



Hyaluronidase inhibitors as skin rejuvenating agents from natural source

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Received 21 Feb. 2020

Revised 19 Mar. 2020

Accepted 23 Mar. 2020

ePublished 10 Apr. 2020



Abstract

With age, a decrease of original elasticity of the skin due to enzyme elastase leads to the appearance of fine lines, age spots, irregular pigmentation and wrinkles showing saggy and dull skin. The collagen also decreases and abnormal elastic fibers replace the dermis. Skin aging is a multifactorial process and its signs are influenced by a combination of intrinsic and extrinsic factors. Beside the process of aging, a daily external injury of skin (UV radiation, heat, pollutants, etc) causes loss of moisture. The key molecule involved in skin moisture is hyaluronic acid (HA) that has unique capacity in retaining water. By time, HA diminishes, degraded and skin become dry and wrinkled. Hence, the need to conserve matrix is recommended. Degradation of HA can be occurred either enzymatically or by a free – radical mechanism. Thus, natural agents that delay free – radical catalyzed degradation or acting for as inhibitors of hyaluronidase enzyme are useful to maintain the integrity of dermal HA. The market of cosmeceuticals from natural products is a demand nowadays to maintain a healthy skin instead of the use of harmful synthetic cosmetics. Few reports concerning hyaluronidase inhibitors from natural source. This article presents the reported potent herbal hyaluronidase enzyme inhibitors worldwide and most reported Egyptian products.

Keywords: Skin aging, Wrinkles, Hyaluronidase inhibitors, Herbal cosmeceutical

Introduction

It is reported that the market of natural and organic products of personal care is ~11 billion US\$ and expected to reach 22 billion US\$ by 2022.¹ The market of cosmeceuticals from natural products is a demand nowadays to maintain a healthy skin instead of the use of harmful synthetic cosmetics. With age, the skin loses its original elasticity and suppleness due to enzyme elastase which leads to sagging, the collagen decreases and the dermis is replaced by abnormal elastic fibers. At the same time hyaluronic acid (HA) in the skin also diminishes and skin becomes dry and wrinkled. Degradation of extracellular matrix in epidermal and dermal layers occurs.

Dermal components of the skin are degraded by the enzymes elastase, collagenase and hyaluronidase causing formation of wrinkles. Hence, there is a need to conserve matrix metallo-proteins by inhibiting the activity of these matrix metallo-proteinases.²

Physical changes in the skin

Aging usually results in a leathery, dry, discoloration, unsmooth, skin with wrinkles (rhytides), fine lines, age spots, saggy skin and wrinkles begin to show, making the skin appear dull and lifeless.^{3,4} The main signs of skin aging include wrinkling and irregular pigmentation, which are influenced by a combination of intrinsic (genetic, hormones) and extrinsic (e.g., UV rays, heat, smoking,

and pollutants) factors.⁵ Reactive oxygen species (ROS) cause oxidative stress and contribute aging, inflammation and cell proliferation. Then the use of antioxidants is important to manage oxidative stress and neutralizing ROS.

Vital role of hyaluronic acid

HA has a unique capacity in holding water as it is hydrophilic; it has a unique ability to hold 6000 mL of water/1 mg of HA.^{6,7} It is the key compound responsible for maintaining lubricant, smooth and hydrated skin.⁸

HA, also called hyaluronan, is the main component of extracellular matrix of soft connective tissues of dermis in human skin (backbone of cartilage matrix). 15 g HA/70 kg individual.⁹ HA is a mucopolysaccharide (high molecular weight glycosaminoglycan) can be found in significant quantities in skin, brain and central nervous system.¹⁰ HA plays a vital role in maintaining structural and functional integrity, reducing wrinkles and helps to keep smooth, youthful and hydrated appearance of human skin. HA concentration depends primarily on both its enzymatic synthesis by hyaluronate synthase which breakdown into small oligosaccharide molecules and enzymatic degradation occurs by hyaluronidase enzyme and results by loosening the subcutaneous tissue bonds. It promotes diffusion and absorption of injected drug via the interstitial space.

