

**FORMULATION, DEVELOPMENT AND EVALUATION APPROACH FOR TOPICAL
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ABSTRACT

Cosmeceuticals means combination of cosmetics and pharmaceuticals. Cosmeceuticals are cosmetic products with biologically active ingredients purporting to have medical or drug-like benefits. Cosmeceuticals are used to improve and nourish the skin appearance and known to treat different dermatologic conditions. Like cosmetics, cosmeceuticals are also applied topically having ingredients that influence the skin's biological function. Cosmeceuticals are meant to improve appearance by delivering nutrients necessary for healthy skin. Cosmeceuticals usually claim to reduce wrinkles and to improve tone, texture and radiance of the skin. Cosmeceuticals products of herbal origin are most liked among clients as they are mostly nontoxic and holding strong antioxidant activity. Cosmeceutical product can be a drug, a cosmetic, or a combination of both. But the term "cosmeceuticals" has no meaning under the law". Cosmeceuticals are not subject to be reviewed by the Food and Drug Administration (FDA) and the term cosmeceuticals is not recognized by the Federal Food Drug and Cosmetic Act. Although cosmetics and cosmeceuticals both are being tested for their safety and tested to determine whether beneficial ingredients actually live up to a manufacturer's claims is not compulsory. The "cosmeceuticals" label applies only to products applied topically, such as creams, lotions and ointments. Cosmetic labels do not have any division between active ingredients and other ingredients that are essential, they are all listed together.

KEYWORDS: Cosmeceuticals, performance cosmetics, functional cosmetics, dermaceuticals, active cosmetics, nutricosmetics.

INTRODUCTION

The importance of beautification to the mankind has been known since the pre historic time and the desire to look beautiful and healthy has been developing in the society. In recent times fitness, good health, looks, way of presenting oneself are being counted as one of qualities of personality, now a day people are also being judged on these factors. Hence today there is a necessity and desirable requirement to give more attention to the looks and beautification for social acceptance as well as professional success, which is also overemphasized by the media.

On the other hand life span of an average individual has been increased and factors such as sedentary lifestyle and dietary excesses associated with genetic determination, pregnancy and the aging process, contribute to alterations of the face and body that result in the loss of the individual's self-image.^[1] The cosmetic surgery industry is dynamic and growth levels reached record height in 2006, the total UK cosmetic surgery was worth an estimated L 528.9 million, a rise of 47.4% on 2005. In recent times cosmetic surgery market is booming due to the development of various different

technologies especially due to non-surgical technique's being developed. In such technique the time required for recovery is very less comparatively to that of undergoing surgical procedures and thus the patient or consumer can return to his work in shorter span of time. One of mankind's greatest problems is the lack of communication. The basis of successful plastic surgery operation is the consultation. The possible and likely results should be described to the patient as exactly and wholly as possible. Particularly it is of great importance to give a rational advice to the patient who desires a minimally invasive procedure in order to deal with the process of natural and normal aging. The need of scientific measures responds to the requests of all people involved in the demonstration of objective results in comparison to an initial picture.

The development of non-surgical or bio-physical non-invasive methods allows to count on the crucial physiological properties of the skin, such as 1) Moisturization 2) Barrier function 3) Mechanical properties, 4) Micro-circulation 5) Skin colour and even to characterize its topography. Maintenance of skin its improvement recovery of the skin can be evaluated

during time, by registering all variations induced by a product application or by performing an aesthetic treatment. In order to maintain high scientific standards in such evaluations, adequate protocols and statistical tests must be designed and applied.^[2-4] Hence now a day's people are moving towards the non-invasive procedure rather than undergoing surgical procedure. As popularly said –beauty is in the eyes of the beholder!, however money is the important factor for any industry, most often money goes in the pockets of the corporate cosmeceutical shareholders, corporations and their paid entourage of star dermatologists. The cosmetics industry has grown beyond from just focusing on hot pink lipsticks and lash-extending mascara. Cosmeceuticals claim to reduce the skin imperfections rather than just covering up imperfections. Men and women are hurrying to cosmeceuticals counters to anti-wrinkle creams, Alpha Hydroxy Acids, Botox and the like.^[5] Cosmetics are substances used to enhance the appearance or odor of the human body. Cosmetics include skin-care creams, lotions, powders, perfumes, lipsticks, fingernail and toe nail polish, eye and facial makeup. Towelettes, permanent waves, colored contact lenses, hair colors, hair sprays and gels, deodorants, hand sanitizer, baby products, bath oils, bubble baths, bath salts, butters and many other types of products. A subset of cosmetics is called "make-up" which refers mainly to colored products intended to change the user's appearance.^[6] Pharmaceuticals or Drugs are the substance that cure and heal having the disease-fighting or healing properties. A drug is –intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and is —intended to affect the structure or any function of the body.^[7] Cosmeceuticals refers to the mixture of cosmetics and pharmaceuticals. The term cosmeceuticals refer to the substances that exerted both cosmetic and therapeutic benefits. Cosmeceuticals are cosmetic products with biologically active ingredients purporting to have medical or drug-like benefits.^[8] A cosmeceuticals is an ingredient with medicinal properties that manifests beneficial topical actions and provides protection against degenerative skin conditions. It encompasses cosmetic actives with therapeutic, disease-fighting, or healing properties, there by serving as a bridge between personal care products and pharmaceuticals.^[9]

Cosmeceuticals are the development made within the world of dermatological products and the new beckon in skincare. Cosmeceuticals are topical cosmetic pharmaceutical hybrids intended to enhance the health and beauty of skin. Cosmeceuticals products are those poised on the gap between cosmetic products that simply cleanse and beautify, and pharmaceuticals that cure and heal.^[10] ‘Cosmeceuticals’, ‘performance cosmetics’, ‘functional cosmetics’, ‘dermaceuticals’, ‘Active cosmetics’ and ‘nutricosmetics’ are buzzwords in personal care industry. Day by day various innovative terms for cosmeceuticals are being introduced viz.

- Beauty supplements
- Active cosmetics

- Bio-active cosmetics
- Performance cosmetics
- Phytocosmetics
- Functional cosmetics
- Dermaceuticals
- Skinceuticals
- Cosmetic drugs
- Therapeutic cosmetics.^[11]

Cosmeceuticals affects the biological functioning of the skin (medicinal or drug like benefits) depending upon the ingredients present in them. Cosmeceuticals increases the collagen growth in the skin and reduces the harmful effects of free radicals thus maintain the structure of keratin in good condition and making the skin healthier.^[12] There are skin-care products that go beyond coloring and adorning the skin.

Like cosmetics, cosmeceuticals are applied topically; they contain ingredients that influence the skin's biological function. Cosmeceuticals are meant to improve appearance by delivering nutrients necessary for healthy skin. Cosmeceuticals usually claim to reduce wrinkles and to improve tone, texture and radiance of the skin. Cosmeceuticals is the fastest-growing segment of the natural personal care industry.^[13]

Cosmetics and cosmeceuticals are tested only for safety. Efficacy testing is not compulsory. Cosmeceuticals include most of the bioactive food components such as milk peptides certain vitamins and minerals, phytonutrients from herbs, various oils and botanical extracts. Cosmeceuticals market in nowadays more flourished with several botanicals having a history of their use in traditional cultures. More and more cosmeceuticals are being used in cosmetic products due to their less side effects and added advantage of multifunctionality.

More recently the emerging trend of beauty inside and out is becoming increasingly popular, wherein orally consumed nutritional supplements (nutricosmetics) and topically applied cosmeceuticals work in harmony to promote physical appearance and well being. In 2002, the well-known cosmetics company L'Oreal and the food manufacturing giant, Nestlé joined forces to create Innéov, a company established to formulate and market nutritional supplements for beauty benefits.^[9] Several other cosmetics companies, large and small, are currently active in this area as well. In recent times men too unlike women are becoming more conscious about their looks and hence different ranges of men beauty products are being introduced. Recently the market is flooded with large number of cosmeceuticals products like anti-wrinkle creams, sunscreens, moisturizers, bleaching agents, medicated lotions, hair growth stimulants, antidandruff shampoos, eye wrinkle creams, collagen infections, skin care, hair care, and sun care products, etc. The consumers are more often in a state of dilemma when it comes to choose between the various ranges of

competing products, because one does not know which product can do the trick for them. Certain plant-based substances have been claimed to be used in cosmeceuticals products by companies marketing them.

