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# COSMECEUTICALS-A REVIEW

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**Abstract**

Cosmeceuticals are used for nourishing as well as improving the appearance of the skin, and are also documented as effective agents for treating various dermatologic conditions. Cosmeceutical preparations from herbal origin are most popular among consumers, as these agents are mostly non-toxic and possess strong antioxidant activity. Since oxidative stress is one of the major mechanisms for skin aging and dermatological conditions, the phytochemicals, such as silibinin, with proven antioxidant activity, could be useful for treating many dermatologic conditions as well as skin aging. Silibinin is a flavonolignan compound from milk thistle plant which possesses strong antioxidant activity and also modulates many molecular changes, caused by xenobiotics and ultraviolet radiation, to protect the skin.

**Keywords:** Cosmeceuticals, Hydroxy acids, Retinoids, Antioxidants

## Introduction[1]:

Cosmeceuticals are cosmetic products with biologically active ingredients purporting to have medical or drug-like benefits.

**Example:** The products typically labeled as cosmeceutical including anti aging creams and moisturisers.

In June 2008, the first cosmaceutical television advert broadcast took place in the UK, featuring Restylane, an injectable dermal filler that classification of Restylane is medical device by law, but it's frequent, unofficial classification as a 'cosmeceutical' arises from its cosmetic and pharmaceutical function.

**COSMETICS Vs DRUG:**

There are multiple slightly variable definitions of both ‘drugs’ and ‘cosmetics’, but some commonalities do exist. The term cosmetic refers to a preparation designed to enhance the body superficially to hide a real comprehended deficiency or flaw, by direct application. This application is considered to be decorative, lacking in depth or significance, as opposed to a response to a medical requirement.

The definition of a drug is more complex. Generally, a drug is a chemical substance which, when absorbed into a living organism, alters normal function. organism, tissue or cell by their introduction into body from outside the organism.

The pharmacology definition of a drug will apply -" a chemical substance used in the treatment, cure, prevention or diagnosis of disease or used to otherwise enhance physical or mental well-being, for a limited duration or indefinite period of time."

Individual governments regulate the availability or drugs to the public.

**1**: Over-the-counter (OTC) medication is available from pharmacies.

**2**: Behind-the-counter medication (BTC) medication must be dispensed by pharmacist, but does not require the authority of a doctor, and finally

**3**: Prescription-only medicine (POM) can only be prescribed by a licensed medical professional.

- There are also numerous bodies that regulate drugs in the market place:

**1:** The Medicines and Healthcare products Regulatory Agency (MHRA)- is a government agency responsible for ensuring that medicines and medical devices work and are acceptably safe. They are responsible for public information as well the investigation and handling of complaints and patient feedback.

**2:** The National Biological Standards Board (NBSB)- is a non-departmental public body, established in 1975 by Act of Parliament. The board takes responsibility for safe-guarding and advancing public health by assuring the

quality and safety of biological.

**3:** National Institute for Biological Standards and Control (NIBSC)- This organisation conducts independent testing of biological medicines for the UK market and both bodies respond to and advise on public health issues.

Visually, the difference between a cosmetic and a drug is defined by the manufacturer by its intended use, using product labelling. Claims made on labels, in advertising, press releases, on the internet or in any form of promotional material serve to define the use of the product. Use may also be determined by abstract factors, such as the perception of the product in the eyes of the consumer. Ingredients also determination use; a good example of which would be toothpaste which contains fluoride. These are all key indicators for cosmeceutical product.

**Some Common Types of Cosmeceuticals:**

1) Hydroxy acids.

2) Botanicals.

3) Depigmenting agents.

4) Exfoliants.

5) Moisturizers.

6) Topical peptides.

7) Retinoids.

8) Sunscreens.

9) Antioxidant

**1. HYDROXY ACID[1]:**

Also referred to as fruit acids, they are a common ingredient found in cosmeceutical products. Examples include: citric acid,malic acid,lactic acid.

AHAs improve skin texture and reduce the signs of aging by promoting cell shedding in the outer layers of the epidermis and by restoring hydration. One hypothesis suggests that AHAs reduce the calcium ion concentration in the epidermis and, through chelation, remove the ions from the cell adhesions, which are thereby disrupted, resulting in desquamation. This is enhanced by cleavage of the endogenous stratum corneum chymotryptic enzyme on the catherins, which are otherwise protected from proteolysis by conjugation with calcium ions. The resulting reduction of the calcium ion levels tends to promote cell growth and slow cell differentiation, thus giving rise to younger looking.

**Introduction:** Formulations containing hydroxy acids (HAs) have been used in clinical practice for decades to treat a variety of skin conditions. The most prominent representatives in this class of compounds are glycolic acid, lactic acid, and salicylic acid (SA).

**1**: They have been used, in concentrations ranging from 2% to 70%, to treatacne, ichthyosis, keratose, warts, psoriasis, photoaged skin, and other disorders.

