

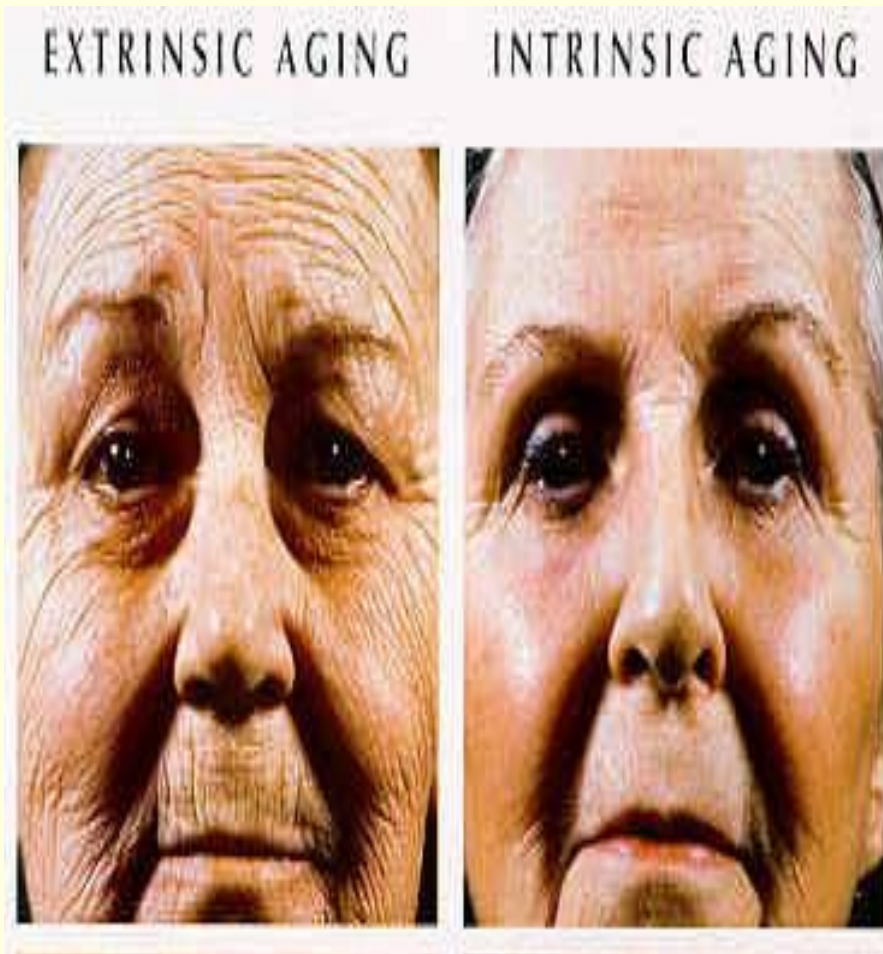
Skin Aging

And Its Modulation

Introduction

- Two main processes of skin aging: intrinsic and extrinsic
- Intrinsic aging: reflects the genetic background of an individual and results from the passage of time. It is inevitable
- Extrinsic aging (premature skin aging): caused by external factors such as smoking, poor nutrition, alcohol, and sun exposure. It is not inevitable

Two 70 year old women



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Intrinsic aging vs. Extrinsic aging:

Intrinsic aging:

- Smooth and unblemished
- Exaggerated expression lines but preservation of the normal geometric patterns of the skin
- Under microscope:
 - a. Epidermal atrophy
 - b. Fattening of the epidermal rete ridges
 - c. Dermal atrophy
 - d. Increase in the collagen III/ collagen I ratio

Intrinsic aging

- The superficial muscles on the face begin to shrink, which causes lines to appear.
- Typical facial wrinkles forming the areas where muscles contract to make facial expressions. These include “worry lines” spanning the forehead, laugh lines around the eyes and mouth, and crow’s feet radiating from the outside corners of the eyes

Intrinsic Aging

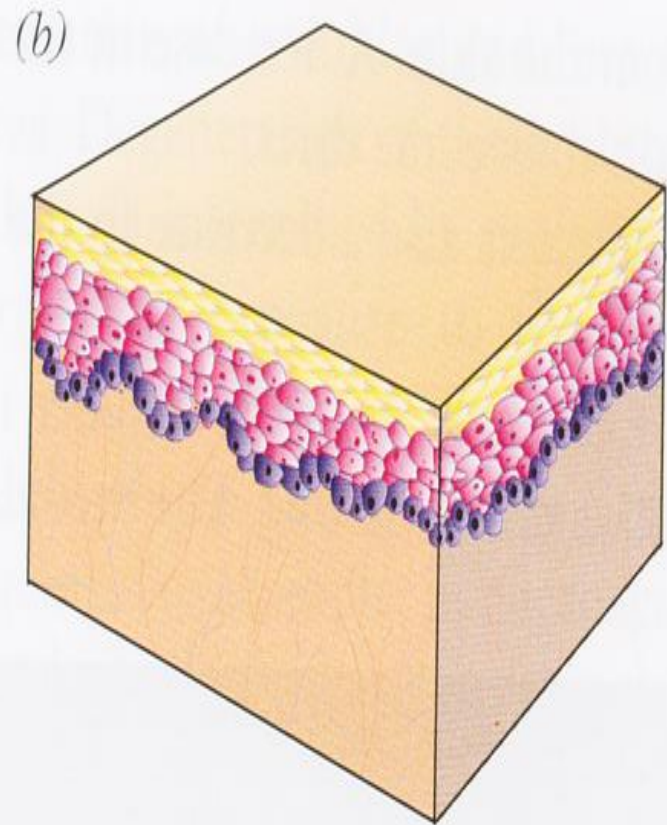
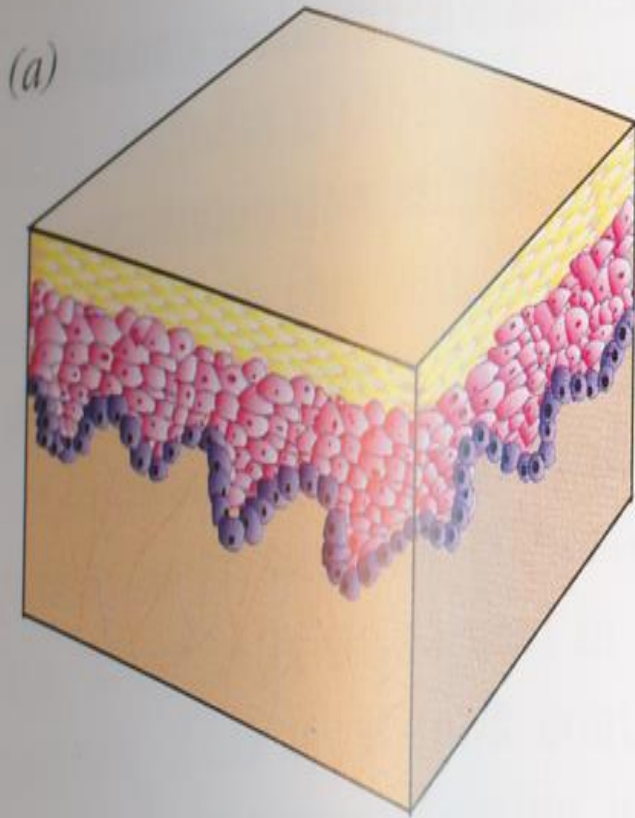
- The production of immune cells decrease overtime which contribute to the compromised wound healing process
- Gradual flattening of the wavy attachment between epidermis and dermis due to reduced production of keratinocytes → increase skin fragility and reduce nutrient transfer

