The Science of Cosmeceuticals
Prof. Zoe Diana Draelos

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Creams and the pursuit of youthful skin

What are the most important skin care ingredients?
Active ingredients enhance skin functioning

The skin and active ingredients: moisturization

Moisturization and anti-aging

- The important effect of any skin cream
- Improves skin smoothness, softness, texture, and luminosity
- Provides environment for barrier repair
- Still the basis for all anti-aging skin care creams
Photoprotection and anti-aging

Sunscreens

• New sunscreen FDA guidance allows anti-aging claims when organic and inorganic filters in products.
• Many cosmeceuticals will now include anti-aging claims.
• Anti-aging is based on the prevention of DNA damage.

Melanin DNA protection
Melanin and anti-aging

- Melanin forms a cap over nuclear DNA.
- Melanin stabilizes reactive oxygen species by donating an electron.
- Melanin becomes oxidized resulting in immediate pigment darkening reaction.
- Oxidation consumes melanin and protection mechanisms overwhelmed.

UV-induced DNA damage induces pyrimidine dimers

DNA damage, p53 activation and apoptosis

- Tumor suppressor protein - known as “the guardian of the genome”
- Activates DNA repair proteins
- Halts cell cycle until DNA repair occurs
- If the DNA cannot be repaired, it initiates cell death apoptotic cycle.
DNA damage and aging

- DNA damage
- Cell cycle abnormalities
- Hypoxia

\[ \text{mdm2} \rightarrow \text{p33} \rightarrow \text{p53} \]

Cell cycle arrest
DNA repair
Cell cycle restart

Apoptosis
Death and elimination of damaged cells

Cellular and genetic stability

Melanin antioxidant failure: apoptotic cell

Sun protection and anti-aging

- Sunscreen the basis for anti-aging skin care.
- Sunscreens protect the DNA of the cell from damage.
- DNA damage can cause young skin cells to age prematurely.
- Severe DNA damage causes skin cancer.
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**Sunscreens, DNA damage and the comet assay**
Demonstrates protection against UV induced damage

- **Control**
- **Exposed, no protection**
- **Exposed, effectively protected**
- **Exposed, ineffectively protected**

*In vitro comparison of the protection from UV-induced DNA damage in cultured human keratinocytes.*

Shorter comet tails mean less DNA damage, and longer comet tails mean more DNA damage.

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**The skin and active ingredients: antioxidants**

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**Antioxidants**

- Important in preventing damage to DNA and structural body proteins by highly energetic oxygen molecules
- Antioxidants are necessary for humans to survive in an oxygen rich environment.
- Oxidative damage is the key insult on young skin leading to the appearance of old skin.
Skin vitamin antioxidants

ROS

Vitamin E
Vitamin C

Diet and antioxidant defenses

<table>
<thead>
<tr>
<th>Micronutrient</th>
<th>Antioxidant function</th>
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</thead>
<tbody>
<tr>
<td>Vitamin C</td>
<td>Water-soluble free radical scavenger</td>
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<tr>
<td>Vitamin E, CoEnzyme Q (not a micronutrient)</td>
<td>Lipid-soluble free radical scavengers</td>
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<tr>
<td>Riboflavin (B2)</td>
<td>FAD (glutathione reductase)</td>
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<td>Selenium</td>
<td>Glutathione peroxidases, thioredoxin reductase, etc.</td>
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<td>Iron</td>
<td>Catalase</td>
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<tr>
<td>Manganese</td>
<td>Mitochondrial superoxide dismutase</td>
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<tr>
<td>Copper, zinc</td>
<td>Cu, Zn superoxide dismutase</td>
</tr>
<tr>
<td>β-carotene, carotenoids (not micronutrients)</td>
<td>Singlet oxygen quenchers</td>
</tr>
</tbody>
</table>

Assessing topical antioxidant efficacy
Antioxidant capacity

- Oral cosmeceuticals do not necessarily function in the same way as topical antioxidants.
- Very difficult to clinically assess the benefits of antioxidants
  - Antioxidants prevent damage that has yet to occur, preventative more than treatment
- ORAC scale proposed, but developed to assess nutritional value of food, not proven relevant to skin or diet.

ORAC scale

- Oxygen radical absorbance capacity (ORAC)
- Measures oxidative degradation of fluorescein after mixed with free radical generator
- Addition of antioxidant allows preservation of fluorescence.

Assessing antioxidants

- Vitamin E is not the best performer on ORAC scale, but it is the primary antioxidant of the body.
- Vitamin C is a better food antioxidant.
- Vitamin C is a secondary antioxidant of the body, there are many tertiary antioxidants (ubiquinone, etc.).
- No model exists and no study done on topical antioxidant effects.
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### ROS and oxidative stress

**What are ROS?**
- Reactive Oxygen Species
- Produced during respiration  
  (transformation of O$_2$ into water)

**How do ROS act inside cells?**
1. Minor quantities ➔ Normal metabolism
2. Excessive quantities ➔ oxidative damage to cellular constituents

3 targets:
- DNA: strand breaks and aberrant cross-links ➔ cellular mutations
- Proteins: structural alterations and enzymatic inactivation ➔ loss in cell function
- Lipids: structural and barrier function alterations in cellular membranes ➔ loss of cell viability

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### Inflam-aging: a cosmeceutical target

