acids <sup>[209][210][211]</sup>                                                                                                                                   | 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 <sup>[209][210][212][213]</sup>                                                       | allergic contact dermatitis <sup>[214]</sup>                                                                                                             |
| <i>Pfaffia paniculata</i>         | saponins (pfaffosides), pfaffic acid, sterols, allantoin <sup>[180][215]</sup>                                                                                                                                                                                     | anti-inflammatory and anti-cellulite effect, antioxidant capacity, protective effect against photo-ageing <sup>[180][215]</sup>                                                                                                                                                                                                     | * N                                                                                                                                                      |
| <i>Picea abies</i>                | diterpene, stilbene glycosides (E-astringin, E-isorhapontin, flavonoids (catechin, taxifolin, taxifolin-3'-O-glucoside), lignin (pinoresinol) phenolic acid derivatives, saccharose <sup>[216][217]</sup>                                                          | 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) <sup>[216][217][218][219][220]</sup> | possible allergic skin reactions (e.g., contact dermatitis) <sup>[220]</sup>                                                                             |

| Active Ingredient/Plant Species                                                                                                                                  | Bioactive Components                                                                                                                                                                                                                               | Biological Role and Benefits for Skin                                                                                                                                                                                                                                                                                                                                                        | Toxicity of Topical Products                                                                                                                                                    |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Porphyridium cruentum</i>                                                                                                                                     | exopolysaccharide, phycoerythrins, phycoerythrocyanins, phycocyanins, sterols, superoxide dismutase, polyunsaturated fatty acids <sup>[221][222][223]</sup>                                                                                        | antioxidant capacity, anti-inflammatory, anti-redness effect<br>restores skin barrier permeability, photo-protection, regenerative and anti-wrinkles effect<br>natural dye for cosmetics (creams, powders, lipsticks, make-up, eye shadows) <sup>[222][223][224][225][226]</sup>                                                                                                             | * N                                                                                                                                                                             |
| <i>Ptychopetalum olacoides</i>                                                                                                                                   | fatty acids, saponins, flavonoids (rutin), sterols, aromatic oil, alkaloids, lupeol <sup>[180][227]</sup>                                                                                                                                          | antioxidant capacity, anti-cellulite effect <sup>[180]</sup>                                                                                                                                                                                                                                                                                                                                 | * N                                                                                                                                                                             |
| <i>Punica granatum</i>                                                                                                                                           | anthocyanins, ellagic acid, tannins <sup>[120]</sup>                                                                                                                                                                                               | improves viscoelasticity, anti-ageing effect, anti-inflammatory and antioxidant capacity<br>antimicrobial activity <sup>[120][228][229]</sup>                                                                                                                                                                                                                                                | no adverse effects <sup>[230]</sup>                                                                                                                                             |
| <i>Rosa</i> sp.<br>( <i>R. damascena</i> ,<br><i>R. canina</i> ,<br><i>R. centifolia</i> ,<br><i>R. davurica</i> ,<br><i>R. mosqueta</i> ,<br><i>R. rugosa</i> ) | 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) <sup>[231][232]</sup> | anti-inflammatory effect (suppressing proinflammatory cytokines) <sup>[233][234][235][236]</sup><br>antibacterial against skin bacteria ( <i>Propionibacterium acnes</i> ) <sup>[233][234][235][236][237]</sup><br>antioxidant capacity <sup>[234][236][238]</sup><br>antiproliferative and chemopreventive effects <sup>[234]</sup><br>fragrance in the perfumery industry <sup>[239]</sup> | well tolerate <sup>[240]</sup><br>no toxicity on human keratinocyte HaCaT cells <sup>[233]</sup><br>contact dermatitis to Rosa mosqueta oil applied for 3 days <sup>[232]</sup> |