Intrinsic Aging

- It affects the skin on the entire body, including the photoprotected areas in a similar manner
- Slow, continuous, and irreversible tissue degradation
- People of identical chronological age may appear to have younger or older looking skin due to different genetic make up

Intrinsic Aging

- Both the mortar and bricks of the skin are affected which leads to a reduction in the SC lipid content, damaged barrier functions, increased epidermal water loss and drier skin
- Changes in skin pigmentation and size of the sebaceous glands:
 - Decrease in melanocytes density → pale appearance which also related to decrease vascularity of the skin → more susceptible to sun damage because of less melanin
 - Number of sebaceous glands remain approx. the same throughout life but their size tends to increase with age → the skin pores may widen

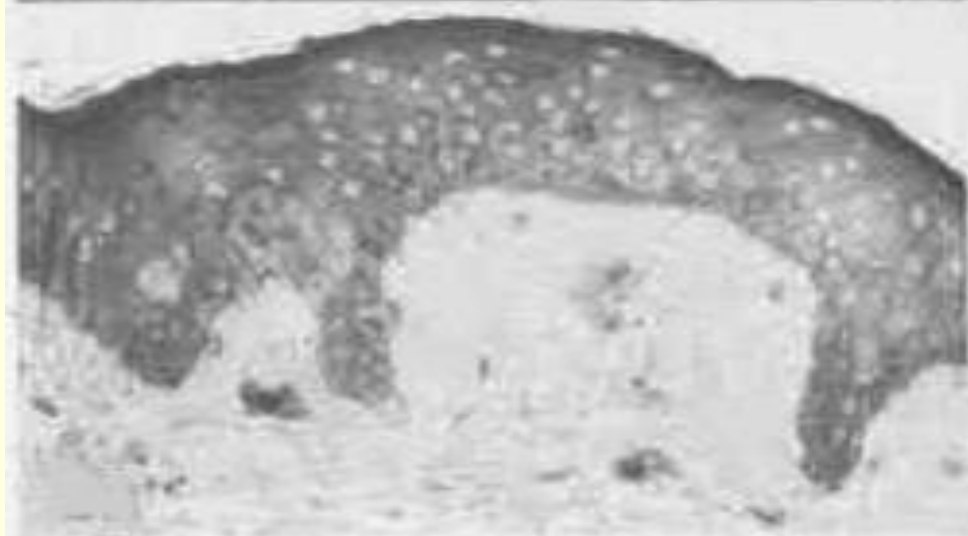


Flattening of the attachment between epidermis and dermis in older skin (b), compared with the wavy attachment in younger skin (a).

Young and aged dermis



Aged



Young

Intrinsic Aging

- Flattening of the dermal-epidermal junction:
 - Fragility
 - Less nutrient transfer
- Decreased cell turnover:
 - Slows from 30 to 50% between the third and eighth decades of life
 - Prolonged SC replacement rate
 - Decelerated wound healing
 - Less effective desquamation in age 65 years or older
→ heaps of corneocytes lead to dull and rough surface

Intrinsic Aging

- Number of melanocytes decreases from 8 to 20% per decade
- Loss of dermal thickness:
 - It is known that the overall collagen content per unit area of the skin surface decreases about 1 percent per year
 - GAC's production particularly HA decreases also
 - -

Intrinsic aging vs. Extrinsic aging:

Extrinsic aging:

- Appears predominately in exposed areas such as the face, chest, and extensor surfaces of the arm
- It is a results of the total effects of a lifetime of exposure to UVR and other factors such as smoking
- Wrinkles, pigmented lesions (i.e. freckles, lentigines, and patchy hyperpigmentation), and depigmented lesions
- Loss of tone and elasticity, increased skin fragility, area of purpura caused by blood vessels weakness, and benign lesions such as keratoses, telangiectasias, and skin tag

Intrinsic aging vs. Extrinsic aging:

Extrinsic aging:

