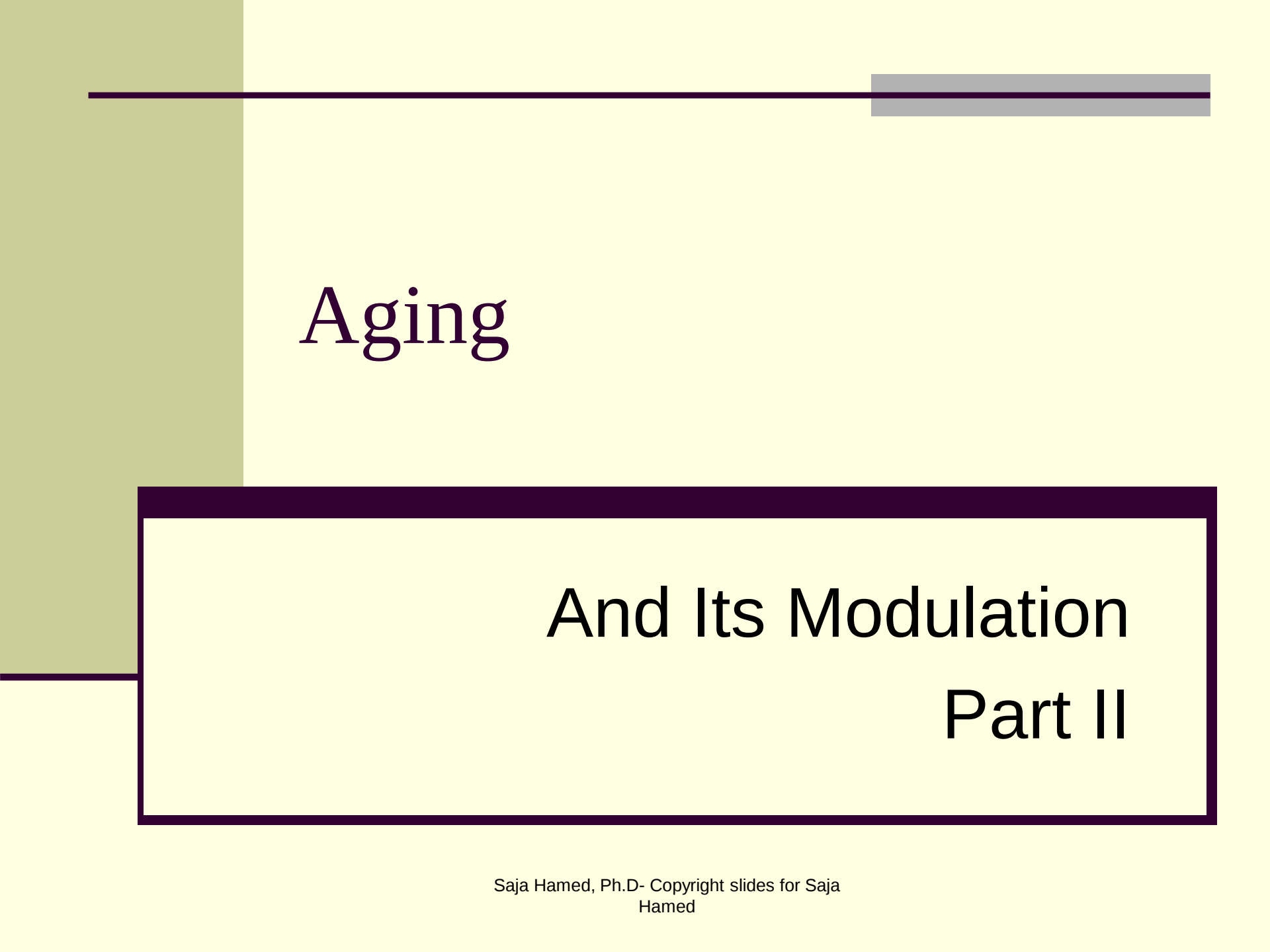




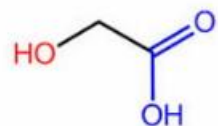
Aging

And Its Modulation Part II

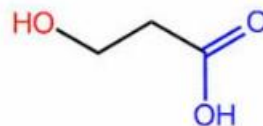
Hydroxy acids

- Organic carboxylic acids:
 - AHAs: lactic acid, glycolic acid, malic acid, tartaric acid, citric acid, mandelic acid
 - BHA: salicylic acid
 - Polyhydroxy acids (PHAs): gluconolactone

- “Alpha” and “beta” describe how far apart the two groups are.
- If the two groups are one carbon apart, then they’re alpha to each other, and if the two groups are two carbons apart, then they’re beta.



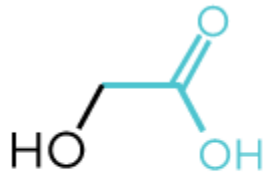
alpha hydroxy acid



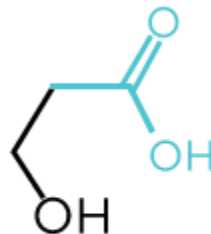
beta hydroxy acid

FOUR TYPES OF HA'S

AHA

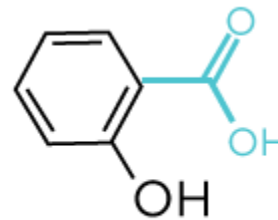


BHA



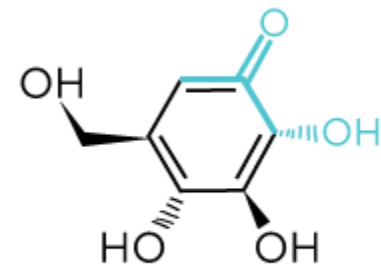
SA

(salicylic acid)



PHA

(gluconolactone)



types of chemical exfoliants

AHAs

- glycolic acid
- lactic acid
- mandelic acid
- malic acid
- tartaric acid
- citric acid

BHAs

- salicylic acid
- salicylate
- tropic acid
- betaine salicylate
- willow bark extract

PHAs

- gluconolactone
- lactobionic acid
- maltobionic acid

BEAUTY AFFAIRS

CURATED SKINCARE & COSMETICS

Numerous skin effects for HAs

- Exfoliation
- Moisturization (humectant effect due to OH groups)
- Reduce melanin synthesis
- Antiinflammatory (SA)

Hydroxy acids

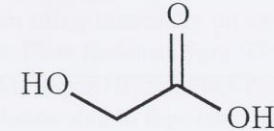
- Low conc (4-10%) in nonprescription creams → promoted for skin aging
- High concentration (>20%) can be used as chemical peels to treat calluses, acne, photo-aging

Exfoliants: AHAs and BHAs

- *Exfoliation*: in *latin* meaning falling off in scales or layers
- Cosmetic benefits attributed to skin exfoliation has been long known since the time of ancient Egyptians
- AHA and BHA are naturally occurring organic acids that help induce exfoliation and speed the cell cycle

AHAs

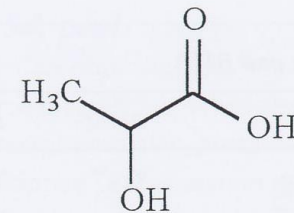
- A group of compounds that contain the hydroxy group in the alpha position
- Glycolic acid (sugar cane), lactic acid (sour milk), citric acid (citrus fruits), and phytic acid (rice)



Glycolic acid
(2-Hydroxyethanoic acid)

Figure 20-3.

Chemical structure of glycolic acid. The OH group is in the alpha position; therefore, this is in the α -hydroxy acid family.



Lactic acid
(2-Hydroxypropanoic acid)

Alpha- hydroxy acids (AHA):

- The effect of AHA depends on their concentration. The higher the concentration the more effective the treatment:
 1. Low concentrations- up to 10%
 2. Moderate to high concentrations up to 70%

Alpha- hydroxy acids (AHA):

1. Low concentrations- up to 10%:
 - These preparations can be bought freely over the counter at cosmetics departments
 - AHA are safe to use in cosmetic preparations in concentrations up to 10% provided that the pH of the preparation is not less than 3.5

2. Moderate to high concentrations – up to 70%:
 - They require physician supervision
 - Are used for superficial chemical peeling

Effects of low concentrations of AHA- up to 10%:

1. Exfoliation: They weaken the bond between dead cells of the outer layers of the skin and enhance desquamation of the outer layer of the skin → the replacement of the dry outer layer by a new layer gives the skin a smooth appearance
1. Humectants (absorb water)

Effects of moderate to high concentrations of AHA- up to 70%:

- Their use require medical supervision
- They are used to achieve superficial chemical peeling of the skin → by dissolving the outer layer of the epidermis
- It usually takes at least four superficial peels before patients can begin to see improvement of photodamage, sun spots, and melasma
- Higher concentrations of AHA have a high acidity level → can burn the skin

Effects of moderate to high concentrations of AHA- up to 70%:

- Higher concentrations at low pH values cause epidermolysis to produce varying degrees of exfoliation

AHAs:

- AHAs are useful in the management of dry skin, acne, scarring, actinic keratoses, as well as photodamaged skin
- At least 1 billion US dollars in sales, maybe more
- Long known as skin conditioners, on the market only since 1993 as 'anti-aging' products.
- Moderate effects on skin hydration.

BASIC CHEMICAL PEELS

Very superficial

- AHA: glycolic 20 – 35%, lactic 50%
- BHA: salicylic acid 20 –30%
- TCA 10 –20%
- Jessner's 1–3 coats
- Tretinoin and retinol
- (Microdermabrasion 2 passes)

Superficial

- AHA: glycolic 70%
- TCA 20 –30%
- Jessner's 4–7 coats
- Solid carbon dioxide

Injury to epidermis
Minimal downtime
All skin types

ADVANCED CHEMICAL PEELS

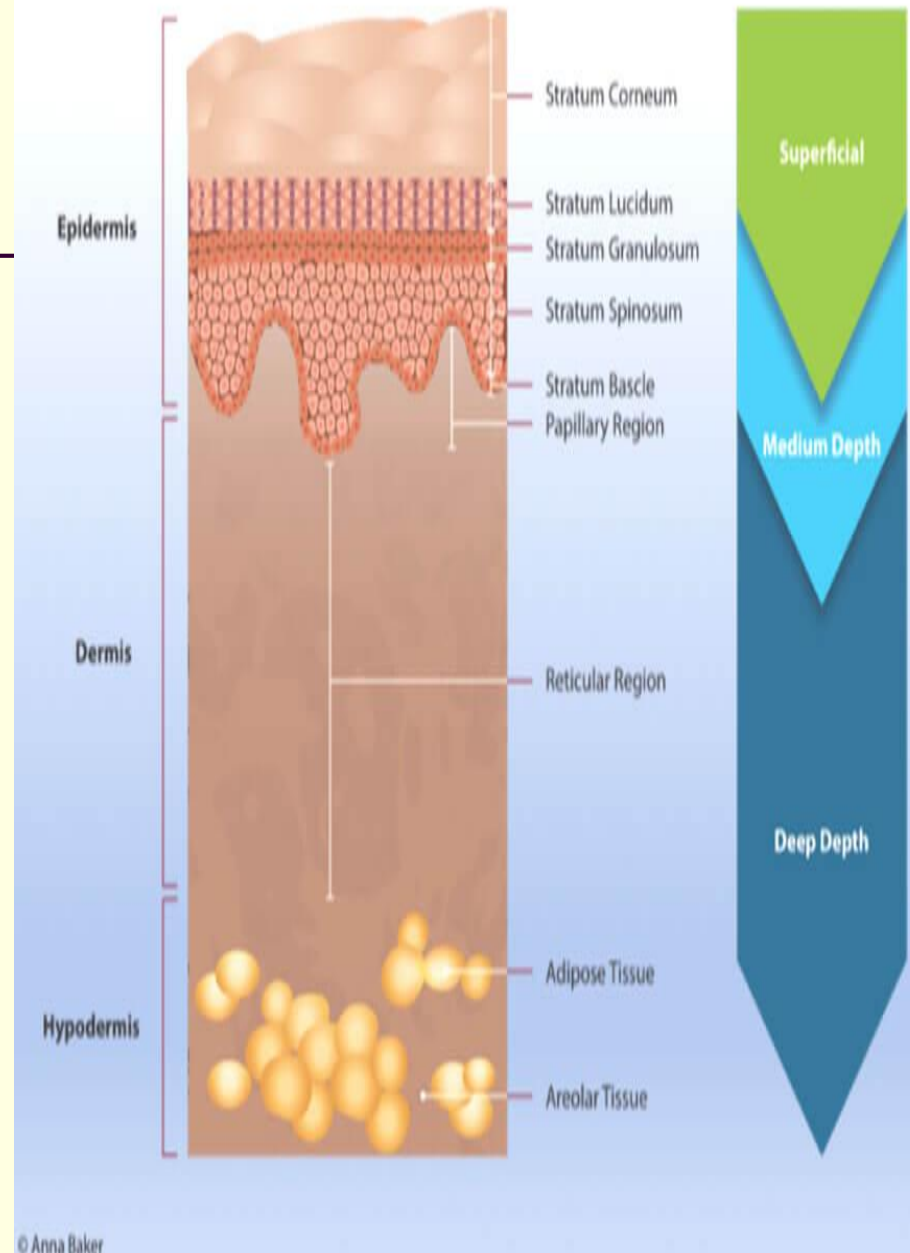
Medium

- TCA 35 –40%
- TCA 35% with:
 - Glycolic 70%
 - Jessner's
 - Solid carbon dioxide

