Skin Lightening & Management of Hyperpigmentation

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1. Background

Skin bleaching, a practice to chemically lighten the skin, has become increasingly more common around the world in the past 40-60 years. Historically, skin bleaching actually starts in the Victorian era with the age of powder and paint, the precursor to us wearing foundation. Queen Elizabeth (1st) was known to take arsenic complexion wafers, which were essentially little bits of poison to give her that ghostly look. Her early and meticulous efforts to appear ghostly white and nearly transparent during her 16th century rule soon became known as the "Elizabethan ideal of beauty". To great surprise, the history of skin whitening practice actually began within the white community itself. European women were literally painting their faces with lead paint. Even fair look women were involved in whiteness because it was their way of communicating purity. And at that time, race was being solidified as a concept and whiteness was being defined as pure. The 1920s were the heyday of the French colonial empire. At that time France controlled more land in Africa than any other European country. During the colonization process they imported their language, norms and traditions to Africa, where they imposed on local populations. Colonized populations sought to imitate the light skin of their colonizers in an effort to enhance their quality of life and improve their self-image. Black women in the Western Cape Province in particular, were more likely to find employment as domestic workers and cooks if they appeared to have a lighter complexion. European colonization practices from Asia to Africa to India during the latter half of the second millennium rapidly began to spread these beliefs to all corners of the globe. Among such ideologies were associations of darkness and blackness with primitiveness, unrestrained sexuality, and pollution, while whiteness was associated with purity, power, and beauty. Throughout medieval and modern history, the Indian subcontinent has been on the radar of various European settlers and traders, including, from the 15th to 17th centuries, the Portuguese, Dutch and French. The subcontinent was invaded and partly ruled by the Mughals in the 16th century, and colonized by the British from the 17th century onwards until independence in 1947. All these foreign "visitors" were of relatively fair complexion, and many claimed to be superior. According to a study we conducted from 2013 to 2016, 70% of the 300 women and men we interviewed reported wanting a date or partner with someone who had light skin. This colorism is what pushes so many Indians to lighten their skin, creating a phenomenon termed "bleaching syndrome". "Let's scrub out that tan" is a common refrain in beauty parlors in Indian subcontinent, where girls grow up with constant reminders that only fair skin is beautiful. Even sentiments like, "She got lucky that he married her despite her [dark] complexion" are still whispered around. Skin fairness products include whitening and skin-lightening creams, face washes, deodorants, and lotions. This industry is one of the fastest growing segments of the global beauty industry, particularly in Asia and Africa, with marketing forecasters predicting it will be worth an estimated $US 31.2 billion by 2024.

2. Abstract

Skin color, along with hair and eye color, is genetically determined by the amount of melanin found in the top layers of skin. Its varied presence – which accounts for different skin colors – is linked to a population's historic levels of sun exposure. Skin-lightening is just one of the multiple options for augmenting the skin's surface appearance, including but not limited to tanning, scarification, makeup, tattooing, face lifts, nose jobs, botox, lip extensions, and piercings. Skin-bleaching practices, such as using skin creams and soaps to achieve a lighter skin tone, are common throughout the world and are triggered by cosmetic reasons that oftentimes have deep historical, economic, sociocultural, and psychosocial roots. The cosmetics industry has traditionally relied on convincing people that they are incomplete without a particular product. Yet, unlike makeup or fake tan, skin-whitening creams base beauty on a racial hierarchy, fueling intolerance and causing serious social harm. Lighter and fairer skin is something that everyone craves for, and celebrities play a massive part in paving the way. Just like ladies, men also aspire to get immaculate, glowing and healthy-looking skin to accentuate their personality and overall looks. It's for everyone to understand that men really feel shy to discuss the skincare routines as they feel it's all-girl stuff. But there is no denying that even boys need to uplift and improve their skin texture to feel good. Studies have documented the use of skin fairness products, sometimes referred to as "skin whitening products," "skin bleaching products," "depigmenting agents," in Africa, Europe, North America, and Asia, with prevalence of use ranging from 30 to 80% among various community samples. Skin fairness products include whitening and skin-lightening creams, face washes, deodorants, and lotions. These agents act in different ways to lighten skin, but generally work by suppressing the production of melanin, the pigment which gives human skin its color. While traditionally a female practice, use has become more popular also among men in recent years. These agents selectively target hyperplastic melanocytes and inhibit key regulatory steps in melanin synthesis. Historically marketed to women, companies have recently expanded their offerings to include products designed and marketed specifically for men. Advertisements and packaging overtly claim that products will make consumers' skin fairer and more even-toned, while product names and the use of well-known models and actors in advertisements imply that they will enhance consumers' cultural capital via improvements in attractiveness, youthfulness, confidence, and success. The relevance of skin fairness products to public health is highlighted by the scope of the industry, the widespread use of these products, and the potential health risks associated with their use. Skin-whitening cosmetics are a multi-billion-dollar industry pushing the idea that beauty equates with white skin and that lightening dark skin is both achievable and preferable.