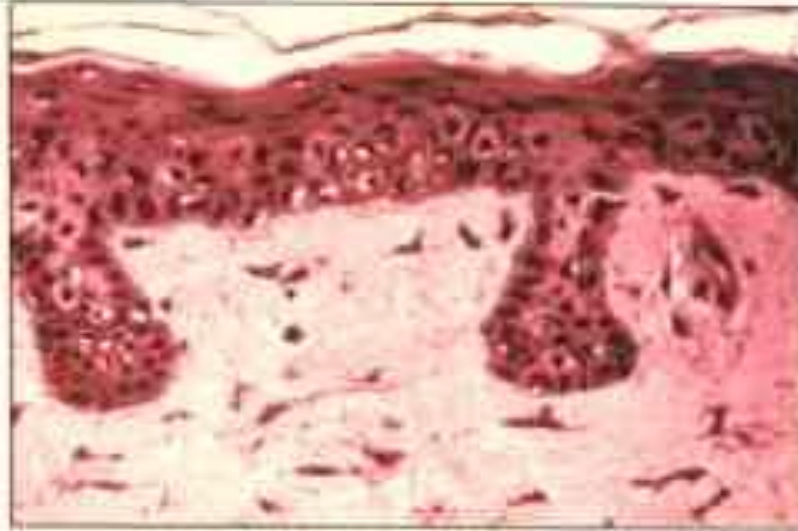
- Histopathologically:
 - Elastosis
 - Epidermal atrophy
 - Changes in collagen and elastin fibers: in severely photoaged skin the collagen & elastin fibers are fragmented.

Intrinsic aging vs. Extrinsic aging:

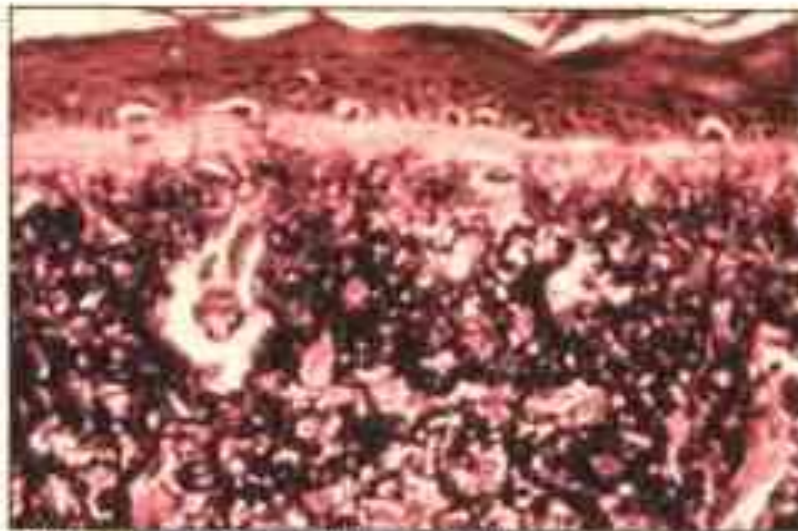
Extrinsic aging:

- Elastosis:
 - A hallmark of photoaged skin
 - An accumulation of amorphous elastin material
 - Results in reduced elasticity of the skin that may account for sagging skin in elderly

Severely damaged elastin in photoaged skin



INTRINSICALLY AGED EPIDERMIS



SOLAR ELASTOSIS- PHOTOAGED SKIN

Solar Elastosis



Solar Elastosis. Yellowing and furrowing of the skin result from chronic solar exposure. The area under the chin which is protected from the light is undamaged.

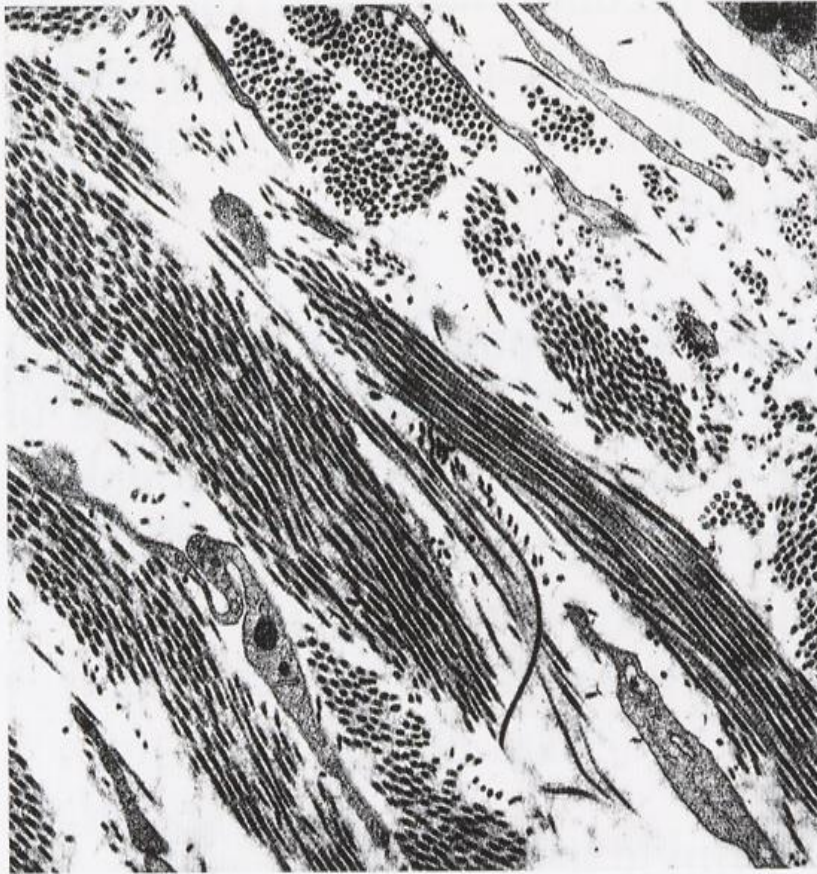
Extrinsic Aging

- The acceleration of intrinsic aging caused by exposure to various environmental factors such as sun, wind, smoking, and air pollutants
- The primary factors are UV radiation and smoking
- When the process is called photoaging when it is caused by the sun
- Photoaging is a cumulative process, which means that exposure adds up over the years
- Smoking leads to premature aging
- Smokers look older than their true age. Smoking has been shown to be a great contributor to facial wrinkling than sun exposure
- (J Invest Dermatol. 2003 Apr;120(4):548-54. Effect of smoking and sun on the aging skin. Kennedy C(1), Bastiaens MT, Bajdik CD, Willemze R, Westendorp RG, Bouwes Bavinck JN; Leiden Skin Cancer Study).