Deep

- TCA $\geq$ 50%
- Phenol 88%
- Baker-Gordon formula

Injury to dermis
Significant downtime
Risk of pigmentary
changes and other
complications



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<https://clinicalgate.com/chemical-peels/> Hamed <https://www.thepmfajournal.com/features/features/post/an-overview-of-chemical-peel-formulations>

- Chemical peels are categorized based on the depth of the procedure: superficial, medium, or deep
- Superficial peels induce necrosis of all or parts of the epidermis
- Medium-depth peels create necrosis of the epidermis and part or all of the papillary dermis in the treatment area
- Deep peels create necrosis deep in the reticular dermis

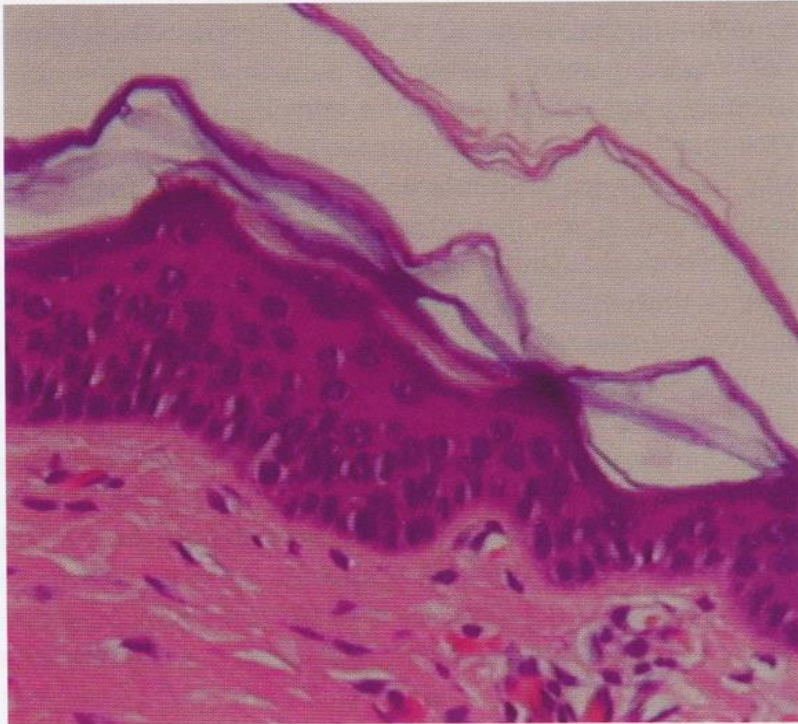


Figure 20-1.

A hematoxylin and eosin (H&E) stain of untreated normal bovine skin.

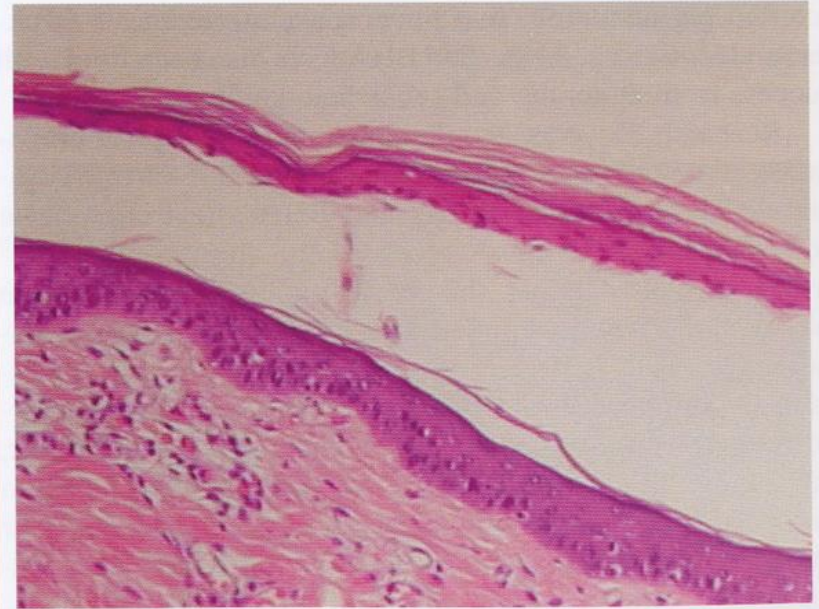


Figure 20-2.

A hematoxylin and eosin (H&E) stain of bovine skin treated with a superficial chemical peel (two coats of the Pigment Peel Plus. This biopsy demonstrates a split in the spinous layer of the epidermis.

- AHAs and BHA are classified as superficial chemical peeling agents
- Superficial and medium-depth peels do not significantly enhance deep wrinkles or sagging skin
- But can improve color and texture of the skin
- Authors have reported success using such products in the treatment of photoaging by improving mottled pigmentation, fine lines, surface roughness, freckles, and lentigines

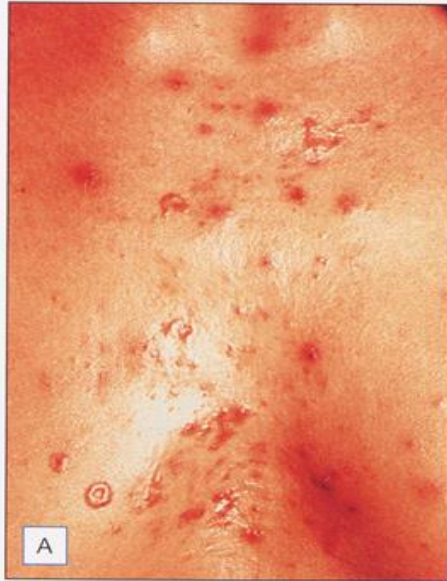


Fig. 16.4 Alpha hydroxy acid peels can be used on the chest to improve acne and skin texture. **(A)** Before. **(B)** After



Fig. 16.5 Improvement in skin texture following an alpha hydroxy acid peel is demonstrated. **(A)** Before. **(B)** After

AHAs:

- Glycolic acid is the simplest molecule with the lowest Mwt and a pK_a of 3.83:
 - Water soluble
 - It is used in its partially neutralized form for topical home care products and in a free acid form in peeling products
- Combination with other antiaging agents

AHAs:

- GA and LA might work on pigmentary lesions not only by accelerating the turnover of the epidermis but also by directly inhibiting melanin formation in melanocytes
- GA and LA in doses of 300 or 500 µg/ml suppressed melanin formation by directly inhibiting tyrosinase activity

ALPHA-HYDROXY ACIDS

Cherie *et.al* investigated the effects of alpha-hydroxy acids (AHAs) on photo-aged skin.

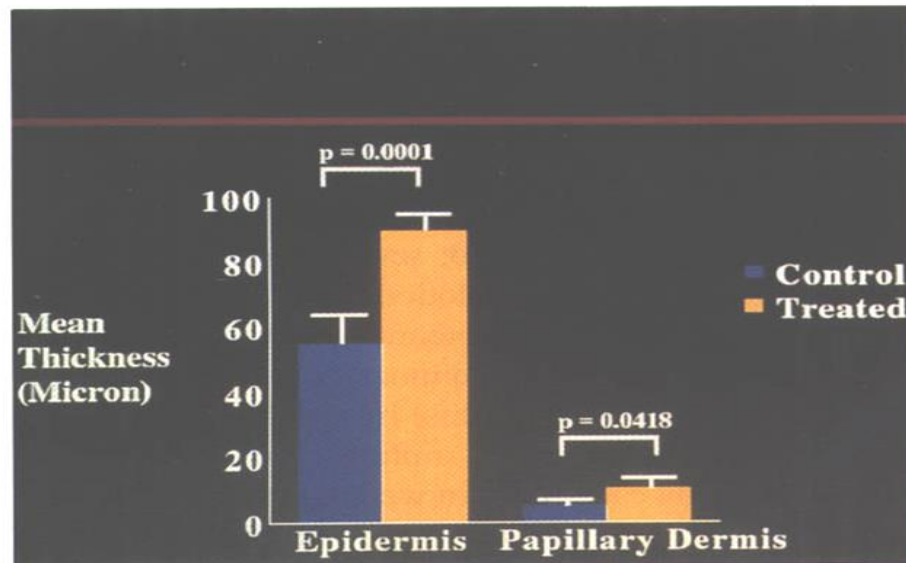
- 17 white subjects with moderate photo-aged skin were selected.
- Subjects were randomly assigned 25% of AHA lotion, (5 each were given lactic acid and glycolic acid and 7 were given citric acid).

(J. Amer. Acad. Dermatol 34: 187-195,1996)

ALPHA-HYDROXY ACIDS

- Subjects were instructed to apply the given lotion to one forearm and the placebo lotion to the other forearm.
- Subjects were observed monthly for 6 months.
- 4mm punch biopsy specimens were obtained at the end of the study period.

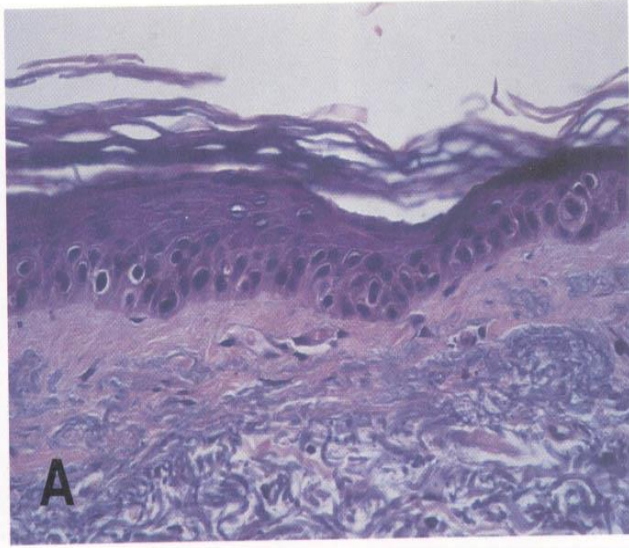
ALPHA-HYDROXY ACIDS



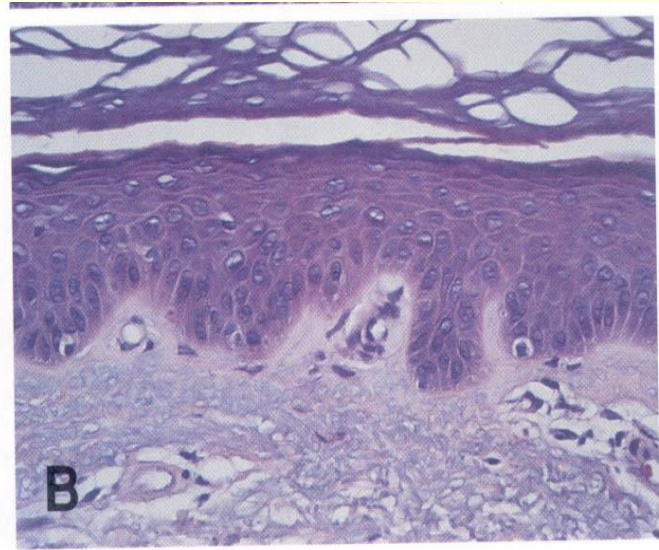
Quantitative histometric analysis of mean thickness of epidermis and papillary dermis.

- There was an increase in the epidermis and papillary dermis thickness in AHA treated specimens than in the control specimens.

ALPHA-HYDROXY ACIDS



A = control arm



B = treated arm

- There was a return to more undulating rete pattern in AHA treated specimen.

ALPHA-HYDROXY ACIDS



A = control arm



B = treated arm

- The elastic fibers tended to be longer, thicker and less fragmented in AHA treated specimens compared with the control.

ALPHA-HYDROXY ACIDS

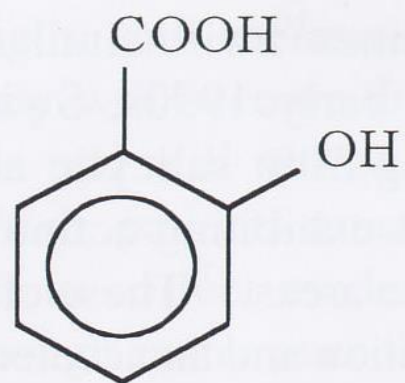
CONCLUSIONS

- Topically applied AHAs cause significant improvements in both epidermal and dermal components.
- Clinical and histological findings suggest that AHAs reverse photo-aging.