Key Terms: skin bleaching; whiteners; hyperpigmentation; fairness creams; melasma; tyrosinase inhibitors; dark skin; melanosomes

A typical advertisement pointing at a sensitive issue of Indian unwed women. But recently, researchers have found that skin whitening or fairness cream advertisements are playing a major role in creating skin-based discrimination in society and disgracing womanhood. The manufacturers broadcast enticing advertisements to attract customers. Most of the time, advertisers make false and misleading promises.

3. Introduction

Global aesthetic regimes continue to place emphasis on, and preference for, lighter shades of brown. Consumer choice now fashions lightening as a form of human agency, where the surface of the skin can be manipulated to conform to, or resist global and local beauty standards. Capitalism is thus implicated in the process of commodification identity politics. The belief and practice to have lighter skin has been rooted from ancient times. For instance, Chinese myth believes that pearls can lighten one's complexion by taking a small amount of pearl powder together with hot water every day. Children are grown up with stories like “Snow White” a princess skin as white as snow and lips red as blood and hair black as ebony. Sure, for a little girl who wants to be a fairy princess the idea of ethereal, magical, mystical and winged creatures all come to mind. TV, movies, radio, and general culture give us the tools to draw these pictures, however, they also give us, directly or indirectly, a standard by which to live, think, and believe. Every time we turn on the TV, listen to the radio, read a magazine, or simply go out somewhere, we get our daily dose. Women are going to extremes to enhance their body image. Curvier, lighter-skinned women are considered more beautiful, more successful and more likely to get married. Skin color bias affects

people psychologically. It affects how a child performs in school because their confidence level goes down: they feel they are not good enough. And when it comes to marriage, we again find skin color plays such a vital role. Women are now embracing anything thrown at them to increase the size of their breasts, hips and change their complexion to suit the community 'standard of beauty'. However, skin lightening products are readily available from major cosmetics companies, from local convenience stores, and widely over the internet. Although both men and women engage in the skin lightening practice, of various sorts, women generally have higher rates of practice than men. Hyperpigmentation-related diseases include melasma, lentigines, nevus, ephelis, freckles, post-inflammatory hyperpigmentation, and age spots. Post-inflammatory hyperpigmentation appears in many skin conditions, including acne, eczema, and contact dermatitis. Multiple agents are available for the treatment of hyperpigmentation, a cosmetically important condition seen most often in middle-aged and elderly individuals and resulting from exposure to ultraviolet light, certain drugs or chemicals, or the existence of disease. Therapeutic interventions include whitening agents, chemical peels, lasers, and physical methods. Many skin-lightening agents cause skin irritation and require months of use before results appear, and some agents are only partly effective. Although multiple interventions are available, skin-whitening agents, due to their simplicity and convenience, continue to be the mainstay of approach to either lighten skin (individuals who wish to change or modify their skin color) in the cosmetic field or depigment skin (treatment for abnormal hyperpigmentation skin such as melasma, freckles, and actinic lentigines) in the clinical therapy. Chromameter measurements are useful in measuring skin tone and color in products claiming evenness of skin tone or skin whitening as well as the reduction of redness when measuring anti-irritant and anti-inflammatory benefits. There are two types of whitening creams – those that ‘lighten’, and those that ‘bleach’. Bleaching creams contain harsh chemicals that inhibit the production of melanin, and quite rapidly make the skin whiter. Lightening creams, however, don’t necessarily contain these chemicals, but will promise to whiten the skin with long-term use. Skin whitening is a lucrative business in many countries where beauty clinics proliferate and skin-whiteners account for more than half of the sales in facial creams. The ideal depigmentation compound should have a potent, rapid, and selective bleaching effect on hyperactivated melanocytes, carry no short- or long-term side effects, and lead to a permanent removal of undesired pigment. Depigmentation can be achieved by regulating (a) the transcription and activity of tyrosinase, tyrosinase related protein-1 (TRP-1), tyrosinase related protein-2 (TRP-2), and/or peroxidase, (b) the uptake and distribution of melanosomes in recipient keratinocytes, and (c) melanin and melanosome degradation and turnover of “pigmented keratinocytes.