| <i>Rosmarinus officinalis</i>                                                                                                                                    | triterpes (rosmarinic acid, oleanolic acid, ursolic acid) <sup>[116][241]</sup>                                                                                                                                                                    | antioxidant capacity, photoprotective effect, anti-aging, wound healing, anti-inflammatory, increases skin elasticity, wrinkles reducing effect <sup>[101][241][242]</sup>                                                                                                                                                                                                                   | eczema, contact dermatitis <sup>[116][243]</sup>                                                                                                                                |
| <i>Rubus chamaemorus</i>                                                                                                                                         | ellagitannins, proanthocyanidins, fenolic acids, flavonoids, lignans, vitamin C, fatty acids (oleic, linoleic, linolenic etc.) <sup>[244]</sup>                                                                                                    | antioxidant capacity<br>antimicrobial effect (Staphylococcus aureus skin infections)<br>reduces periorbital inflammations and ameliorates pruritus <sup>[244][245]</sup>                                                                                                                                                                                                                     | no irritation after an 48 h occlusive patch testin of a cosmetic product incorporating 2.5% <i>Rubus chamaemorus</i> Seed Oil (25 µL testing product quantity) <sup>[246]</sup> |
| <i>Saccharum officinarum</i>                                                                                                                                     | fatty acids, fatty alcohols, acids, esters, aldehydes, ketones, sterols, terpoides, phenolic acids, flavonoids (flavones glycosides) <sup>[247][248][249]</sup>                                                                                    | antioxidant capacity, anti-tyrosinase activity<br>photo-protection effect <sup>[248][249]</sup>                                                                                                                                                                                                                                                                                              | low toxicity after in vitro cytotoxicity assay <sup>[248]</sup>                                                                                                                 |
| <i>Sambucus nigra</i>                                                                                                                                            | phenolic acids (caffeic, chlorogenic, ferulic, rosmarinic), flavonoids (quercetin, rutin, kaempferol), anthocyanins, tannins, triterpenes, organic acids <sup>[250][251][252]</sup>                                                                | antioxidant capacity, reduces tyrosinase activity antiseptic, anti-inflammatory, anti-psoriatic, photoprotective effects <sup>[250][251][252][253][254][255][256]</sup>                                                                                                                                                                                                                      | * N                                                                                                                                                                             |
| <i>Sideritis</i> sp.<br>( <i>S. perfoliata</i> ,<br><i>S. raeseri</i> )                                                                                          | terpenes, phenolic compounds (flavonoids, phenylpropanid glycosides), tannins <sup>[257][258][259][260][261]</sup>                                                                                                                                 | antioxidant capacity, anti-elastase, anti-melanin and anti-tyrosinase activity (anti-wrinkle and depigmentation effect)<br>anti-inflammatory and antibacterial capacity<br>photo-protection effect <sup>[257][258][260][261]</sup>                                                                                                                                                           | * N                                                                                                                                                                             |
| <i>Sophora japonica</i>                                                                                                                                          | flavonoids (rutin, quercetin etc.), tripterpenoids, alkaloids, saponins, polysaccharides <sup>[262][263][264]</sup>                                                                                                                                | antioxidant capacity, photo-protection, anti-melanin and anti-tyrosinase activity (skin-whitening) <sup>[262][263][264][265]</sup>                                                                                                                                                                                                                                                           | * N                                                                                                                                                                             |
| <i>Triticum aestivum</i>                                                                                                                                         | oligosaccharides <sup>[266]</sup>                                                                                                                                                                                                                  | stimulates hyaluronan synthase, fibronectin synthesys, restores the skin barrier integrity (wound healing: decubitus ulcers, skin lesions and burns), anti-inflammatory effect, antioxidant capacity <sup>[266][267][268][269]</sup>                                                                                                                                                         | possible hypersensitivity reactions <sup>[270]</sup>                                                                                                                            |

| Active Ingredient/Plant Species | Bioactive Components                                                                                                                                                 | Biological Role and Benefits for Skin                                                                                                                                                                                                   | Toxicity of Topical Products              |