Intrinsic aging vs. Extrinsic aging:

Extrinsic aging:

- UVR up-regulates the production of several types of collagen-degrading enzymes known as matrix metalloproteinases (MMP)



(a)



(b)

(a) Collagen fibres in the dermis of 'young skin'. (b) Collagen fibres in the dermis of 'old skin'.

Extrinsic Aging

- Skin type significantly influences the clinical signs of photoaging
- In general the epidermis becomes thinner over the years with thicker coarse areas.
- Blood vessels can be easily seen through the skin where it is thinner and in these areas the skin bruises and bleeds more easily than normal

Extrinsic Aging

Motoyoshi, Ota *et.al* investigated the mechanism of wrinkle formation caused by long-term exposure to UVA radiation.

OUTLINE OF THE EXPERIMENT

- Hairless mice (9-10weeks old) were used as the animal model.
- Animals were irradiated 5 times weekly for 6 months.

(Cosmetic and Toiletries 113:51-58,1998)

MECHANISM OF WRINKLE FORMATION (CONTD...)

Visual Examination:

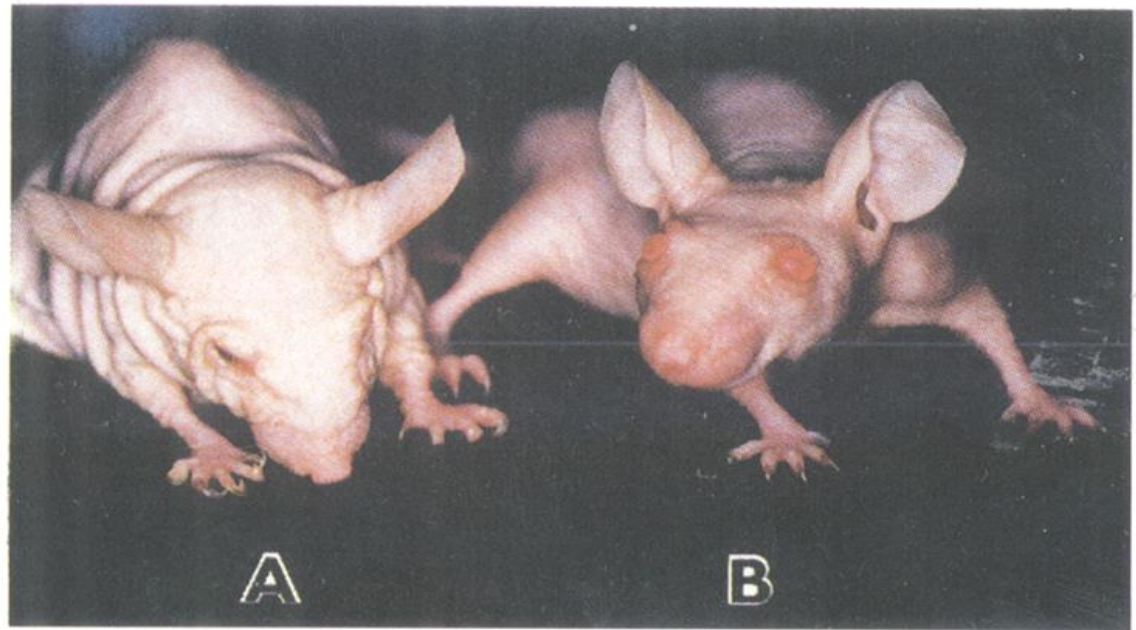


Figure 1-3. Visible changes at 24 weeks
A = UVA-irradiated hairless mouse
B = nonirradiated hairless mouse

- At 6 months, there was complete blanching of skin, nodular texture and loose folds.

Skin Appearance

Skin tags



Solar Lentigo (Sun spots)



Figure 3-6.

Seborrheic keratosis and other benign neoplasms often occur in areas with significant sun exposure.

Seborrheic keratosis

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Extremely thin atrophic skin.



Bruise (local haemorrhage) in an older man's forearm.



Figure 3-1.

The extensor (sun-exposed) surface of the arm shows much more photodamage than the flexor (unexposed) surface of the arm. This can be used to demonstrate to patients the importance of photoprotection.

The Role of Free Radicals in Aging

- Reactive oxygen species (ROS) are a major contributor to aging process
- Composed of oxygen with an unpaired electron
- Are created by UV exposure, pollution, stress, smoking, and normal metabolic processes
- Evidence suggests that free radicals lead to degradation of collagen and accumulation of elastin that is characteristics of photoaged skin.

The Role of Free Radicals in Aging

- A certain number of free radicals in the skin is perfectly normal, our bodies are well equipped to fight off these vicious molecules with natural antioxidants such as superoxide dismutase, glutathione and melanin, also can get help from vitamins A, C and E which give up their electrons for the greater good of our cells. But when the number of free radicals overwhelms the natural antioxidant systems, healthy cells are the victims

Cigarettes and Aging Skin

- Smokers manifest greater facial aging and skin wrinkling than nonsmokers
- lower SC water content has been reported in smokers which is likely caused by the diuretic effect of nicotine
- Increased levels of MMPs in the skin of smokers
- Smoking-induced alterations occur deeper in the reticular dermis as opposed to the solar damage to the papillary dermis

Cigarettes and Aging Skin

- Chronic smoking diminishes capillary and arterial blood flow leading to local dermal ischemia, this leads to less nutrients and oxygen in the skin with a buildup of toxic waste products that can damage the skin
- It is well known that smoking slows wound healing and that patients should stop smoking prior to any elective cosmetic surgery

Cigarettes and Aging Skin

- Smoker's face (Cigarette skin):
 - Increased facial wrinkling
 - Slightly red/orange complexion
 - Pale or gray overall skin appearance
 - Puffiness
 - Prematurely older appearance
 - Look older than their stated age
 - Increased incidence of precancerous lesions and squamous cell carcinomas on lips and oral mucosa



Figure 4-1.

Smoker demonstrates premature wrinkling around the mouth known as "smoker's mouth."