**2**: In the last three decades, α-hydroxy acids (αHAs) have been widely incorporated into a variety of cosmetic products for daily use over long periods of time. These improvements have been measured as decreases in roughness, discoloration, solar keratoses, and overall pigmentation and also as increased density of collagen and improved quality of elastic fibers.

**3**: The antiaging effects of HA have become a prominentfactor in cosmetic dermatology, leading to the proliferation of HA-containing cosmetic products and skin care systems.

More recent research in this field led to the discovery of polyhydroxy acids (PHAs) and aldobionic acids (BAs) which are presently widely used in cosmetic and dermatologic applications. Many Clinical, Cosmetic and preparations that contain HAs are both exfoliants and moisturizers. In low concentrations (4%–10%), they are ubiquitous components of nonprescription creams and lotions that are promoted as being effective for ameliorating skin aging. In high concentrations (.20%), these preparations\are used as chemical ‘peels’ to treat

calluses, keratoses,acne, psoriasis, and photoaging.

- **Types/classes of HAs[2]:**

**1. αHAs:**These are carboxylic acids with one hydroxyl group attached to the alpha-position of the carboxyl group. Glycolic acid (chemical name-hydroxyacetic acid), which was first of this class of compounds to be introduced into skin care products. Lactic acid, with optimal biological activity in its 1-form, is also used in various topical formulations to exfoliate the skin and also to provide antiaging properties.

**2. PHAs:** Bionic acids (PHBAs), provide effects similar to αHAs but with less irritation responses. PHAs, such as lactobionic acid are carboxylic acids with two or more hydroxyl groups attached to carbon atoms or an alicyclic chain. It is essential that at least one hydroxyl group be attached to the α-position. Attaching a sugar molecule to the PHA structure results in a polysaccharide known as bionic acid.Multiple skin benefits have been proven for the PHAs and PHBAs, making them ideal ingredients for use in dermatologic and cosmetic procedures.

**3. β-Hydroxy acids:** β-Hydroxy acids (βHAs) are carboxylic acids having one hydroxyl group attached to the β-position of the carboxyl group.The most common βHA is β-hydroxybutanoic acid. A lipid soluble βHA is tropic acid (2-phenyl-3-hydroxypropanoic acid) . Some βHAs are also considered αHAs as they contain a hydroxyl group in the α-position to one carboxyl group and in the β-position to the other carboxyl group. Malic acid and citric acid are prominent representatives in this category . Citric acid is widely used in topical formulations as an antioxidant, and its antiaging benefits are well established.

**4. SA:** Described as a βHA, but that classification is incorrect.In SA, both the hydroxyl and the carboxyl groups are directly attached to an aromatic benzene ring and both exhibit acidic properties. In contrast, the hydroxy groups in αHAs, βHAs,and PHAs are neutral under the conditions used in clinical and cosmetic settings. SA is used in cosmetic formulations for a variety of applications, more specifically, it is fat soluble, which makes it useful in subjects with oily skin.

**ALPHA HYDROXY ACIDS ( AHAs)[2]:**

**α-Hydroxy acids**, or **alpha hydroxy acids** (**AHAs**), are a class of chemical compounds that consist of a carboxylic acid substituted with a hydroxyl group on the adjacent carbon. They may be either naturally occurring or synthetic. AHAs are well-known for their use in the cosmetics industry. They are often found in products claiming to reduce wrinkles or the signs of aging, and improve the overall look and feel of the skin. They are also used as chemical peels available in a dermatologist's office, beauty and health spas and home kits, which usually contain a lower concentration. Although their effectiveness is documented numerous cosmetic products have appeared on the market with unfounded claims of performance. Many well-known α-hydroxy acids are useful building blocks in organic synthesis: the most common and simple are glycolic acid, lactic acid, citric acid, mandelic acid.

- **Cosmetic applications:**

Understanding skin structure and cutaneous aging is helpful to a discussion of the topical action of AHAs. Human skin has two principal components, the vascular epidermis and the underlying vascular dermis. Cutaneous aging, while having epidermal concomitants, seems to involve primarily the dermis and is caused by intrinsic and extrinsic aging factors.

AHAs are a group of organic carboxylic compounds. AHAs most commonly used in cosmetic applications are typically derived from food products including

a) Glycolic acid(from sugar cane),

b) Lactic acid (from sour milk),

c) Malic acid (from apples),

d) Citric acid (from citrus fruits),

e) Tartaric acid (from grape wine).

For any topical compound, including AHA, it must penetrate into the skin where it can act on living cells. Bioavailability (influenced primarily by small molecular size) is one characteristic that is important in determining compound's ability to penetrate the top layer of the skin. Glycolic acid having the smallest molecular size is the AHA with greatest bioavailability and penetrates the skin most easily; this largely accounts for the popularity of this product in cosmetic applications.