BHA:

Salicylic acid

- SA is both oil soluble and water soluble
- 2%-12% causes keratolysis of SC
- Found in the OTC home products usually at 2% concentration
- Most physicians use preparations of 20% or 30% for the in-office peels
- Such peels have been shown to fade pigment spots, to decrease surface roughness, and to reduce fine lines
- SA, unlike AHAs, exhibits anti-inflammatory capabilities by affecting arachidonic acid
- The anti-inflammatory effects of BHA make it a useful peel in patients with acne and rosacea



Salicylic Acid

BHA:

Salicylic acid

- It is able to penetrate the sebaceous material in the hair follicle and exfoliate the pores
- AHA do not exhibit this comedolytic feature because they are water soluble
- *Kligman* evaluated the ability of 2% BHA to improve comedones compared to 8% glycolic acid
- GA did not decrease the density of microcomedones, whereas a statistically significant decrease was seen after SA application (*Kligman A.: A comparative evaluation of a novel low-strength salicylic acid cream and glycolic acid products on human skin. Cosmet Dermatol., Sept (Suppl): 11, 1997*)

BHA:

Salicylic acid

- There is no published data examining BHA's effect on collagen production
- There have been case reports of children with multiple excoriations and elderly patients with ichthyosis that were treated with topicals containing SA who developed salicylism
- Therefore, large body surfaces should be treated with care and the physician should watch for the signs of salicylism that include nausea, disorientation, and tinnitus
- BHA is contraindicated in patients who are pregnant, breast-feeding, or allergic to aspirin
- Home-care products that contain SA (typically labeled as “acne washes”) should also be avoided in patients who are pregnant, breast-feeding, or allergic to aspirin

Table 20-1.

Comparison of AHAs and BHA

	<i>AHAs</i>	<i>BHA</i>
Useful in photoaging	Yes	Yes
Useful in acne	Yes	Yes
Useful in melasma	Yes	Yes
Useful for dry skin	Yes	Yes
Speeds cell cycle	Yes	Yes
Enhances exfoliation	Yes	Yes
Lipophilic	No	Yes
Inhibits arachidonic acid	No	Yes
Anesthetic properties	No	Yes
Anti-inflammatory properties	Maybe	Yes
Must be neutralized	Yes	No
Visible frost	No	Yes
Risk of salicylism	No	Yes
Variety of available concentrations	Yes	Minimal
FDA approved for home use	No	Yes (dry skin)
Shown to increase collagen synthesis	Yes	No
Use in pregnancy/breast feeding	Unknown	No

Disadvantages of HAs:

- Irritation and skin dryness can result from AHA and BHA products
- Patient should alternate between hydroxy acid containing products and regular moisturizers that do not contain hydroxy acids
- It usually takes at least four superficial peels before patients can begin to see improvement of photodamage, solar lentigo, and melasma
- Superficial peels are unable to correct moderate to severe wrinkles and scars
- Many cosmetic companies noted an increase of sunburn cells in patients treated with AHA preparations → should be used in combination with a sunscreen
- Some experts suggest that continued use of hydroxy acids might show a decrease in efficacy with continued use as a result of accommodation by the skin. Thus, it may be beneficial to have patients stop their AHA preparations periodically to enhance the efficacy of these products when used for long-term

-
- Smith 1995 found that while skin thickness, firmness and improvement in wrinkle characteristics continued to improve beyond a 26-week treatment period, after 20 weeks of use both glycolic and lactic acids are 60% less effective at increasing cell renewal as they were during the initial period of use

The accommodation effect with AHAs

Test Material (3.0%), pH 3	Renewal Rate*, Start	Renewal rate after 10 Weeks Treatment	Renewal rate after 20 Weeks treatment
Control	4.7	4.9	4.8
Lactic Acid	28.6	17.3	10.3
Glycolic Acid	29.3	16.8	11.6
Salicylic Acid	33.2	26.7	17.2

*** Rates are expressed as % increase from pretreatment values.**

Evaluating and comparing hydroxy acid preparations

- The amount of available free acid:
 - Concentration of hydroxy acid
 - pKa of acid preparation
 - pH of the solution
 - Whether or not the preparation is buffered
- Because of too many factors, it is difficult to compare one brand of chemical peel to another
- Differences in vehicle can affect the clinical response
- Urea may affect the efficacy of these products because it increases their penetration

Evaluating and comparing hydroxy acid preparations

- pKa is the pH at which the level of free acid is the same as the level of the salt form of the acid
- When pH is less than the pKa the free acid form predominates
- Acid form is the “active form”
- It is necessary to have the proper balance of the salt and acid form to have an efficacious peel with minimal irritation
- pKa for SA= 2.97
- pKa for AHAs= 3.83
- It is difficult to formulate a combination product that reaches an optimal pH
- AHA-BHA combination product with a pH of 3.5??

Evaluating and comparing hydroxy acid preparations

- Lower pH= increased irritation and efficacy
- Buffered solutions:
 - When a base such as sodium bicarbonate is added to the solution
 - This produces an increased amount of the salt form
 - Less free acid and a higher pH: decrease side effects and decrease efficacy
 - They are resistant to pH changes

Cumulative irritation scores for AHA formulations and products

AHA	%	pH	N	Score
GA	8.0	4.40	21	1/882
GA	8.0	3.80	21	49/882
GA	8.0	3.25	21	119/882
LA	12.0	4.40	21	30/882
GA	13.0	4.40	21	33/882
GA	10.0	3.80	21	21/882
GA	9.0	3.80	21	7/882
GA	10.0	4.40	23	18/966
GA	10.0	3.80	23	38/966
GA	10.0	3.25	23	404/966
GA	10.0	3.00	23	631/966
GA	10.0	2.50	23	746/966
GA	10.0	2.00	23	768/966
GA**	5.0	2.40	23	770/966
GA**	9.0	3.25	23	481/966
GA**	8.0	3.60	23	258/966
GA	8.0	3.60	23	148/966
GA	15.0	3.80	23	14/966
GA	20.0	3.80	23	37/966

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** Commercial products

Smith's Data on SC turnover and irritation

Test Material	pH	SC turnover	Irritation
Lactic acid, 4%	3	+35%	2.8
	5	+24%	2.1
	7	+13%	1.2
Glycolic acid, 4%	3	+34%	2.9
	5	+23%	2.1
	7	+10%	1.1
Salicylic acid, 4%	3	+42%	3.0
	5	+28%	2.3
	7	+12%	1.2

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Smith, Soap *Chem Cosmet Spec.* (1993) **69**, 54

-
- In 1997, the Cosmetic Ingredient Review Panel (CIR) concluded that AHAs (glycolic acid, lactic acid, and their related chemical compounds) are safe for use in products intended for cosmetic use when:
 - The AHA conc. is 10% or less
 - The final product has a pH of 3.5 or greater
 - The final product is formulated in such a way that it protects the skin from increased sun sensitivity or its package directions tell consumers to use sunscreen products

-
- FDA is cautioning persons using AHA products to avoid sun exposure when possible and or to use adequate sun protection as these products increase skin sensitivity to sun

Remarks about HA

- When to use
- Conc
- Frequency
- Do I really need them
- AHA vs BHA vs PHA
- What about physical exfoliation!

Skin Aging Modulations: Antioxidants



Antioxidant



Free radical



Healthy cell

Antioxidants:

- The free radical theory of aging, proposed in 1956, is one of the most widely accepted theories to explain the cause of aging
- ROS take electrons from vital components (DNA, proteins, and membranes) leaving them damaged
- ROS are involved in the aging process and are believed to be involved cutaneously in causing photoaging, carcinogenesis, and inflammation
- UV-induced skin damage is partly mediated by ROS
(Black HS: Potential involvement of free radical reactions in ultraviolet light-mediated cutaneous damage. Photochem Photobiol, 46: 213, 1987)

Antioxidants:

- Natural antioxidants in the skin: superoxide dismutase, catalase, α -tocopherol (vitamin E), ascorbic acid (vitamin C), ubiquinone, and glutathione
- UV light exposure:
 - Inhibit many of these defense mechanisms (*Fuchs et al.: Acute effects of near ultraviolet and visible light on the cutaneous antioxidant defense system. Photochem Photobiol, 50: 739, 1989 & Fuchs et al.: Impairment of enzymic and nonenzymic antioxidants in skin by UVB irradiation. J Invest Dermatol, 93: 769, 1989*)
 - Cause an increase in free radical formation (*Dreher F & Maibach H: Protective effects of topical antioxidants in humans. Curr Probl Dermatol, 29: 157, 2001*)

Antioxidants:

- Topical antioxidants are currently marketed for:
 - Prevention of premature-aging and photoaging
 - Treatment of wrinkles (No evidence for this claim)
 - and treatment of erythema caused by inflammation
- the free radical theory of aging explains why antioxidants are thought to prevent wrinkles but it does not justify the use of antioxidants to treat wrinkles that are already present

Network antioxidants:

- Most of antioxidants used in the cosmetic industry are “network antioxidants”
- They work synergistically to “enhance the power” of each other
- After an antioxidant “disarms” a free radical it is unable to function further as antioxidant unless it is recycled
- Five known network antioxidants: vitamins C & E, glutathione, lipoic acid, and coenzyme Q₁₀ (CoQ₁₀)
 - Vitamin C or CoQ₁₀ can recycle vitamin E
 - Lipoic acid can recycle vitamin C or glutathione

Fat-Soluble Antioxidants:

Vitamin E

- vitamin E is the primary lipid soluble antioxidants in skin that protect cells from oxidative stress
- ROS induce changes in the biosynthesis of collagen and GAGs in cultured human dermal fibroblasts. This alteration was prevented with the addition of α -tocopherol to the fibroblasts
(Tanaka et al.: the effect of reactive oxygen species on the biosynthesis of collagen and glycosaminoglycans in cultured human dermal fibroblasts. Arch Dermatol Res, 285: 352, 1993)
- vitamin E lowers prostaglandin E2 production and raises IL-2 production leading to anti-inflammatory and immunostimulatory activity

Fat-Soluble Antioxidants:

Vitamin E

- Topical D- α -tocopherol acetate diminish erythema caused by sunburn, edema, and skin sensitivity in mice when applied after exposure to UVB (*Trevithick et al.: Topical tocopherol acetate reduces post-UVB, sunburn-associated erythema, edema, and skin sensitivity in hairless mice. Arch Biochem Biophys, 296: 575, 1992*)
- 5% tocopherol applied to mice prior UVB exposure lead to 75% decrease in skin wrinkling and reduction in cutaneous tumors (*Bissett et al.: Photoprotective effect of superoxide-scavenging antioxidants against ultraviolet radiation-induced chronic skin damage in the hairless mouse. Photodermatol Photoimmunol Photomed, 7: 56, 1990*)

Fat-Soluble Antioxidants:

Vitamin E

- A double-blind, placebo-controlled study examined the protective effects of orally administered vitamin E (400 IU per day) against UV-induced epidermal damage in humans for a 6 months period. There was no significant difference between the placebo group and those treated with vitamin E in MED and histologic response (*Werninghaus et al.: Evaluatin of the photoprotective effect of oral vitamin E supplemenation. Arch Dermatol, 130: 1257, 1994*)

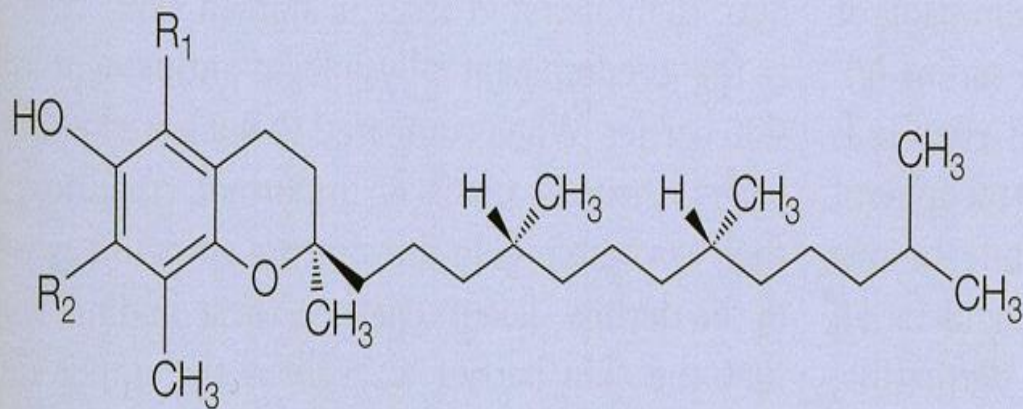
Fat-Soluble Antioxidants:

Vitamin E

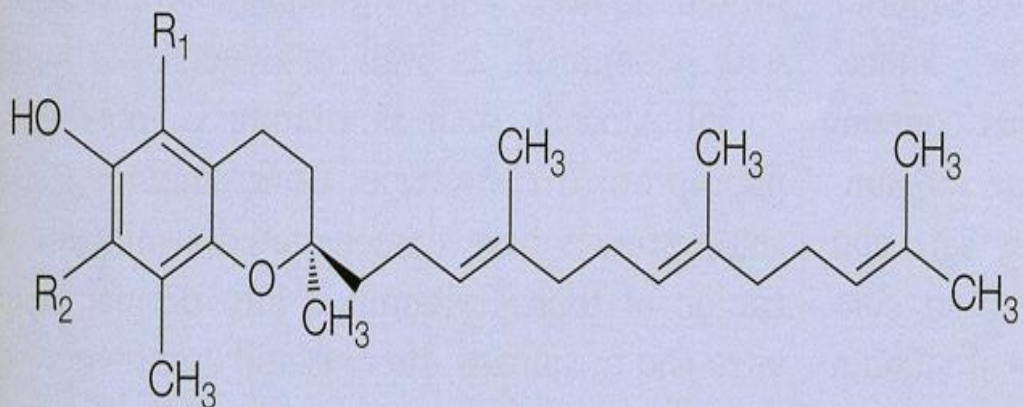
- It is suggested that vitamin E may require to interact with other antioxidants such as vitamin C to provide photoprotection (*Chan AC: Partners in defense, vitamin E and vitamin C. Can J Physiol Pharmacol, 71: 725, 1993*)
- In a study that assessed the cosmetic benefit resulting from the use of topically applied vitamin E to a surgical scars patient applied 320 IU of D- α -tocopheryl per gram of Aquaphor to one side of the scar and Aquaphor alone to the other side of the scar for 6 months. Vitamin E preparation failed to improve the cosmetic appearance of surgical scars (*Baumann & Spencer: The effects of topical vitamin E o the cosmetic appearance of scars. Dermatol Surg, 25: 311, 1999*)

Forms of vitamin E

- Vitamin E is a family of compounds called tocopherols (α , β , γ -, and δ - tocopherol)
- α -tocopherol is the most active form and is the form that the recommended daily allowance (RDA) is based on
- The names of all types of vitamin E begin with either D or DL
- The natural form (D-) is more active and better absorbed
- Synthetic supplements contain α -tocopherol
- Food sources contain several different tocopherols



Tocopherols



Tocotrienols

Fig. 7.1 Chemical structure of tocopherols and tocotrienols.