Cigarettes and Aging Skin



Figure 4-1.

Smoker demonstrates premature wrinkling around the mouth known as "smoker's mouth."



مظهر جلد المدخن؟



Reference: <http://www.webmd.com/smoking-cessation/ss/slideshow-ways-smoking-affects-looks>

Age spots



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Damaged Teeth and Gums



Stained Fingers



Hair Loss



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Crow's Feet Eye Wrinkles





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Modulation of aging sign

1. Primary prevention: healthy life style, no smoking, use sunscreen, balanced diet, adequate water, exercise
2. Chemical peels, topical injections of chemicals such as Botox, laser, corrective surgeries, topically applied products

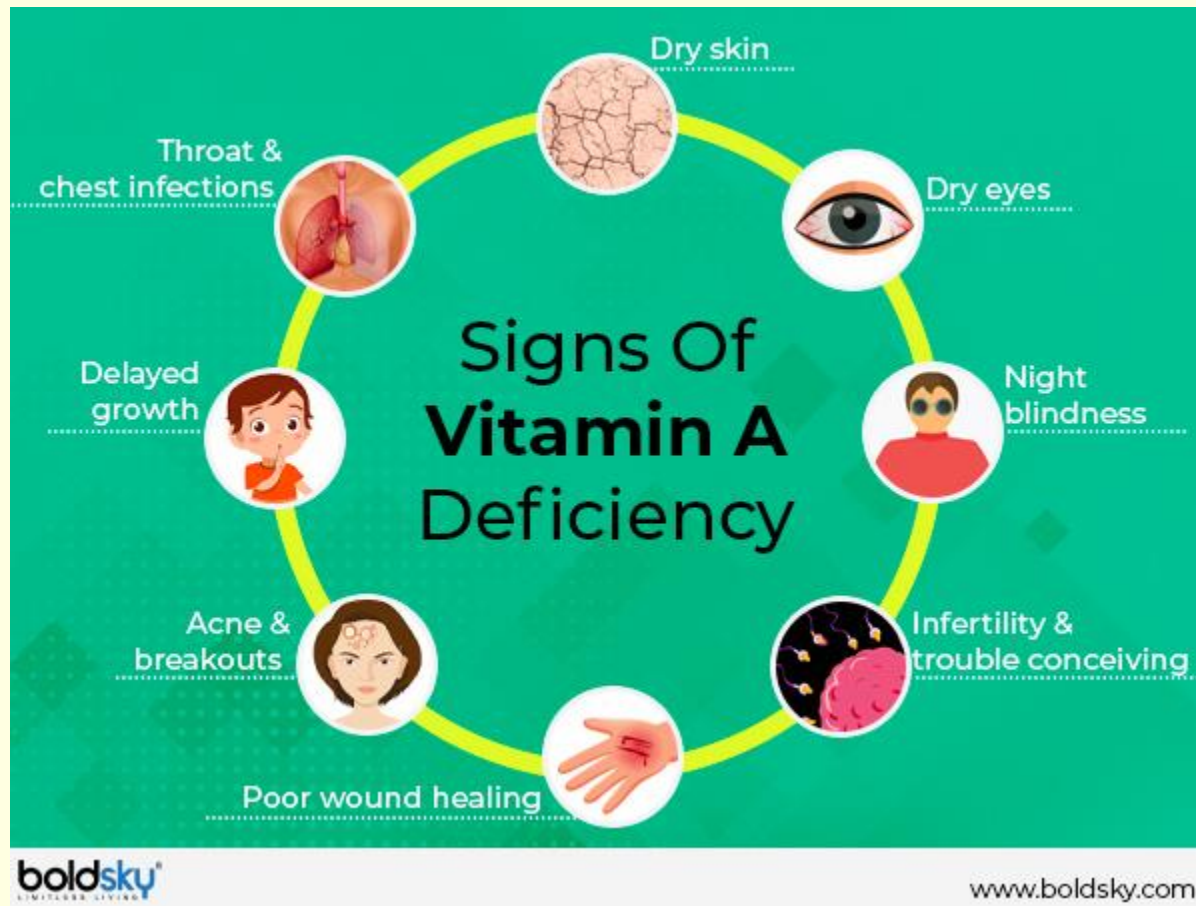
Many topical products are claimed to prevent oxidative reactions and the formation of free radicals

Retinoids

- Retinoic acid and its derivatives: adapalene, tazarotene, Tretinoin → Drugs
- Topical retinol derivatives: retinyl esters, retinol, retinaldehyde → cosmetics
- Retinoids in general are lipophilic that can reach the dermis
- They work at the molecular level through receptors in the cells
- Side effects:
 - Retinoid reaction
 - or retinoid dermatitis
 - limit its use in the first weeks

Retinoids:

- The role of vitamin A (retinol or all-trans-retinol) is well known in human nutrition
- As relates to the skin: the vitamin is an important regulator of epidermal cell growth and can alter or modulate total collagen synthesis
- The most striking symptom of vitamin A deficiencies is an alteration of the epithelium that is visible as atrophy and dry skin



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<https://www.mcisaachealthsystems.com/3923-2/>

Retinoids

- Derivatives of beta-carotene and are called vitamin A and its direct metabolites
- It include: retinol, retinaldehyde, retinyl esters, and retinoic acid
- The role of topically applied retinoids in regulation of skin development seems most efficiently accomplished by retinoic acid
- Retinoic acid occurs in two isomeric forms: all-trans retinoic acid (tretinoin) and 13-cis retinoic acid (isotretinoin).

