Review Article

# The cosmetic treatment of wrinkles

**C Rona,[1] F Vailati[1] & E Berardesca[2]**

[1]*Department of Dermatology University of Pavia, Pavia, Italy and* [2]*San Gallicano Dermatological Institute, Rome, Italy*

## Summary

Wrinkles now have a greater social impact because people live longer. Science and hedonism overlap in the search for causes, treatments and prevention of wrinkles.

The cosmetic approach to wrinkles includes:

i Cleansing
ii Photoprotection
iii Active ingredients

Active ingredients go well beyond simple moisturisers and exert a more complex activity in protecting skin from external injuries, nourishing it and removing its superficial layers. Transport systems and excipients are increasingly effective. Functional agents currently include alpha hydroxy acids (AHAs), poly-AHAs, complex poly-AHAs, retinoids, fish polysaccharides, anti-enzymatic agents, antioxidants (including ascorbic acid, pycnogenol, ursolic acid, vegetable isoflavones, vitamin E, coenzyme Q10, lipoic acid, resveratorol, l-carnosine and taurine) as well as agaricic acid and various plant extracts. All are reviewed in this text. Most are topical, some can be given by mouth, even as food supplements.

Cosmetics are becoming closer to drugs in preventing and treating wrinkles. Included amongst the cosmeceuticals are the anti-wrinkle agents described herein.

*Keywords*: AHAs, antioxidants, fish cartilage, pycnogenol, retinoids, skin ageing, wrinkles

## Introduction

Wrinkles, as a sign of skin ageing, have an important social impact, especially because of longer lifetimes and more frequent social relationships; consequently, they are an important factor influencing our way of communication.

Nevertheless, the scientific interest of dermatologists and cosmetologists overlaps the merely hedonistic problem to find both cause and treatment/prevention opportunities.

## Wrinkles

Wrinkles represent the more evident outcome of cutaneous ageing. Their onset is linked to a variety of events, resulting from both chrono- and photoageing, among which are: dermo-epidermal junction thinning, due to decrease of laminine 5[1] and loss of collagen, GAG and subcutaneous fat; in turn, gravity and muscle/articular movements play an important role. Both *intrinsic* (hormones, racial and genetic factors, oxidative stress, systemic disease) and *extrinsic* (temperature, air pollution, smoke, alcohol) factors worsen skin condition.

Often the term 'wrinkle' is misused and it is difficult to establish classification, histological correspondence and pathogenesis in a unique way. In fact, people call 'wrinkles' all skin features different from a baby's perfectly smooth skin: expression lines, more or less deep microrelief furrows, articulation and mimic-muscle lines, laxity folds and in general all lines or folds recognizable on a no longer young face and body.

However, wrinkles deriving from skin texture, or microrelief, modification afflict women more than all

Correspondence: Enzo Berardesca, San Gallicano Dermatological Institute, Via Chianesi 53, 00144 Rome, Italy. E-mail: berarde@unipv.it

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other wrinkles as signs of ageing in the common mind. Actually, young skin microrelief is made of many lines, superficial and tidily arranged, whereas old/ageing skin is featured by less deep and untidy lines.

Even if skin ageing is well and widely described in the literature, a precise definition of the word 'wrinkle' does not exist. The only concrete attempt to precisely define the term 'wrinkle' can be attributed to Griffiths: an extension of the skin perpendicular to the axis of the wrinkle leaves a marked line representing the bottom of the wrinkle.[2] In general, to address skin-ageing features we can speak of 'coarse wrinkles', which resist a transversal traction made on the skin; 'fine lines', which, instead, disappear; and 'facial lines', whose appearance depends mainly on stratum corneum moisture.[3]

## The cosmetic approach to wrinkles

Even if the cosmetic market features many anti-wrinkle products also among detergents, contact time during *cleansing* is too little to ensure any anti-wrinkle effect. Nevertheless, cleansing can be a moment of treatment or prevention of wrinkles depending on the cosmetic form chosen: oily or cream detergents prevent further injury of skin natural defence systems, giving some sebum-like ingredients that exert an emollient/restoring effect.[4]