Tocopherols (α : $R_1 = R_2 = \text{CH}_3$, 430.7 g/mol; β : $R_1 = \text{CH}_3$, $R_2 = \text{H}$, 416.7 g/mol; γ : $R_1 = \text{H}$, $R_2 = \text{CH}_3$, 416.7 g/mol; δ : $R_1 = R_2 = \text{H}$, 402.7 g/mol); **Tocotrienols** (α : $R_1 = R_2 = \text{CH}_3$, 424.7 g/mol; β : $R_1 = \text{CH}_3$, $R_2 = \text{H}$, 410.6 g/mol; γ : $R_1 = \text{H}$, $R_2 = \text{CH}_3$, 410.6 g/mol; δ : $R_1 = R_2 = \text{H}$, 396.6 g/mol)

Forms of vitamin E

- The vitamin E forms typically used in cosmetics are α -tocopheryl acetate and α -tocopheryl linoleate
- Tocopheryl esters are more poorly absorbed by the skin than the tocopherol forms
- α -tocopheryl acetate and α -tocopheryl succinate failed to prevent photocarcinogenesis in a study (*Gensler et al.: Importance of the form of topical vitamin E for prevention of photocarcinogenesis. Nutr Cancer, 26: 183, 1996*)

Vitamin E

- A study demonstrated that even the use of rinse-off products containing α -tocopherol in concentrations of less than 0.5% leads to significantly increased levels of vitamin E in the SC of human skin
- Therefore, topical formulations with α -tocopherol (but not vitamin E ester) at concentrations ranging from 0.1 to 1% are very likely to be efficient in improving antioxidant protection of the skin barrier.

(Ekhanayake-Mudiyanselage et al.: Vitamin E delivery to human skin by a rinse-off product: penetration of alpha-tocopherol versus wash-out effects of skin surface lipids. Skin Pharmacol Physiol. 2005 Jan-Feb;18(1):20-6)

Vitamin E

- A clinical placebo controlled study on 96 atopic dermatitis patients were treated with either placebo or oral vitamin E (400IU/day) for 8 months
- An improvement and near remission of atopic dermatitis and a 62% decrease in serum IgE levels in the vitamin E treated group

(Tsourelis-Nikita et al.: Evaluation of dietary intake of vitamin E in the treatment of atopic dermatitis: a study of the clinical course and evaluation of the immunoglobulin E serum levels. International Journal of Dermatology, 41: 146-150, 2002)

Vitamin E:

Side effects

- The incidence of contact dermatitis due to vitamin E topical application may be relatively high (*Jenkins et al.: Failure of topical steroids and vitamin E to reduce postoperative scar formation following reconstructive surgery. J Burn Care Rehabil, 7: 309, 1986*)
- In 1992, Swiss researchers evaluated 1000 cases of an atypical contact dermatitis provoked by vitamin E linoleate that was an additive to cosmetics and found that oxidize vitamin E derivatives can operate *in vivo* as haptens or irritants (*Perrenoudet al.: An epidemic outbreak of papular and follicular contact dermatitis to tocopheryl linoleate in cosmetics. Swiss Contact Dermatitis Research Group. Dermatology, 189: 225, 1994*)

Vitamin E



VITAMIN E
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Hamed

Vitamin E:

Conclusion

- Vitamin E has been used to protect against a variety of dermatologic conditions
- Research results have varied just as widely as the range of diseases treated
- The most promising reason for research into the dermatologic use of vitamin E appears to be its antioxidant activity
- This antioxidant potency can be increased through combination with other antioxidants

Coenzyme Q₁₀ or Ubiquinone:

- Is a naturally occurring nutrients
- Fish and shelfish
- It is a fat-soluble compound found in all cells as part of the electron transfer chain responsible for energy production
- It is also an antioxidants
- The “Q” = member in quinone family
- The “10” identifies the number of isoprenoid units on its side chain

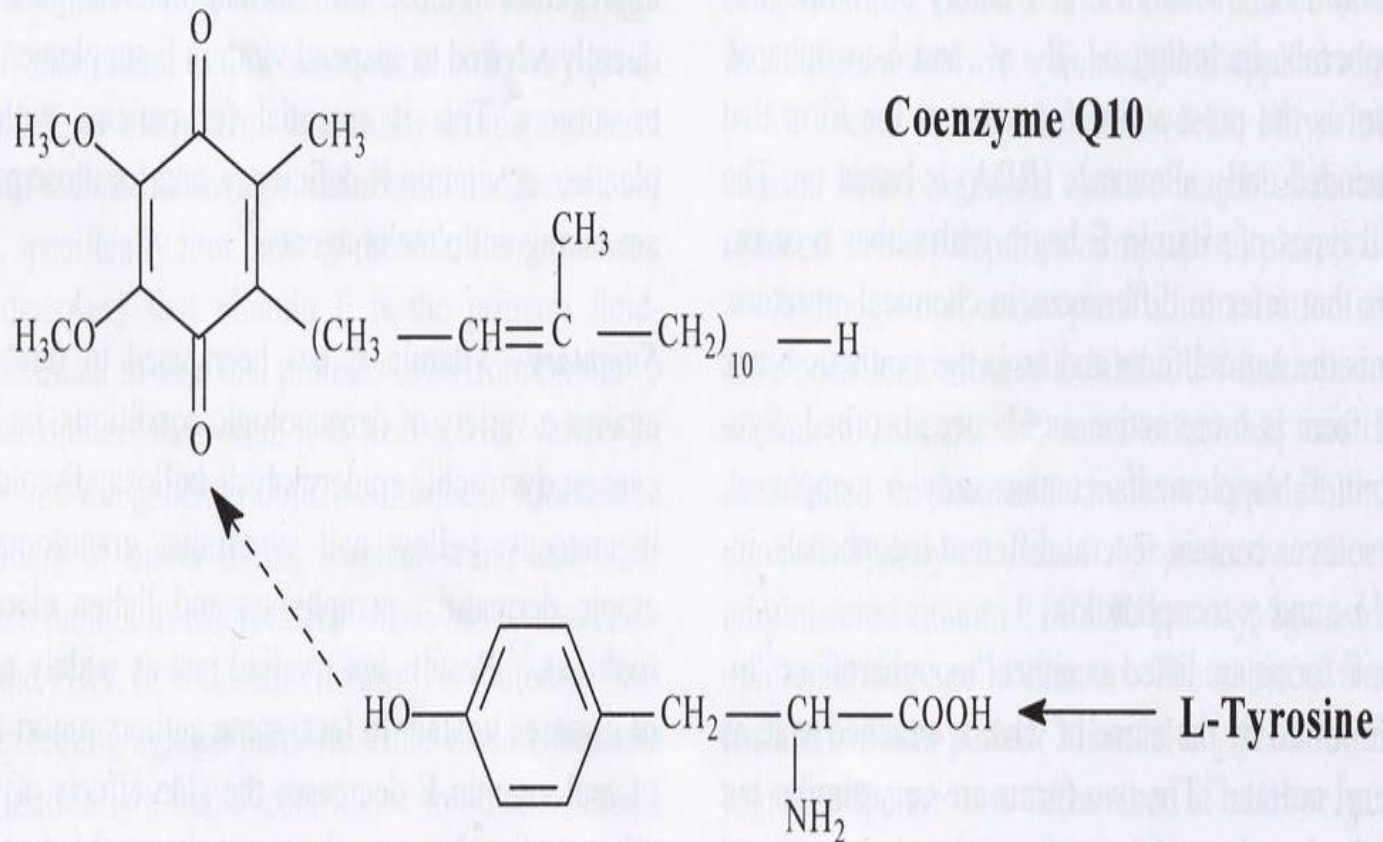


Figure 15-1.

The chemical structure of coenzyme Q_{10} . It has 10 isoprenoid units side units and requires tyrosine for biosynthesis.

Coenzyme Q₁₀ or Ubiquinone:

- Age-related decline of CoQ₁₀ levels in animals and humans
- Hoppe et al. demonstrated that CoQ10 penetrated into the viable layers of the skin and significantly suppressed the expression of collagenase in human dermal fibroblasts following UVA irradiation (*Hoppe et al.: Coenzyme Q10, a cutaneous antioxidant and energizer. Biofactors 9: 371, 1999*)
- There is a need for more research to examine the long-term preventive effects of these products to see if they are truly able to prevent signs of aging seen in the skin



Water (Aqua) ⓘ, Aloe Barbadensis Leaf Juice* ⓘ, Glycerin ⓘ, Bidens Pilosa Extract ⓘ, Elaeis Guineensis (Palm) Oil ⓘ, Gossypium Herbaceum (Cotton) Seed Oil ⓘ, Linum Usitatissimum (Linseed) Seed Oil ⓘ, Tocopherol (Soy)] ⓘ, Xanthan Gum ⓘ, Soy Lecithin ⓘ, Ubiquinone (Coq10) ⓘ, Persea Gratissima (Avocado) Oil ⓘ, Prunus Amygdalus Dulcis (Sweet Almond) Oil ⓘ, Triticum Vulgare (Wheat) Germ Oil ⓘ, Sodium Hyaluronate (Hyaluronic Acid) ⓘ, L-Carnosine ⓘ, Benzyl Alcohol ⓘ, Phenoxyethanol ⓘ, Natural Aroma, Natural Hinokitiol, Camellia Sinensis (Green Tea) Leaf Extract ⓘ

Coenzyme Q₁₀ or Ubiquinone:

Side effects

- Oral Q₁₀ supplementation is associated with a caffeine-like side effect and may cause a nervousness
- It is recommended that CoQ₁₀ not to be taken at night
- No side effects have been reported with topical application

Water-Soluble Antioxidants:

Vitamin C

- Topical vitamin C has been used as a topical antioxidant to:
 - Prevent sun damage (*Darr et al.: Topical vitamin C protects porcine skin from ultraviolet radiation-induced damage. Br J Dermatol, 127: 247, 1992*)
 - ameliorate melasma (*Kameyama et al.: Inhibitory effect of magnesium L-ascorbyl-2-phosphate (VC-PMG) on melanogenesis in vitro and in vivo. J Am Acad Dermatol, 34: 29, 1996*)
 - Ameliorate striae alba (*Ash et al.: Comparison of topical therapy for striae alba (20% glycolic acid/0.05% tretinoin versus 20% glycolic acid/10% L-ascorbic acid). Dermatol Surg, 24: 849, 1998*)
 - To treat postoperative erythema in laser patients (*Alster et al.: Effect of topical vitamin C on postoperative carbon dioxide laser resurfacing erythema. Dermatol Surg, 24: 31, 1998*)
- Topical vitamin C was first studied as a photoprotectant by using a porcine skin model (*Darr et al.: Topical vitamin C protects porcine skin from ultraviolet radiation-induced damage. Br J Dermatol, 127: 247, 1992*)

Water-Soluble Antioxidants: Vitamin C

- Oral supplementation with vitamin C produces only a limited increase in skin concentration
- Because even with ingestion of massive doses, the absorption of vitamin C is limited by active transport mechanisms in the gut

Water-Soluble Antioxidants:

Vitamin C

- Topically applied vitamin C has been shown to enhance collagen production in human skin
- Skin biopsies taken from postmenopausal women who applied 5% L-ascorbic acid to one forearm and vehicle to the other showed an increase in mRNA levels of collagen I and III

(Nusgens et al.: Topically applied vitamin C enhances the mRNA level of collagens I and III, their processing enzymes and tissue inhibitor of matrix metalloproteinase 1 in the human dermis. J Invest Dermatol. 2001 Jun;116(6):853-9)

Water-Soluble Antioxidants:

Vitamin C

- Sunscreens even when applied properly block only 55% of free radicals produced by UVA exposure *(Haywood et al.: Sunscreens inadequately protect against ultraviolet-A-induced free radicals in skin: implications for skin aging and melanoma?. J Invest Dermatol. 2003 Oct;121(4):862-8)*
- These data suggest that in order to optimize UV protection, sunscreens should be used in conjunction with topical antioxidants