Retinol (Vitamin A) and the retinoid has a history of efficacy in the handling the aging of skin. Retinoid is known for stimulation of collagen synthesis there by growing and transforming growth factor (TGF)-beta and procollagen. Growth factors represent an increasingly popular component of cosmeceuticals. Results of *in-vitro* studies have shown that by adding kinetin, a plant growth factor to human fibroblasts in culture, biological and morphological changes associated with cellular aging may be slowed down. Antioxidants such as alpha-lipoic acid have the ability and capability to penetrate cellular lipid membranes and to scavenge the intracellular free radical. Copper peptide is gaining recognition and in recent studies, enhancement in skin roughness, fine lines, wrinkles, elasticity and overall photo damage versus control were documented by ultrasound evaluation.^[15] Unfortunately the Food and Drug Administration (FDA) the agency that administrates the requirements of the Food Drug and Cosmetics Act of 1906 does not actively review the overstated claims of cosmeceuticals manufacturers. Recognizing this escape in FDA guideline, cosmetics companies have engaged dermatologists to legitimize their overstated claims before consumers. Consumers in turn rely on the recommendations of these medical professional in paying upwards of \$25 to \$400 per bottle to cosmeceuticals companies.

Generally cosmeceuticals are the OTC (Over the counter) sold products that claim to offer a health benefit in addition to conventional cosmetic qualities. Scientific developments will maintain enlargement in the market. Cosmeceuticals products can be purchased from mass market, direct marketing retailers as well as from prestige retailers including increasingly popular -spas. The cosmeceuticals consumer is becoming more complicated; demanding outstanding quality from these products and thus scientific innovations will have to keep up with this demand. Innovations in cosmeceuticals products over the next few years will come primarily in the following areas:

- Proof of effectiveness of ingredients, particularly natural extracts will become more vital because consumers have a broad variety of choices and will discontinue use of unproductive products.
- Botanical products and extracts will continue to substitute chemical materials and plants and fermentation will increasingly substitute animals as ingredient sources.
- Delivery systems will be more complex and effective. Offering triggered and controlled release of actives and the research and development of nanostructure delivery systems will continue.
- Sunscreen actives will be gradually more present in daily wear products and new actives will offer

broad-spectrum UV coverage and/or higher sun protection factors.

- Guideline of cosmetic and drug products will be coordinated globally, particularly between North America, the European Union, and Japan Technology Catalysts. Consumer care research and business strategy staff has completed an extensive analysis of the technologies representing the next-generation ingredients, formulations and delivery systems for cosmeceuticals. They have identified business opportunities in the cosmeceuticals segment of the cosmetic and toiletries industry via personal interviews with inventors, companies and organizations around the world.

HISTORY

The health-giving property of cosmetics was first identified by the Egyptians. The cosmetics were first used by Egyptians in 4000 B.C whose records are being available.^[16] Up to the beginning of 19th century, there was no clear separation between cosmetics and pharmaceuticals, the separation occurred when the first modern pharmaceutical industry was developed. In 1980's there was a rapid expansion of the cosmeceuticals due to hydroxy acids (natural fruit acids) used as exfoliants against wrinkles. In 1961 the term cosmeceuticals was coined by the Raymond Reed, founding member of the United States Society of Cosmetic Chemists. Albert Kligman in 1971 developed a formula to improve the appearance of UV damaged and wrinkled skin, using retinoic acid thereby reactivated interest of the people in cosmeceuticals.^[17] World-renowned dermatologist Dr. Kligman made a long-lasting contribution to the world of skincare by discovering that topical retinoic acid (or tretinoin) can be used for both an acne and wrinkle treatment. Kligman may be described as the father of cosmeceuticals, a term he popularized.^[18] but cosmeceuticals first appeared in the world market in 1996.^[19]

The several cosmetic jars have been unearthed by the Archaeologists whose hieroglyphics say "good for sight" and "stops bleeding". A medical papyrus "Ebers," which was written in 1600 BC, makes frequent reference to a number of cosmeceuticals-type products. The favorite was the one prepared using honey and milk that claimed to help cure skin diseases, while different product mentioned in the Ebers, claiming to "expel wrinkles from the face", were made from frankincense, balantine oil, rush oil and wax in equal proportions.^[20]

A dark powder known as Kohl was being applied around the eyes in an almond shape with a stick. Kohl was made of different colors of copper ore, lead, ochre, ash, burnt almonds and oxidized copper. Red clay mixed with water was the choice of make-up, for the cheeks and lips. Henna was used to paint the finger-nails yellow or orange. Egg whites, gum Arabic, beeswax and gelatin were used to create nail color in ancient China. As time moved on cultures were fused and the Greeks began to

move into cosmetics history and accept the use of Egyptian cosmetics. They did it just simply to look good and not for spiritual purposes. Centuries later, as the Romans moved in they started the use of cosmetic formulas for other purposes, such as creating aphrodisiacs. They started to use blood mixed sheep fat for nail polish and instead of just using the traditional body oils created by Egyptians, they took baths in mud and crocodile excrement.^[21]

NEED FOR STUDY ON COSMECEUTIALS

Now a day it's not just the interest of people but certainly has become the need of the people to maintain a youthful & healthy appearance. Ultimately as the population in the world of the median age increases there is rise in the demand of the cosmeceuticals. Over 560 million people in India are in the age group of 18-35 years. As median age increases, the market is going to boom, especially growing number of women in the workforce feeling the hassle to maintain a youthful and vibrant appearance. This resulted into a rapid growth of cosmeceuticals in the natural personal care industry.

As there is constantly growth in global market a lot of money is playing in hands of people at the same there is increase in the population with higher qualification and knowledge thus this class of population has become more beauty-conscious and thus is spending a high amount of their earning in maintaining a youthful appearance i.e. in cosmeceuticals. Thus cosmeceuticals market has become one of the fastest growing markets throughout the globe. Development in technology and invention of new ingredients has further contributed to the progress in the commercialization of cosmeceuticals products world-wide. The market that reached to the mark of US\$ 27.2 Billion in 2010 is likely to augment at a rapid pace in the coming years with anti-aging skin care taking the top spot in revenue patterns.

The cosmeceuticals demand in US is estimated to grow by 7.4% per year to \$8.2 Billion in 2012. The skin care segment will account for 63% of all cosmeceuticals product demand through 2012 and is expected to grow to \$22.1Billion in worldwide sales by 2013.^[22]

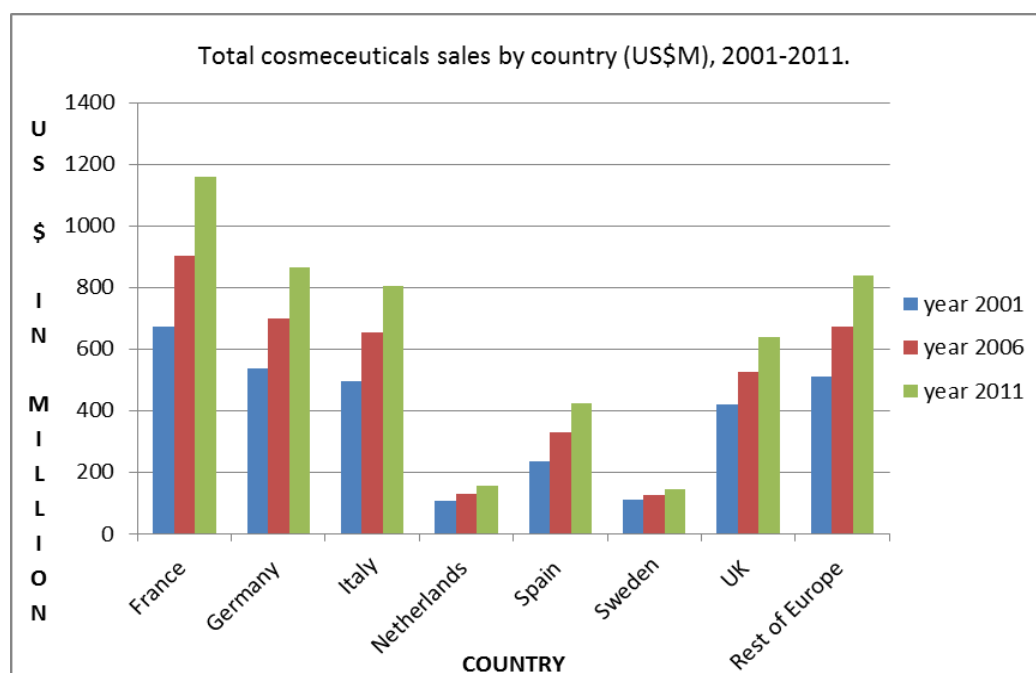


Figure 1: The graphical representation of sales in cosmeceuticals.

Source-data monitoring analysis^[25]

According to new research report –Global Cosmeceuticals Market Analysis, the global cosmeceuticals market offers enormous potential in the Asian countries, such as China, Japan and India, which are also set to magnetize major players in future. Though the market is at the emerging stage in India and China, there remains an untouched large population, with the desire to look young and fair. A mark in the global cosmetics market has already been made by the Japan and its position in the cosmeceuticals (having quasi drug status) segment is effectively improving.