- **Epidermal effect**

AHA's have a profound effect on keratinization; which is clinically detectable by the formation of a new stratum corneum. It appears that AHAs modulate these levels of the stratum corneum.

- **Dermal effects**

AHAs with greater bioavailability appear to have deeper dermal effects. Glycolic acid, lactic acid and citric acid, on topical application to photodamaged skin, have been shown to produce increased amounts of mucopolysaccharides and collagen and increased skin thickness without detectable inflammation, as monitored by skin biopsies.

- **Alpha hydroxy acids at different concentrations**

a] In low concentrations( between 5 - 10%) as is found in many over the counter products, glycolic acid reduces cell adhesion in the top layer of the skin. This action promotes exfoliation of the outermost layer of the skin accounting for smoother texture following regular use of topical GA. This relatively low concentration of glycolic acid lends itself to daily use as a monotherapy or a part of a broader skin care management for such conditions as acne, photo-damage, wrinkling as well as miasma. Care to be taken to avoid irritation as this may result in worsening of miasma or other pigmentary problems. Newer formulations combine glycolic acid with an amino acid such as arginine and form a time-release system that reduces the risk of irritation without affecting glycolic acid efficacy. The use of an anti-irritant like allantoin is also helpful. Because of its safety, glycolic acid at the concentrations below 10% can be used daily by most people except those with very sensitive skin.

b] In higher concentrations(between 10 and 50%) its benefits are more pronounced but are limited to temporary skin smoothing without much long lasting results. This is still a useful concentration to use as it can prepare the skin for more efficacious glycolic acid concentrations (50 - 70%) as well as prime the skin for deeper chemical peels such as TCA peel (trichloroacetics acid).

c] At higher concentrations(between 50-70%) applied for 3 to 8 minutes under the supervision of a physician, glycolic acid promotes slitting between the cells and can be used to treat acne or photo-damage (such as mottled dyspigmentation, melasma or fine wrinkles). The benefits from such short contact application (chemical peels) depend on the pH of the solution (the more acidic the product, or lower pH, the more pronounced the results), the concentration of GA (higher concentrations produce more vigorous response), the length of application and prior skin conditioning such as prior use of topical vitamin A products.

Although single application of 50 - 70% GA will produce beneficial results, multiple treatments every 2 to 4 weeks are required for optimal results. It is important to understand that glycolic acid peels are chemical peels with similar risks and side effects as other peels.

**Side effects of AHAs chemical peeling:** can include hyper-pigmentation, persistent redness, scarring as well as flare up of facial herpes infections ("cold sores").

- **Safety:** AHAs are generally safe when used on the skin as a cosmetic agent using the recommended dosage. The most common side-effects are mild skin irritations, redness and flaking. The severity usually depends on the pH and the concentration of the acid used. Chemical peels tend to have more severe side-effects including blistering, burning and skin discoloration, although they are usually mild and go away a day or two after treatment.

The FDA has also warned consumers that care should be taken when using AHAs after an industry-sponsored study found that they can increase photosensitivity to the sun.

**BETA HYDROXY ACID[4]:**

Beta hydroxy acid is not a single substance; instead, it is a term used to describe a family of organic acids. These organic compounds may either be naturally occurring or synthetic. In their natural chemical state, beta hydroxy acids are found in the body, in fruits, and in the bark of the willow tree.

Synthetic versions have proven to be as effective as the natural forms and are used in an array of medicines and commercial products. The beta hydroxy acid family consists of salicylic acid, carnitine, beta-hydroxybutyric acid, 3-hydroxypropionic acid, and beta-hydroxy beta-methylbutyrate acid.

Salicylic acid is the most well-known beta hydroxy acid and the only one used in dermatology. Derived from aspirin, it is widely used in both cosmetics and skin care products. For decades, salicylic acid has functioned as the main ingredient in acne treatment medicines. Since beta hydroxy acids are oil soluble, they are able to penetrate beneath the skin into the pores. Due to this, beta hydroxy acid is an effective ingredient in modern anti-aging products and skin cleansers.

Carnitine is biosynthesized from amino acids in the body. It is used during the metabolic process that breaks down fats. Outside of the body, carnitine is found in high concentrations in dairy products and red meat. As a supplement, this beta hydroxy acid is mainly used to treat heart-related conditions and symptoms of kidney disease. Carnitine is also marketed as a weight-loss supplement, although its effectiveness in helping dieters has yet to be determined.

Beta-hydroxybutyric acid is used as a source of energy by the brain when blood glucose levels are low. Industries use the synthetically developed form of this acid, which is produced by bacteria, as part of the manufacturing process in making biodegradable plastics. Another beta hydroxy acid, 3-hydroxypropionic acid (3-HP), is also produced in the body, but has been synthesized in laboratories by using microbes. It is an important component in the industrial production of specialty chemicals such as polyesters.