|---------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| <i>Ulmus davidiana</i>          | saccharides (galactose, rhamnose, glucose), succinic acid, terpenoids (epifriedenolol), lignans, flavonoids (catechin) <sup>[271][272][273]</sup>                    | moisturizing, photoprotective, anti-ageing, anti-allergic and anti-inflammatory effect <sup>[271][272]</sup>                                                                                                                            | * N                                       |
| <i>Vaccinium myrtillus</i>      | anthocyanins (cyanidin, delphinidin, malvidin, peonidin, petunidin), flavonoids, phenolic acids <sup>[274]</sup>                                                     | antioxidant capacity, photoprotective and anti-inflammatory effect (anti-psoriatic, anti-erythematous), astringent properties, wound healing, restores and protects the skin barrier function <sup>[274][275][276][277][278][279]</sup> | * N                                       |
| <i>Vitis vinifera</i>           | polyphenols (resveratrol, anthocyanins), coumarn, carotenoids, flavonoids, tartaric acid, tannins, terpene alcohols <sup>[280][281][282]</sup>                       | anti-ageing effect, antioxidant capacity, anti-melanogenic activities, sunscreen protection <sup>[101][120][282][283]</sup>                                                                                                             | allergic dermatitis <sup>[280][284]</sup> |
| <i>Voandzeia subterranean</i>   | alkaloids, flavonoids, glycosides, saponins, steroids, triterpenoids, phenols, anthocyanins, carotenoids, proteins, crude fiber, carbohydrates <sup>[285][286]</sup> | anti-wrinkle effects, photoprotective, anti-irritant, anti-pollution, hydrating effects, antioxidant capacity, anti-ageing activity, inhibits proteases, elastases, collagenases and catalase <sup>[287]</sup>                          | * N                                       |

\* N—No article reported.

### 3.2. Other Active Ingredients in Commercially 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 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                                                    |
|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| <i>Probiotics</i>                      | prevention and improvement of skin conditions (e.g., external signs of ageing, acne, rosacea, yeast and bacterial infections, psoriasis, dermatitis) <sup>[288][289][290][291][292][293][294]</sup>                                                                                                                                                                | no side effects <sup>[288][294]</sup>                                           |
| Bifida Ferment Lysate                  | improves the skin's epidermal renewal process <sup>[295]</sup><br>diminishes clinical signs and symptoms of atopic eczema <sup>[296][297][298]</sup><br>regulates skin reactivity and dryness <sup>[299]</sup>                                                                                                                                                     | non-sensitizing <sup>[300]</sup>                                                |
| Lactococcus Ferment Lysate             | stimulates the skin's self-renewal <sup>[301]</sup><br>significant improvement of atopic dermatitis (AD) <sup>[298]</sup>                                                                                                                                                                                                                                          | non-irritant, no allergenic potential <sup>[302]</sup>                          |
| Pseudoalteromonas Ferment Extract      | reduces skin shininess, pores, spots, and sebum <sup>[303][304]</sup>                                                                                                                                                                                                                                                                                              | non-sensitizing, non-irritating <sup>[305]</sup>                                |
| <i>Amino acids, Peptides, Proteins</i> | common ingredients in cosmetics, as they function as natural moisturizing factors which act as water-binding molecules<br>stimulating collagen and elastin synthesis in skin and improving surface healing<br>anti-ageing effect,<br>increase hydration of the skin which helps to reduce wrinkles and improves the functions of the skin barrier <sup>[306]</sup> | safe in cosmetics <sup>[306]</sup>                                              |
| Alanine                                | natural moisturizing factor which acts as a water binding molecule <sup>[306]</sup>                                                                                                                                                                                                                                                                                | safe for cosmetic use<br>no dermal irritation or sensitization <sup>[307]</sup> |

| Active Ingredient                                  | Cosmetic Claim and Skin Benefits                                                                                                                                                                                                                                                                                                                                                                                                                                   | Toxicity of Topical Products                                                                                        |
|----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|
| Arginine                                           | moisturizing effect<br>increases skin hydration and alleviates the condition of skin dryness <sup>[308]</sup>                                                                                                                                                                                                                                                                                                                                                      | no dermal irritation or sensitization <sup>[307]</sup>                                                              |
| Isoleucine                                         | an essential amino acid known for its ability to support tissue repair<br>effective in the treatment of mild to moderate chronic lesion of atopic eczema of the face <sup>[309]</sup>                                                                                                                                                                                                                                                                              | safe for cosmetic use <sup>[307]</sup>                                                                              |