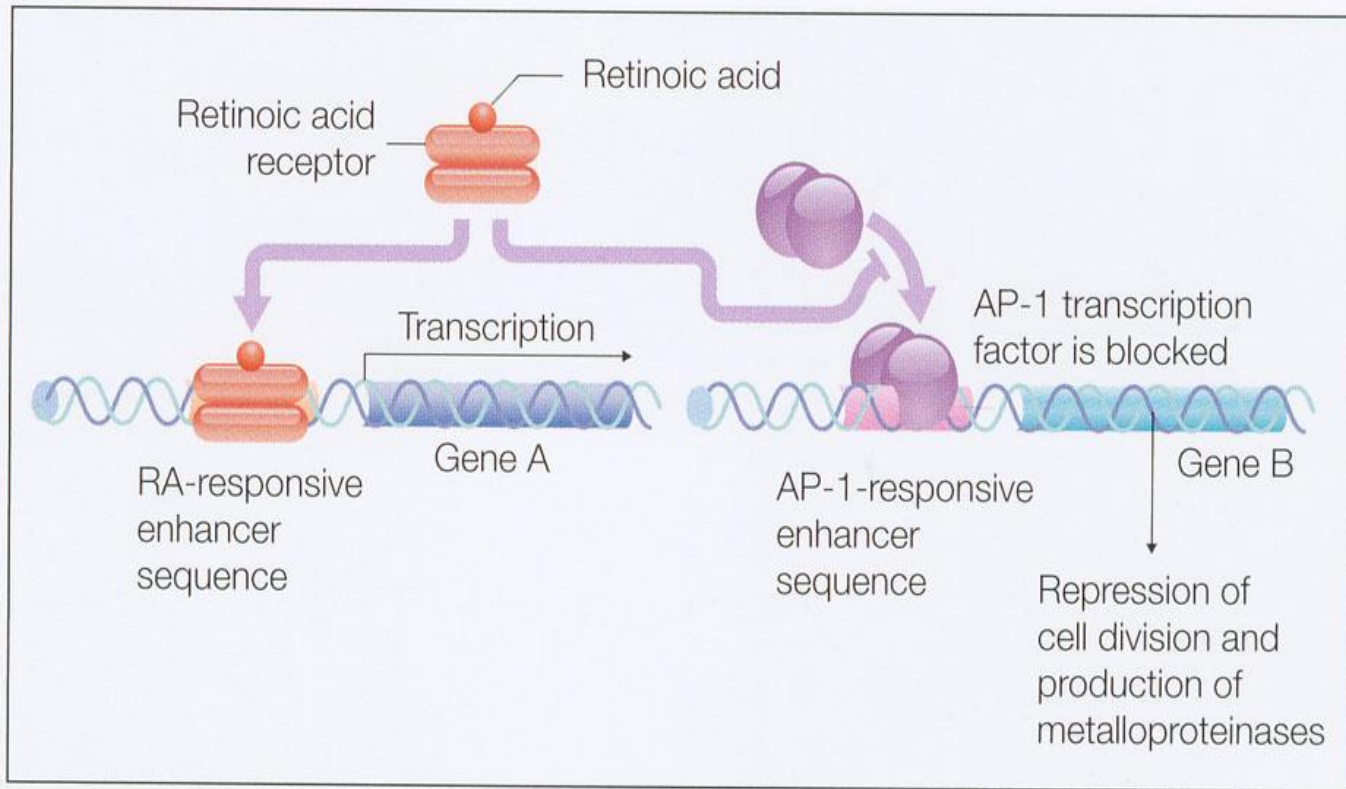


Fig. 6.2 Retinoic acid regulation of gene expression

- Retinoids elicit their effects at the molecular level by inducing transcription from genes with promoter regions that contain retinoid response elements or indirectly by inhibiting the transcription of certain genes

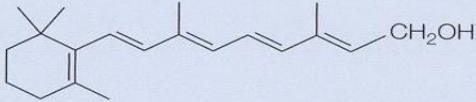
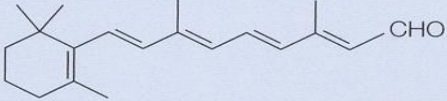
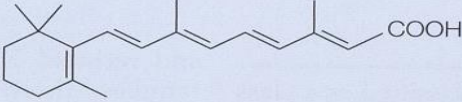
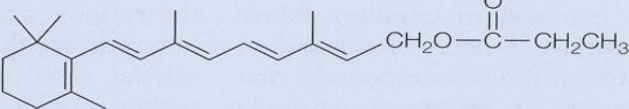
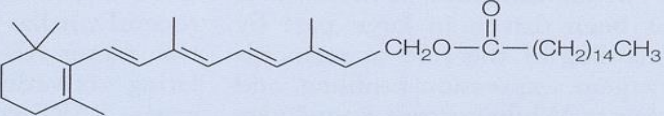
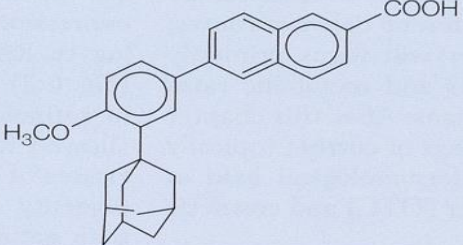
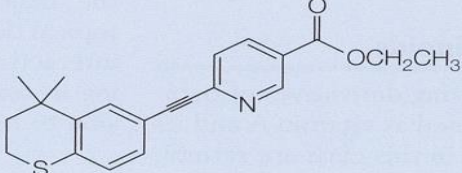
Retinoid	Structure
retinol	
retinaldehyde	
tretinoin	
retinyl propionate	
retinyl palmitate	
adapalene	
tazarotene	

Fig. 6.1 Chemical structures of key retinoids

-
- Topical usage of retinoids has shown a high degree of efficacy against acne, photodamage, and psoriasis
 - Side effects: skin irritation, desquamation, redness and teratogenic effects

Retinol (vitamin A):

- Current cosmetics contain relatively low levels of retinol due largely to intolerance amongst consumers for the irritation side effects
- It is hypothesized that its efficacy occurs via its conversion to retinoic acid
- Retinol is 20 times less potent than retinoic acid
- Not all retinol-containing products are equal
- Retinol must be manufactured, formulated, and packaged properly to avoid oxidation and loss of potency. In addition the amount of retinol in the product must be high enough to be effective
- Roc Retino Actif-pur and Neutrogena Healthy Skin contain 0.04 to 0.07% retinol
- Alustra (drug): 4% HQ and 0.3% retinol