Hyaluronidase (HAase) is an enzyme present in the



dermis which depolymerizes HA, ending with drying, hence wrinkling of skin, decreases the viscosity of body fluids and increases the permeability of connective tissues.⁵ HAase plays an important role in allergic reactions by stimulation of anti-inflammatory genes expression, granulation of mast cells and release of chemical mediators.^{11,12}

Synthetic antiaging and their side effects

Antiaging formulations are either synthetic or herbal. Synthetic anti-aging products often contain varying amounts of vitamins C, vitamin E, ubiquinone (co-enzyme Q10), ferulic acid, idebenone, α -hydroxy acid, glycolic acid, oestrogen, silymarin or retinol.^{3,4,13} Most of these synthetic cosmeceuticals may cause side effects such as phototoxicity, irritant contact dermatitis, photoallergic reactions and sometimes skin cancer. Some of these synthetic products are not validated, not proven scientifically and expensive. Their long-term use is not established in term of safety, efficacy and modes of actions.^{3,4,13}

Importance of hyaluronidase inhibitors

HAase inhibitors are effective regulating agents, that maintain the balance between the anabolism and

catabolism of HA,¹ and this keep skin smooth and hydrated. HA degradation is correlated with pathogenesis of joint diseases (arthritis, osteoarthritis, etc) and can support cancer cells by leaving 1ry tumor and forming metastasis.¹⁰ HA deposition and its presence in high level increases the growth of tumor.¹⁵ Thus a balance is required in HA concentration.

Natural hyaluronidase inhibitors

The reported class of compounds as inhibitors of HAase enzymes are polyphenols,^{10,11,16} phenolic acids and tannins,^{1,16} flavonoids,^{10,16} alkaloids, polysaccharides, oligosaccharides and Chikusetsu-saponins.¹⁷ As well as the reported isolated natural compounds which proved also their activity are ellagitannins, catechin, epigallocatechin gallate (EGCG), protocatechuic acid, gallotannins, tannic acid; phenolic acids as: *p*-coumaric acid, ferulic acid; flavonoids as: apigenin, kaempferol, quercetin and ascorbic acid.^{16,18}

Some plants belonging to different families proved their activity and efficacy as natural inhibitors of HAase enzyme. The active components of these variety of potent herbal HAase inhibitors are mostly the polar fraction. The tested organ and the active chemical content are presented in Table 1.