- The purpose of this study was to see if a combination of topical vitamins C and E is better for UV protection to skin than an equivalent concentration of topical vitamin C or E alone.
- Vitamin C and E were applied alone or in combination for 4 days to pig skin and then irradiated with a solar simulator.
- Either 15% L-ascorbic acid or 1% alpha-tocopherol alone also was protective but the combination was superior

Water-Soluble Antioxidants:

Vitamin C

- Histological examination revealed that animals treated with topical ascorbic acid exhibited fewer sunburn cells than did those animals treated with vehicle alone when exposed to both UVA and UVB irradiation
- Sunburn cells are basal keratinocytes undergoing programmed cell death as a result of irreparable DNA damage and represent a method to quantifying the damaging effects of UV irradiation

Water-Soluble Antioxidants:

Vitamin C

- In addition, they observed a decrease in erythema in areas treated with vitamin C
- Darr et al. found that topical vitamin C combined with either a UVA or UVB sunscreen improved sun-protection as compared to sunscreen alone (*Darr et al.: Effectiveness of antioxidants (vitamin C and E) with and without sunscreens as topical photoprotectants. Acta Dermatol Venereol, 766: 264, 1996*)
- Vitamin C also reduced oxidized vitamin E back into its active form so it amplify the antioxidant capabilities of vitamin E (*Chan AC: Partners in defense, vitamin E and vitamin C. Can J Physiol Pharmacol, 71: 725, 1993*)

- Vitamin C may help in lightening hyperpigmentation
- Magnesium-L-ascorbyl-2-phosphate suppressed melanin formation by tyrosinase and melanoma cells
- Topically applied 10% magnesium-L-ascorbyl-2-phosphate cream caused a significant lightening of melasma and lentigenes when applied to the face

(Kameyama et al.: Inhibitory effect of magnesium L-ascorbyl-2-phosphate (VC-PMG) on melanogenesis in vitro and in vivo. J Am Acad Dermatol. 1996 Jan;34(1):29-33)

Water-Soluble Antioxidants:

Vitamin C

- There are no studies that demonstrate that ingestion of oral vitamin C increases the levels of vitamin C in the skin

- Unfortunately

- Stability issues

Most preparations of topical vitamin C do not come in airtight containers that are protected from UV radiation

- many of the currently available topical preparations are unable to penetrate the stratum corneum (Since AA is hydrophilic)

So yes Vitamin C has many biochemical & Physiological cutaneous effects

Does it have a
biochemical &
physiological
cutaneous function?

Will it Get to the
Skin?

Has it Shown to be
Stable?

Has it Shown to be
Effective?

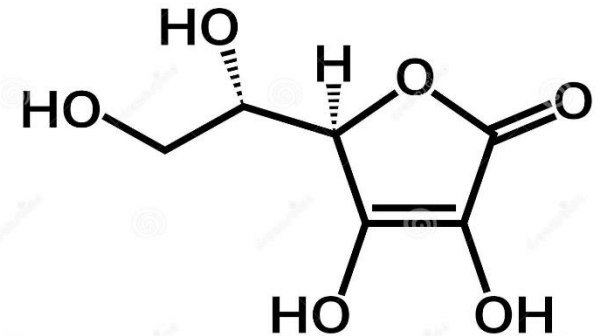
**Questions we need to ask about
Vitamins in Cosmetics**

Will Ascorbic Acid Get to the Skin?

■ Mwt: 176 g/mol

Hydrophilic→

Ascorbic Acid has poor skin penetration potential

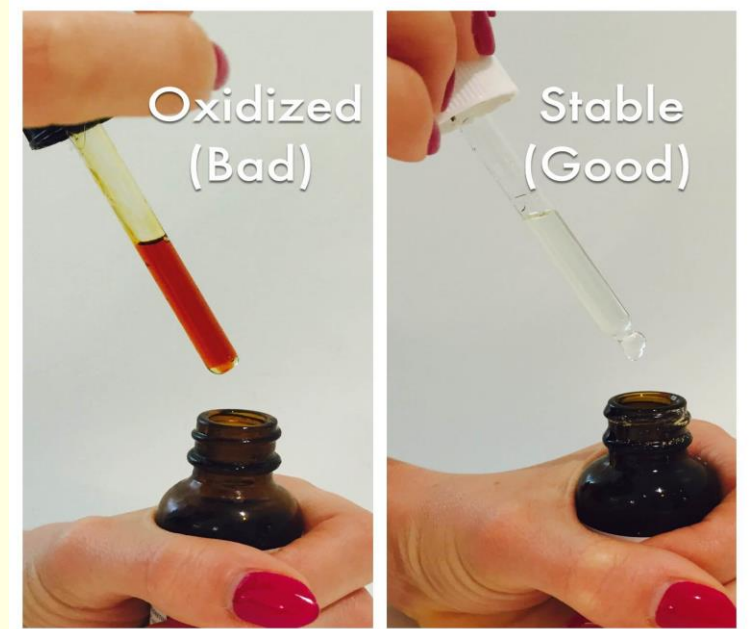


ascorbic acid

Has it Shown to be Stable?



- It is easily degraded in aqueous medium, at high pH, in the presence of oxygen and metal ions.
- This process is usually accompanied by a color change in the formulations, which become gradually more yellowish



<https://skinscience.md/evidence-proof-why-we-are-picky-about-retail/>

So Ascorbic Acid has two challenges when used topically?

- Hydrophilic so it is difficult to penetrate the stratum corneum
- Easily oxidized and degraded → Reduced stability in the formulation

How to enhance penetration & stability of Ascorbic Acid?

- Controlling the presence of oxygen during formulation and storage and the use of oxygen impermeable packaging
- Low pH
- Reduction of water content through the use of anhydrous/ non-aqueous formulations.
- The addition of antioxidants and anti-chelating agents also prevents the degradation of the Vit C → ferulic acid and sodium metabisulfite have shown good results
- The development of micro and nanoencapsulated delivery systems.
- Utilization of more stable derivatives of Vit C

Caritá AC, Fonseca-Santos B, Shultz JD, Michniak-Kohn B, Chorilli M, Leonardi GR. Vitamin C: One compound, several uses. Advances for delivery, efficiency and stability. Nanomedicine. 2020 Feb;24:102117.



INGREDIENTS

2021561 9 - INGREDIENTS: AQUA/WATER/EAU, ASCORBIC ACID, GLYCERIN, DIMETHICONE, CETEARYL ETHYLHEXANOATE, ALCOHOL DENAT., SODIUM HYDROXIDE, AMMONIUM POLYACRYLOYLDIMETHYL TAURATE, PANTHENOL, CERAMIDE NP, CERAMIDE AP, CERAMIDE EOP, CARBOMER, CETEARYL ALCOHOL, BEHENTRIMONIUM METHOSULFATE, SODIUM HYALURONATE, SODIUM LAUROYL LACTYLATE, CHOLESTEROL, PHENOXYETHANOL, TOCOPHERYL ACETATE, DISODIUM EDTA, ISOPROPYL MYRISTATE, CAPRYLYL GLYCOL, XANTHAN GUM, PHYTOSPHINGOSINE, ETHYLHEXYLGLYCERIN [CODE F.I.L. D231277/1]

WATER-BASED SERUMS

C/ E /FERULIC SERUM



Look for vitamin C loaded delivery system



Water- Free (anhydrous) Products

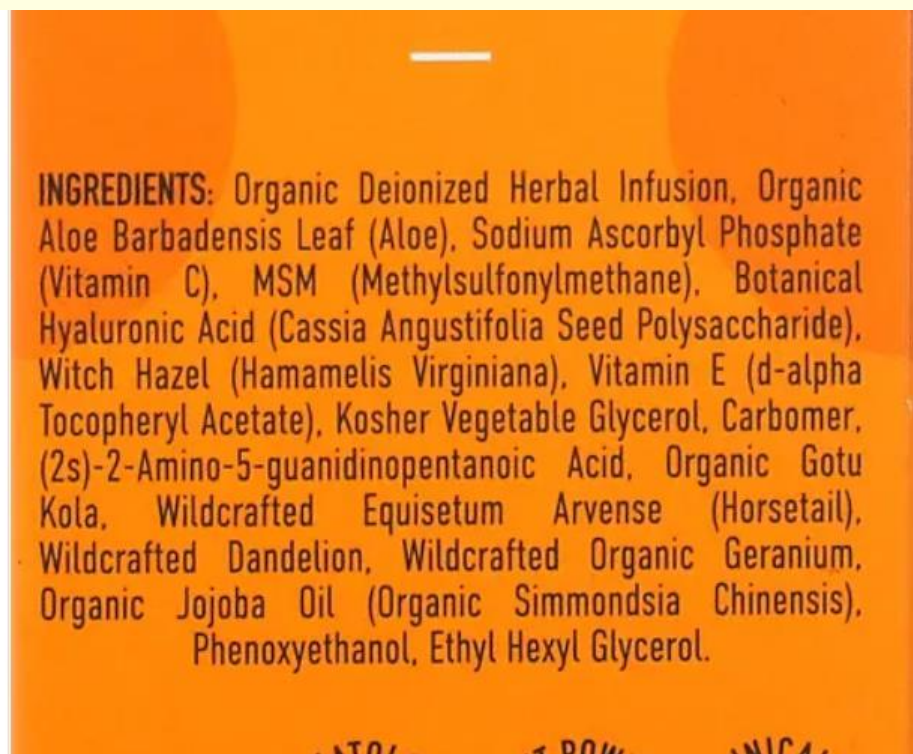
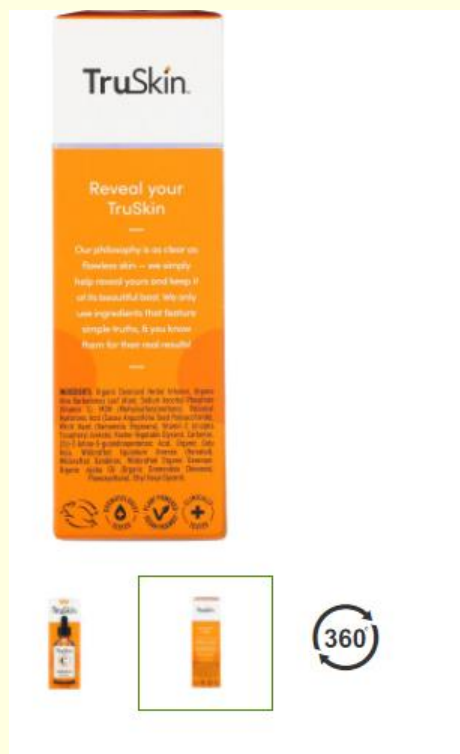


Dimethicone, Ascorbic Acid, Polysilicone-11, Peg-10 Dimethicone.

The ascorbic acid isn't dissolved yet, and they usually don't have any pH adjusters in them
tiny, low pH pool of very concentrated ascorbic acid on your skin

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What about derivatives of Ascorbic Acid?



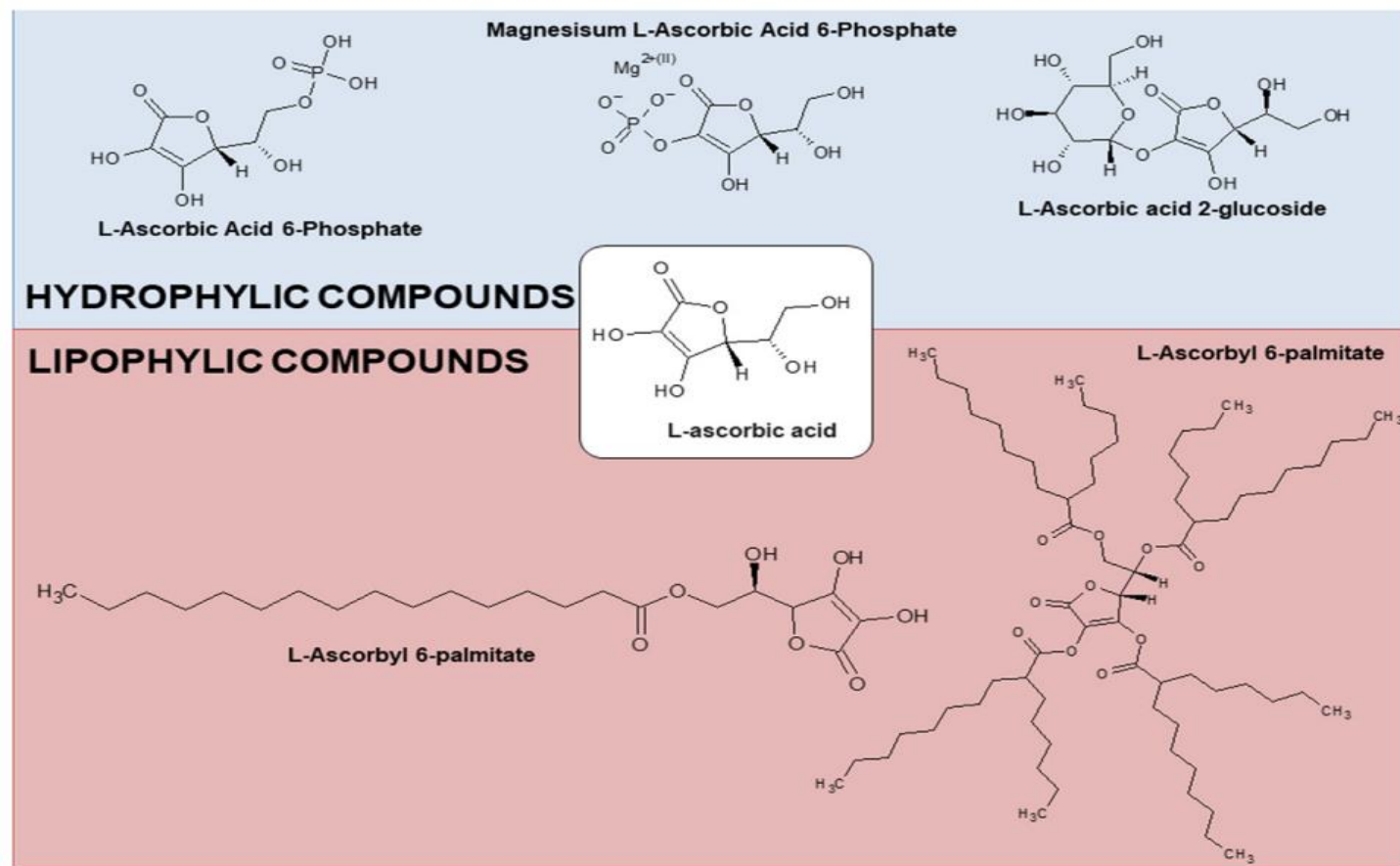


Figure 2. L-ascorbic acid molecule and its derivatives.