- Retinol (all-trans-retinol) is somewhat difficult to formulate into products (the free alcohol being sensitive to air oxidation) while oil solutions are quite stable, at least until combined with other ingredients to form an emulsion. At that time, sensitivity to air and light may precipitate degradation of the material

-
- For this reason, cosmeceuticals containing this material are often packaged in metal or opaque glass containers with a vacuum-sealed pump applicator to minimize entry of light and air during dispensing
 - On the manufacturing side, sensitive constituents components should be weighed as much as possible in darkness using black light if necessary with a nitrogen blanket to serve as a barrier to oxygen while mixing
 - Packaging the finished product require also special care



Aqua ⓘ, Dimethicone ⓘ, Glycerin ⓘ, Butylene Glycol ⓘ, Isononyl Isononanoate ⓘ, Castor Isostearate Succinate, Glyceryl Stearate ⓘ, C12-15 Alkyl Benzoate ⓘ, Dimethicone Crosspolymer ⓘ, PEG-33 ⓘ, Polysorbate 20 ⓘ, Behenyl Alcohol ⓘ, Retinol ⓘ, Tetrahexyldecyl Ascorbate ⓘ, Ceramide 2 ⓘ, Palmitoyl Oligopeptide ⓘ, Palmitoyl Tetrapeptide-7 ⓘ, Sodium Hyaluronate ⓘ, Dipotassium Glycyrrhizate ⓘ, Glycyrrhiza Glabra (Licorice) Root Extract ⓘ, Avena Sativa (Avena) Kernel Extract ⓘ, Arctium Lappa (Burdock) Root Extract ⓘ, Salix Alba (Willow) Bark Extract ⓘ, Glycine Soja Sterols ⓘ, Lecithin ⓘ, Allantoin ⓘ, Tocopheryl Acetate ⓘ, Hydrolyzed Soy Protein ⓘ, Sorbitan Laurate ⓘ, Acetyl Dipeptide-1 Cetyl Ester ⓘ, Disodium EDTA ⓘ, Hydroxyethylcellulose ⓘ, Sodium Hydroxide ⓘ, Tribehenin ⓘ, Caprylyl Glycol ⓘ, Ethylhexylglycerin ⓘ, Pentylene Glycol ⓘ, PEG-100 Stearate ⓘ, PEG-75 Shea Butter Glycerides ⓘ, PPG-12/Smdl Copolymer ⓘ, PEG-10 Phytosterol ⓘ, PEG-8 Dimethicone ⓘ, PEG-14 ⓘ, Pentaerythrityl Tetraisostearate ⓘ, Polymethylsilsesquioxane ⓘ, Magnesium Aluminum Silicate ⓘ, Arachidyl Glucoside ⓘ, Sclerotium Gum ⓘ, Arachidyl Alcohol ⓘ, Benzoic Acid ⓘ, Sodium Carbomer ⓘ, Phenoxyethanol ⓘ

Read more on [how to read an ingredient list >>](#)



Aqua (Water) ⓘ, Glycerin ⓘ, Ethyl Linoleate ⓘ, Propanediol ⓘ, Caprylic/Capric Triglyceride ⓘ, Cetearyl Isononanoate ⓘ, Bisabolol ⓘ, Hydroxypinacolone Retinoate ⓘ, Retinol ⓘ, Tasmannia Lanceolata Fruit/Leaf Extract ⓘ, Dimethyl Isosorbide ⓘ, Inulin Lauryl Carbamate ⓘ, Glyceryl Stearate ⓘ, Ceteareth-12 ⓘ, Ceteareth-20 ⓘ, Cetearyl Alcohol ⓘ, Carrageenan ⓘ, Xanthan Gum ⓘ, Acacia Senegal Gum ⓘ, Cetyl Palmitate ⓘ, Sucrose Laurate ⓘ, Polysorbate 20 ⓘ, Behentrimonium Chloride ⓘ, Potassium Citrate ⓘ, Trisodium Ethylenediamine Disuccinate ⓘ, Disodium EDTA ⓘ, Dehydroacetic Acid ⓘ, Benzoic Acid ⓘ, Ethylhexylglycerin ⓘ, Phenoxyethanol ⓘ, Chlorphenesin ⓘ

INGREDIENTS



2021547 8 - INGREDIENTS: AQUA/WATER/EAU, PROPANEDIOL, DIMETHICONE, CETEARYL ETHYLHEXANOATE, NIACINAMIDE, AMMONIUM POLYACRYLOYLDIMETHYL TAURATE, DIPOTASSIUM GLYCYRRHIZATE, HYDROGENATED LECITHIN, POTASSIUM PHOSPHATE, CERAMIDE NP, CERAMIDE AP, CERAMIDE EOP, CARBOMER, CETEARYL ALCOHOL, BEHENTRIMONIUM METHOSULFATE, DIMETHICONOL, LECITHIN, SODIUM CITRATE, RETINOL, SODIUM HYALURONATE, SODIUM LAUROYL LACTYLATE, CHOLESTEROL, PHENOXYETHANOL, ALCOHOL, ISOPROPYL MYRISTATE, CAPRYLYL GLYCOL, CITRIC ACID, TRISODIUM ETHYLENEDIAMINE DISUCCINATE, PENTYLENE GLYCOL, PHYTOSPHINGOSINE, XANTHAN GUM, POLYSORBATE 20, ETHYLHEXYLGLYCERIN (CODE F.I.L. D233672/1)