| Acetyl Hexapeptide-8                               | cosmetic application for wrinkles, working by relaxing of superficial dermal muscles <sup>[310]</sup><br>decreases hyperkinetic facial lines or expression wrinkles, effective in reducing skin roughness <sup>[311]</sup><br>neurotransmitter inhibitor peptide, used in anti-wrinkle formulations applied to the periorbital area <sup>[312]</sup>                                                                                                               | well tolerated, with lack of burning and discomfort to the patient<br>safe for topical application <sup>[313]</sup> |
| Acetylglycyltryptophyl<br>Diphenylglycine          | enhances skin elasticity and tightness,<br>increases type I collagen synthesis <sup>[314]</sup>                                                                                                                                                                                                                                                                                                                                                                    | * 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 <sup>[315]</sup>                                                                                                                                                                                                                                                     | safe for cosmetic use <sup>[316]</sup>                                                                              |
| Dipeptide Diaminobutyroyl<br>Benzylamide Diacetate | a small tripeptide with anti-ageing and mattifying effect,<br>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 <sup>[317]</sup>                                                                                                                                                | * N                                                                                                                 |
| Palmitoyl Tripeptide                               | improvement of facial wrinkles, elasticity, dermal density and skin tone <sup>[318]</sup>                                                                                                                                                                                                                                                                                                                                                                          | safe in cosmetic products <sup>[319]</sup>                                                                          |
| Vitamins                                           | useful role in the treatment of skin ageing and protection of human skin against UV induced ageing <sup>[320]</sup>                                                                                                                                                                                                                                                                                                                                                |                                                                                                                     |
| Ascorbyl Tetraisopalmitate                         | antioxidant and anti-inflammatory properties, increases skin hydration and smoothness <sup>[321]</sup>                                                                                                                                                                                                                                                                                                                                                             | contact dermatitis <sup>[322][323]</sup>                                                                            |
| Niacinamide                                        | antipruritic, antimicrobial, vasoactive, photoprotective, sebostatic capacity, lightening effect depending on its concentration <sup>[324]</sup>                                                                                                                                                                                                                                                                                                                   | safe for cosmetic use <sup>[325]</sup>                                                                              |
| Panthenol                                          | hydrating and softening potential, significantly accelerating epidermal regeneration <sup>[326]</sup>                                                                                                                                                                                                                                                                                                                                                              | allergic contact dermatitis <sup>[327][328]</sup>                                                                   |
| Retinoids                                          | antioxidant capacity, anti-wrinkle, depigmentation, anti-roughness, keratolytic effects, improve skin texture and laxity, protective effect against photo-ageing <sup>[329][330]</sup>                                                                                                                                                                                                                                                                             | photosensitization, irritation, erythema, dermatitis, pruritus, burning sensation <sup>[330]</sup>                  |
| Tocopherol<br>Tocotrienols                         | antioxidant capacity, anti-wrinkle effect, improving skin moisture <sup>[301][329][331]</sup>                                                                                                                                                                                                                                                                                                                                                                      | erythema, oedema, local irritation <sup>[331]</sup>                                                                 |
| Saccharides                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                     |
| Trehalose                                          | moisture retaining agent in several cosmetic creams and lotions <sup>[332][333]</sup>                                                                                                                                                                                                                                                                                                                                                                              | safe for use in cosmetic products <sup>[332]</sup>                                                                  |