*Photoprotection* is the second step of a proper cosmetological approach to wrinkles treatment: use of UVA/B filters, which are more and more frequently formulated in daily skin care products and make-up, must be considered as a good daily practice, in consideration of the scientific evidence that sun damages skin continuously, not only during summer vacations, but also during unintentional sun exposure.[5–9]

Thus, wrinkle cosmetic *treatment* is exerted by a variety of active functional ingredients: modern anti-ageing cosmetics go well beyond the simple moisturizing function of traditional anti-wrinkle creams, by exerting a more complex function in protecting the skin from external injuries, nourishing it, and removing its superficial layers. That is the reason why the term 'cosmeceuticals' is increasingly used: there are many cosmetic products that fit into this category defined in the regulatory systems of some countries. Excipients also have an important role: cosmetic carriers that make cosmetics closer to drugs, with a prevalence of controlled-release carriers, like liposomes, nanosomes, cyclodestrins, phytosomes, oleosomes, ensuring a more specific and long-lasting action. Recently, food supplements with anti-wrinkle purposes have been introduced to the market.

## Functional agents

Many product categories, for topical or oral use, can be helpful in restoring and repairing functional properties of the skin to treat or prevent skin wrinkles.

### Alpha hydroxy acids (AHAs)

Together with retinoids, the AHAs play a major role in skin care and dermatological therapy: they include glycolic, citric and lactic acids, the so-called 'fruit acids'. AHAs act both on epidermis and dermis,[11–19] exerting opposite effects: they have a thinning effect on the stratum corneum (s.c.), inducing desquamation and promoting cell renewal as well as stimulating collagen synthesis at the dermal level, increasing dermal thickness.

When applied to the skin, at the epidermal level, they weaken intercorneocitary cohesion and stimulate s.c. desquamation by interfering with the formation of ionic bonds and desmosomes by inhibiting transferases and kinases. This leads to a reduction of the polarity of sulphate and phosphate groups on the corneocyte membrane; application of AHAs reduces pH even in the deeper layers of s.c., contributing to desmosome dissolution. Furthermore, they stimulate epidermal turnover. On the dermis, which contributes mainly to skin biomechanical properties, AHAs increase glycosaminoglycan deposition in the ground substance and replace collagen and elastic degradation by promoting new collagen synthesis, without any sign of inflammation.[11,16] This effect is responsible for wrinkle improvement and recovery of the dermal mechanical properties like elasticity and 'tone', as shown by Smith and co-workers.[20] These effects induce an increase in s.c. flexibility.[18]

### Poly-AHA (gluconolactone): complex poly-AHA (polylactic acid)

Gluconolactone – delta lacton gluconic acid – is the main molecule of the second AHA generation. It is present in the skin as a metabolite of cell-renewal processes. Its ring structure is hydrolyzed to gluconic acid, which is both AHA, due to a OH group in the alpha position, and poly-AHA, due to the presence in its molecule of five OH groups. Therefore, it keeps the keratolytic property of AHA, adding moreover a stronger moisturizing action. Thanks to the lactonic structure, this agent hides its acid nature, being suitable even for sensitive skin and for particular skin areas like eye and lip contours. It is also a natural antioxidant, contributing to the enhancement of anti-wrinkle efficacy, and anti-ageing action in general.[21,22] Moreover, the third AHA generation has been developed: complex poly-AHA, lactobionic acid

for first, conserve AHA's peculiar capacity to promote cellular turnover, enhancing stratum corneum exfoliation process, but moreover exerting a deeper moisturizing effect. Such properties make them specific for the treatment of ageing signs and of wrinkles of sensitive skin. In particular, lactobionic acid is made by a polyhydroxy acid, gluconic acid, which is present in cells as an acid form of gluconolactone, together with a sugar molecule, galactose, which is a natural component of dermal glucose amino glycan (GAG).

