# Astaxanthin

## *To delay skin aging*

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## SUMMARY

Oxidative stress caused by UV-light, smoking and pollution has been explained to have a major impact in the process of skin aging. Free radicals damage skin cells and destroy the collagen network which leads to sagging and wrinkles. The interest of astaxanthin as an anti-wrinkle agent is growing among researches due to its natural capacity to protect cells from irradiation and oxidation. Astaxanthin is produced by the alga *Haematococcus pluvialis* to protect its cells from sun radiation, UV-light and oxidation. Several human studies demonstrated that astaxanthin reduced wrinkles and improved skin elasticity and moisture. The results are confirmed by animal studies. The mechanism of action of astaxanthin is explained by its strong antioxidant capacity and its protective effects against sun irradiation. *In vitro* studies have demonstrated that astaxanthin improves the function of mitochondria and has good protective effects on human fibroblasts. In that way, it can protect skin cells from free radicals and preserve the collagen layer which result in smooth and youthful appearance of the skin. The results indicate that astaxanthin has promising anti-wrinkle effects and that it can be helpful in reducing the skin aging process.

## INTRODUCTION

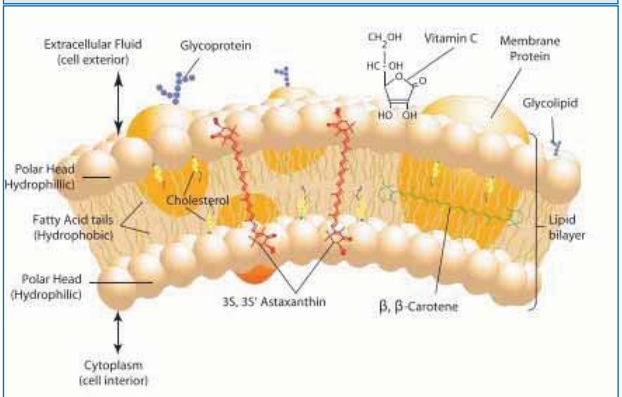
### Skin aging

Aging of the skin is commonly associated with increased wrinkling, sagging and loss of elasticity. Due to the cosmetic disfigurement it produces and its psychological impact, aging of the skin has become an issue of great social significance and concern. Skin aging is a continuous and complex process explained by genetic factors as well as environmental components such as UV-light, exposure to smoke and pollution (**1,2**). These environmental factors, and especially the UV-light, generate free radicals in the skin. Free radicals are reactive molecules that exert a multitude of effects such as lipid peroxidation, activation of pro-inflammatory transcription factors, DNA damage, and by such processes damage skin cells and the collagen fibers (**3**). As we become older, the antioxidants in the skin are reduced, and consequently, we are more dependent on antioxidants from food or supplements (**4,5**).
In addition, it has been demonstrated that fibroblasts from old donors are much more vulnerable to the accumulation of oxidized proteins following oxidative stress and are unable to remove them as efficiently as young fibroblasts (**6**). Damage on skin, dryness and wrinkles are therefore not only determined by our genes, but it seems also to be a result of an unbalanced diet with too low levels of antioxidants.

### Astaxanthin

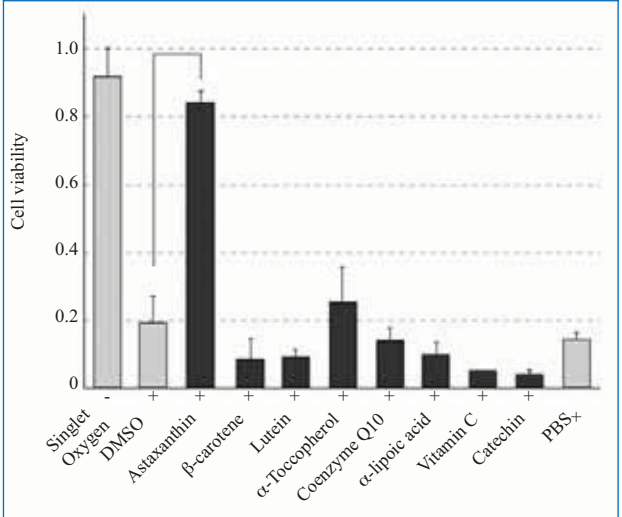
Astaxanthin is a red carotenoid pigment contained in seafoods such as salmons and crabs. Astaxanthin is related chemically to other lipid antioxidants of the carotenoid family like lutein, zeaxanthin, beta-carotene and lycopene (**7**). Astaxanthin, classified as a pure antioxidant, has not shown any pro-oxidative effects. Other antioxidants may show pro-oxidative effects under certain conditions which increase oxidative stress and cause damage on cells. Astaxanthin is a fat soluble antioxidant and its unique structure with the presence of hydroxyl and keto moieties on each ionone ring, enables it to go through the membrane and protect the cell membrane in a way that no other antioxidant can (***Fig 1***).
This unique structure of astaxanthin is one explanation why its antioxidant capacity has been shown to be significantly higher compared to other antioxidants (**8**). In fact, astaxanthin has demonstrated antioxidant capacity up to 500 times higher than vitamin E and 10 times stronger than β-carotene (**9**). Tominaga *et al* (**10**) found that astaxanthin had the greatest protective effect against singlet oxygen on human dermal fibroblasts compared to seven other common antioxidants (***Fig 2***).

