Skin is the first business card in human social life. Its structure, texture, and color transmit our status of health and wellness. Unfortunately, wrinkles and sagginess appearing is a natural phenomenon of life that can affect the human psychological status. Especially with the increase of the lifetime, and the focus on improving the lifestyle, there is an increase of patients demanding solutions for the aging signs. Cosmetics act in a scientific way to find those molecules aiding to maintain the health status of the skin. The purpose of this review is to consider the wrinkles origin and the treatments that cosmetology and aesthetic medicine offered so far.

Wrinkles classification
The wrinkles are distinguished in (Kligman et al., 1985):
• Texture
  The skin, even the infants’ one, show on its surface a...
texture composed by depressions or groves, which intersecting form small rhomboid area.

• Expressional
These are those lines forming on the face where skin has to adapt to the facial muscles movements. Indeed, the facial muscles find their insertion beneath the skin. Consequently, the skin moves together with them. These cranes are visible at the age of 30, but they do not increase in number during the years; instead, they become deeper. Their direction is perpendicular to the muscular fibers direction. Due to their dynamism and position, they can be sub classified in (Figs. 1-2):
- horizontal wrinkle on the forehead, connected to the activity of frontalis;
- periocular wrinkles, related to the muscle orbicularis oculi. They result marked in elderly due to the lateral fall;
- glabellar folds run vertically from the nose root towards to the forehead. They are due to the corrugator and procerus muscles hyperactivity;
- the nasolabial folds, run laterally from the nose to the lips angles. The nasolabial fold un-aesthetic when it is more marked, giving an older aspect to the face. This accentuation is due to the cutaneous atrophy and to the ptosis of soft tissues, in particular the malar fat pad of Owsley. In addition, the mimic activity of elevator labii gives a great contribution;
- the commissural fold, due to the genien inferior region ptosis and to the activity of the depressor anguli oris muscle;
- the peri-labial wrinkles are due to the mimic of orbicularis oris muscle;
- the geniene wrinkle run vertically from the lateral canthus of the lips and the mandibular angle. They can be highlighted by the atrophy of the Bichat corpus.

• Joint lines
They are located in the scheletic articulations place and necessary for the natural movements of the skin.

• Grooves from muscolar skin laxity
They normally appear as part of ageing process, due to the loss of elasticity of collagen texture. Therefore, dermis is no more able to contrast the gravity and the muscle tissue is reduced. This kind of groove appears normally on the face as the natural fall of the skin. The treatment in this case is just surgical.

• Lines from sleeping
These folds are created from the lateral position during the sleep. They appear later on the photo damaged skin.

Treatments and cosmeceutics molecules in skin aging

Treatments
The continuous increase of length of life depicts the necessity to maintain a healthy and young aspect. So the population look at the aesthetic medicine. When plastic surgery is not necessary, so-called “non-invasive” treatments are available (Table 1). These options are:
- filler;
- peeling;
- botulin toxin;
- lasers;
Table 1. Summary of the methods of treatments in skin aging (Ganceviciene et al., 2012)

<table>
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<th>Non invasive treatments</th>
<th>Filler</th>
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<td>Restoration (redistribution) of fat and volume loss, skin augmentation and contouring</td>
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<tr>
<td>Cosmetic Care</td>
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The fillers
The filler is a biological or syntactical mean to inject in hypoderm or in derma tissue, so to implement or enhance a limited area of body (usually face) for aesthetic purpose (Kusin and Lippitz, 2009).

The currently available injectable skin fillers can be divided into three categories: those that function to replace tissue lost by the aging process and temporary duration (collagen, hyaluronic acid, and biologic fillers); those that stimulate endogenous connective tissue growth (poly-L lactic acid and calciumhydroxyapatite); and permanent fillers (polymethylmethacrylate, silicone, and hydroxyethylmethacrylate).

- Temporary filler: they are the most used due to their temporary effect. The filler is processed and re-absorbed by the local enzymes. The used substrates are bovine collagen, autologous collagen, cadaveric collagen, cell-cultured collagen, hyaluronic acid and agarose gel (Kusin and Lippitz, 2009).
- Partially absorbable filler: they are constituted by an absorbable part (usually hyaluronic acid or collagen) and the other not absorbable (usually composed by synthetic materials such as dextran beads or polymethyl-methacrylate).
- Permanent filler: they are synthetic, injectable and ideally aiming to be permanent without any side. They are indicated in volumetric correction of deep defects. They are constituted by acrylics material, hydroxyapatite and silicones (Buck et al., 2009; Kusin and Lippitz, 2009).

Peelings
Peeling is a medical treatment consisting in a micro-abrasion of epidermis or the superficial and medium derma, by means of chemical or physical agents. This kind of treatments aim to the revitalizing and rejuvenating the skin (Fischer et al., 2007; Sánchez-Carpintero et al., 2010). Both physicians and nonmedical personnel to improve or correct enlarged pores, photo-damages, hyperpigmentation, superficial rhytides, stretch marks, tattoo removal, scar revision, and acne scarring are using it.