Lactobionic acid exerts a very strong antioxidant action, due to its ability to seize iron ions; in addition it has an important moisturizing effect, thanks to its molecule with eight OH groups. Topically applied, this ingredient contributes to the improvement of skin tone and to the reduction signs of ageing, especially wrinkles, both clinically and histologically.[23,24]

### Retinoids

Originally used for acne treatment, today retinoids are a 'standard' for the cosmetic treatment of ageing signs. Initial studies of topical tretinoin were concentrated on photoageing: LH Kligman[25] showed, in hairless mice irradiated with UVA and UVB, that topical tretinoin was capable to reverse the histological changes induced by UV irradiation and recover the dermal structure by increasing fibroblast activity and collagen deposition. Later A. Kligman[26] published the first paper on human volunteers, suggesting that tretinoin can have the same effects on human photoaged skin. He described histological and physiological changes in skin treated with tretinoin 0·05% cream: in particular, the skin showed replacement of atrophic epidermis by hyperplastic tissue, elimination of dysplastic and atypical keratinocytes, disappearance of microscopic actinic keratoses and uniform dispersion of melanin granules. Tretinoin-treated skin also showed new collagen formation in the papillary dermis, new vessels and exfoliation of retained follicular horns.

Ellis[27] *et al.* performed a double-blind, randomized, vehicle-controlled trial to assess the efficacy of 0·1% tretinoin cream in the treatment of photoaged skin: clinically, patients were graded on face and forearm skin for fine and coarse wrinkles, teleangiectasia, tactile roughness, pinkness and dermal oedema. On 30 patients who completed the treatment, a significant improvement was found for all parameters investigated in treated sites, whereas no changes were found in vehicle-treated sites.

### Fish polysaccharides

Fish polysaccharides, when taken orally, are reported to be effective in treating photoageing (with particular regard to elastosis, and wrinkles) and chronological ageing (especially thinning of the skin).

Their mechanism of action is still basically unknown: previously reported data suggest a possible role in promoting collagen synthesis, in particular procollagen and Type III collagen, which stimulate repair processes within the dermis. The high content of mucopolysaccharides can improve dermal ground substance thus improving skin mechanical behaviour and skin thickness.[28,30] A study[29] reported clinical improvement of skin ageing and some biophysical parameters such as thickness, microcirculation, trans-epidermal water loss (TEWL) and wrinkles. Other studies reported both improvement of skin mechanical properties and skin thickness.[31] In particular, when taken orally at a dose of at least 500 mg in combination with flavonoids and antioxidants, they seem to exert a thickening effect at the dermal level, with significant reduction of deep lines. From a mechanical viewpoint, a significant increase in viscoelasticity is detectable, compared to placebo treatment. This seems to be a peculiar marker of their effect on the dermis.[32] As a consequence other mechanical parameters such as elasticity are also improved.

These results confirm that polysaccharides of fish taken orally can be helpful in ameliorating some aspects of skin ageing. Due to their peculiar properties, combination treatments in association with topical retinoids/AHAs could be interesting to investigate.

## Anti-enzymatic agents

More recently, some anti-enzymatic agents to inhibit elastases, metalloproteinases and collagenases have been introduced in anti-wrinkle treatments. Antioxidants, both by topical and systemic routes, and immunoenhancing agents are increasingly used to make the skin look younger. In particular, *Lentinus edodens*, rich in ergosterols which stimulate fibroblasts, and lentinan, a specific beta-glucan, are endowed with immunoenhancing properties and moisturizing properties.

The matrix metalloproteinases[33] are enzymes present in the skin and are responsible for the degradation of extracellular components. The extracellular matrix (EMC) establishes the three-dimensional integrity and functionality of the skin, so that it plays an essential homeostatic role whose damage causes important alterations in the different biological functions of the skin. In healthy skin, the balance of the homeostasis of collagen fibres depends on a few factors, among which are the synthesis of collagen fibres themselves, the slow basal matrix methallo proteinases (MMP) action necessary to proceed to the natural and planned degradation of old or deranged fibres, and the tissue inhibitors action to control the MMP-degrading activity.

The enzymatic balance of the metalloproteinases is indeed naturally controlled and ensured by tissue inhibitors (TIMPs). Ageing and environmental insults, such as long-term exposure to UV rays, alter the physiological balance, increasing enzyme activity, and decreasing TIMPs expression and collagen fibre synthesis. These events give rise to the collapse of the meshwork in the ground substance and contributes to the visible effects of UV damage: wrinkling, loss of elasticity and tone, and teleangectasias. Matrix metalloproteinase inhibitors represent new and interesting tools that can be used by formulators in addressing different cosmetic issues and to protect the skin from external injury. In particular, improvement in EMC properties could help in promoting skin tone, thereby reducing wrinkles and fine lines; cosmetics aimed to improve skin firmness and elasticity could in turn take benefit from the addition of such active ingredients in their formulation.