Table 1. Reported Plants as Hyaluronidase Inhibitors

Name (Reference)	Organ/Family	Active Extract or Compounds
<i>Eleutherococcus henryi</i> (15)	Roots/ Araliaceae	Phenolic acids (protocatechuic, caffeic, <i>p</i> - coumaric, ferulic acids)
Coffee silverskin (byproduct of the roasting procedure for coffee beans (19)	Seeds/Rubiaceae	Phenolic acids – alkaloids
<i>Curcuma aromatica</i> (20)	Rhizomes/Zingiberaceae	Polyphenol – curcuminoids
<i>Styrax japonica</i> (21)	Stem/Styracaceae	MeOH
<i>Deutzia coreana</i> (21)	Stem/Hydrangeaceae	MeOH
<i>Osmanthus insularis</i> (21)	Stem/Oleaceae	
<i>Artocarpus altilis</i> (1)	Bark/Moraceae	Flavonoids
<i>Artocarpus nobilis</i> (1)	Bark/Moraceae	
<i>Artocarpus heterophyllus</i> (1)	Bark/Moraceae	
<i>Camellia sinensis</i> (5)	Leaves & buds/ Theaceae	Flavonoids (water soluble)
<i>Chamaerhodos erecta</i> (10)	Aerial parts/Rosaceae	BuOH fraction (of MeOH ext.)
<i>Chamaerhodos altaica</i> (10)	Aerial parts/Rosaceae	Aqueous fraction (of 80% acetone ext.)
<i>Dracocephalum foetidum</i> (10)	Aerial parts/Lamiaceae	Aqueous fraction (of 80% acetone extract)
<i>Gaultheria procumbens</i> (eastern teaberry) (10)	Leaves/Ericaceae	Polyphenolics
<i>Oenothera biennis</i> (Evening-primrose) (10)	Aerial parts/Onagraceae	Ellagitannins
<i>Canavalia gladiata</i> (10)	Seeds/Fabaceae	80% MeOH ext.
<i>Payena dasyphylla</i> (10)	Bark/Sapotaceae	Flavonoids & phenolics
<i>Padina pavonica</i> (22)	Brown seaweed/Dictyotaceae	Flavonoids
<i>Malaxis acuminata</i> (23)	Leaves & stem/Orchidaceae	Flavonoids, polyphenols, alkaloids & terpenoids
<i>Panax japonicas</i> (18)	Roots & rhizomes/Araliaceae	Chikusetsusaponins
<i>Prunus salicina</i> (18)	Fruit/ Rosaceae	Phenolic acids
<i>Fraxinus rynchophylla</i> (24)	Outer bark/Oleaceae	Aesculin (phenolic)
<i>Areca catechu</i> (25)	Arecaceae	Phenolic content
<i>Terminalia chebula</i> (26)	Fruit rind/ Combretaceae	Collagen
<i>Terminalia arjuna</i> (26)	Bark/ Combretaceae	Collagen
<i>Naja naja</i> (Indian cobra) venom (12)		anti-NNH1/aristolochic acid
<i>Garcinia indica</i> (9)	Fruit rind/ Guttiferae	Phenolic content
<i>Vitis rotundifolia</i> (11)	Skin & seeds/Vitaceae	Polyphenol
<i>Lythrum salicaria</i> (10)	Flowering herb/ Lythraceae	Aqueous extract:elagitanin

***Ravenala madagascariensis* as an example of natural hyaluronidase inhibitor in cosmetic products**

Ravenala madagascariensis, is also called traveler's tree or traveler's palm. It is one of nature's most distinctive and remarkable plants for the arrangement of its leaves in a fan shape. The common name is thought to refer to how travelers could be refreshed in an emergency by drinking the water that has collected in the cup-like leaf bases. It belongs to the bird-of-paradise family, Strelitziaceae. It is native to Madagascar²⁷; cultivated in tropical countries, in particular as an ornamental tree. Culturally, it is the primary materials used for house construction in Madagascar. Medicinally, it is used in relief of dizziness, stomach-ache and regulates albumin levels. Its hydro-alcoholic extract is used as a hydrating agent in cosmetic products,²⁸ to retrieve the skin hydration by regulating the flow of water in the epidermis. Its major chemical constituents are flavonoids and steroids. This plant was

tested as HAase inhibitor (under publication) and as antioxidant (accepted for publication) and proved its potent activity which was correlated to its polyphenolic constituents.

Herbal skin products for hydration available worldwide in market

Several antiaging and cosmeceuticals formulations are available in market in the form of serum, lotion, creams, powder, oral, etc.^{4,5} Some plants showed their efficacy in skin care and are available as products in market; selected examples are presented in Figure 1; but no clear or statistical data are available till now for natural HAase inhibitors.

Conclusion

This article collects the natural hyaluronidase inhibitors which proved their efficacy and could serve as natural



Figure 1. Selected Examples of Herbal Skin Hydration Available as Products Worldwide.

skin care antihyaluronidase products. The effect is mainly correlated with their content of polyphenols, flavonoids, phenolic acids and tannins. They could be a benefit source in herbal cosmeceutical industry.

Competing Interests

None

Acknowledgement

The author appreciates the effort of Mrs. Marwa Fathalla in formatting the references. .

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