4. Global Demand for Skin Lightening

Global industry analysts (GIA) have predicted that the universal market for skin lighteners will reach $23 billion by 2020, driven by new markets in Asia, particularly India, Japan and China. This industry is one of the fastest growing segments of the global beauty industry, particularly in Asia and Africa, with marketing forecasters predicting it will be worth an estimated $US 31.2 billion by 2024. Approximately $13 billion spent on skin care products and cosmetics in Asia Pacific’s. This is particularly relevant in Asian countries, including India, Japan, Korea, China, and Thailand, where skin fairness has been understood to be a cultural marker of class, wealth, and social status for centuries. Studies located in Asia, USA, U.K., India, China and the Caribbean indicate the prevalence of a thriving skin lightening cream industry. The regular and sustained use of skin bleaching products has been practiced in African and Asian contexts for decades, with prevalence estimates from 25% to 96%. China accounts for about 40% of sales in Asia, Japan 21%

and Korea approximately 18%. Whitening creams account for half of the $320 million Thai market for facial creams, according to research firm Nielsen. The preference to have white skin has driven the skin lightening industry. This phenomenon was reflected in the domination of skin lightening products in Asian skincare market with 60% of sales. A WHO survey found that nearly 40% of women polled in nations including China, Malaysia, the Philippines and South Korea said they regularly used whitening products. In India, 60% of the skincare market consisted of whitening products, with estimates of its worth varying between $US 450–535 million. A nearly 40% of the sample reported currently using skin fairness products, with women being two times more likely to use these products. Among current users, 17% reported past experiences of adverse side effects, and "Media/TV/Adverts" were the most common prompts for using fairness products, followed by "Friends" and "Family." Men were significantly more likely than women to endorse beliefs about fairness being more attractive and were more likely to perceive family and peers as viewing fairness as beneficial for cultural capital. A recent survey showed that 80% of Indian men use fairness creams and the number of consumer's are growing 18% annually. There were no differences between women and men currently using products in their desire to look as fair as media celebrities. Among non-users, women were significantly more likely than men to report concerns about product efficacy and side effects as reasons for non-use, while men were significantly more likely to report socioeconomic reasons for non-use. In three different African countries, the statistics demonstrate that 25% of women in Bamako, Mali a further 52% in Dakar, Senegal, and 77% in Lagos, Nigeria use skin lighteners. Such practices are reinforced by a belief that fairer skin is associated with beauty, self-esteem, and financial and social advantages among Saudi women. Aside from how gender plays important role in practicing skin lightening, range of age is also an important factor. A study shows that the majority of samples focus on female age ranging between 20 and 30 years (more than 50% in one study and more than 70% in another one). The sales of skin lightening products increase 100% every year (2007-2012) in Malaysia. In a study of 450 Nigerians who confessed the use of lightening creams, a nearly 70% were women and around 30% were men. Lighter skin not only enhances the perception of greater attraction but also enhances the appearances of tattoos on skin as the darker colored tattoos contrasts better with light skin than dark skin [1-10].