## Antioxidant agents

Antioxidants are a very heterogeneous class of functional substances: they include vitamins, minerals, and essential amino acids, all endowed with a specific property, among others, of fighting free radicals. These result from oxidative stress and are responsible for cell-structure damage, in particular to DNA, lipids and proteins, leading to skin relaxation and wrinkled appearance.[34–37]

Cosmetic treatments of the latest generation, developed against wrinkles, rely on antioxidant properties of some ingredients, especially those derived from plants. Among them, we remember *Vitis vinifera*, olive-tree, tomato, orange, green and white tea, and saw palmetto extracts, which exert antioxidant effects on the skin both by topical application and systemic supply of food supplements. In particular, a study by Purba *et al.*[38] conducted on 453 volunteers illustrates that skin wrinkling measured using a cutaneous microtopographic method in a sun-exposed site in older people of various ethnic backgrounds may be influenced by the types of foods consumed. A high intake of vegetables, legumes and olive oil appeared to be protective against cutaneous actinic damage, because of their high content of active antioxidants.

### Ascorbic acid

Among topical anti-ageing treatments, ascorbic acid has been introduced only recently because of its instability. It is an essential nutrient involved in many physiological processes and functions, thanks to its excellent reducing capacity, which explains its antioxidant efficacy.[38] Thus, ascorbic acid can protect tissues and cells of living organisms from oxidative damage caused by free radicals and oxygen-derived species. In particular, it works synergistically with vitamin E[39,40] by serving as a donor antioxidant to restore the tocopheroxil radical, whose reaction represents the most important way to export oxidative free radicals from cell membranes. This capability offers an important tool to prevent skin ageing, with particular regard to tone and elasticity: indeed, ascorbic acid can preserve dermal components from sun damage by inhibiting free radical injuries to collagen and elastin. It has been reported to stimulate dermal deposition of new collagen.[41]

### Pycnogenol

Procyanidins from French Maritime Pine bark (Pycnogenol®) are among the most powerful natural antioxidants that recycle and prolong the effects of vitamins C and E.[43,44] These bioflavonoids neutralize collagenases and elastases,[45] improving skin disorders in general and skin ageing in particular. Pycnogenol®, in use as a health supplement since 1853, is a proven free radical scavenger[46] 50 times more potent than Vitamin E and 20 times more potent than Vitamin C against free radicals, according to European researchers. It protects efficiently against ultraviolet-radiation-induced oxidative stress injury (lipid peroxidation and cytotoxicity). These protective effects are related to dose, with the highest concentration providing the greatest benefits.[47,48] The ingredient is effective even in protecting the skin from UVB-induced erythema.[49,50] When topically applied, it is quickly absorbed into the skin and is retained for as long as 72 h while it neutralizes free radicals and prevents oxidation. This results in slowing the effects of ageing, improving circulation and strengthening the immune system.[44] It also has effects on collagen and elastin binding, thus improving vascular permeability.[45,51]

### Ursolic acid

Ursolic acid is used in the formulation of oils and creams developed to revitalize the skin. It exerts an antioxidant effect which prevents cell damage;[52] moreover, it inhibits elastase, an enzyme activated by UVA rays, which is responsible for solar elastosis and onset of wrinkles,[53] and which stimulates collagen and ceramide synthesis. In this respect, a study conducted by Both *et al.*[54] showed that skin wrinkling and xerosis associated with ageing result from decreases in dermal collagen and stratum corneum ceramide content. This study demonstrated that ursolic acid incorporated into liposomes (URA liposomes) increased both the ceramide content of

cultured normal human epidermal keratinocytes (NHEK), and the collagen content of cultured normal human dermal fibroblasts. In addition, URA liposomes increased the ceramide content of the skin of human subjects, with increases in hydroxyceramides occurring after only 3 days of treatment. Both URA liposomes and retinoic acid decreased the markers of keratinocyte differentiation (keratin 1, keratin 10 and involucrin) in cultured NHEK. Thus, URA liposomes have effects on keratinocyte differentiation and dermal fibroblast collagen synthesis similar to those of retinoids. URA liposomes have the potential to be used alone or in combination with other agents to restore or maintain skin ceramide and collagen content.