Beta-hydroxy beta-methylbutyrate acid (HMB) has a long name and a major role in health. HMB is

formed naturally in the body during the breakdown of an amino acid. Plants such as alfalfa and animals such as catfish also contain HMB. Scientific studies have established its ability to increase muscle mass and decrease body fat. It has become a popular bodybuilding dietary supplement.

- **Alpha Hydroxy Acids and Chemical Peels[3]**

Alpha hydroxy acids in various concentrations are used in chemical peels. The concentration determines who can use it. Alpha hydroxy acid products sold to consumers must have a concentration of less than 10%. Trained cosmetologists can use alpha hydroxy acid products that have a concentration of 20% to 30%. These chemical peels give results that are similar to microdermabrasion - erasing fine lines and giving the skin a smoother appearance with 1 to 3 application.These treatments must be repeated every 3 to 6 months to maintain this skin appearance. Doctors can use alpha hydroxy acid products that have a concentration of 50% to 70%. These treatments also erase fine wrinkles and remove surface scars, but the effects last longer - up to 2 to 5 years. The higher the alpha hydroxy acid concentration used in a chemical peel, the more skin irritation occurs. At the 50% to 70% concentration, a person could expect to have severe redness, flaking, and oozing skin that can last for 1 to 4 weeks.

- **The Difference Between Alpha and Beta Hydroxy Acids[2]:**

The main difference between alpha hydroxy acids and beta hydroxy acid is their lipid (oil) solubility.Alpha hydroxy acids are water soluble only, while beta hydroxy acid is lipid (oil) soluble. This means that beta hydroxy acid is able to penetrate into the pore which contains sebum and exfoliate the dead skin cells that are built up inside the pore. Because of this difference in properties, beta hydroxy acid is better used on oily skin with blackheads and whiteheads. Alpha hydroxy acids are better used on thickened, sun-damaged skin where breakouts are not a problem.

**2. BOTANICALS:**

Botanicals comprise the largest category of cosmeceutical additives found into the marketplace today.

Some botanicals that may benefit the skin include: green tea extract, ferulic acid, and grape seed extract.

**Examples:**

**a] Ferulic acid:** This compound, which is derived from plants, is considered to be a potent antioxidant, and has been shown to provide photoprotection to skin.Furthermore, when ferulic acid is combined with vitamins C and E, the product has been shown to provide substantial UV protection for human skin.Moreover, Murray et al. report that because its mechanism of action is different from sunscreens, ferulic acid could be expected to supplement the sun protection provided by sunscreens.

**b] Grape Seed Extract:** This botanical has been established as a potent antioxidant and has been shown to speed wound contraction and closure.Topical application of grape seed extract has also been shown to enhance the sun protection factor in humans.

**3. DEPIGMENTING AGENT:** Skin-lightening agents added to product formulations have become increasingly popular. Common depigmenting ingredients include hydroquinone, ascorbic acid (vitamin C), kojic acid, and licorice extract (glabridin).

**Examples:**

**a] Hydroquinone:** Hydroquinone has been the agent of choice for skin lightening.The US FDA has proposed concentrations between 1.5% and 2% in skin lighteners.A recent report suggested that this concern has been based mainly on studies with animal models utilizing long-term exposure at high dosages are carcinogenic. Routine topical application may pose no greater risk than that from levels present in common foods.

**b] Ascorbic Acid (Vitamin C):** Ascorbic acid is a naturally occurring antioxidant found in citrus fruits and leafy green vegetables. It is hydrophilic, so skin penetration is low.

**c] Kojic Acid:** Kojic acid is a less commonly used bleaching agent. When combined with dipalmitate, there is improved skin penetration and greater stability, but there is little research to support its efficacy.

**d] Licorice Extract (Glabridin):** Several studies on miasma have shown good efficacy with only mild irritation that disappeared with discontinuation.

**4. EXFOLIANTS:**

Exfoliants promote skin turnover by removing adherent cells in the stratum corneum. Common exfoliants found in cosmeceutical preparations include salicylic acid (SA), lactic acid, and glycolic acid. There are concerns that repeated use of SA and AHAs could cause the dermis and epidermis to be more vulnerable to penetration by UV radiation. Therefore, patients should be advised to use adequate sun protection. The Cosmetic Ingredient Review Expert Panel concluded that SAs are safe to use when formulated to avoid skin irritation and to be non-photosensitizing, or when directions for use include the daily application of sun protection.