Through in-depth and prudent analysis of the developments taking place at the global level, it is observed that skin care and hair care cosmeceuticals dominates the market presently. However, injectable and various other major sub-segments, such as tooth whitening, lip protection, etc are also garnering considerable amount of profits for cosmetic companies. In addition, research into new ingredients such as stem cell and peptides for skin care-based cosmetics is projected to modify the market supremacy in the days to come.

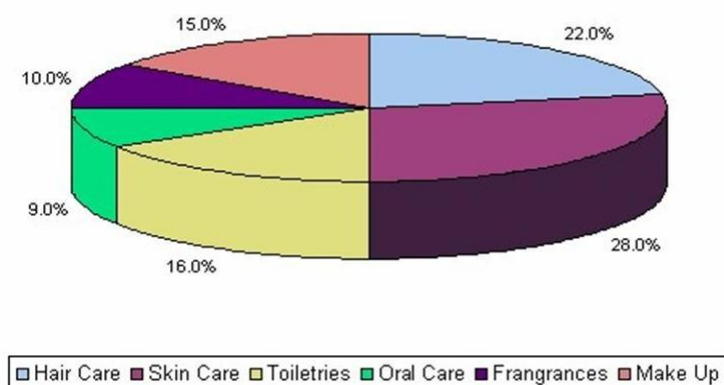


Figure 2: The pie diagram of various cosmeceutical product depending upon their demand.

The concept propounded by Dr. Albert Kligman states that –The Cosmeceuticals are topical agents that are distributed across a broad spectrum of materials lying somewhere between pure cosmetics they partake of both categories^[23]. In India very slight research is carried out to prove the use and benefits of cosmeceuticals. At global level many companies, such as Procter and Gamble Biersdorf and L’Oreal, are advancing and understanding the structure of skin and role of cosmeceuticals. An extremely strict research standard has been set by these company and they evaluate cosmeceuticals in the same manner as drugs. None of this work is being done in academic dermatology.^[24] Tiny research has been carried out to prove the effectiveness, efficacy and safety of these products and a lot of questions remain unanswered. It is primarily viewed as marketing efforts to enhance the use of these products.

Effect of ROS (Reactive oxygen species) on skin

Ultraviolet (UV) radiation are portion of the electromagnetic spectrum that lies between X rays and visible light, i.e., between 40-400 nm (30-3 eV). The UV spectrum is mainly divided into five spectrum, i.e.

Vacuum UV (40-190 nm), Far UV (190-220 nm), Ultraviolet C [UVC] (220-290nm), Ultraviolet B [UVB] (290-320), and Ultraviolet A [UVA] (320-400 nm). UVA can be further divided into two sub-section i.e. UVA I (340-400 nm) and UVA II (320-340 nm).^[26] Solar UVR at the earth's surface comprises roughly about 95-98% of UVA and 2-5% of UVB, all the UVC being absorbed by stratospheric ozone. The frequency of ultraviolet type B or UVB is mainly responsible for erythema of sunburn and suntan of the skin. Once human skin is exposed to UVB, it is absorbed by DNA of keratinocyte.^[27] Its high energy radiation, which is dependent on its wavelength, causes not only sunburn but also skin ageing, skin cancer, etc.^[28] To avoid the harmful effects of repeated exposure to ultraviolet radiation, personal protection, Personal measures are needed. The interaction of UVR with skin surface causes biochemical changes in collagen, elastin and connective tissues, there by resulting into break down of collagen and elastin fibers of the skin by enzymes collagenase and elastase that are responsible for maintaining the skin firmness and elasticity, and skin deterioration start to occur.^[29] As skin becomes less elastic, it gradually becomes drier and looks wrinkled.

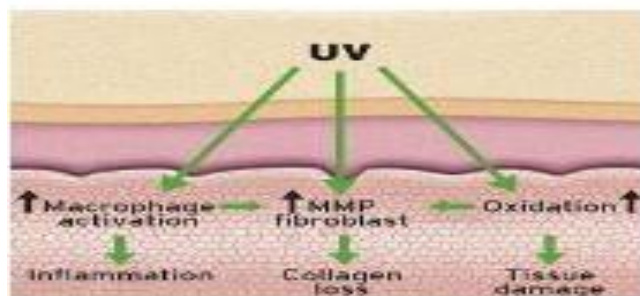


Figure 3: A schematic illustration of UV-induced inflammation, collagen loss and tissue damage.

CLASSES OF COSMECEUTICAL

Major Classes of Cosmeceuticals are as follows

Sunscreens

These are considered as OTC drugs: sun protection factor must be proven by *in-vitro* and *in- vivo* studies.

These are regarded by dermatologists as the single most important formulation that should be applied daily. These are the products formulated to meet individual preferences, such as scent and feel, can improve compliance.

Retinoids

These are the natural and synthetic derivatives of vitamin A.

Drugs: retinoic acid (tretinoin). Adapalene and tazarotene. Substantial scientific data confirm their anti-aging and anti-acne benefits. Retinoic acid is considered by dermatologists to be the anti-aging gold standard. These are available only through a doctor's prescription.

Cosmeceuticals: retinol, retinaldehyde, retinylpropionate, retinylpalmitate. In many cases, bioavailability and activity are unproven when formulated.

Moisturizer

Moisturizer includes emollients, occlusives, and humectants. They are considered to be the most useful product for the management of various skin conditions (e.g. atopic dermatitis, psoriasis, pruritus, aging skin).

Antioxidants

These include vitamins A, C and E; alpha lipoic acid; Ubiquinone (coenzyme Q-10); idebenone; polyphenols (e.g. catechins, flavonoids); kinetin; botanicals (e.g. teas, grape seed, grape skins and stems, coffeeberry). They enhance the skin's natural antioxidant protection system with topical application. They reduce free-radical damage by blocking the oxidative processes in cells. Antioxidants inhibit inflammation that causes collagen depletion. They protect against photo damage and skin cancer. They do reverse signs of photo aging.

Hydroxy' Acids (alpha. beta, poly)

These include glycolic acid, tartaric acid, citric acid, malic acid, pyruvic acid and lactic acid. They can improve depigmentation and skin texture. They can induce actual structural changes in skin, so the potential exists for regulatory scrutiny.

Lightening Agents

At best, depigmenting agents can achieve modest levels of efficacy. Hydroquinone is considered to be the most effective. They are presently under re-evaluation by the US FDA. Sunscreen use is required due to drug-induced photosensitivity, other examples include kojic acid, glabridin (licorice extract), arbutin, azelaic acid, n-acetyl glucosamine and vitamin C.

Botanicals /Plant Extracts

They have experienced a rapid rise due to the popularity of natural compounds. These represent the largest group of additives found in marketed products. They have limited scientific data to support efficacy and safety.

Epidermal Growth Factors

These are the naturally occurring chemicals in the body that influence cellular proliferation and differentiation.

The potential applications include regeneration of damaged or aged skin.

Proteins/ Peptides

They can trigger skin repair as needed. There are some indications that they can reduce the signs of aging and accelerate the skin's healing processes.

Other vitamins and Minérales

Recently, the market is swamped with too many cosmeceuticals products like anti wrinkle creams, medicated lotions, hair growth stimulants, antidandruff shampoos, eye wrinkle creams, collagen injections, etc.^[30]

There are **three primary categories of ingredients** in cosmeceuticals that have the capability to modify the biologic function of the skin

- Botanicals,
- Retinoids and
- Hydroxy Acids.

Each offers its own unique benefits.

Botanical extracts: including teas, soy, pomegranate, date, grape seed, horse chestnut, German chamomile, curcumin, comfrey, allantoin and aloe, these are natural plant-based ingredients that can contribute to generate refreshing, aromatic formulas to soothe, hydrate, and balance the skin. Some are designed to soothe and calm inflamed or irritated skin. Botanicals are typically not the primary ingredient of a cosmeceutical but are combined with retinoids and Hydroxy Acids to create effective skin care products.

Retinoids: Retinoids include Vitamin A and its derivatives, which act as antioxidants and help the skin in its natural processes of circulation, exfoliation and cellular regeneration. Retinoids can reverse the signs of aging, reducing fine lines and wrinkles, tightening and smoothing the skin surface and restoring a youthful glow.