Carità AC, Fonseca-Santos B, Shultz JD, Michniak-Kohn B, Chorilli M, Leonardi GR. Vitamin C: One compound, several uses. Advances for delivery, efficiency and stability. Nanomedicine. 2020 Feb;24:102117.

Sodium Ascorbyl Phosphate

- Ascorbyl 2-phosphates, which are formulated with sodium (SAP) or magnesium (MAP) salts:
 - hydrophilic in character
 - More stable than Ascorbic Acid
 - do not have direct antioxidant activity and must be converted, in vivo, by enzymatic reaction into L-ascorbic acid.



Ascorbic acid 2-glucoside (AA-2G)

- Hydrophilic character
- increased stability of the molecule
- When applied topically, AA-2G is hydrolyzed by a cellular α -glucosylase and is converted to L-ascorbic acid.
- Formulation of AA-2G in a microemulsion indicates that the system has higher permeability when compared to commercial emulsions.



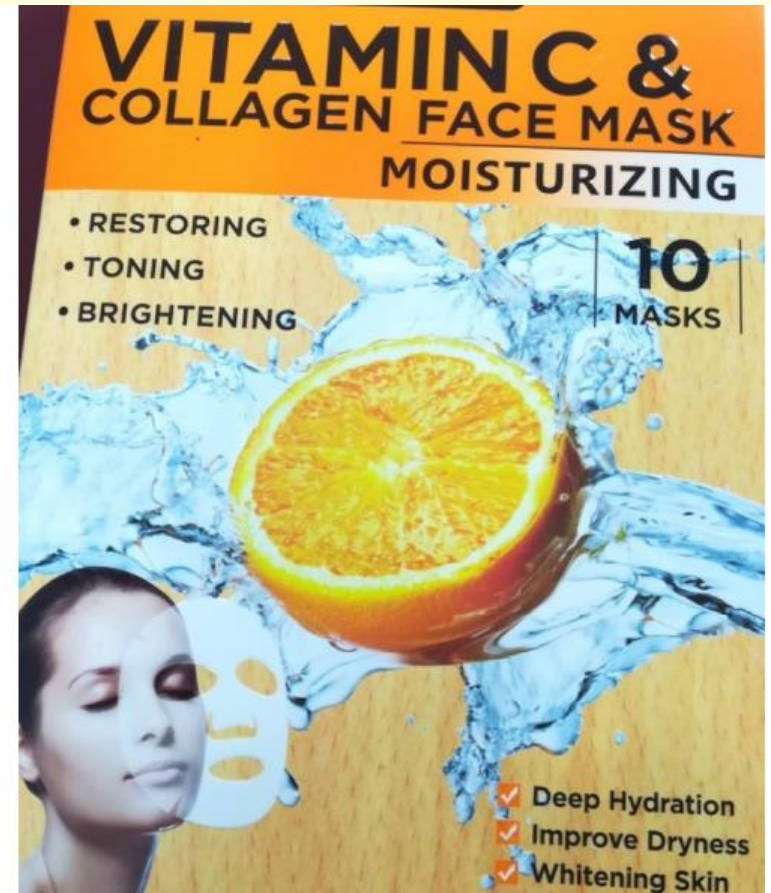
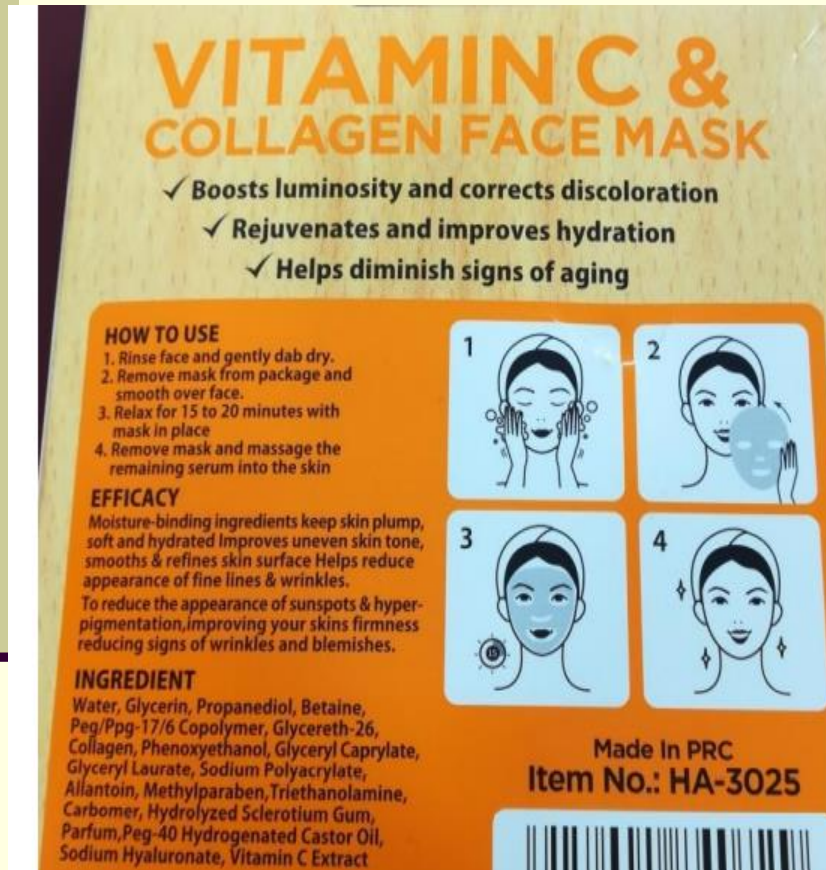
Ascorbic Acid Derivatives?

- Formulation challenges of Ascorbic Acid →
 - Stability
 - Permeability
 - Antioxidant properties is lower than AA itself
 - Cost (delivery system, concentration, low oxygen level during manufacturing..etc)
 - Questionable efficacy and insufficient scientific evidence (in vitro/ex vivo/animal studies)

Take home message

- Oral supplementation with vitamin C produces only a limited increase in skin concentration
- Ascorbic acid is a potent antioxidant that can neutralize Free Radicals
- Free Radicals are known to be involved in photoaging, carcinogenesis, and inflammation
- A small number of patients may experience minimal discomfort (stinging and mild irritation) from the topically applied formulations
- Major disadvantages of the various formulations include:
 - High cost
 - Questionable efficacy
- When it might help? Smokers, Photoprotectants (with other antioxidants like vitamin E)

Make sure it is not a claim ingredient



Take home message

- **LAYERING**
- As close as you can to bare skin since it's not great at absorbing into skin.
- Use it as one of the first steps of your routine after cleansing.
- be careful with other irritating ingredients like hydroxy acid exfoliants and retinoids. You can use them together, but if you're not really careful you'll probably burn your face off.
- You can use vitamin C morning or night. In the morning you'll probably get more of the sun protection benefits,
- Vitamin C is NOT photosensitizing. It actually decreases UV sensitivity!

The Fat- and Water- Soluble Antioxidants: α - Lipoic Acid

- Synthesized in the mitochondria of plants and animals, including human
- It is a good candidate for topical application:
 - A small, stable molecule
 - A potent antioxidant
 - Soluble in both aqueous and lipid environment
- A split face study was done on 33 women. Topical application twice daily of 5% lipoic acid cream for 12 weeks decreased skin roughness by 50.8% when compared with the placebo. In addition, reduction in lentigenes and fine wrinkles were noted (*Beitner H: Randomized, placebo-controlled, double blind study on the clinical efficacy o a cream containing 5% alpha-lipoic acid related to photoaging of facial skin. Br J Dermatol, 149: 841-849, 2003*)

Skin Aging Part III

Saja Hamed, Ph.D

-
- Botox
 - Dermal Fillers
 - Botox Like cream

Dermatologic Use of Botulinum Toxin

- Botulinum toxin is the product of *Clostridium botulinum*.
- The bacteria are found in soil and marine sediments; the spores can be detected on fruits and vegetables and in seafood.
- The growing bacteria produce the neurotoxin botulinum toxin, which is often referred to as the most poisonous substance known to mankind.
- The neurotoxin inhibits the release of acetylcholine and results in the flaccid paralysis of the affected muscles.

Botulism FREE

Jeremy Sobel ✉

Clinical Infectious Diseases, Volume 41, Issue 8, 15 October 2005, Pages 1167–1173,
<https://doi.org/10.1086/444507>

Published: 15 October 2005 **Article history** ▼



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Cite



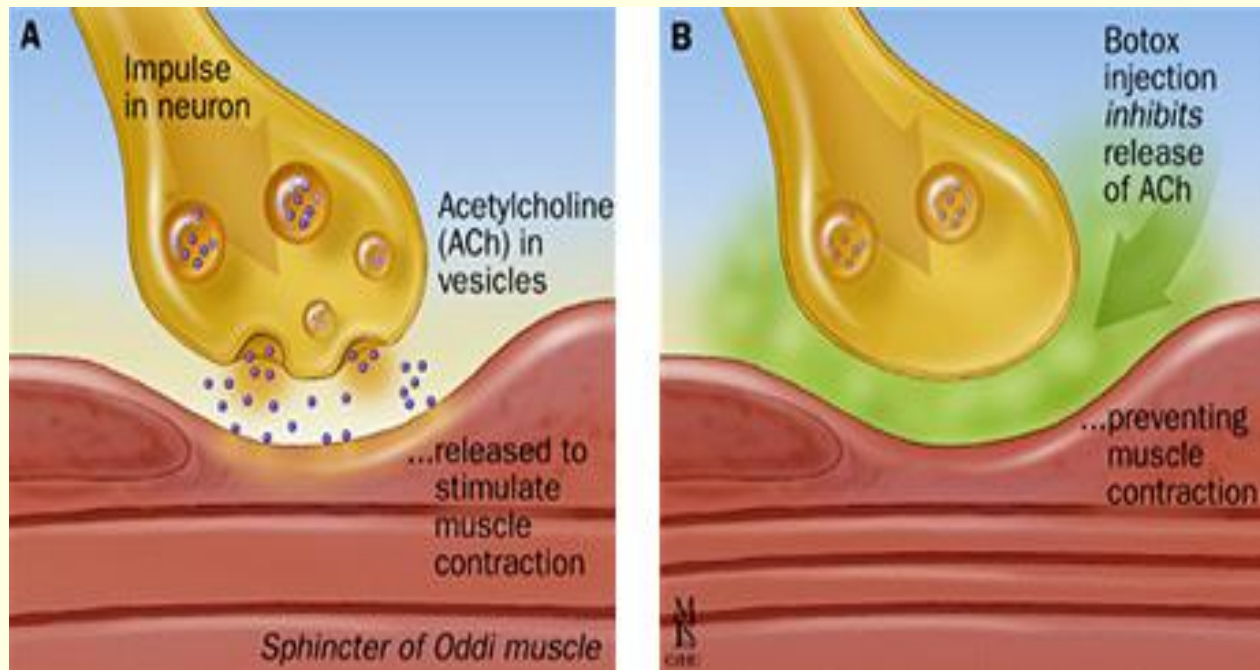
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Abstract

Botulism is a rare disease with 4 naturally occurring syndromes: foodborne botulism is caused by ingestion of foods contaminated with botulinum toxin, wound botulism is caused by *Clostridium botulinum* colonization of a wound and in situ toxin production, infant botulism is caused by intestinal colonization and toxin production, and adult intestinal toxemia botulism is an even rarer form of intestinal colonization and toxin production in adults. Inhalational botulism could result from aerosolization of botulinum toxin, and iatrogenic botulism can result from injection of toxin. All forms of botulism produce the same distinct clinical syndrome of symmetrical cranial nerve palsies followed by descending, symmetric flaccid paralysis of voluntary muscles, which may progress to respiratory compromise and death. The mainstays of therapy are meticulous intensive care (including mechanical ventilation, when necessary) and timely treatment with antitoxin.