5. Skin Brightening vs. Lightening vs. Whitening

The terms lightening, whitening, brightening and bleaching are often used interchangeably. Skin bleaching is a term that was more popular in the 80's than it is today, and is essentially the same as skin whitening. The difference between skin lightening and whitening is largely based on the degree/severity with which melanin production is reduced. *Skin lightening* is used when the method is more gradual and the effect less obvious while whitening is used to describe a more aggressive technique. Both techniques use tyrosinase inhibitors to block the skin's production of melanin. Lightening creams work to reduce the melanin pigmentation in a particular area on the skin. It has to do with discoloration and evening of skin tone. Skin lighteners can be both over-the-counter products or skin care products that target brown spots, dark spots, age spots, freckles, etc. Instead of affecting the whole face, skin lightening agents seek to reduce the darkness in one area or spot on the face. These spots usually occur from sun damage, so it can take time to see results. Lightening reduces pigmentation, lightens discoloration and evens skin tone. Skin lightening products target particular areas of discolorations like age spots and hyperpigmentation from acne breakouts and bruising. Lightening products are best used for a limited period of time. *Skin whitening* uses stronger inhibitors such as hydroquinone or mercury to strip the skin of its

melanin. Skin Brightening is an entirely different concept. Our skin is continuously creating new skin cells to replace older skin cells, and often, these dead skin cells remain on the skin's surface and can cause it to appear dull. Exfoliation removes these dead skin cells from the skin's surface, thereby revitalizing it and making it look more radiant and "brighter". Brightening here is achieved with ingredients such as alpha and beta hydroxy acids, vitamins A, E and C that help the skin to naturally shed dead skin cells. Some brightening products may also contain natural extracts and antioxidants that have lightening properties e.g. licorice root extract to help gradually fade dark spots. *Skin brighteners* are skin care products that make skin brighter and more even throughout the entire face. Brightening is more about restoring vibrancy to the skin. Hydroquinone, Kojic Acid, Arbutine, Vitamin C, retinol, Niacinamide, Licorice Extract act as skin brighteners. Brightening can also be used to describe products that help to increase cell turnover and therefore speed up the flaking away of damaged upper layers of the skin to reveal the beautiful baby-soft skin below. There is overlap between ingredients for both. Using all those ingredients can address both issues. In addition to stimulating collagen production, which will soften lines and wrinkles, peels firm skin and even our skin tone. Repetitive peels can also help to reduce pore size, fade discolorations, improve rosacea, as well as treat and prevent acne [11-17].

6. Skin Pigmentation

Visible pigmentation of the skin, hair, and eyes depends primarily on the functions of melanocytes, a very minor population of cells that specialize in the synthesis and distribution of the pigmented biopolymer melanin. Melanocytes are melanin-producing precursor cells (called melanoblasts) cells embryological development found in skin, hair follicles, eyes, inner ear, bones, heart and brain of humans. They arise from pluripotent neural crest cells and differentiate in response to a complex network of interacting regulatory pathways. Melanins are pigment molecules that are endogenously synthesized by melanocytes. The light absorption of melanin in skin and hair leads to photoreceptor shielding, thermoregulation, photoprotection, camouflage and display coloring. Melanins are also powerful cation chelators and may act as free radical sinks [18,19]. The number of melanocytes is relatively comparable among different ethnicities and variations in skin color are mainly dependent on the type (the relative quantity of pheo and eumelanins) and the amount of melanin produced within melanosomes. Size, quantity, distribution and degradation of these structures in the surrounding keratinocytes are also determinants in ethnic color differences. In light skin, melanosomes are smaller and mainly at an early stage of maturation (stages I and II). They are transferred to keratinocytes (**Figure 1**) as clusters and are degraded at the level of the spinous layer. In dark skin, these structures are larger, at stage IV and are singly transferred to the surrounding cells. Their degradation appears also slower than that in the light skin, being some melanins yet observed in the stratum corneum. Moreover, the ratio between pheo and eumelanins appears higher in dark versus light skins [20].