Hydroxy Acids: They are often referred to as -fruit acids and are further classified into two sub-categories according to their molecular structure: 1) alpha hydroxy acids (AHAs) and 2) beta hydroxy acids (BHAs). AHAs such as Glycolic acid, Citric acid, Lactic acid, Malic acid, Mandelic acid and Tartaric acid, are the uppermost anti-aging skin care ingredients today. Alpha hydroxyl acids (AHAs) act by normalizing cell turnover in the top layers of the skin (i.e. epidermis), and by boosting the formation of normal and healthy skin. They also result in the diminishing of fine lines and wrinkles by helping in reversing the sun damage to the dermis (the deeper layers of the skin). The most commonly used beta hydroxyl acid (BHA) is salicylic acid, which works well as an exfoliant and is helpful in the treatment of acne and dry skin.^[31]

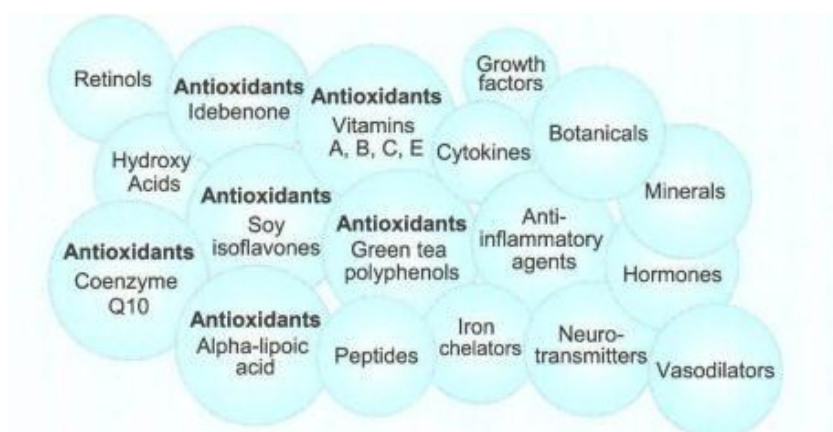


Figure 6: Some topical cosmeceuticals ingredient touting anti-aging claims.

Skin Care Cosmeceuticals

Cosmetics and skin care products have become the part of everyday grooming of the people. It is essential to Protect and preserve the skin for good health. Our skin, which is the largest organ of the body acts by separating and protecting the internal environment from the external one. UV radiations coming from the sunlight penetrate the skin and accelerated damage due to free radicals, which consist of wrinkling, inflammation and hyper pigmentation. The collagen and elastin fibres of the skin due to prolonged exposure to UV radiation are broken down by enzymes collagenase and elastase and thus the texture of skin deteriorates. Collagen and elastin are responsible for maintaining the elasticity and integrity of the skin. Numerous plant extracts and antioxidants that are obtained from natural sources are able to prevent the aging and also improving the appearance of the skin.^[32]

The most important botanicals pertaining to dermatologic uses, such as cosmeceuticals, include teas, soy, pomegranate, date, grape seed, Pycnogenol, horse chestnut, German chamomile, curcumin, comfrey, allantoin, and aloe; of all these only green and black tea, soy, pomegranate, and date have been studied to the extent that clinical trials for the treatment of parameters of extrinsic aging have been published.^[33] Potential cosmeceuticals agents in this category include green tea, grape seed extract, vitamin E and beta-carotene.

The following ingredients are most commonly used in cosmeceuticals:

Boswellic acids

These are obtained from *Boswellia serrate* and the key function is to inhibit the enzymes responsible for inflammation (5-lipoxygenase) and damage of the skin.^[34]

Tetrahydro-curcuminoids

These are obtained from white (colour free) curcuminoids of turmeric (*curcuma longa*) carnosic acid, cosmarinic acid, ursolic acid from rosemary extract. *Rosemarinus officinalis* as antioxidants are the other compounds which are used to facilitate the tissue damage and restoring the healthy status of skin.^[34]

Hydroxy acids

Hydroxy acids are organic carboxylic acids classified into alpha hydroxy acids (AHAs) and beta hydroxyl acids (BHAs) polyhydroxy acids, and bionic acids according to their molecular structure. Many are derived from natural sources and are often referred to as fruit acids. The various hydroxy acids are found in most of the marketed cosmetic preparation but they are used in very low concentration. Hydroxy acids are found to be present in anti-aging formulations, moisturizers, and peels, and in treatment products to improve hyper- pigmentation and acne.

Alpha hydroxyl acids (AHAs) range from simple aliphatic compounds to complex molecules. The product can be derived either from natural or non-natural origin, those product's that are derived from natural origin are known as fruit acid. Alpha hydroxyl acids (AHAs) include the following: glycolic acid, lactic acid, citric acid, mandelic acid, malic acid, and tartaric acid. AHAs have been shown to decrease the signs of aging. The skin appears smoother and more uniform. The likely cause of these changes is the property of AHAs to enhance epidermal shedding. Some claim that AHAs increase the synthesis of glycosaminoglycans (GAGs), there by improve the quality of elastic fibers, and increase the density of collagen.

BHAs are aromatic compounds. Salicylic acid is the reference of BHA; it has dermolytic properties and also aids in various xerotic and ichthyotic disorders. Other BHAs include 2- hydroxy-5-octanoyl benzoic acid, also known as beta-lipohydroxy acid (B-LHA), and tropic acid.

The exact mechanism of action of hydroxyl acid is still unknown however one finding of its biological activities may be attributed to the inherent acid strength of the compounds. AHAs sensitivity to UV radiation has been proved and thus sunscreen application may be advisable when these products are used.^[35]

Vitamins

Exposure to the UV radiations hastens the aging effect of the skin. The progressive telomere shortening and finally its disruption by low-grade oxidative damage are related to the aging. Damage is started by the generation of reactive oxygen species (free radicals). It is a progressive process whose consequences are DNA damage.

The topical treatment of acne vulgaris with vitamin A is very well supported by evidence. Vitamin B3, which is commonly known as nicotinamide or niacinamide, is available in cosmetic and also in cosmeceuticals products and can be used as a complementary agent for some types of acne, as well as in skin aging.

Activation of toll-like receptors may also be involved in the scarring process by activating the metallo-proteinases.^[36-38] The retinoids are vitamin A derivatives constituting the most effective comedolytic agents. They function by normalizing desquamation of the follicular epithelium, preventing the formation of new microcomedo, and minimizing the formation of comedones and inflammatory lesions.

Nicotinamide is useful as a complementary drug because of its mild anti-inflammatory activity and its possible action in the reduction of sebum production and improvement of the skin barrier.^[39-41]

Vitamin A

Vitamin A (all-trans-retinol) in significant amounts is present in the human epidermis. The metabolism and transport of vitamin A can be damaged by both UVA and UVB. This may lead to deficiency of vitamin A in the skin.^[42] A small amount of retinol in the body gets converted to all-trans retinoic acid also called tretinoin (active form) and rest of the retinol is converted into retinyl ester (storage form).

Acne has been successfully treated by use of Topical retinoids. The effectiveness of topical tretinoin in the treatment of photo aged and intrinsically aged skin is sufficiently recognised. The effects are believed to be mediated through its binding to the nuclear retinoid acid receptors. It induces type I and type III procollagen gene expression in human skin, resulting in increased deposition of collagen fibrils in the dermis. The effects result in an improvement in the clinical and histologic skin appearance.^[43,44] Tretinoin cream in appropriated concentrations of 0.025%, 0.05% and 0.1% as well as 0.1% isotretinoin and 0.1% tazarotene, frequently produce moderate to severe skin irritation. For the treatment of photo aged skin Retinaldehyde (0.05%) is another useful topical agent. It has a poorer frequency of irritation but fewer efficacies than tretinoin.^[45] The problem to be dealt in case of tretinoin is photosensitivity. The advantageous concentration of topical retinol ranges from 0.3% to 1%. Most of the over-the-counter products available usually contain lower levels of retinol (about 0.08% or less), compared

with the concentration used in the few clinical studies available.^[46]

Of all other retinoids, Vitamin A (retinol) is the prototype and is necessary for proper growth, development of bone, and integrity of mucosal and epithelial surfaces. Deficiency of vitamin A, can severely affect, the eyes and the skin. The conjunctiva and the cornea develop metaplasia and keratinization, leading to night blindness.

Vitamin A exists in three isomeric forms i.e. alpha, beta, and gamma. Among which beta form found to be more active than alpha and gamma isomer. The deficiency of beta form may lead to dry rough skin. In the 1970s the introduction of synthetic analogs of vitamin A brought new interest into their biological activity, especially on the skin. Since then, vitamin A along with its derivatives have been beneficial in the treatment of many skin disorders, including ichthyosis, acne, and psoriasis. Abundant amount of research has concentrated on its use as an anti-aging compound as well as its use for other cutaneous disorders. As antioxidants, they protect cells from oxidative damage. They protect it by 3 different mechanisms: 1) By scavenging peroxy radicals 2) By quenching singlet oxygen 3) By triplet-state sensitizers. Vitamin A and its derivatives have two important functions: i) Act as antioxidants, ii) Activate specific genes and proteins. A hormone like effect is also exerted by Vitamin A on the skin, thus activating specific genes through nuclear receptors. The receptors bind to target sequences called hormone response elements on DNA and activate gene transcription. Retinoic acid receptors (RARs) bind all-trans retinoic acid and retinoic X receptors (RXRs) bind 9-cis retinoic acid. Vitamin A and its derivatives inhibit lipid peroxidation; there by increasing the levels of alpha-tocopherol (vitamin E); and also activate growth factors, oncogenes, keratins, and trans-glutaminases.