**Figure 1** *How astaxanthin, β-carotene and vitamin C are positioned in the phospholipid cell membrane*




Astaxanthins unique molecular structure enables it to stay both inside and outside the cell membrane which gives better protection as compared to β-carotene and vitamin C which respectively can only be positioned inside or outside the lipid bilayer (**7,8**) (Figure, Copyright Bioreal)

**Figure 2** *Viability of human dermal fibroblasts treated with different antioxidants for 24 h before exposure to singlet oxygen*




Cell damage was induced by exposure to visible light for 10 min using rose bengal as a singlet oxygen generator.
DMSO, dimethyl sulfoxide. PBS, phosphate-buffered saline.
*p<0.01 vs control, paired t-test; Data are the means ± SD (n=3);
Data are taken from (**9**)

Due to the capacity of astaxanthin to neutralize free radicals, it has potential for a number of health related benefits such as cardiovascular health, diabetes, gastric health and muscle endurance (**11**). The alga *Haematoccus pluvialis* produces astaxanthin to protect its cells from sun radiation and UV-light. It is possible that astaxanthin has the same protective effects against UV-light in human skin cells. In the process of skin aging, exposure to UV-light is especially harmful for skin cells and therefore, the interest of the anti-wrinkle properties of astaxanthin is growing among researchers.
This article reviews the current available scientific literature regarding the effect of astaxanthin on skin health.

## RESEARCH STUDIES ON ASTAXANTHIN

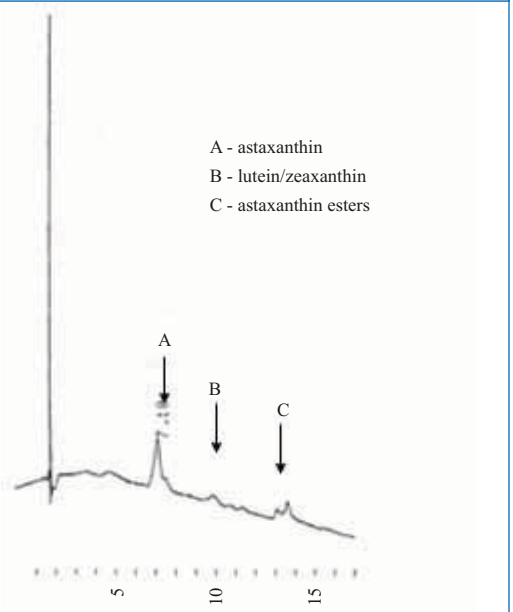
### HPLC profile

Astaxanthin is detected by HPLC as a major carotenoid in the skin after oral supplementation which indicates an efficient uptake of astaxanthin in human skin (***Fig 3***) (**12**). It is absorbed through the GI tract and is then taken up by the skin cells.