**5. MOISTURIZERS:** Moisturizers restore water content to the epidermis, and provide a soothing protective film. They improve the appearance and tactile properties of dry and aging skin, restore the normal barrier function of the skin, and reduce the release of inflammatory cytokines. Moisturizers comprise an important therapeutic component in the management of various skin conditions (e.g., eczema, psoriasis, pruritus, and aged skin)

**6. TOPICAL PEPTIDES[9]:**

Topical peptides are regarded as cellular messengers that are formed from amino acids and are designed to mimic peptide fragments with endogenous biologic activity. These pentapeptides (e.g., KTTKS) are comprised of a subfragment of type I collagen propeptide, and play a role in signalling fibroblasts to produce collagen in the skin,which can improve the appearance of wrinkles. One variation, the palmitoyl pentapeptide known as Pal-KKTKS (Matrixyl™, Sederma) was tested in a controlled, double-blind, left-right randomized, split-face study of 93 women between 35 and 55 years of age who had Fitzpatrick I-III type skin. Pal-KTTKS concentration was 3ppm; both groups were treated twice daily for 12 weeks. Improvements in wrinkle appearance and length were observed.

**7. RETINOIDS[10]:**

Retinoids are among the most common ingredients found in cosmeceuticals. In fact, they are the most studied and have the most data behind them. They consist of natural and synthetic derivatives of vitamin A that reduce hyperpigmentation and inhibit enzymes from breaking down collagen. Many of their cosmeceutical claims are based on data derived from studies on tretinoin and other classes of retinoid drugs. Some key retinoids include retinoic acid (tretinoin), retinol, retinaldehyde etc.

**Examples:**

**a]Retinoic Acid (Tretinoin):** There is extensive literature on the use of tretinoin, which is considered to be one of the most potent compounds for treating the signs of aging and/or photodamaged skin, including fine lines, hyperpigmented spots, and wrinkles.However, side-effects such as burning and scaling have limited its acceptance. In order to minimize these side-effects, various novel drug delivery systems are being developed.

**b] Retinol (Vitamin A).**:Retinol is oxidized into retinaldehyde and then into retinoic acid, the biologically active form of vitamin A. In vivo studies showed that topical retinol had only a modest retinoid-like biologic activity compared with topical retinaldehyde and retinoic acid.Two randomized, controlled trials reported significant improvement in fine wrinkles after 12 and 24 weeks of treatment, respectively.

**c] Retinaldehyde:** Retinaldehyde is viewed in a large part as an intermediate form during the conversion of retinol to retinoic acid. Studies have shown that it does have activity in human skin.Moreover, some studies have reported that this retinoid can produce significant clinical improvement in the appearance of fine and deep wrinkles.

The **retinoids** are a class of chemical compounds that are related chemically to vitamin A. Retinoids are used in medicine, primarily due to the way they regulate epithelial cell growth.

Retinoids have many important and diverse functions throughout the body including roles in vision, regulation of cell proliferation and differentiation, growth of bone tissue, immune function, and activation of tumor suppressor

genes.

Research is also being done into their ability to treat skin cancers. Currently 9-cis retinoic acid may be used topically to help treat skin lesions from Kaposi's sarcoma.

**Types:**

There are three generations of retinoids:

- First generation retinoids which include retinol, retinal, tretinoin (retinoic acid, Retin-A), isotretinoin and alitretinoin.
- Second generation retinoids which include etretinate and its metabolite acitretin.
- Third generation retinoids which include tazarotene , bexarotene and Adapalene.
- **Structure:**

The basic structure of the retinoid molecule consist of a cyclic end group, a polyene side chain and a polar end group. The conjugated system formed by alternating C=C double bonds in the polyene side chain are responsible for the color of retinoids (typically yellow, orange, or red). Hence, many retinoids are chromophores. Alternation of side chains and end groups creates the various classes of retinoids.

First and Second generation retinoids are able to bind with several retinoid receptors due to the flexibility imparted by their alternating single and double bonds.

Third generation retinoids are less flexible than first and second generation retinoids and therefore, interact with fewer retinoid receptors.

- **Absorption[11]:**

The major source of retinoids from the diet are retinyl esters derived from animal sources. Retinyl esters are hydrolyzed in the intestinal lumen to yield free retinol and the corresponding fatty acid (i.e. palmitate or stearate). After hydrolysis, retinol is taken up by the enterocytes. Retinyl ester hydrolysis requires the presence of bile salts that serve to solubilize the retinyl esters in mixed micelles and to activate the hydrolyzing enzymes .

Several enzymes that are present in the intestinal lumen may be involved in the hydrolysis of dietary retinyl esters. Cholesterol esterase is secreted into the intestinal lumen from the pancreas and has been shown in vitro to display retinyl ester hydrolase activity. In addition, a retinyl ester hydrolase that is intrinsic to the brush-border membrane of the small intestine has been characterized in the rat as well as in the human. The different hydrolyzing enzymes are activated by different types of bile salts and have distinct substrate specificites. For example, whereas the pancreatic estrase is selective for short-chain retinyl esters, the brush-border membrane enzyme preferentially hydrolyzes retinyl esters containing a long-chain fatty acid such as palmitate or stearate. Retinol enters the absorptive cells of the small intestine, preferentially in the all-trans-retinol form.