Structural changes underlying the cosmetic benefits include correction of epidermal atrophy, enhancement of mitogenesis, generation of new vessels, and deposition of new collagen. This improved mitogenesis promotes the shedding of melanin-laden keratinocytes, resulting in bleaching and subsequent depigmentation. The capability of topical tretinoin to improve the appearance of aged and photo-damaged skin by reducing wrinkles, bleaching hyper-pigmented spots, decreasing laxity, and bringing about a smoother surface have been well studied and documented. Further remedial qualities of retinoids remain to be elucidated.

Vitamin E

The physiological function of vitamin E, if applied dermally is to contribute to the antioxidant defence of the skin, due to its tendency to absorb UV light in the solar spectrum region that is mainly responsible for most of the harmful biologic effects of the sun.^[47] Vitamin E inhibits lipid peroxidation in tissues, cells and it is a good

antioxidant. It aids to improve the performance of UV filters, moisturizes and softens skin. Vitamin E is the important lipid-soluble antioxidant of the body and if oxidized, vitamin E can be regenerated back to its reduced form by L-ascorbic acid.

In topical OTC (over-the counter) products Vitamin E as alphanatocopherol or tocopherol acetate is used in concentration of 1-5%. Alphanatocopherol has been found to be helpful in reducing minimal erythema and the number of epidermal sunburn cells, which marks skin damage related to oxidative stress caused by UVB.^[48]

The effect of vitamin E after sun exposure seems to have no benefit.^[49] Vitamin E can minimise UV-induced erythema and edema when applied before UV exposure. Topical application of vitamin E may raise stratum corneum hydration and improves water-binding capability. Alpha-tocopherol also shows synergistic effect with vitamins A (retinol) and C (ascorbic acid) in combined products, providing an significant photo protection and antioxidant action that suggests a potential effect in the protection against photo aging and skin cancer.^[50,51] Topical application of vitamin E before UV irradiation has been shown to decrease erythema, edema, sunburn cells, immunosuppression caused by sunlight, and DNA adduct formation.

Vitamin B3 (niacinamide or nicotinamide)

Nicotinamide is a part of the coenzymes nicotinamide adenine dinucleotide (NAD), NAD phosphate (NADP) and its reduced forms are NADH and NADPH. These molecules are vital in many cellular metabolic enzyme reactions.^[46,52] Nicotinamide is one of the newly discovered vitamin-based components of cosmeceutical products. It is found to have anti acne and anti-inflammatory actions.^[43] Its anti-inflammatory action may improve skin appearance by decreasing leucocyte peroxidase systems that may lead to localized tissue damage as well as enhance the stratum corneum barrier. The amelioration of facial depigmentation is mediated by the suppression of melanosome transfer from melanocytes to keratinocytes.^[53] In fibroblast culture nicotinamide increases collagen production and this effect may lead for the improvement of skin elasticity and reduction of fine wrinkles.^[54]

Vitamin C

The rise of vitamin C in skin concentration is limited even with enormous oral supplementation. Vitamin C has become a popular topically applied cosmeceutical because topical application of L-ascorbic acid is the only way to further increase skin concentration. Free radical scavengers has grasped the attention of researchers on vitamin C. L-ascorbic acid which was first used as cosmeceutical creams is the active form of vitamin-C. Due to the oxidation of the vitamin exposed to air previous formulations of L-ascorbic acid were very unstable. Esterified derivatives of L-ascorbic acid in topical formulations has been used to overcome this

problem and to improve stability. Ascorbyl-6-palmitate and magnesium ascorbyl phosphate are the most commonly used derivatives.^[55]

All the researchers, despite these controversies, agrees that topically applied vitamin C has several benefits, such as promoting collagen synthesis, lightening hyper-pigmentation, anti-inflammatory and photo-protective properties.^[56-58] Vitamin C and its derivatives are believed to show reducing effects on melanin intermediates. They stop the oxidative chain reaction from tyrosine/dihydroxyphenylalanine (DOPA) to melanin. It is necessary for the hydroxylation of pro-collagen, proline, and lysine. Its insufficiency can cause keratotic follicles, purpura and bleeding gums. It is a significant regulator of collagen expression, stimulating its synthesis, a water-soluble antioxidant that clenches free radicals and regenerates Vitamin E and Vitamin C levels on the skin are rigorously depleted after UV irradiation and it recovers and normalizes the changes caused by light damage.

Vitamin B5

It is also known as pantothenic acid and is known to help in the production of the lipoproteins of the skin, accelerating its healing time, nourish the skin.^[59]

Vitamin P

It comprises of bio-flavonoid, which are not vitamins but they are nutritional supplements that contain antioxidants like grape's, ginkgo biloba and citrus derivatives. These function as antioxidants to eradicate free radicals that can damage skin cells. They eliminate the redness and irritation in skin. Vitamins are good for the body. Practicing the habit of taking vitamin's everyday is good for a more healthy body and mind.^[59]

Panthenol

Panthenol, which is the alcoholic analog of vitamin B-5, is a water-soluble humectant commonly found in different commercial skin creams, lotions, lipsticks and hair preparations. It is unstable in the presence of acids, bases and high temperatures but stable in the presence of oxygen and light.^[17] Panthenol is converted in the skin to pantothenic acid, which is a significant component on coenzyme A that is essential for normal cellular metabolism.

Green Tea Extract

Research has shown that green tea (*Cammeliasinensis*) poly phenols are powerful suppressors of carcinogenic activity from UV radiation and can exert wide protection against other UV-mediated responses, such as immuno-suppressant, sunburn and photo aging.^[60]

Ferulic Acid

These are the compound that are derived from plants, and are considered to be a potent antioxidant and has been shown to provide photo protection to skin.^[61,62] Moreover, when ferulic acid is mixed with vitamins C

and vitamin E, the product has been shown to provide substantial UV protection for human skin.^[63,64] Furthermore, 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.^[65]

Grape Seed Extract

These are the botanical that has been well recognised as a potent antioxidant and has been shown to enhance wound contraction and closure.^[66] Topical application of grape seed extract has also been shown to boost the sun protection factor in humans.^[67]

Arbutin

Arbutin is derived from the leaves of bearberry, cranberry, mulberry or blueberry shrubs, and also is present in most types of pears. It can have melanin-inhibiting properties.^[68] Arbutin along with other plant extracts are considered to be the safe alternatives to commonly used depigmenting agents to make the skin fairer. Medical studies have publicized the effectiveness of Arbutin for skin lightening.^[61]

Kojic acid

There are patents controlling its use for lightening of skin. Kojic acid is a by-product in the fermentation process of malting rice for use in the manufacturing of sake, the Japanese rice wine. Some research shows kojic acid to be effective in stopping melanin production.^[69]

5% Inyline

They act by Reduces Fine Lines – Wrinkles.

Inyline (Hexapeptide-30 and Arginine) mainly target's the agrin/Musk post-synaptic pathway blocking the mechanism of Musk (Muscle-Specific Kinase) in reducing muscle contraction. Thus by blocking these neurotransmitters, the formation of fine lines and wrinkles is reduced and prevented. When repetitive movements are impaired a collaborative effect is achieved - reduced depth of wrinkles and younger looking skin.^[70]

Antioxidants

Along with the external insults like UV radiation, drugs, air pollutants and heat and/or cold, the skin also has to cope with endogenous mitogens, most importantly reactive oxygen species (ROS) and other free radicals. These species are constantly generated during physiological cellular metabolism. To respond to the harmful effects of ROS, the skin is armed with an antioxidant system to maintain equilibrium between the pro-oxidants, or damaging agents and the antioxidants, or protective agents; these antioxidants mediate at different levels in the protective process.

Here some of the antioxidants are listed below:

Lipoic acid

Lipoic acid is an exclusive free radical protector that is fat and water soluble. Once lipoic acid crosses the cell

membrane, it is broken down into dihydrofolic acid, which is also an antioxidant. Alpha lipoic acid also reuses other important antioxidants, such as vitamin C, vitamin E and glutathione.^[17]

Dimethylaminoethanol

Topical preparations comprising dimethylaminoethanol (DMAE) have been advertised for their ability to improve skin firmness and to lift sagging skin. DMAE is able to diminish the cross-linking of proteins that occurs during aging, probably acting as a free-radical scavenger.^[71]

Spin traps

Free radical spin traps are species that react with reactive free radicals to create fairly stable, unreactive free radicals, thus blocking the free radicals from damaging cellular components.