### Effect of oral supplementation on wrinkles

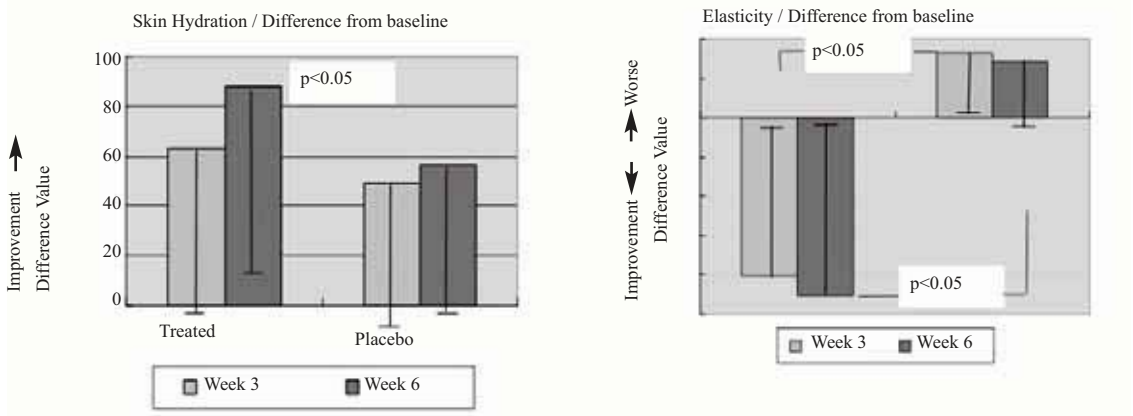
The effect of astaxanthin on the skin condition has been investigated in several studies on humans and animals. In a placebo controlled, double blind study (**13**), 49 women, between forty-five to fifty years of age, were supplemented with 4 mg of astaxanthin or placebo for 6 weeks. Self assessment questionnaires, clinical examinations by dermatologists and instrumental assessment were used to evaluate the effect of astaxanthin on skin dryness, elasticity, roughness, moisture and wrinkles. Over 50% of the subjects in the treated group had subjective improvements of all items in the self assessment questionnaire. According to the blinded judgments of dermatologists, the wrinkles were significantly reduced with astaxanthin. These results were also confirmed by objective results from the instrumental measurements. The value of moisture content in treated group was significantly higher at week 6 compared to baseline. The elasticity in the treated group was improved both at week 3 and 6, while the elasticity in the placebo was worse at week 3 and week 6 (***Fig 4***).

**Figure 3** *HPLC profile of carotenoids in human skin after supplementation of astaxanthin*




Oral supplementation leads to an accumulation of astaxanthin in the human skin. Data are taken from (**12**)

**Figure 4** *Effect of astaxanthin on moisture and elasticity of the skin*




The placebo controlled, double blind study was performed on 49 women supplemented with 4 mg/day astaxanthin or placebo for 6 weeks. Skin moisture content (skin hydration) (electrical conduction MS) was measured using the Dermal Phase Meter 9003 (NOVA meter); elasticity of the skin was measured by using the Dermalab (Cortex Technology, Denmark). Data are the means ± SD. ($p<0.05$ paired t-test). Data are taken from (**13**)

An earlier, double blind study by the same authors demonstrated similar results (**14**). In that study, 16 women took 2 mg of astaxanthin in combination with vitamin-E or placebo for four weeks. Several aspects of skin condition were significantly improved, such as moisture and pimples. Magnified skin surface photographs showed that wrinkles were significantly reduced. The beauty effects of astaxanthin are also supported in an animal model (**15**). In hairless mice exposed to UV-light, supplementation of astaxanthin inhibited wrinkle formation and the decrease of skin elasticity. The authors claimed astaxanthin to have significant protection against photoaging.

## Effect of topical treatment on wrinkles

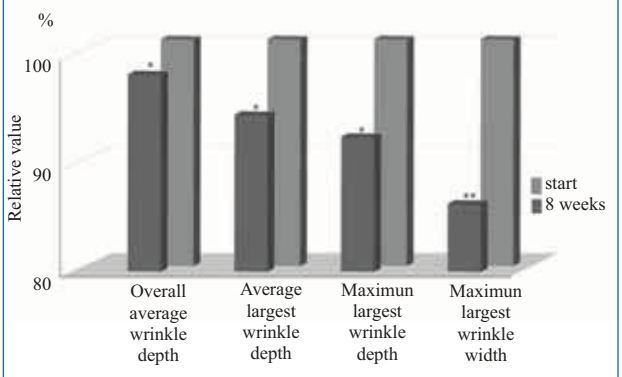
It appears that astaxanthin not only is efficient as a supplement, but also has potential as a topical treatment. In an open study, 11 women applied a face cream containing astaxanthin every morning and evening (**16**). Skin moisture content was measured by using instrumental assessment and questionnaires were made to evaluate symptoms on skin condition. By three weeks, 8 of the women already observed improvements in symptoms on skin-dryness as evaluated by the questionnaires. This was also confirmed in the instrumental assessment which showed significantly enhanced moisture content on the skin. In the same study, dermatological inspection was done on three subjects and the result demonstrated anti-wrinkle observations.