Dermatologic Use of Botulinum Toxin

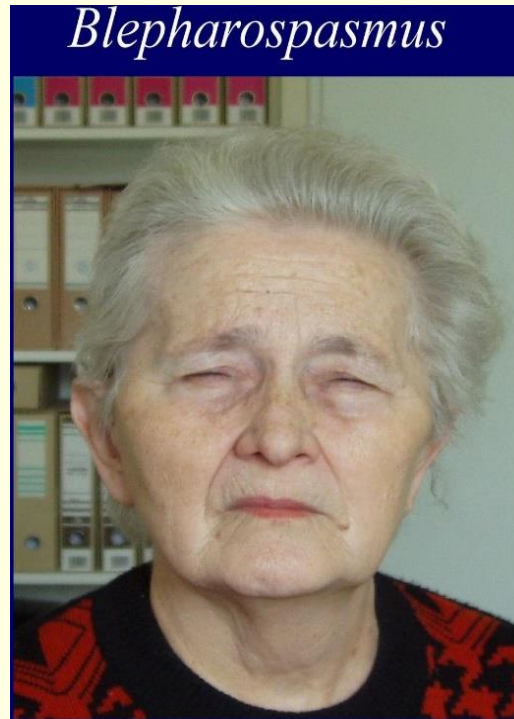
- Botulinum toxin (Botox, onabotulinumtoxinA) is a material that has been known for over a century and used for medical purposes for more than 50 years.
- Its initial uses were for lazy eye, blepharospasm (inability to move the eyelids in certain ways), and wry neck (cervical dystonia).
- In 2002, it was approved for improving and relaxing frown lines in the area (the glabella) between the eyes on the forehead.
- In 2004, Botox was approved for excess sweating (hyperhidrosis)
- and in 2010, Botox was approved for the treatment of migraine headaches.

http://www.emedicinehealth.com/botox_injections/article_em.htm

TABLE 1. Comparison of botulinum toxin preparations⁵

	ONABOTULINUMTOXINA	ABOBOTULINUMTOXINA	CBTX-A	BONTA
COMMERCIAL NAMES	Botox [®] , Botox Cosmetic [®] , Vistabel [®] , Vistabex [®]	Dysport [®] , Reloxin [®] , Azzalure [®]	Prosigne [®] , Lantox [®]	Neuronox [®]
COMPANY	Allergan Inc.	Medicis Pharmaceutical Corp.	Lanzhou Institute of Biological Products, China	Medy-Tox Inc., South Korea
TYPE	A	A	A	A
COUNTRIES	Worldwide, including United States and Canada	> 65 countries, including United States and Canada	> 10 countries including China, not in the United States or Canada	South Korea, India, South America, not in the United States or Canada
ACTIVE SUBSTANCE (MOLECULAR WEIGHT)	BTX-A complex (900 kD)	BTX-A complex (500–900 kD)	BTX-A (900 kD)	BTX-A (940 kD)
STRENGTH (BTX-A: PRODUCT)	1:1	1:2–1:4		
INDICATIONS	Blepharospasm, cervical dystonia, glabellar lines, hyperhidrosis, chronic migraine, urinary incontinence, etc.	Blepharospasm, cervical dystonia, glabellar lines	Blepharospasm, cervical dystonia, glabellar lines, hyperhidrosis	Blepharospasm
FDA APPROVAL	Botox[®] : cervical dystonia, severe primary axillary hyperhidrosis, blepharospasm, neurogenic detrusor overactivity (urinary incontinence), chronic migraine, upper limb spasticity Botox Cosmetic[®] : glabellar lines (moderate to severe)	Cervical dystonia, glabellar lines (moderate to severe)	None	None

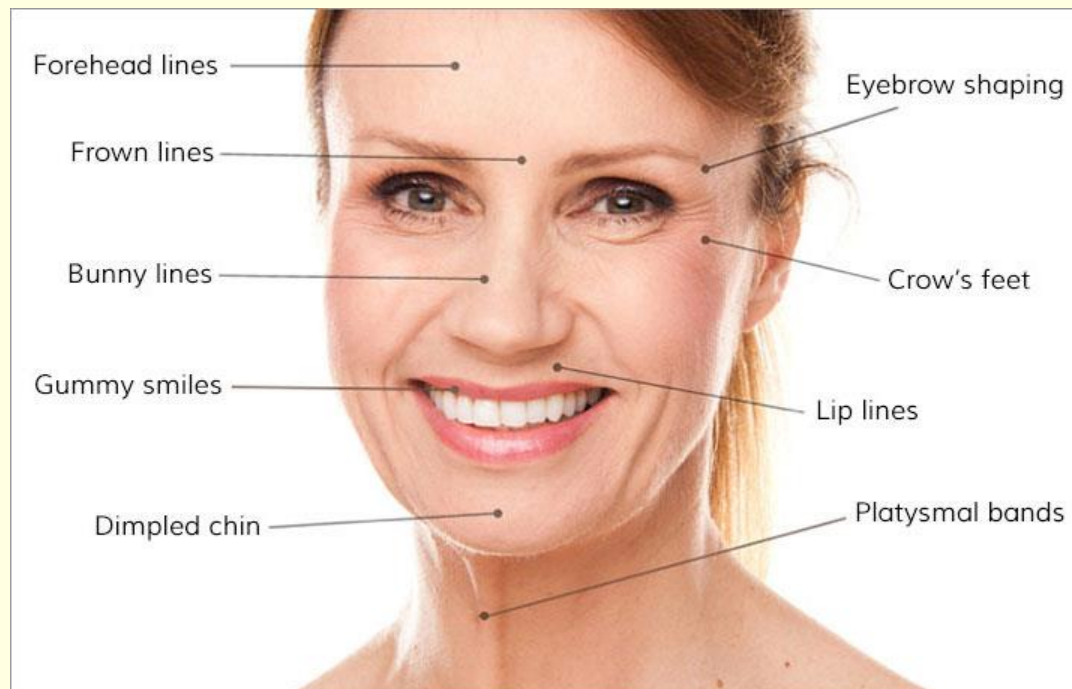
Dermatologic Use of Botulinum Toxin



Dermatologic Use of Botulinum Toxin

- Seven serologically distinct types of botulinum toxin exist: A, B, C1, D, E, F, and G.
- Botulinum toxin type A (BOTOX®; Allergan) was the first commercially available type in the United States.
- Botulinum toxin is used in dermatology for the treatment of facial wrinkles caused by muscular contractions. These wrinkles are commonly referred to as crow's feet, frown lines, and bunny lines
- Botulinum toxin is not an appropriate treatment for wrinkles caused by solar exposure or other degenerative processes of the dermal tissues.

Dermatologic Use of Botulinum Toxin



MINOR'S STARCH-IODINE TEST

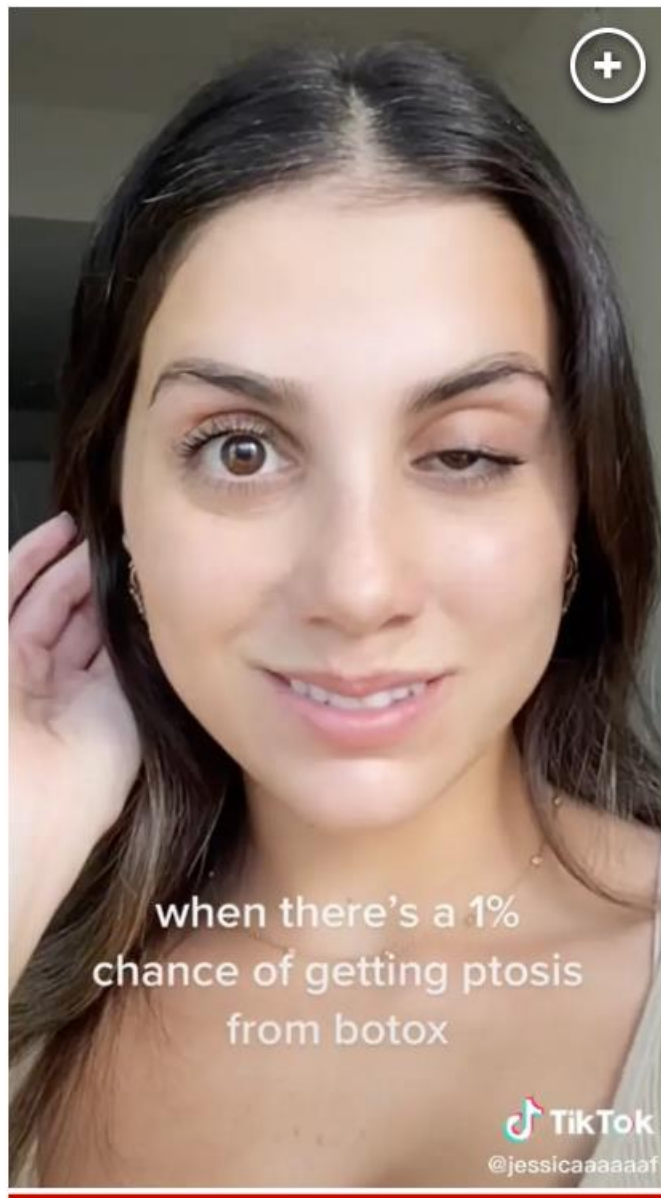


The starch-iodine combination turns a dark blue color wherever there is excess sweat



Dermatologic Use of Botulinum Toxin

- As with any injection, pain, mild bruising, and infection can occur.
- Diffusion of botulinum toxin can lead to weakness of the muscles adjacent to the injection site. Therefore, advising the patient not to massage the injected areas is important.
- Delayed eyelid closure, a decreased blink response, and excessive tearing can occur when injections into the orbicularis oculi muscle in the temporal region are too close to the eyelid.
- there may be a drooping lid
- Asymmetry of the face can occur because of differences in injection techniques or doses between the 2 sides of the face.



There's just a 1 percent chance of getting ptosis from Botox and Jessica was horrified that this happened to her.

- Hooded or drooping eyes.
- Lack of facial expression when talking, smiling, or feeling strong emotions. This is that classic “frozen face” that so many celebrities seem to wear

...But Too Much, Too Fast Will Age You

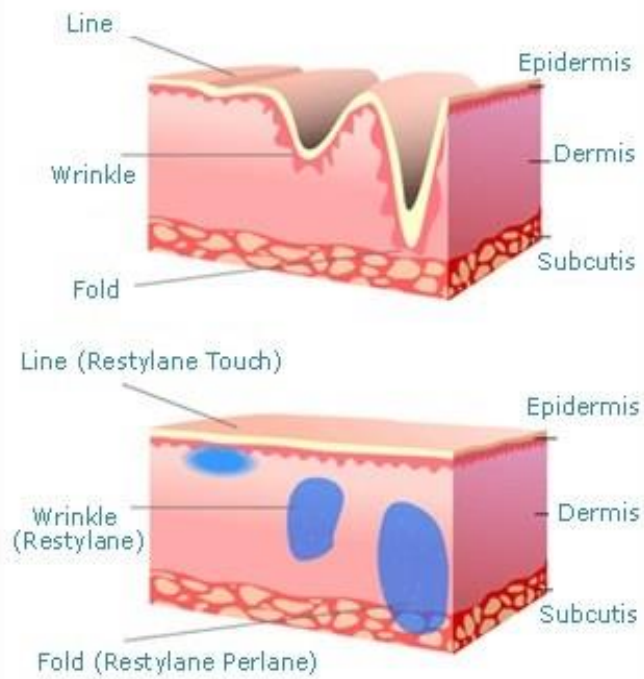
Botox only lasts three to six months—and yet what's less commonly discussed is this: Facial muscles naturally weaken over time and going overboard in a certain area could have unwanted consequences. “If you do too much Botox on your forehead for many, many years, the muscles will get weaker and flatter,” cautions Wexler, adding that the skin can also appear thinner and looser. Moreover, as your muscles become weaker, they can start to recruit surrounding muscles when you make facial expressions. “If one stops using their forehead muscles, they may start squinting using their nose and have wrinkles along the side of their nose,” she explains. Translation: You need even more

Dermal fillers

- Injectable **filler** (injectable cosmetic **filler**, injectable facial **filler**) is a soft tissue **filler** injected into the skin to help fill in facial wrinkles, restoring a smoother appearance. Most of these wrinkle **fillers** are temporary because they are eventually absorbed by the body
- Since its approval in 1981, bovine collagen had been the only US Food and Drug Administration (FDA)–approved dermal filler more than a decade. Then more fillers were approved (HA containing fillers)

Restylane

How It Works



Dermal Fillers

■ Caution

- In May 2015, the FDA issued a warning to healthcare providers and the public about serious complications that can occur if dermal fillers are inadvertently injected into blood vessels in the face.
- The complications could possibly include vision impairment, blindness, stroke, and damage and/or necrosis of the skin and underlying facial structures.
- Caution should be used to ensure proper placement of the filler material, and patients should be informed about the potential adverse effects and how to recognize symptoms of impending serious complications.