| <i>Bee products (Honey, Propolis)</i>              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                     |
| Honey Extract<br>Propolis Extract                  | antimicrobial and immunomodulatory effect, antioxidant capacity, wound healing (stimulates angiogenesis, granulation, epithelialization, TNF- $\alpha$ (tumor necrosis factor- $\alpha$ ) production, increasing collagen and fibroblasts synthesis), emollient, humectant, moisturizing, nourishing and protective effects against photo-ageing, restoration capacity of skin barrier function <sup>[334]</sup><br><sup>[335][336][337][338][339][340][341]</sup> | contact dermatitis, acute sensitization <sup>[335]</sup><br><sup>[340][341]</sup>                                   |
| <i>Other Chemical Compounds</i>                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                     |



| Active Ingredient                | Cosmetic Claim and Skin Benefits                                                                                                                                                                                                                                                                                                   | Toxicity of Topical Products                                                                                                                                                                                                                                 |
|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Allantoin<br>(5-ureidohydantoin) | anti-inflammatory effect and anti-irritation, wound healing and keratolytic properties, hydration effect, tissue regeneration and cell proliferation capacity <sup>[342][343]</sup>                                                                                                                                                | no adverse effects <sup>[343]</sup>                                                                                                                                                                                                                          |
| Ceramide 3                       | increases SC hydration, enhances the barrier function and reduces inflammation <sup>[344][345]</sup>                                                                                                                                                                                                                               | safe for use in cosmetic products <sup>[346]</sup>                                                                                                                                                                                                           |
| Gold                             | anti-inflammatory and antioxidant effect, tissue regeneration capacity, restores skin elasticity, reduces signs of stress and ageing <sup>[347][348][349]</sup>                                                                                                                                                                    | 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 <sup>[348]</sup>                        |
| 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 <sup>[350][351]</sup><br>peeling agent used in the amelioration of acne vulgaris and in the treatment of melasma <sup>[352]</sup> | good skin compatibility, showing only minor reactions <sup>[351]</sup>                                                                                                                                                                                       |
| Lecithin                         | antioxidant effect, dispersing agent for pigments <sup>[353]</sup>                                                                                                                                                                                                                                                                 | safe as used in rinse-off products<br>safe for use in leave-on products at concentrations of 15%<br>insufficient data to determine the safety for use in cosmetic products where Lecithin or Hydrogenated Lecithin are likely to be inhaled <sup>[353]</sup> |
| Malachite Extract                | a copper complex extracted from the malachite stone, being a powerful free radical scavenger, boosting cellular defenses, offering protection and detoxifying benefits <sup>[354]</sup>                                                                                                                                            | * N                                                                                                                                                                                                                                                          |
| Sodium Pyrrolidone Carboxylate   | skin moisturizing effect <sup>[355]</sup>                                                                                                                                                                                                                                                                                          | safe in cosmetics<br>non-irritating in a reconstructed human epidermis model test using the EpiSkin model <sup>[356]</sup>                                                                                                                                   |
| Superoxide Dismutase (SOD)       | reduces UV-induced erythema, free radical scavenger, anti-irritant effect, anti-ageing capacity <sup>[357]</sup>                                                                                                                                                                                                                   | non-irritating and non-sensitizing <sup>[357]</sup>                                                                                                                                                                                                          |
| Urea                             | humectant, decreases TEWL in normal skin and especially in xerotic skin disorders (AD patients) <sup>[358]</sup><br>moisturizing effect, desquamating actions (urea dissolves the intercellular cementing substance in the SC), antimicrobial action <sup>[359][360][361]</sup>                                                    | safe as used in cosmetic products <sup>[359]</sup> .                                                                                                                                                                                                         |

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

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