The anti-wrinkle effect with topical treatment of astaxanthin has also been evaluated in an animal model (**17**).The effect of topical astaxanthin on appearance of wrinkles and skin elasticity were examined in hairless mice irradiated with UV-light to produce photoaged skin. The mice were irradiated five times weekly with UV-light over 18 weeks. In the group exposed to UV-light, wrinkling was significantly increased compared to non-irradiated controls. On the other hand, the group treated with astaxanthin had significantly reduced wrinkles compared to the placebo group.

## Effect of a combination of topical and oral treatment

Conceivably, a combination of oral and topical astaxanthin might enhance the effect produced by astaxanthin alone on skin condition. In a recent open study on 30 healthy women, the effect of combining 6 mg per day oral supplement with topical treatment during 8 weeks was investigated (**18**). Skin surface photographs were used to evaluate the effect of astaxanthin. Significant improvement in four different parameters was observed (***Fig 5***): the mean depth of the deepest wrinkle and the mean depth of all wrinkles were significantly reduced in

**Figure 5** *Wrinkle analysis: effect of astaxanthin*



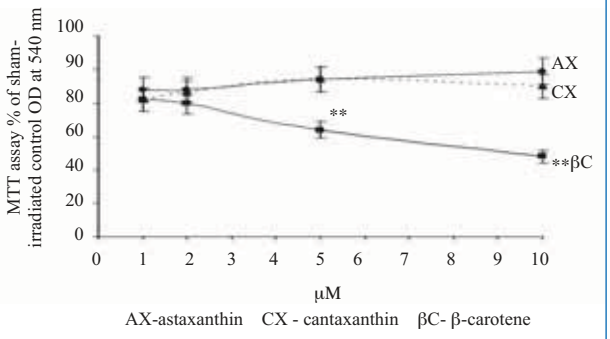

Wrinkle topography of the subjects crow´s feet was evaluated with replica by image analysis before and after treatment. In this open study, 30 participants were supplemented with 6 mg per day astaxanthin combined with topical cream for 8 weeks. *$p<0.05$, **$p<0.01$, (paired t-test). Data are taken from (**18**)

the first 4 weeks ($p<0.01$ and $p< 0.05$, respectively); the deepest point of the deepest wrinkle and the maximum width of the deepest wrinkle were significant reduced after 8 weeks ($p<0.01$).

## Mechanism of action

While the mechanism of skin aging is not well understood, there is compelling evidence that damage from UV-light has a major impact (**1-3**). Exposure to UV radiation increases free radical activity in the cell membrane which causes damage to skin cells through complex and multiple steps. The anti-wrinkle properties of astaxanthin are basically explained by its capacity to protect human skin cells from oxidative stress. Astaxanthin has demonstrated better protection of human fibroblasts exposed to UV-light than other antioxidants in several *in vitro* studies (**10,19-20**). Camera *et al* (**19**) even found that β-carotene acts as a pro-oxidant and increased membrane damage, whereas astaxanthin had photoprotective effects (***Fig 6***).

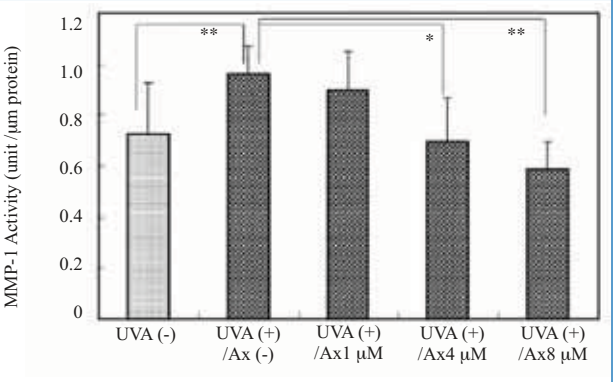
**Figure 6** *Effects of carotenoids on cell survival on human fibroblasts after exposure to UV-light*