### Vegetable isoflavones

Phytoestrogens are so called because they act like oestrogens within new anti-ageing formulations by stimulating fibroblasts to produce new structural proteins and exerting their main property, namely the antioxidant and immunostimulant one. Phytoestrogens, in particular soy isoflavones, showed *in vitro* the capacity to improve epithelial cell proliferation, and collagen synthesis, and also showed a protective effect on collagen and elastic fibres against enzymatic degeneration.[55,56]

### Vitamin E

Preclinical studies showed that topical application of vitamin E protects against oxidative stress damage produced by solar exposure,[57–63] both against UVB and UVA rays.[64] Kanimoura[65] confirmed that topical application of vitamin E in an alcoholic vehicle is readily absorbed by the skin, and that it appears in the dermis within 6–24 h. Record[66] demonstrated that topical supplementation is more effective in enhancing skin natural antioxidant properties. Vitamin E topically applied produces a plateau of concentration that lasts at least 24 h.

Vitamin E possesses moreover a strong anti-collagenic activity.[67] In effect, the cosmetological use of this ingredient during recent decades was based on its remarkable moisturizing properties.[68–70] Topical application contributes to improving the length, width and frequency of fine lines and wrinkles.[71]

Actually, the term 'vitamin E' is a generic word indicating a family of substances with antioxidant activity, which involves two classes of agents: *tocopherols* and *tocotrienols*. In general use, vitamin E refers to the tocopherol group, and in particular to alpha-tocopherol; but tocotrienols are increasingly gaining popularity in dermocosmetical applications, such that they are considered to be the third millennium vitamin E. They are stronger as antioxidants than tocopherols and show a better cutaneous biodisponibility. Moreover, they accumulate in the stratum corneum and exert a very important action against free radicals, thereby protecting against actinic damage and environmental pollutant injury in general; the delta-tocotrienol form is particularly effective. They born as nutraceuticals, but are suitable for formulating both topical products and cosmetofoods, or food supplements that claim specific and positive effects on the skin, intended for the prevention or treatment of skin ageing.[72–76]

### Coenzyme Q10

Coenzyme Q10, ubiquinone, allows cells to better utilize oxygen, in this way reducing free radical production within the cell energetic cycle. It is an important lipophilic antioxidant against peroxides. Although it is synthesized by human cells, its production decreases with age, making it advisable to provide a topical supplement to promote cellular regeneration. It works synergistically with vitamin E, which results in protection from oxidation.[77–82]

In particular, Hoppe *et al.*[79] have investigated whether topical application of CoQ10 has the beneficial effect of preventing photoageing. In particular, they were able to demonstrate that CoQ10 penetrated into the viable layers of the epidermis and reduced the level of oxidation measured by weak photon emission. Furthermore, a reduction in wrinkle depth following CoQ10 application was also shown. CoQ10 was determined to be effective against UVA-mediated oxidative stress in human keratinocytes in terms of thiol depletion, activation of specific phosphotyrosine kinases and prevention of oxidative DNA damage. CoQ10 was also able to significantly suppress the expression of collagenase in human dermal fibroblasts following UVA irradiation. These results indicate that CoQ10 has the ability to prevent many of the detrimental effects of photoageing.

### Lipoic acid

Physiologically present into human cells,[83] lipoic acid is now frequently added to cosmetic formulations addressed to people particularly prone to premature ageing, and especially wrinkling, among which are heavy smokers and sun lovers.

Lipoic acid showed remarkable antioxidant properties by:

- Free-radical scavenging;
- Heavy-metal chelating;

  

- Synergistic action with other antioxidant species, like vitamin C, which it protects from oxidation, vitamin B, CoEQ10 and glutathion.[84]

Lipoic acid shows a high level of penetration (topical)/absorption (systemic), and very good balanced hydrophilic/lipophilic properties, which allow it to exert its effect on different compartments. In particular, Podda *et al.*[85] showed that 2 h after topical application a plateau of lipoic acid is achieved. Ninety-five percent of lipoic acid is located in the stratum corneum, 1% in the residual epidermis and 4% in the dermis and fatty layer. Topical application of 5% cream onto hairless mice 2 h before UVA/B irradiation significantly protects the skin against oxidation.