- DMPO (5, 5-dimethyl-1-pyrroline-N -oxide)
- DEPMPO(5-diethoxyphosphoryl-5-methyl-1-pyrroline-N-oxide)
- TEMPONE-H (1-hydroxy-2, 2, 6, 6-tetramethyl-4-oxo-piperidine)

Melatonin

Melatonin is a hormone secreted by the pineal gland. The advantageous action of melatonin has been enlightened in terms of its ability to scavenge free radicals and to augment the activities of antioxidant enzymes. It has been shown to suppress UV radiation-induced erythema.^[17]

Catalase

Catalase is an enzyme present in almost all cells of the human body, which catalyse the decomposition of hydrogen peroxide to water and oxygen. High quantities of this enzyme in the skin can impart ant oxidative activity.^[17]

Glutathione

Glutathione is a tripeptide of glutamic acid, cysteine, and glycine. It is found in all active animal tissue. It is important as an antioxidant, and significantly reduced amounts of glutathione are found after UV exposures.^[17]

Superoxide dismutase

Superoxide dismutase (SOD) is an enzyme that destroys superoxide (a highly ROS). Superoxide dismutase is a large molecule and has trouble in penetrating deep into the skin. In theory, once in the lower epidermis and dermis, SOD should decline UV erythema and damage and act as an excellent antioxidant.^[17]

Glucopyranosides

Resveratrol and polydatins are glucopyranosides found in various fruits and vegetables, the maximum concentrations being found in grape skins, which synthesize these compounds in response to exposure to UV-A and UV-B and fungal pathogens.^[17]

Polyphenols

Polyphenolic compounds (eg. catechins, flavonols, thioflavins, thearubigins), also recognised as epicatechins, are antioxidant by nature. These compounds, when tested against human keratinocyte cells stressed by UV-B irradiation, showed high antioxidant properties.

Cysteine

Numerous recent studies have shown that cysteine derivatives can shield against the negative effects of UV exposure. In particular, N-acetylcysteine (NAC) is shown to be an effective protector against UV-Induced immunosuppression.^[17]

Allantoin

Allantoin stimulates cell proliferation, assisting in the healing process. Allantoin has long been known to improve the effectiveness and desirability of cosmetic creams and lotions by its action as a skin protectant. Allantoin has been merged into shampoos, lipsticks, shaving creams, sun tanning products, bath foams, hair gels, baby powders, and various aerosol preparations. Allantoin has been named as a cell proliferant, an epithelization stimulant, and a chemical debrider. It is said to clean away necrotic tissue, rushing the growth of new healthy tissue.^[17]

Furfuryladenine

Furfuryladenine (Kinerase) is a natural plant growth factor that slows down the aging process in plants. Cut leaves when immersed in a solution that contains furfuryladenine remain green, while untreated leaves turn brown. It is promoted as the natural evolution of anti-aging treatment with similar effects *in-vitro* on human skin cells as that in plants, aiding to slow and reverse alterations that naturally occur in the cell-aging process.^[17]

Uric acid

In the past, uric acid was generally looked upon as simply an end product of purine metabolism. More recently, uric acid has become gradually recognised as an important biological antioxidant.^[17]

Carnosine

Carnosine (beta-alanyl-L-histidine) is a physiological dipeptide that can restore senescent cultured human fibroblasts. Carnosine has been shown to contain antioxidant, free radical and metal ion-scavenging activities.^[17]

Depigmenting Agent

Hyperpigmentation is the result of an increased amount of melanin in the epidermis, the dermis, or both. This change in pigmentation can be divided into two pathophysiologic processes: 1) Melanocytosis (increased number of melanocytes) and 2) Melanosis (increased amount of melanin). Depigmenting agents work best when melanosis or melanocytosis is restricted to the

epidermis.^[17] Depigmenting agents can be further divided into several groups:

Phenolic compounds include the following

- Hydroquinone
- Monobenzylether of hydroquinone
- 4-Methoxyphenol
- 4-Isopropylcatechol
- 4-Hydroxyanisol
- N -acetyl-4-S-cysteaminylphenol

Nonphenolic compounds include the following:

- Corticosteroids
- Tretinoin
- Azelaic acid
- N -acetylcysteine
- L-ascorbyl-2-phosphate
- Kojic acid

Combination formulas include the following

- Kligman's formula
- Pathak's formula
- Westerhof's formula.^[72]

Hormones

Hormonal creams claim to be the most effective means to halt or slow the aging process by reversing the loss in tone and elasticity of the skin.

Estrogens

One of investigation found that after 6 months of application of 0.01% estradiol and 0.3% estriol compounds, the elasticity, firmness, wrinkle depth, and pore sizes of the skin were markedly improved. However, better studies are needed before these agents are routinely used for their anti aging effects.

Progesterone

Progesterone cream claims to heal skin conditions, such as acne, psoriasis, rosacea, seborrheal, and keratosis.^[17]

Botulinum A exotoxin

An exotoxin is a neurotoxin synthesised by the bacterium *Clostridium botulinum*. This toxin is now being used by cosmetically oriented specialists for the treatment of a huge variety of movement-associated wrinkles on the face and neck.^[17]

Exfoliants

Exfoliants stimulate skin turnover by removing adherent cells in the stratum corneum. Exfoliants that are commonly found in cosmeceutical preparations include salicylic acid (SA), lactic acid and glycolic acid. There are worries that frequent use of SA and AHAs could cause the dermis and epidermis to be more susceptible to penetration by UV radiation. Therefore, patients should be instructed 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.^[73] Adequate data is not available to establish a limit on SA concentration or to detect the minimum pH of formulations to inhibit skin irritation.^[74]

Regenerating Agents

There are multiplicities of ingredients that have slight anti-inflammatory properties able to soothe irritated and stressed skin. Typical examples include are aloe Vera, allantoin and rose hip oil which all are widely used in skin care preparations for sensitive or irritated skin. Many of these agents like provitamin B5 and hyaluronic acid have also effective regenerating properties promoting the growth of new skin cells and supporting wound healing. Both provitamin B5 and hyaluronic acid are thus frequently used in after-peeling treatments, anti-aging formulations and in all treatments aiming to provide smoothness & softening to the skin.^[75]

Moisturizers

The cutaneous permeability barrier is localized in the stratum corneum interstices, and it is mediated by the lamellar bilayers enriched in cholesterol, free fatty acids and ceramides. Formulations containing skin-identical lipids have been suggested to facilitate a cascade of physiologic events in keratinocytes, normalizing damaged skin. When applied to the skin for a prolonged period, water can cause the elimination of cytokines. These pro inflammatory molecules induce edema, vasodilatation, and frank inflammation; therefore, water alone may modify both the structure and the function of the skin under certain conditions. By the same token, moisturizers that make the stratum corneum softer and more pliant by increasing its hydration could be considered cosmeceuticals.^[59]

Probiotics

Probiotics are a relatively novel classification of skin care ingredients that are being used in numerous topical products. Lactobacillus cultures are used to produce molecules that aid repair the skin barrier after laser treatment or chemical peels. One product line (Clinique Medical (Estee Lauder, New York) uses mild cleansers, sun protection, moisturizers and a calming balm to provide an integrated skin care regimen for patients undergoing skin treatments. In one study of this product line, patients treated with powerful pulsed lights or fractional laser treatments had a noteworthy decrease in post treatment erythema and more speedy recovery.^[76] This study reported objective findings that included a 28% decline in skin redness and 55% enhancement in skin radiance after treatment with 30% trichloroacetic acid (TCA) when this regimen was compared with a control regimen. These verdicts suggest that probiotic technology may hold important potential for improving outcomes with procedures commonly performed by facial plastic surgeons, plastic surgeons, and dermatologists.^[77]

Growth Factors

Growth factors are molecules used to stimulate cellular proliferation. This proliferation may be profoundly useful when it produces epidermal and dermal structures that are more systematized and less senescent. Two widespread product lines (Skin Medica, Carlsbad, CA and Neocutis, San Francisco, CA) use different version of growth factors to produce commercially successful product. The product developed by Neocutis incorporate growth factors derived from a proprietary stem cell line. The product from Skin Medica use epidermal growth factors originating from cellular cultures. Each has their own hypothetical benefits, and both have data to support their results. One study using topical growth factors demonstrated that it resulted in smoother skin with less visible wrinkles.^[78] However, the versions that are currently available are relatively early versions that are still evolving. Purification of growth factors as well as a better understanding of the actions of the molecules will produce more targeted growth factor cosmeceuticals. In the nearby future, we are expected to see cosmeceuticals that target skin thickness and organization and others that attempt to stimulate collagen and elastic growth.^[77]