- **Uses**

Retinoids are used in the treatment of many diverse diseases and are effective in the treatment of a number of dermatological conditions such as inflammatory skin disorders, skin cancers, disorders of increased cell turnover.

- **Toxicity**

Toxic effects occur with prolonged high intake. The specific toxicity is related to exposure time and the exposure concentration. A medical sign of chronic poisoning is the presence of painful tender swellings on the long bones. Anorexia, skin lesions, hair loss, hepatosplenomegaly, papilloedema, bleeding, general malaise, pseudotumor cerebri, and death may also occur.

Chronic overdose also causes an increased lability of biological membranes and of the outer layer of the skin to peel.

Systemic retinoids (isotretinoin, etretinate) are contraindicated during pregnancy as they may cause CNS, cranio-facial, cardiovascular and other defects.

**TOPICAL RETINOID[12]:**

**DEFINATION:** Topical retinoids are creams, lotions and gels containing one or other of group of medicines derived from Vitamin A. These compounds result in proliferation and reduced keratinisation of skin cells

independent of their functions as a vitamin.

Many brand-name creams containing the retinoids retinol and retinaldehyde can be obtained over the counter at pharmacies and supermarkets.

The more potent topical retinoids available on prescription in New Zealand are:

- ReTrieve™ cream (tretinoin)
- Retin-A™ Cream (tretinoin or retinoic acid)
- Retinova™ Cream (tretinoin emollient)
- Isotrex™ Gel (isotretinoin)
- Differin™ Gel, Cream (adapalene)
- **Uses:**

1: Topical retinoids are effective treatments for mild to moderately severe acne. The effect is often noticeable within a few weeks, but it may take 6 weeks or longer before improvement occurs.

2: Tretinoin has also been shown to reverse some of the changes due to photo-aging, i.e. sun damage.

3: If used long term, it may reduce some fine wrinkles, freckles, solar comedones (whiteheads and blackheads), and solar keratoses (tender, dry sun-spots).

4: They may also be used in bleaching creams to reduce pigmentation in melasma.

Topical retinoids can be applied to any area but are most often used on the face, the neck and the back of hands.

- **Side effects:**

a] When used for first time,retinoids can irritate the skin. This is more likely in those with sensitive skin, resulting in stinging. It may cause or aggravate eczema, particularly atopic dermatitis.

b] 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.

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

d] Retinoids taken by mouth may cause birth deformities. Manufacturers recommend that topical retinoids are not used in pregnancy or breastfeeding as negative animal studies are not always predictive of human response.

**8. SUNSCREEN:**

Sunscreens are the single most important cosmeceutical, because they protect skin against solar radiation, which is the most important damaging environmental agent. As a result, they help to prevent the signs of aging. To be effective, sunscreens should provide broad spectrum coverage that includes both UVA and UVB blocking agents to inhibit photoaging and be part of a daily skin care regimen. Sunscreens contain active ingredients that act as ultraviolet filters. The recommended application is $2mg/cm^2$, though this is rarely achieved in real-life practice.

**9. ANTIOXIDANTS[20]:**

Antioxidants reduce free-radical damage, thereby preventing impairment at the cellular level. They inhibit inflammation, which leads to collagen depletion, and they offer protection against photodamage and skin cancer.

Common antioxidants include alpha-lipoic acid (ALA), L-ascorbic acid (vitamin C), niacinamide (vitamin B3), N-acetyl-glucosamine (NAG), α-tocopherol, and ubiquinone (CoQ10).

**1: Alpha-lipoic Acid (ALA).** Alpha-lipoic acid has anti-inflammatory properties and acts as an exfoliant. Topical 5% ALA applied b.i.d. for 12 weeks reduced skin roughness, lentigines and fine wrinkles. This agent does not protect against UV-induced erythema or reduce the number of sunburn cells.

**2: L-ascorbic Acid (Vitamin C).** There is clinical data to support the use of topical vitamin C to improve fine lines and reduce both pigmentation and inflammation, and many cosmeceutical formulations contain this antioxidant. However, many of these formulations are not effective on the skin because:

- The concentration of L-ascorbic acid is too low.

- Exposure of the product to air and light compromises the stability of the product.
- The L-ascorbic acid molecule (in the form of an ester or a mixture of isomers) cannot be absorbed or metabolized effectively by the skin.

In high enough concentrations (i.e., at least 10%) of the nonesterified, optimal isomer, this antioxidant does inhibit UV damage. A formulation that has an acid pH of approximately 3.5 may optimize vitamin C absorption. Newer formulations of stabilized ascorbic acid derivatives may prove to be more efficacious.