The chemical agents can be distinguished in:
- Superficial peels, affecting the epidermidis and stimulating the papillary derma. The peels used in these treatments are pyruvic acid, salicylic acid, retinoic acid, tricloroacetic acid (T.C.A.) at 10%-20%;
- Intermedium peels, affecting the superficial derma. They are T.C.A. at 25%, T.C.A. 35%, glycolic acid and T.C.A. 35%
- Deep peels, affecting the intermedium derma. These peels are TCA 50% and fenolic based solution.

Botulinum toxin
Botulinum toxin injection for treatment of facial wrinkles is one of the most common entry procedures for clinicians seeking to incorporate aesthetic treatments into their practice. Botulinum toxin is a potent neurotoxin that inhibits release of acetylcholine at the neuromuscular junction. Injection of small quantities of this molecule into overactive muscles determines a localized relaxation that smooths the overlying skin and consequently reduces wrinkles. The effects take two weeks to fully develop and last three to four months. Treatment of frown lines and crow’s feet, which are the cosmetic indications approved by the U.S. Food and Drug Administration, and horizontal forehead lines, offers predictable results, has few adverse effects, and is associated with high patient satisfaction (Bhalla and Thami, 2006).

Lasers
The cosmetic use of the laser represents a valid non-invasive intervention for the aged skin. The used lasers are the CO2 laser and the Er-Yag. They are indicated for treatments of aesthetic lesions, for resurfacing, for non-ablative rejuvenating and for hair removal. These lasers usually are implemented for face rejuvenating and in acneic patients. The goal is to vaporize the superficial layers of the skin (epidermidis
and papillary derma) to smooth the external skin. The side effect of this treatment is the longtime of healing (Camargo Cristina et al., 2014; Humphreys, 2006; Sharad, 2013).

**Molecules in cosmetology**

Vitamin C (I.N.C.I.: Ascorbic Acid-Ascorbil Palmitate) is well-known and fundamental for its antioxidant actions as well as being a cofactor in hydroxylation reactions of collagen production. Vitamin C is also considered an antiaging ingredient because of its potential to stimulate collagen production (Hruza et al., 1993; Telkemeier and Goldberg, 1997). There are three forms commonly available in cosmetics: ascorbyl palmitate, magnesium ascorbyl phosphate, and L-ascorbic acid.

Ascorbyl palmitate, a fat-soluble synthetic ester of vitamin C, is stable in cosmetic formulas at neutral pH.

Topical ascorbyl palmitate in one study was found to be thirtyfold more effective than Ascorbic palmitate, applied after UV burning, reduced redness 50% sooner than areas on the same patient that were left untreated (Manela-Azulay and Bagatin, 2009). The suspected mechanism is that the ascorbyl palmitate acted as both an antioxidant and anti-inflammatory agent.

The Magnesium-L-ascorbyl-2-phosphate, was found to protect against UVB radiation-induced lipid peroxidation in hairless mice. The authors found in vitro evidence that magnesium ascorbyl phosphate crossed the epidermis and is converted to ascorbic acid. In an in vivo study of human skin showed 10% magnesium ascorbyl phosphate cream determined a clinical improvement of melasma and senile freckles (Yuan et al., 2005).

L-ascorbic acid is the most bioactive form of vitamin C and has been found to have numerous benefits for the skin. This form of vitamin C is water soluble but it must be formulated at low pH to be stable. In cultured human skin fibroblast, it increases type I and type III procollagen mRNA (Kameyama et al., 1996; Lupo, 2011).

Retinol (I.N.C.I.: Retinol-Retinyl Palpitate), or vitamin A, and its derivates are very popular in cosmetics. It is particularly indicating for aged skin. The primary benefit of vitamin A and its derivates in cosmetic products consist in the normalizing the keratinization and in the regulation of epithelial cell growth and differentiation. This family of compounds showed to have receptor-specific effects on the skin organ, resulting in a consequent decreased roughness and decreased facial wrinkling (Geesin et al., 1988).

Vitamin E (I.N.C.I.: Tocoferol-Tocoferyl Acetate), potent antioxidant ability. Because of this ability to quench free radicals, especially lipid peroxyl radicals, the term “protector” has been used to describe the actions of vitamin E and its derivatives. Several studies showed their property to reduce UV-radiation-induced erythema and edema, sunburn cell formation, and lipid peroxidation (Pinnel et al., 1987).

Alpha Lipoic Acid (I.N.C.I.: Thiocytic Acid) is known to be one of the most natural powerful antioxidant, the alpha lipoic acid (LA) is well-defined as a therapy for preventing diabetic polyneuropathies, and scavenges free radicals, chelates metals, and restores intracellular glutathione levels which otherwise decline with age. Enzymes containing lipoamide are typically mitochondrial multi-enzyme complexes catalyzing the oxidative decarboxylation of α-keto acids (e.g. pyruvate dehydrogenase, 2-oxo-glutarate dehydrogenase, and transketolase) and glycine cleavage (Serri and Iorizzo, 2008).