Human dermal fibroblasts were irradiated with 0, 5, 10 and 15 J/cm ² UVA. The 3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide (MTT) toxicity assay denoting cell viability was performed 24 h after irradiation by measuring the optical density (OD) at 540nm.
** p<0.0.05, Student´s t-test. Data are taken from (**19**)

Based on astaxanthin's capacity to protect skin cells from oxidation, astaxanthin inhibits several steps involved in the process of skin aging. The skin is composed of three layers and the second layer, the dermis, consists of collagen and elastin fibers which are largely responsible for the strength and elasticity of the skin. UV-light from the sun penetrates into the skin, and through generation of reactive oxygen species (ROS) activate matrix-degraded metalloproteinases (MMPs) (**1-3**), a group of enzymes able to degrade matrix proteins such as collagen. In fact, Fischer *et al* (**21**) found that in human skin multiple exposures to UV-irradiation led to sustained elevation in MMP activity that degrades skin collagen and may contribute to photoaging. Furthermore, it has been demonstrated that astaxanthin can reduce the levels of these degrading enzymes in both fibroblasts (**22**) and macrophages (**23**). In fact, Suganuma *et al* (**22**) found that UV-light increased the level of matrix-degraded MMPs in fibroblasts, while fibroblasts with astaxanthin had a significantly lower amount and reduced activity of these degrading enzymes (***Fig 7***).

**Figure 7** *Effect of astaxanthin on metalloproteinases (MMP) activity*




Effect of astaxanthin(AX) on MMP-1 activity in UVA-exposed human fibroblasts assessed by ELISA at 48h post irradiation. UVA irradiation: 10 J/cm²
*p<0.05; **p<0.01, Student´s t-test. Data are taken from (**23**)

Activation of MMPs is not only stimulated directly by the oxidative stress from UV-light, but also indirectly through transcription factors such as NF-kB (**2**) which produces pro-inflammatory cytokines. Lee *et al* (**24**) found that astaxanthin inhibited NF-kB activity. It seems, therefore, that astaxanthin can protect the collagen and elastin fibers from MMPs by protecting cell membrane from oxidation and by deactivating NF-kB.
In addition to activation of MMPs, and its damage on collagen and elastin fibers, a second pathophysiological pathway has been suggested in the pathway of skin aging and is focused on the mitochondria (**2**), cell-organelles whose main function is to generate energy for the cell. This process is not completely error-free and as a consequence leads to the generation of ROS. Free radicals in the mitochondria can cause mitochondrial dysfunction by damaging lipids, proteins and mitochondrial DNA. In a recent study by Koziel *et al* (**25**), analysis on mitochondrial function in dermal fibroblasts obtained from healthy young (23-39 years old), middle age (52-68 years old) and old donors (90 years old), demonstrated a significant decrease in mitochondrial membrane potential among the older donors compared to the younger, accompanied by a significant increase of oxidative stress.
Membrane potential is necessary for respiration to work and essential for normal mitochondrial function. A declined function of mitochondria can lead to an inadequate energy production which can damage dermal fibroblasts. Wolf *et al* (**26**) found that astaxanthin can enhance the function of mitochondrion by reducing oxidative stress. Cells that were exposed to oxygen decreased the membrane potential in mitochondria. How-

ever, the cells that were treated with astaxanthin had significantly improved membrane potential compared to placebo. The results indicate that the ability of astaxanthin to enhance mitochondrial function combined with its capacity to protect the collagen and elastin fibers from oxidation can be considered two mechanisms for its effect on skin condition.

## CONCLUSIONS

Dietary supplementation and topical application of astaxanthin resulted in increased skin moisture content, improved skin elasticity, and reduced fine lines and wrinkles shown in several studies on humans. The mechanism of astaxanthin is explained by its antioxidant capacity and its protective effects against sun irradiation. *In vitro* studies have demonstrated that astaxanthin improves mitochondrial function, has significant protective effects on fibroblasts and reduced MMP. In these ways, it can preserve the collagen layer which results in smooth and youthful appearance of the skin. In conclusion, astaxanthin has shown promising anti-wrinkle effects and can be helpful in reducing the process of skin aging. For these reasons, astaxanthin can benefit those people concerned about their skin health.

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