**3: Niacinamide (Vitamin B3)**

Niacinamide is a potent antioxidant that is generally well tolerated. It improves the lipid barrier component of the epidermis, thus reducing transepidermal water loss, and acts as an inhibitor of melanosome transfer, resulting in reduced hyperpigmentation. Studies have revealed significant reduction in fine lines and wrinkles, hyperpigmented spots, red blotchiness, and skin sallowness, as well as improved skin elasticity.

**4: N-acetyl-glucosamine (NAG).** NAG is a more stable form of glucosamine, and may prevent new signs of photodamage from occurring, and fade existing imperfections by interrupting the chemical signals that promote melanin production.

**5: α-tocopherol (Vitamin E).** When taken orally, α-tocopherol protects membrane lipids from peroxidation. It has been shown to reduce sunburn cells after UV exposure, neutralize free radicals, and act as a humectant. Its activity can be renewed by combining it with a vitamin C preparation.

As a component in topical formulations, has shown some limited efficacy; however, when a stable formulation delivers a high concentration of the nonesterified, optimal isomer of this antioxidant, vitamin E does inhibit the acute UV damage of erythema, sunburn, and tanning, as well as chronic UV photoaging and skin cancer. Because vitamin C regenerates oxidized vitamin E, the combination in a cosmeceutical formulation is synergistic - particularly with regard to UV protection.

**6: Ubiquinone (CoQ10).** Ubiquinone is a naturally occurring, fat-soluble antioxidant and there is good in vitro

evidence that it can suppress fibroblast production of UVA-induced collagenase, thereby reducing collagen breakdown.It has been shown to be effective against UVA mediated oxidative stress in human keratinocytes. Ubiquinone was also able to significantly suppress the expression of collagenase in human dermal fibroblasts following UVA irradiation.Another study showed that ubiquinone can strongly inhibit oxidative stress in the skin induced by UVB. It is an effective antioxidant protecting the dermal matrix from both intrinsic and extrinsic agent.

**Some Antioxidants[23]:**

**1. Vitamin C:** – Also known as ascorbic acid. The most bioavailable form of Vit C is Ester-C, it has been shown to last longer in the body and comes with calcium (10% of the weight of Vit C) as this helps with cellular uptake. Humans, other primates and guinea pigs are the few animals that cannot synthesize Vitamin C as we lack a critical enzyme in the synthesis. 1-2 grams daily maintenance, 4-6 grams during active infection.

**Good for**: fighting stress; detoxifying poisons; antiviral properties and antihistamine (this is the inflammation response I talked about); repair and growth of tissue cells, blood vessels, teeth and bones; prevention of viral and bacterial infections.

**Deficiency symptoms**: Appetite loss; bruising easily; fatigue; GI problems; nose bleeds, slow wound healing; bleeding gums (loose teeth usually accompany this).

**1. Vitamine E** – Alpha tocopherol, also important and should be consumed with the gamma-tocopherol. Enhances the activity of Vit A (since both of these are lipid soluble). 400 IU maintenance daily, 800IU during detox or active infectious periods. Its important not to take too much as this vitamin will hang out longer due to the fact that it is lipid soluble and is excreted less easily.

- **Good for**: endurance; protecting the lungs against pollution; anticoagulant (be careful if someone is already on an anticoagulant); accelerating the healing of burns.
- **Deficiency symptoms**: Muscle degeneration; reproductive disorders; miscarriages; premature or low birth

weight in infants, anemia.

**3. Vitamine A** – retinol – derived from the cleavage of beta-carotene, very similar to lycopene.10,000 IU for maintenance; 25,000 IU daily during active infection.

- **Good for***:* healthy function of intestinal flora, sinuses, ears, eyes, urinary tract, and respiratory organs; reduces duration of disease; healthy skin, hair; treatment of acne and boils (note the allopathic application of Retin-A, an analog of retinol); helpful in the treatment of emphysema.
- **Deficiency symptoms**: ear, sinus, and eye infections; anemia; lower resistance to infections.

**4. CoQ10** – coenzyme Q 10 – a quinone found in the mitochondria of every cell. Carries electrons in the electron transport chain. This is extremely important for cellular energy. Heart cells require the most energy and thus CoQ10 is found in the most abundance here.

- **Good for**: low energy levels, heart troubles (especially where there is muscular insufficiency). Applied topically actually reduces photoaging ; may actually modify cancer mediated cytokines (messengers). Helps in recovery of heart ischemia

**5. Lycopene** – This molecule is so similar to Vitamine A in structure. Found in concentrated tomato products 10mg/day would be a minimum.

**6. Alpha Lipoic Acid** – AKA Lipoate - Vitamin like cofactor found in mitochondria. Here's another cofactor found in and around the mitochondria. This lipoate has had excellent effects for neurodegenerative processes and diseases. It does this by raising the glutathione levels. Glutathione is an extremely important biological compound that destroys harmful oxidizing agents, it does this by reducing them (adding a hydrogen), but in the process forms a disulfide bridge to another oxidized glutathione, an enzyme then reduces this molecule. Glutathione is actually three amino acids chained together. Alpha Lipoic acid is a substrate that the reducing enzyme is attached to.