A vicious circle with cascade effect:
- Excessive level of ROS can induce inflammation and ROS are inflammatory effectors
- Loss of cellular homeostasis
- Premature aging

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### 2 types of inflam-aging

- Low-grade chronic inflammation
  - Chronic ➔ No resolution; Harmful doesn’t allow healing
  - Low-grade ➔ Asymptomatic; Detectable at cellular level
  
A response to prolonged repetitive « aggressions »

Since inflammation induce high ROS production, its modulation and resolution is essential for cellular homeostasis

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Alphabet vitamins: A, B, C, D, E, F

Vitamin A: carotenoids

Carotenoids: tertiary antioxidant

- Mean concentration of carotene, retinol and dehydroretinol in human back skin was 13, 0.4, and 0.4 micrograms/gm of protein (no age or sex difference noted)
- 90% vitamin A reserve in the liver, 1% in the plasma

Vahlquist A, et al., Vitamin A in human skin: II concentrations of carotene, retinol, dehydroretinol in various components of human skin. JID 1982;75:94-7

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Retinol activity

- Retinyl esters
- Hydrolysis → Esterification
- Oxidation → Reduction

Topical retinol
- Retinol most widely used in currently marketed cosmeceuticals
- Highly susceptible to oxidation
- Must be manufactured in an oxygen free environment
- Active products in amber bottles, metal tubes, or one way pump dispensers


Cosmeceutical retinol
- 2% maximum tolerable concentration due to irritation
- Demonstrated to induce benefit beyond moisturization
- Confusing studies showing efficacy equivalent to tretinoin in 12 weeks, but moisturizer effect important
Vitamin B: niacinamide

Niacinamide derivatives

- Niacinamide also known as nicotinamide
- Niacinamide in skin care products speeds cell turnover acting as a vitamin exfoliant.
- May have some anti-inflammatory properties, used in male shaving cosmeceuticals
- Part of NADPH pathway of mitochondrial energy production

Vitamin C: ascorbic acid
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Vitamin C: secondary antioxidant

Neutralization of a free radical by an antioxidant

Vitamin C: prevents antioxidant chain reaction

Vitamin C and pigmentation

- Interrupts melanogenesis by interacting with copper ions to reduce dopaquinone
- Blocks dihydrochiniindol-2-carboxyl acid oxidation
- Body reservoir is only 1500mg


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Vitamin C and the skin

- Promotes fibroblast proliferation and migration
- Cofactor for lysyl and prolyl hydroxylase
- Modulates replication-associated base excision repair of potentially mutagenic DNA lesions


Vitamin D and skin

- Vitamin D3 major factor canthelicidin expression, inducing cutaneous inflammation in rosacea, producing a cosmetically unattractive red face
- Vitamin D linked to the regulation of p53, a tumor suppressor protein important in skin cancer
- Speculative relationship between vitamin D deficiency and melanoma

Vitamin E: primary antioxidant

Skin vitamin antioxidants

Vitamin E: antioxidants and skin aging

- UV damage rapidly depletes vitamin E
- Very difficult to consume vitamin E, found in nuts primarily
- The optimal amount of vitamin E uptake is unknown, and it is most likely depends on sex and age.
- Antioxidant minimize apoptotic cell formation and need to activate p53 by preventing lethal DNA insult.

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Vitamin E and oxidative protection

- Vitamin E epidermal content is only 1.0 nmol/g.
- Alpha tocopherol terminates lipid radical chain reactions, stabilizes membranes against damage by phospholipase A, free fatty acids, and lysophospholipids.

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Oral vs. topical vitamin E

- Vitamin E is fat soluble, hard to penetrate skin topically, may be penetration enhancer intercalating within the lipid bilayer of SC.
- Vitamin E inexpensive antioxidant to prevent lipids in moisturizers from rancidity
- Excellent emollient to smooth skin surface

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Vitamin F: essential fatty acids

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Essential fatty acids:
linolenic and linoleic acids

- Linolenic acid is omega-3
- Linoleic acid is omega-6
- Number indicates position of the first double bond
  continuing from the terminal methyl group on the molecule

Linolenic omega-3

- Alpha linolenic acid converted to eicosapentaenoic acid
  and then into docosahexaenoic acid
- Used in cell wall formation
- Deficiency leads to decreased mental abilities,
  poor vision, diminished immune function,
  increased triglycerides, increased LDL, hypertension,
  skin disease resembling eczema

Linoleic omega-6

- Gamma linoleic acid, which combines with eicosapentaenoic
  acid to form eicosanoids
- Found in topical preparations as borage oil
  and evening primrose oil
- Orally present with omega-3 in canola oil, hempseed oil,
  walnuts, sesame seeds, avocados, salmon, and albacore tuna
- Important in cell wall formation

Horrobin DF. Essential fatty acids in clinical dermatology.

Simopoulos AP. Omega-3 fatty acids in inflammation and autoimmune disease.

Miller CC, et al. Dietary supplementation with ethyl ester concentrations of fish oil and borage oil.
JID 1991; 96: 98-103
Summary: *cosmeceutical science*

- The moisturizer vehicle accounts for 50-70% of the perceived efficacy.
- Sunscreens are important to prevent DNA damage leading to premature aging.
- Vitamins and other antioxidants are added to quench reactive oxygen species resulting from UV exposure.