Soft-tissue Filler–associated Blindness: A Systematic Review of Case Reports and Case Series

Vandana Chatrath, MSc*†
Pooja S. Banerjee, MPharm‡
Greg J. Goodman, MD, FACDS§
Eqram Rahman, MBBS, MS,
PhD¶

Background: With the increase in the use of soft-tissue fillers worldwide, there has been a rise in the serious adverse events such as vascular compromise and blindness. This article aims to review the role of fillers in causing blindness and the association between hyaluronic acid (HA) filler and blindness.

Methods: The Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines were used to report this review.

Results: A total of 190 cases of blindness due to soft-tissue fillers were identified, of which 90 (47%) cases were attributed to autologous fat alone, and 53 (28%) cases were caused by HA. The rest of the cases were attributed to collagen, calcium hydroxylapatite, and other fillers.

Conclusions: Autologous fat was the most common filler associated with blindness despite HA fillers being the most commonly used across the globe. However, the blindness caused by other soft-tissue fillers like collagen and calcium hydroxylapatite was represented. It was also evident through the review that the treatment of HA-related blindness was likely to have better outcomes compared with other fillers due to hyaluronidase use. (*Plast Reconstr Surg Glob Open* 2019;7:e2173; doi: 10.1097/GOX.0000000000002173; Published online 2 April 2019.)



Many skincare products use peptides to treat wrinkles. But what are peptides? And do they actually make you look younger?

Introduction

- you've probably heard at least a couple of companies make claims about the miraculous benefits of peptides in their products.
- Those claims range from the ability to plump lips and lift sagging skin, to getting rid of dark circles and puffy eyes.

http://www.paulaschoice.com/expert-advice/anti-aging/_/peptides-for-skin



palmitoyl
pentapeptide-3.
Price: \$18.00



oligopeptide
palmitoyl. Price:
\$135

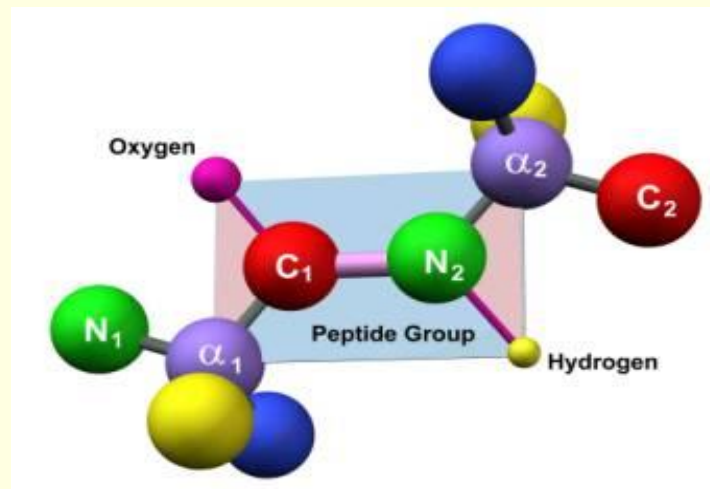


argireline
(acetyl
hexapeptide-3)



What Are Peptides?

- Peptides are molecules made up of two or more amino acids linked together by the same peptide bonds found in proteins.



What Are Peptides?

- Peptides may be natural or synthetic. Most peptides used in cosmetics are synthetic because lab engineering these ingredients gives chemists greater control on their stability and effectiveness in skin-care products.
- Peptides break down easily, and it is important they are only used in products with ingredients that do not cause them to break down.

What Are Peptides?

- The major obstacles to the use of synthetic peptides in cosmetic products are related to the question of:
- Penetration and diffusion,
- long-term stability

Penetration and diffusion

- As peptides and proteins:
 - contain many amide bonds
 - and because of their large molecular size
 - And they often charged at physiological pH
 - They are hydrophilic
- → they have low diffusivity in the skin

Type of Peptide	Name of Peptides
Matricins peptides	Carnosine, Copper tripeptide, Trifluoroacetyl-tripeptide-2, Tripeptide-10 citrulline, Acetyl tetrapeptide-5, Acetyl tetrapeptide-9, Acetyl tetrapeptide-11, Tetrapeptide PKEK, Tetrapeptide-21, Hexapeptide, Hexapeptide-11, Palmitoyl pentapeptide-4, Palmitoyl tripeptide-3/5, Palmitoyl tetrapeptide-7, Palmitoyl hexapeptide-12, Palmitoyl oligopeptide, Palmitoyl tripeptide-1, Pentamide-6
Carrier peptides	Copper tripeptide, Manganese tripeptide-1
Peptide mimetics or neurotransmitter-inhibiting peptides	Acetyl hexapeptide-3, Pentapeptide-18, Pentapeptide-3, Tripeptide-3
Enzyme inhibitor peptides	Soybean peptide, Silk fibroin peptide, Black rice oligopeptides
Structural protein digestion	Keratin peptide

Schagen, Silke Karin. "Topical Peptide Treatments with Effective Anti-Aging Results." Cosmetics 4 (2017): 16.

Carrier Peptides

- Copper peptides can be found in pricey product lines such as Neova or Osmotics as well as less expensive products like Neutrogena's Visibly Firm Night Cream.
- While the wound healing effects of copper peptide have been investigated and documented in many studies, much less research has been done so far on their cosmetic and anti-aging use.

Carrier Peptides

- **Caution:**
- **excessive use** of copper peptides can have an opposite effect by increasing the levels of free copper and/or by triggering excessive production of metalloproteinases.
- Free copper promotes free radical damage and collagen breakdown leading to accelerated skin aging. Metalloproteinases can digest collagen and elastin, weakening the skin and causing sag.
- **A sufficiently large study is needed to better quantify these risk.**

[Mutat Res.](#) 1999 Mar 8;424(1-2):23-36.

Oxidative DNA damage mediated by copper(II), iron(II) and nickel(II) fenton reactions: evidence for site-specific mechanisms in the formation of double-strand breaks, 8-hydroxydeoxyguanosine and putative intrastrand cross-links.

[Lloyd DR¹](#), [Phillips DH](#).

⊕ Author information

Abstract

The role of metal ion-DNA interactions in the Fenton reaction-mediated formation of putative intrastrand cross-links, 8-hydroxydeoxyguanosine (8-OHdG) and single- and double-strand breaks was investigated. Salmon sperm DNA and pBluescript K+ plasmid were incubated with hydrogen peroxide and either copper(II), iron(II), or nickel(II), which differ in both their affinity for DNA and in the spectrum of oxidative DNA damage they induce in Fenton reactions. EDTA was included in these incubations according to two different strategies; the first (strategy 1) in which DNA and metal ions were mixed prior to the addition of EDTA, the second (strategy 2) in which EDTA and metal ions were mixed prior to the addition of DNA. The formation of the putative intrastrand cross-links, monitored by 32P-postlabelling, was not affected by the addition of between 10 microM and 5 mM EDTA to the copper(II) Fenton reaction according to strategy 1. In contrast, the level of cross-links declined significantly upon inclusion of 20 microM EDTA and above when added according to strategy 2. Similarly, formation of these lesions declined in the iron(II) Fenton reaction more dramatically upon addition of 5 mM EDTA when added according to strategy 2 compared to strategy 1, while the yield of cross-links formed in the nickel(II) Fenton reaction declined equally with both strategies with up to 25 mM EDTA. The formation of single- and double-strand breaks was investigated in plasmid DNA by agarose gel electrophoresis and subsequent densitometry. The formation of linear DNA in the iron(II) Fenton reaction decreased dramatically upon inclusion of EDTA according to strategy 2, while no such decline was observed using strategy 1. In contrast, the formation of linear DNA in the copper(II) Fenton reaction decreased upon inclusion of EDTA according to both strategies. A decrease in the formation of open-circular DNA was also observed upon inclusion of EDTA according to both strategies; however this decrease occurred at a lower EDTA concentration in strategy 2 (100 microM) compared to strategy 1 (200 microM), and the level of open-circular DNA reached a lower level (8.5% compared to 24.2%). The nickel(II) Fenton reaction generated only open-circular DNA, and this was completely inhibited upon addition of 25 microM EDTA according to both strategies. There was less formation of 8-OHdG in the copper(II) and iron(II) Fenton reactions when EDTA was added according to strategy 2 than according to strategy 1. These results suggest that a site-specific mechanism is involved in the formation of double-strand breaks and, to a lesser extent, 8-OHdG and the putative intrastrand cross-links, while the formation of single-strand breaks is more likely to involve generation of hydroxyl radicals in solution.

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Neurotransmitter affecting peptides

- Some peptides might block transmission of signals from nerves to your facial muscles. In particular, a **neuropeptide** called **argireline** has been shown in **in vitro** to block the release of neurotransmitters from nerves.
- Neuropeptides are sold in products often called wrinkle-relax creams

Shop by Product

Treatments
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Eye Treatments
Serums
Exfoliators & Toners
Neck & Body

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Fine Lines & Wrinkles
Loss of Firmness
Hydration
Enlarged Pores
Redness
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Shop by Science

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Cold Plasma
Vitamin C Ester
DMAE
Alpha Lipoic Acid
Neuropeptides
Tocotrienols
Olive Polyphenols



Neuropeptides

Neuropeptides transform skin showing signs of advanced aging such as deep lines, wrinkles and crepiness. Elasticity and firmness are restored while aging skin is rapidly revived and infused with nourishing hydration.

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Neuropeptide Facial
Cleanser



\$48.00



Neuropeptide Firming
Moisturizer



\$280.00



Neuropeptide Facial
Conformer 1 oz



\$325.00



Neuropeptide Facial
Conformer 2oz



\$495.00

ACETYL HEXAPEPTIDE-8

(trade name Argireline and technically known as acetyl hexapeptide-3)

- A synthetically derived peptide that is being used in a wide range of skin-care and makeup products, especially those claiming to have a muscle-relaxing effect similar to Botox injection

ACETYL HEXAPEPTIDE-8

- The company selling acetyl hexapeptide-8, Centerchem, is based in Spain.
- According to their Web site, "Argireline works through a unique mechanism which relaxes facial tension leading to a reduction in superficial facial lines and wrinkles with **regular use**. Argireline has been shown to **moderate excessive catecholamines release**."
- If **acetyl hexapeptide-8** really worked to relax facial muscles, it would work **all over the face** (assuming you're using the products as directed).



Perricone Recommends

◀ BROWSE ▶

Neuropeptide Face Activator

A fast-acting toner formulated with liquid Neuropeptides to restore loss of elasticity and firmness. With Neuropeptides and DMAE.

4 fl oz / 118 mL

★★★★☆

This unique, powerful and effective serum delivers high concentrations of DMAE, combined with proprietary neuropeptides to instantly help tighten the appearance of the skin, smooth its texture and soften fine lines. It delivers the radiance and glow of youthful skin.

Paraben-free.

Item#	Product	Qty	Price
5507	Neuropeptide Face Activator In Stock	1 ▼	\$95.00
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Just Once ▼			



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KEY SCIENCES

APPLICATION

INGREDIENTS

New Q&A

REVIEWS

By none
from missouri

★ ★ ★ ★ ★ sure disappointed me

Comments about Perricone MD Neuropeptide Face Activator:
the price was extreme for no more good than it did. it had an bad odor and oily feeling and after using it for about a year I have seen no difference. however after using another different product I purchased at a local well known dept.store at a lesser price in one week I have seen a difference. sorry would not recommend your product. way way over priced

Was this a gift? No

BOTTOM LINE No, I would not recommend this to a friend

Was this review helpful? [Yes](#) / [No](#) - You may also [flag this review](#)

By Eman
from columbia, mo

(1 of 1 customers found this review helpful)

★ ★ ★ ★ ★ really works,

Comments about Perricone MD Neuropeptide Face Activator:
i had the face activator for a while and forgot about it. Im 54 and my skin is ok for my age, but it looked dull and tired due to the summer months, extensive travelling, and death in the family. I used the activator day and night for 3 days, and noticed a huge difference in tone, radiance and elasticity. Ive been using it for a month with face finishing moisturizer only and Im so happy with the results. will never be without it.

Was this a gift? No

BOTTOM LINE Yes, I would recommend this to a friend

Was this review helpful? [Yes](#) / [No](#) - You may also [flag this review](#)

By Sandra
from Great Falls, VA

(6 of 6 customers found this review helpful)

★ ★ ★ ★ ★ The most amazing toner EVER!!

VERIFIED

There are plenty of anecdotal stories of their efficacy but essentially no controlled published scientific data.

-
- It is prohibited to give drug claim for cosmetics:

Botox-like is a drug claim (not allowed)

Signal Peptides

- **PEPTIDES SIGNAL YOUR SKIN TO MAKE MORE COLLAGEN**
- When collagen breaks down, it forms specific peptides. These peptides act as a signal to tell your skin it was damaged and to make new collagen.
- The signal peptides mimic protein sequences from collagen and elastin structures. They thus stimulate the production of new collagen and elastin.

Signal Peptides

- Applying peptides directly to your skin is a way to trick your skin into thinking that it has lost collagen recently and needs to make more.
- The most popular signal peptide for cosmetic use is palmitoyl pentapeptide (Matrixyl).
- It is linked to palmitic acid in order to enhance delivery through the epidermis for action in the dermis.
- This pentapeptide was shown to stimulate dermal matrix production in fibroblast culture (**in vitro**)