PEPTIDES

Peptide are composed of chains of amino acids themselves the product of DNA transcription. Thus the peptide is in normally cellular enviroing. These are the communication molecules between the DNA and cellular machinery. Thus, they may be used and manipulated to direct cells to behave in a more youthful manner. Peptides might also be the result of protein degradation. As such, they form important feedback inhibition and feedback up regulation loop. One such instance of feedback inhibition is their down regulation of metalloproteinases (MMPs) such as collagenase.^[79] After procedures intended to stimulate collagen production, such as fractional laser treatments, chemical peels, injections of poly L lactic acid (PLLA), and perhaps injections of Evolence (Porcine Collagen, Johnson and Johnson, Skiliman, NJ), it may be helpful to incorporate the use of peptides that will stop MMP thereby increasing the yield of the procedures performed. Peptides that may be useful in this regard include Matrix 1. This molecule is composed of five linked amino acid that have been demonstrated to raise fibroblast production of collagen.^[80] Future peptides will likely be developed from fibroblasts stimulated with controlled injuries such as those from fractional resurfacing. Harvesting these molecules will help not only to prime the skin prior to these procedures but also possibly to enable physicians to obtain the remodelling results using topical agents instead of controlled wounds as is presently the case. Larger-chain peptides are able to perform more complex signalling and transduction within the cells as well as communicate between various cells of the skin. Botulinum toxin type A protein is the one of the most studied among the proteins that control cellular functions. Presently, this protein is injected into the muscle where it stops the SNAP 25 protein and

prevents vesicles containing acetylcholine from transiting the neuromuscular junction. Topical application of this molecule has already been demonstrated and it is likely that future iterations will be more effective than current ones.^[81] Cosmeceutical products derived from this technology will eventually be part of our repertoire, and their use before and after treatments with injectable toxins, lasers, and chemical peels are likely to enhance the outcomes achieved. Peptides such as human growth hormone, estrogen and testosterone are used by many patients to improve the tone and texture of their skin. The exact mechanism of action for these products is not well known but is the subject of increased study. Once the specific benefit from these molecules has been defined, peptides representing the active portions of the molecules will be synthesized. These peptides will likely offer significant advantages for rejuvenation of the skin beyond that of molecules currently available. Combinations of metal ions with peptides are presently marketed and they have been demonstrated to have beneficial activities in reducing the appearance of fine lines and wrinkles. In particular, copper peptide molecules using glycyl-Histadyl-lysine (GHK) have been broadly studied and shown to have various restorative effects.^[82] Copper is not the only metal complexed with peptides, the number of metal/peptide combinations is vast. Elucidation of the benefits linked with some of these complexes will yield effective novel peptides. It is known that low-dose doxycycline will stop some of the matrix metalloproteinase including collagenase. This action is mediated by peptide signals. The peptides associated with this effect are likely to be used as cosmeceuticals in the future thereby eradicating the necessity to ingest oral antibiotics to obtain this effect. Tretinoin and similar retinoids have substantial rejuvenating effect on the skin.

Kinetin

Clinical studies have shown that Kinetin reverses the signs of photo damaged skin and develops the overall appearance of the skin, thereby making it smoother and more even in color and noticeably diminishes the appearance of fine lines and wrinkles. The studies have also showed that Kinetin significantly improves the skin barrier function, assisting skin to retain more moisture, thereby making the skin more softer and smoother.

Kinetin a chemical messenger is a cytokinin that has been shown to reduce the signs of aging that are primarily due to photo damage. Kinetin is a vital plant growth factor that can also be found in the human body involved in tissue repair. It has also been shown to retard age-related changes in human skin cells. As a powerful antioxidant, Kinetin lessens the signs of aging and aids to protect the skin from oxidative damage caused by the sun.^[83]

LipoLight (fumed silica)

Lipo Light is used in selected formulations because almost all approaches to skin correction take time to

achieve full effect. The principle of LipoLight's soft focus technology is based on scattered light. In this light waves are reflected back from wrinkles and enlarged pores. Similarly as proper lighting improves a photograph, rejecting the shadows from wrinkles and pores makes them less visible.^[83]

Sodium Hyaluronate

Hyaluronic Acid (HA) is the naturally occurring and widespread component found within the extra-cellular space within bodily tissues (ECM), especially those of the face. The spaces between the connective fibers collagen and elastin in the dermis are filled up by its water-binding and water attracting qualities. HA function is to hydrate and separate the skin. Dermis layer of skin is made up of about 70% water and claims approximately 50% of body's total HA allotment; there it aids to support and hydrate the skin, resulting in a healthy and eye-catching appearance. As the amount of HA decreases (adults have only 1/20th the amount of HA of a baby), the ECM becomes dehydrated, which further leads to surface roughness, flaking, fine lines, and a whole host of other undesirables. Dry skin also leads to flappy, wrinkly skin. Wrinkles are the result of the loss of three important components in the skin: 1) Collagen 2) Hyaluronic acid and 3) Elastin. The hydrating and nutrient transporting framework necessary for holding up the structure of the ECM in the skin is provided by HA. Elastin if not suffused in water it becomes dry and brittle, invariably leading to dull, loose and less-elastic skin. Dry Skin is aged skin. Molecular size of Sodium Hyaluronate is smaller than HA (making it especially penetrative) and thereby it is able to hold more water than any other natural substance-up to 1000 times its weight in water. Due to these qualities, when applied topically to the skin it can reach deep down into the dermis to combine with, maintain and attract water, as well as to promote skin/blood microcirculation and nutrient absorption and maintain normal metabolism. And also due to its supersized hydrating properties it will result in a smoother and softer skin with reduced wrinkles and an all-around fuller appearance.^[83]

Hair cosmeceuticals

The appearance of hair is a feature of the body over which humans, unlike other land mammals, has direct control. The length, color and the style of the hair can be modified according to one's wish to appear. Styling of hair along with its color plays a vital role in the appearance of people. In ancient times the setting and coloring of hair was done with the help of mud and henna resp. various tonics and ointment for beautification of hair and for curing scalp disease were used in ancient Greece and Rome. Henry de Mandeville first made the distinction between the medical therapies intended for treatment of disease and cosmetic agent for beautification.^[84] But today's delineation of cosmetics from pharmaceuticals has become more complex through the development of cosmetics with physiologically active ingredients, i.e. cosmeceuticals. By far the most frequent form of

cosmetic hair treatment is shampooing. While shampoos have primarily been products aimed at cleaning the hair and scalp, recent formulations are modified to the variations associated with hair quality, hair care habit, and specific problems such as treatment of oily hairs.^[85] dandruff.^[86] and for androgenic alopecia.^[87] related to the superficial condition of the scalp.

For the treatment of hair, cosmetics are applied topically to the scalp and hair. While they can never be used for therapeutic purposes, they must be not be hurtful to the skin and scalp, to the hair, and to the mucous membranes and should have non-toxic effect, general or local, in normal conditions of their use. The compositions of hair-care cosmetic are iodopropynyl butyl carbamate and/or a solution of zinc pyrithione in N-acyl ethylenediamine triacetate which have been patented, which also includes an appropriate carrier and a non allergenic dry extract of yarrow (*Achillea millefolium* L.), which is obtained by oxidation of a water- alcohol solution extract of flower tops of yarrow. These extract contains less than 0.5% by weight of polyphenolic derivatives, and are used for the treatment of hair, especially in oily hair, that is based on extract of yarrow. It is usually acknowledged that genetic hair loss arises from the activation of an inherited predisposition to circulating androgenic hormones.

A hair cosmeceuticals product includes conditioning agents, special care ingredients and hair growth stimulants.