### Resveratorol

Resveratorol is a polyphenolic substance naturally occurring in plants such as red grapes and *Polygonum cuspidatum*, which synthesize it under stress conditions, such as strong UV irradiation. It can be considered an anti-ageing agent, thanks to its antioxidant properties.[86,87] In particular, it can exert its effect on two levels: scavenging free radicals and chelating metal ions, such as iron and copper, which catalyse free radical formation. It works synergically with vitamins C and E.

A USA patent describes its capacity to stimulate *in vitro* cell proliferation and collagen synthesis. Moreover, it would inhibits the degrading action of some proteases on the dermal matrix and proteins.

Thereof, revitalizing fibroblasts, improving their functionality and protecting dermal structures integrity resveratrol reduces skin ageing. Its cosmetic efficacy is enhanced by the screening effect against natural UV rays.

### L-Carnosine

L-Carnosine, a synthetic peptide identical to the natural one (α-alanyl-L-histidine), which naturally occurs in muscle and brain, where it protects tissue from oxidative stress damage, represents an innovative cosmetic ingredient for anti-wrinkle formulations, due to its ability to protect the skin against ROS (radical oxygen species) and RCS (radical carbonylic species) damage, or to reverse such damage.

It fights both ROS, directly and by chelating metal ions that catalyse their formation, and RCS, directly by quenching them, or indirectly by:

- preventing proteins (collagen and elastin) cross-link or by eliminating modified macro-molecules;
- marking of advanced glycation and products (AGEs) for degradation;
- quenching carbonyl compounds;
- promoting modified protein degradation.[88–90]

### Taurine

Beta amino acid ubiquitous, it protects biological membranes from damage due to oxygen free radicals and therefore is essential in man. Derived from methionine and cysteine metabolism, taurin plays a pivotal role in numerous physiological functions, among which is the protection of tissues and membranes;[91–93] this protection is exerted by its direct interaction with membrane proteins to suppress oxidative damage. Of particular notice is its peculiar and unique ability to neutralize ipocloride acid, which destroys cell membranes, leading to a premature skin wrinkling.[94–96]

### Agaricic acid

Agaricic acid is among the newest agents to function in the treatment of wrinkles: it inhibits the cross-linking process which leads to dermal proteins denaturation.

## Plant extracts

Plants represent a very precious and rich source of cosmetic functional agents, today exploited more than ever due to consumers preference for 'natural' products. In particular, lots of plant extracts are employed in cosmetic formulations developed to treat wrinkles. Their efficacy is related to the presence, besides some of the previously described substances, of non-soaping oil fractions and triglycerides.

### Non-soaping oil fractions

These are rich in phytormones, which stimulate fibroblast activity, and in sebum-like substances. These fractions exert a remarkable antioxidant, nutrient and repairing effect. Moreover, they carry out a photoprotective function, thanks to their content of carotenoids, tocopherols, terpenes and sterols.[53]

### Triglycerides

Some vegetable oils are very valuable in relation to their anti-ageing and anti-wrinkle effect, thanks in particular to the presence of vitamins and phytosterols. Among such oils are jojoba liquid wax, karitè butter, and oils from sweet almonds, wheat seed, apricots, *Borago officinalis*, *Macadamia ternifolia*, *Oenothera biennis*, *Persea gratissima*, and so on. A particular oil, increasingly employed in anti-wrinkle cosmetic formulation is lupin oil, which protects cell DNA from free radical injury and inhibits lipoperoxidases and elastases.[53,97]

## Conclusions

The treatment of wrinkles is an open challenge in an ageing society. Many new molecules will appear in the near future, derived both from botanical and pharmaceutical research. Combination treatments, using compounds based on different mechanisms of action, may increase efficacy and specificity of therapy. Research is needed to establish long-term efficacy and safety of anti-wrinkle treatments as well as to develop protocols for prevention.

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