Water ①, Butylene Glycol ①, Glycerin ①, Cetearyl Ethylhexanoate ①, 1,2-Hexanediol ①, Squalane ①, Methylpropanediol ①, Panthenol ①, Polyglyceryl-3 Distearate ①, Betaine ①, Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer ①, Polyacrylate Crosspolymer-6 ①, Caprylic/Capric Triglyceride ①, Macadamia Ternifolia Seed Oil ①, Glucose ①, Chlorella Vulgaris Extract, Acrylates/C10-30 Alkyl Acrylate Crosspolymer ①, Hydrogenated Lecithin ①, Tromethamine ①, Xanthan Gum ①, Fructose ①, Fructooligosaccharides ①, Brassica Campestris (Rapeseed) Sterols ①, Retinol ①, Glyceryl Stearate Citrate ①, Polyglyceryl-10 Laurate ①, Cholesterol ①, Ethylhexylglycerin ①, Adenosine ①, Melia Azadirachta Flower Extract, Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate, Ocimum Sanctum Leaf Extract, Melia Azadirachta Leaf Extract, Allantoin ①, Pentaerythrityl Tetra-Di-T-Butyl Hydroxyhydrocinnamate ①, Aluminum/Magnesium Hydroxide Stearate ①, Curcuma Longa (Turmeric) Root Extract ①, Potassium Cetyl Phosphate ①, Corallina Officinalis Extract, Chitosan, Beta-Glucan ①, Tris (Tetramethylhydroxypiperidinol) Citrate, Sodium Hyaluronate ①, Carbomer ①, Sodium Lactate ①, Bakuchiol ①, Polysorbate 20 ①, Tocopherol ①, Palmitoyl Tripeptide-1 ①, Palmitoyl Tetrapeptide-7 ①, SH-Decapeptide-7 ①, SH-Octapeptide-4 ①, SH-Polypeptide-1 ①, Sh-Polypeptide-22, SH-Oligopeptide-1 ①, SH-Polypeptide-1 ①, Oligopeptide-2

Read more on [how to read an ingredient list](#) >>

- **Retinyl esters:** Storage form of vitamin A in cells (retinyl palmitate is the predominant form)
- retinyl acetate and retinyl palmitate, while somewhat more stable than retinol in cosmetic creams and lotions, are not as efficient at producing remedial cellular effects when delivered topically
- The lower effectiveness of these materials is due to differing bioconversion rates of each in the skin which is dependent upon enzyme activity
- Esterases hydrolyze retinyl palmitate to retinol which is further oxidized in tissue to retinoic acid through alcohol dehydrogenase
- Retinol, retinaldehyde, and retinyl esters attempt to mimic the effect of tretinoin in cosmeceutical formulations

■ **Tretinoin (trans-retinoic acid):**

- Retin A, Renova, Ortho-Neutrogena
- Improve skin photodamage as fine lines, wrinkles, and pigmentation
- Cause significant irritation and dryness
- Retin A was first approved up to 0.1% levels for acne
- Then approved under Renova name at 0.025 and 0.05% for topical treatment of photodamaged skin
- Application of tretinoin inhibits the induction of MMPs (i.e. collagenase and gelatinase) (*Fisher et al., Molecular basis of sun-induced premature skin ageing and retinoid antagonism, Nature, 379, 1996*)
- Topical application of tretinoin 0.1% to photodamaged skin partially restores levels of collagen type I



Long-Term Efficacy and Safety of Tretinoin Emollient Cream 0.05% in the Treatment of Photodamaged Facial Skin

A Two-Year, Randomized, Placebo-Controlled Trial



Fig. 4. Case example of a subject treated with tretinoin emollient cream 0.05%. (a) Baseline. (b) After 24 months of treatment.

■ **Adapalene:**

- Differin, Galderma (0.1%)
- Prescribed for topical acne therapy

■ **Tazarotene:**

- Prescribed for psoriasis and acne at 0.05 and 0.1% under the name Tazorac and Zorac
- Prescribed for treatment of photodamage under the name Avage
- Still cause irritation



Figure 12-2.

Redness, flaking, and tender skin are common symptoms after beginning a retinoid. These symptoms usually improve with time.

Instructions for the Use of Topical Retinoids

Apply to dry skin

Apply only a pea-size amount

Apply every third night in the beginning

After 2 weeks, apply every other night

After another 2 weeks, apply every night

Do not cover with a moisturizer

Do not use with hydroxy acids

Do not use with Vitamin C topical products

Do topical retinoids have any side effects?

Topical retinoids can irritate the skin, especially when they are first used. This is more likely in those with **sensitive skin**, resulting in stinging. Excessive use results in redness, swelling, peeling and blistering in treated areas. It may cause or aggravate **eczema**, particularly **atopic dermatitis**.

By peeling off the top layer of skin, they may increase the chance of sunburn. Irritation may also be aggravated by exposure to wind or cold, use of soaps and cleansers, astringents, peeling agents and certain cosmetics.

Some people have reported a flare of acne in the first few weeks of treatment. This usually settles with continued use.

<http://www.dermnetnz.org/topics/topical-retinoids/>

How to use topical retinoids

Follow these instructions carefully:

- In general, a cream is less irritating than a gel. If there is a choice, start with a lower concentration product.
- Use your topical retinoid on alternate nights at first. If you have sensitive skin, wash it off after an hour or so. If it irritates, apply it less often. If it doesn't, try every night, and if possible twice daily. In most people, the skin gradually gets used to it.
- To reduce stinging, apply it to dry skin, that is, 30 minutes or longer after washing.
- Apply a tiny amount to all the areas affected, and spread it as far as it will go.
- Don't get it in your eyes or mouth.
- Apply a sunscreen to exposed skin in the morning.
- Use gentle cleansers (avoid soap) and apply non-greasy moisturisers as often as required.
- If your skin goes scarlet and peels dramatically even with cautious use, the retinoid may be unsuitable for your sensitive skin.

In conclusion

- In general, retinoids affect cell proliferation during the process of keratinization
- They also affect sebum secretion (orally more than topically)
- Affect inflammatory and immunological reactions
- Retinoic acid reportedly repairs photoaged skin by inhibiting collagenase, and improving dermal vasculature and stimulate new collagen deposition
- topical vitamin A and its analogues inhibit the expression of MMP and stimulate collagen synthesis in both photodamaged and photoprotected aged skin

Approaches have been made to decrease the irritating potential of retinoic acid

- Formulation of specific delivery systems
- Synthesis of new derivatives
- Products should be used at night in small amounts
- Moisturizer use
- Sunscreen
- Retinoids are best used at night
- When using retinoids it has been shown that most of the improvement in aging signs occur within first year of treatment