Conditioning agents are envisioned to impart softness and gloss, to lessen flyaway and to enrich disentangling facility. A number of ingredients may be used, mostly includes fatty ingredients, hydrolyzed proteins, quaternized cationic derivatives, cationic polymers and silicones.^[84] Special care ingredients are targeted at modifying specific problems relating to the superficial scalp. These shampoos are formulated using one or more specific ingredients selected for their clinical effectiveness in these conditions. Thus, present-day antidandruff ingredients are virtually all-effective antifungal agents, zinc pyrithione, octopirox, and ketoconazole.^[88] Due to short-contact time and water dilution, Hair growth stimulants cannot be expected to have any impact on hair growth. A minoxidil-related compound (2, A- diamino-pyrimidine-3-oxide) is a cosmetic agent with claim of acting as a topical hair growth stimulant.^[89] Its target of action has been proposed to be the prevention of inflammation and perifollicular fibrosis.^[90] Some degree of efficacy of 2, A-diamino-pyrimidine-3-oxide has been claimed in the prevention of seasonal alopecia.^[91] Current approval in the United States of two fresh products, Propecia and Rogaine Extra Strength (Minoxidil) 5%, indicated in men to promote scalp hair growth, have added a new facet to treatment options offered by physicians in treating androgenetic alopecia.^[92]

REGULATORY SCENARIO

In the European Union, United States or Japan, Cosmeceuticals are not regulated as such. In the EU, cosmeceuticals are considered cosmetics, In the United States, they are considered as drugs that probably have not been approved by the U.S. Food and Drug Administration (FDA). In Japan, cosmeceuticals are considered as quasi-drugs. There exists no recognized legal definition of a cosmeceuticals, as compared to the legal definition of a cosmetic or a drug, anywhere in the world.

Indian Regulatory Scenario^[59]

Essential issues with the recent Indian cosmetic regulations include the following

- Multiple and complex regulations under different bodies
- Indian cosmetic definition is narrow & restrictive
- Lack of execution guidelines of the D&C Act for regulators for issues related to cosmetics such as
- Non uniform licensing approvals across various states
- Inconsistent approach across authorities in interpretation of a particular issue
- Absence of guidelines on product claim interpretation as well as illustrative lists of cosmetics, cause difference in understanding between licensing authorities on product classification and hence delaying the process of product licensing and product trade cycle.
- Pace of BIS Standards development/ revision are not in line with technological progress thus deterring innovation and growth.

The provisions relating to manufacture, sale, storage, distribution and import of drugs as well as cosmetics in India is governed by Drugs and Cosmetics Act, 1940. There is no term as "Cosmeceuticals" in the Act; the said Act clearly defines the terms –Drug" and "Cosmetic". As such nobody has a legal or statutory right to use the term for drawing benefits of any sort. The terms either "drug" or "cosmetic" have to be used for all intents and purposes and usage of any other term to replace or substitute either of these two terms is simply illegal, there is no rationale. The term "Cosmeceuticals" however may be used for purposes other than legal/statutory/ drawing benefits/seeking relaxations or concessions etc.

Any such category as –cosmeceuticals is not recognized by the FD&C Act. A product can either be a drug, a cosmetic, or a combination of both, but there has no meaning for the term –cosmeceuticals under the law. The Federal Food, Drug, and Cosmetic Act (FD&C Act) defines cosmetics by their intended use as –articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance [FD&C Act, sec. 201(i)]. The products included in this definition are skin moisturizers,

perfumes, lipsticks, fingernail polishes, eye and facial makeup preparations, shampoos, permanent waves, hair colours, toothpastes and deodorants, as well as any material intended for use as a component of a cosmetic product.^[115]

Approval Requirements

For cosmetic products or ingredients, FDA does not have a premarket approval system with the important exception of colour additives. However, Drugs are subject to FDA approval. Generally, drugs must either receive premarket approval by FDA or conform to final regulations specifying conditions whereby they are generally recognized as safe and effective, and not misbranded. Currently, certain-but not all over-the-counter (OTC) drugs (that is, non-prescription drugs) that were promoted before the beginning of the OTC Drug Review (May 11, 1972) may be advertised without specific approval pending publication of final regulations under the on-going OTC drug review. Once a regulation covering a specific class of OTC drugs is final, those drugs must either.

- Be the subject of an approved New Drug Application (NDA) [FD&C Act, sec. 505(a) and (b)], or Comply with the appropriate monograph, or rule, for an OTC drug.^[114]
- Regulations specifically prohibit or restrict the use of the following ingredients in cosmetics. For complete details, refer to the relevant regulations (21 CFR, Parts 250.250 and 700.11 through 700.23).

These products must meet the standards for both cosmetics (colour additives) and drugs, to refer to products that have drug-like benefits. Some cosmetic makers use the term "cosmeceuticals", but FDA does not recognize this term. A product can be a drug, a cosmetic, or a combination of both. But there has no meaning to the term "cosmeceuticals" under the law. While drugs are reviewed and approved by FDA, FDA does not approve cosmetics for the product's acting like a drug, FDA must approve it as a drug.^[116]

The FDA pursued to establish policy on the distinction between a cosmetic and a drug in three ways. First, FDA issued proper trade correspondence that set forward advisory opinions on the classification of products. Second, the pamphlets and other educational materials with examples of product classification were published by the agency. Third, it brought court action to contest the legitimacy of cosmetic products with labelling that contained what the agency concluded to be drug claims. From this body of literature and precedent developed over six decades, a number of well-developed examples:

- A sunscreen product is a drug but suntan product is a cosmetic.
- An antiperspirant is a drug but deodorant is a cosmetic.
- An antidandruff shampoo is a drug but shampoo is a cosmetic.

- The Toothpaste is cosmetic but anticaries toothpaste is a drug.
- A skin peel is a drug but a skin exfoliants is a cosmetic.
- A mouthwash is a cosmetic but an ant gingivitis mouthwash is a drug.
- A hair growth product is a drug but hair bulking product is a cosmetic.
- A skin product to hide acne is a cosmetic but an antiacne product is a drug.
- An antibacterial anti-infective soap is a drug but antibacterial deodorant soap is a cosmetic.
- A wrinkle remover is a drug but skin moisturizer is a cosmetic.
- A lip softener is a cosmetic but a product for chapped lips is a drug.

This list is illustrative, not exhaustive.^[117] How is a product's intended use established?

Intended use may be established in a number of a ways. Among them are:

- Claims stated on the product labeling, in advertising, on the Internet, or in other publicity materials. Certain claims may cause a product to be considered as a drug, even if the product is promoted as if it were a cosmetic. Such claims establish the product as a drug because the intended use is to cure or prevent disease or otherwise affect the structure or functions of the human body. Some examples are claims that products will restore hair growth, reduce cellulite, treat varicose veins, or revitalize cells.
- Consumer perception, which may be established through the product's status. This means inquiring why the consumer is purchasing it and what the consumer presumes it to do.
- Ingredients that may cause a product to be considered as a drug because they have a recognized (to the public and industry) therapeutic use. An example is fluoride in toothpaste.

This belief also holds true for essential oils in fragrance products. A fragrance advertised for encouraging attractiveness is a cosmetic. But a fragrance advertised with certain "aromatherapy" claims, such as assertions that the scent will help the consumer sleep or quit smoking, meets the definition of a drug because of its intended use.^[118]

European Regulatory Scenario

The European cosmetics industry is frequently divided into the following sub-sectors:

1. Skin Care, these includes sun care and other skin-care products
2. Hair Care, these includes shampoos, conditioners and scalp-health products
3. Body Care, these includes deodorants and a wide range of toiletries
4. Decorative, these includes nail care, eye care and colour cosmetics.^[119]

What about “cosmeceuticals”?

Any such category as —cosmeceuticals is not recognized by the FD&C Act. A product can be a drug, a cosmetic, or a combination of both, but there has no meaning for the term —cosmeceuticals under the law.

How a product's intended use established?

Intended use may be established in a number of ways. Among them are:

- Claims stated on the product labeling, in marketing, on the Internet, or in other advertising materials. Certain claims may cause a product to be considered a drug, even if the product is promoted as if it were a cosmetic. Such claims establish the product as a drug because the intended use is to cure or prevent disease or otherwise affect the structure or functions of the human body. Some examples are claims that products will restore hair growth, reduce cellulite, treat varicose veins, or revitalize cells.
- Consumer perception, which may be established through the product's status. This means querying why the consumer is procuring it and what the consumer supposes it to do.
- Ingredients that may cause a product to be considered a drug because they have a renowned (to the public and industry) therapeutic use.

Current Cosmeceuticals Compounds Available

Bo-Peptide Eye Cream—An HCG diet friendly mixture of various peptides and glycosaminoglycans along with the Lipo Light reflecting technology.

Anti-Aging Eye Cream—Powerful mixture of the anti-oxidants melatonin and Idebenone in Glycine Soya Protein solution, designed to restore youthful texture to skin.

Bacopeptide Anti-Aging—HCG diet friendly formulation of Bacopa Monnieri extract, acetyl dipeptide and gluconol-actone in vanishing cream.

Collagen Booster Lotion—HCG diet friendly formula to improve and restore skin matrix contains Palmitoylpentapeptide, glycine soya protein, kinetin and glycosaminoglycans.

Eye Wrinkle Gel—HCG diet friendly formula designed to provide maximum moisture to support skin matrix contains Sodium Hyaluronate, DMAE, Acetyl D Glucosamine and glycine soya protein. Ask pharmacists to help you decide which formulas are best for your skin care needs.

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