It protects the neural cells from glutamate cytotoxicity by reducing the loss of glutathione following a

glutamate challenge. The glutamate challenge follows a stressful neurological event (viruses, injury, hypoxia – lack of oxygen, or general stress). It has been shown that people in chronic pain have mood alterations due to the fact that the constant firing of the pain receptors in the brain cause a glutamate challenge to the mood centers and that these neurons are actually dying off from the damage.

**DOSE**: A good daily dosage is between 50 – 250mg daily, possibly more during challenged times.

**7. Pycnogenol** - This is derived from the Pinus maritima tree of the french coast. In this same class is grape seed extract and other pine tree extracts. What one has to be careful here is the extraction method. If chemical solvents are used then some of the antioxidant properties are lost, this and heat can dilute the properties.

- **Others** [21]- This category includes bioflavenoids, proanthocyanidins, esters, etc.

Most antioxidants have what is known as conjugated double bonds. This is where carbon to carbon double bonds exists every other carbon so that single and double bonds alternate. As a matter of fact the more conjugated the atom the darker the color thus beta-carotenes are yellow to orange in color and red grapes are even darker. The conjugated double bonds act as free radical neutralizers. Double bonds are the connections of two atoms that occupy more than one orbital, in these orbitals are electrons.

There are orbitals that are s and p types (among others), double bonds contain two p orbitals; these p orbitals exist in 3D space above and below the s orbital. When there is a conjugated system these p orbitals will line up and the electrons in them will tend to move about the shared orbitals, this is known as a PI electron cloud, for the electrons don't particularly belong to any one specific atom. Conjugated double bonds exist in carbon chains of vitamin A. When a free radical comes along, the antioxidant will readily give up an electron, but still be stable due to the conjugated bonds, even though that now, this is a free radical itself, but hundreds of times more stable than a hydroxyl radical, let's say (OH ).

**Free Radical theory of disease[25]:**

- **Definition of free radical :** It is any chemical species that has an unpaired electron in one of it's orbitals

(generally the valence or outer shell).

- **Reduction/Oxidation or redox:**

Reduction is the act of neutralizing a free radical (adding an electron) or adding a hydrogen atom to a compound to reduce double bonds between atoms. Oxidation is the act of removing an electron from a stable orbital or reducing the number of single bonds and increasing the number of double bonds, this is usually done by either removing a hydrogen or by adding an oxygen sometimes both, thus the name oxidation. Redox potential is the ease of being oxidized or reduced

**Consequences of free radicals**

They change the molecular characteristic of the victimized molecule, so this in turn effects it's ability to bind properly which can affect all kinds of biochemical reactions, some having to do with the genetic expression of one protein or another. Oxidative damage, another name for the chemical reaction that free radicals cause, can lead to a breakdown or even hardening of lipids, which make up all cell walls. If the cell wall is hardened (lipid peroxidation) then it is impossible for the cell to properly get it's nutrients, get signals from other cells to perform an action (such as firing of a neuron) and many other cellular activities can be affected.

One such interesting consequence of free radicals comes from our own immune system. Neutrophils secrete a chemical toxin that attacks a foreign invader (after a complex immune response has already started) and thus causes the foreign cell complex to lyse (break apart) and thus releases the invader toxins into the surrounding tissue. This not only signals the body to respond with more immune response to increase local inflammation to help neutralize these toxins, but these immune cells use antioxidants (chiefly Vitamin C) to protect themselves from their own toxins, fascinating stuff. The cytochrome p450 pathway converts harmful hydrocarbons to alcohols that then can be eliminated by the liver. It does this because cytochrome p450 is what is known as a porphyrin ring that contains iron within its structure and this iron oxide extracts a hydrogen from the hydrocarbon and becomes FeOH and now the hydrocarbon is a radical. In the next step the OH radical dissociates from the Fe

to combine with the hydrocarbon radical to create alcohol, which then goes through the alcohol dehydrogenase pathway to eventually get eliminated.

**Conclusions**

There are many cosmeceuticals containing synthetic chemicals or botanical agents or a mixture. In this regard, many phytochemicals have antioxidant property and are relatively safer as compared to synthetic chemicals. Investigators continue to search for phytochemicals with greater efficacy in the ability to protect against various deleterious agents to skin, such as radiation. The scientific data available for silibinin's skin protective efficacy against a range of toxic chemicals and ultraviolet radiation with no side effects suggest that silibinin could be an ideal compound for cosmeceutical preparation. Based on preclinical observations, clinical studies with silibinin in various dermatological conditions, including that of skin aging and cancer, are warranted to assess its efficacy and adverse effects.

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