The chemical reactivity of LA is mainly due to its dithiolane ring. The oxidized (LA) and reduced (DHLA) forms determine a potent redox couple with a standard reduction potential of −0.32 V. This determines DHLA one of the most potent naturally occurring antioxidants (Trevithick et al., 1992). In fact, there is evidence that both LA and DHLA are able of scavenging a variety of reactive oxygen species. Both LA and DHLA may scavenge hydroxyl radicals and hypochlorous acid (Devasagayam et al., 1993, 1991; Scott et al., 1994; SEARLS and SANADI, 1960; Shay et al., 2009). Neither species is active against hydrogen peroxide. Furthermore, DHLA appears to regenerate other endogenous antioxidants (e.g. vitamins C and E) and has the property of neutralizing free radicals without itself becoming one in the process.

Hyaluronic acid (I.N.C.I.: Ialuronic Acid-Sodium Ialuronate) is one of the major elements in the extracellular matrix (ECM) of vertebrate tissues. It is available in almost all body fluids and tissues, such as the synovial fluid, the vitreous humor of the eye, and hyaline cartilage (Devasagayam et al., 1991; Fakhari and Berkland, 2013; Suzuki et al., 1991; Vej lens, 1971;
Zheng Shu et al). This biopolymer functions as a scaffold, binding other matrix molecules including aggrecan. It is also involved in several important biological functions, such as regulation of cell adhesion and cell motility, manipulation of cell differentiation and proliferation, and providing mechanical properties to tissues, skin included. It is widely used in cosmetic formulations for its hydration properties and a filler material.

Omega 3 (or PUFA n-3) acids are essential for the correct body functioning. They are crucial at cellular levels for maintaining membrane homeostasis, as ligands for transcription factors thus influencing gene expression, and for an optimal balance with n-6 fatty acids to secure a regulated inflammatory response, a healthy body composition homeostasis and an equilibrated neurological and psychiatric balance. Omega 3 have anti-age property: they maintain whole the cellular membrane avoiding the water loss. In addition they are used for acne, psoriasis and dermatitis (Burri et al., 2012).

**Natural compounds and herbal products**

Phenolic compounds, Flavonoids, and Proanthocyanidins derived from plants are the main characters of antioxidative properties of herbal products. Their chemical structures make them able to donate free electron and hydrogen (Binic et al., 2013). The *Polypodium leucotomos*, extracted from the tropical Cabbage palm fern and the *Camellia sinensis* from the Green Tea act as protection against photodamages (Binic et al., 2013). Polyphenolic ellagic acid mostly from berries prevented proteolytic degradation of existing dermal elastic fibres and efficiently enhanced elastogenesis in aged skin. It revealed to be a promising aid in curtailing skin wrinkling and cutaneous inflammation associated with chronic UV exposure leading to photoageing (Bae et al., 2010).

Always in the topic of photoageing, *Aceriphyllum rossii* extracts have showed to decrease the Matrix metalloproteinases (MMPs) (Ha et al., 2015). *A. lappa, A. catechu, D. villosa, C. xanthorrhiza, and S. japonica* decrease the activity of the tissues’ degradation enzymes. In particular, they inhibit Hyaluronidase, Elastase and Colagenase (Shaheda et al., 2014).

*Aloe vera* (Liliaceae) inhibits the tyrosine hydroxylase and the 3,4dihydroxyphenylalanine oxidase (Shaheda et al., 2014).

The combined formulated fruit extract of *P. granatum, G. biloba, F. carica, and M. alba* showed a much higher rate of collagenase inhibition than the efficacy of individual plant’s fruit extract (Ghimeray et al., 2015). *E. oficinalis, C. asiatica, P. ginseng, and C. zeylanicum* act on the promotion of the synthesis of collagen fibers (Mukherjee et al., 2011).

For what concern the depigmentation and the skin enlightenment, the Licorice extract, induce skin lightening by means of melanin dispersion; Raspberry ketone also inhibits melanogenesis (Binic et al., 2013).

Origanoside from *Origanum vulgare* has a depigmentation properties, being an inhibitor of the melanin synthesis and causing the decline in cellular Dihydroxyphenyl-alanine oxidase (DOPA oxidase) activity (Binic et al., 2013).

**Topical effect**

A good cosmetic product using as ingredient the molecules listed above, has to satisfy the three gold standard questions formulated by Dr. Albert Kligman:

1) Can the active ingredient penetrate the stratum corneum (SC) and be delivered in sufficient concentrations to its intended target in the skin over a time course consistent with its mechanism of action?

2) Does the active ingredient have a known specific biochemical mechanism of action in the target cell or tissue in human skin?

3) Are there published, peer-reviewed, double-blind, placebo-controlled, statistically significant, clinical trials to substantiate the efficacy claims?

To our knowledge, only the Niacinamide is the cosmetic ingredient that is closest to the the “Kligman standards” of cosmeceutical-ingredient analysis (Levin et al., 2010).

**Conclusion**

Cosmetology play a fundamental role in aesthetic medicine, because the modern formulation represents a valid co-adjutant to the minor treatments. Modern cosmetology considers the skin as a proper organ looking at its anatomy, biochemistry and physiology. Cosmeceuticals are cosmetic products with biologically active ingredients with the purpose to have medical or drug-like benefits. Cosmetics act on a healthy skin, contributing to its maintaining and as aid during the ageing process.

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References


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