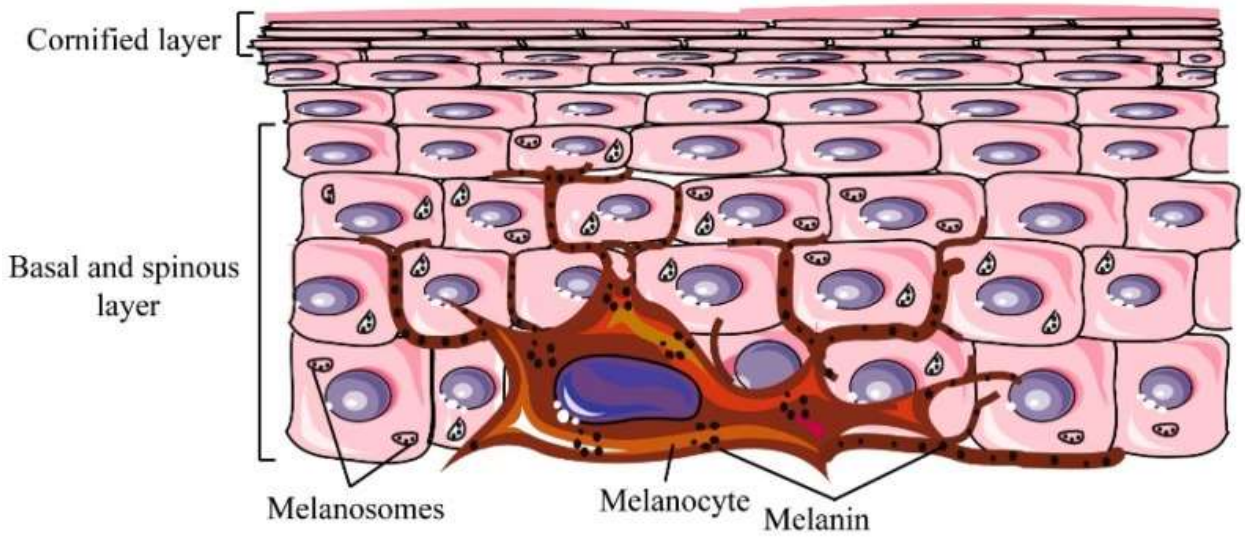


Figure 1. Association of keratinocytes and melanocytes [18]. The dendritic melanocyte is located in the basal layer of skin and produces melanin. Melanin pigments in melanosomes are transferred to keratinocytes.

Cutaneous melanin pigment plays a critical role in camouflage, mimicry, social communication, and protection against harmful effects of solar radiation. Pigmentation in skin is determined by various physiological processes occurring at different stages:
(a) Development of melanocytes
(b) Density of melanocytes
(c) Expression of the enzymatic and structural constituents of melanosomes
(d) Synthesis of melanin
(e) Transport of melanosomes to dendrites
(f) Transfer of melanosomes to keratinocytes
(g) Distribution of melanin in the supra basal layers of the skin [21]
Maranduca et.al, 2019 stated that the melanin molecule plays a role in the skin pigmentation and offers photoprotection to the organism by absorbing the sun ultraviolet radiation, due to its specific chemical structure. The color of the skin, hair and eyes is determined by the melanic pigments, and more precisely the ratio between the two types of melanic pigment. The quantity of melanic pigment offers the skin the color from white (lack of melanic pigment) to black (increased melanin density), and the ratio eumelanin-pheomelanin determines the differences in pigmentation of the human skin (**Figure 2**). If the quantity of pheomelanin produced by the epidermal melanocytes is higher compared to the quantity of eumelanin, then the skin is of lighter color and has a higher susceptibility to the sun burns. In the skin containing a higher quantity of pheomelanin, following the exposure of the sun ultraviolet radiation, a higher quantity of reactive species of oxygen is produced, leading to a cellular lesion and initiating the carcinogen process [22]. The general geographic patterns of skin pigmentation show a strong correlation with latitude and UVR intensity. Skin pigmentation tends to be darker in equatorial and tropical regions (Sub-Saharan Africa, South Asia, Australia and Melanesia) where UVR levels are higher than in regions distant to the equator [23].

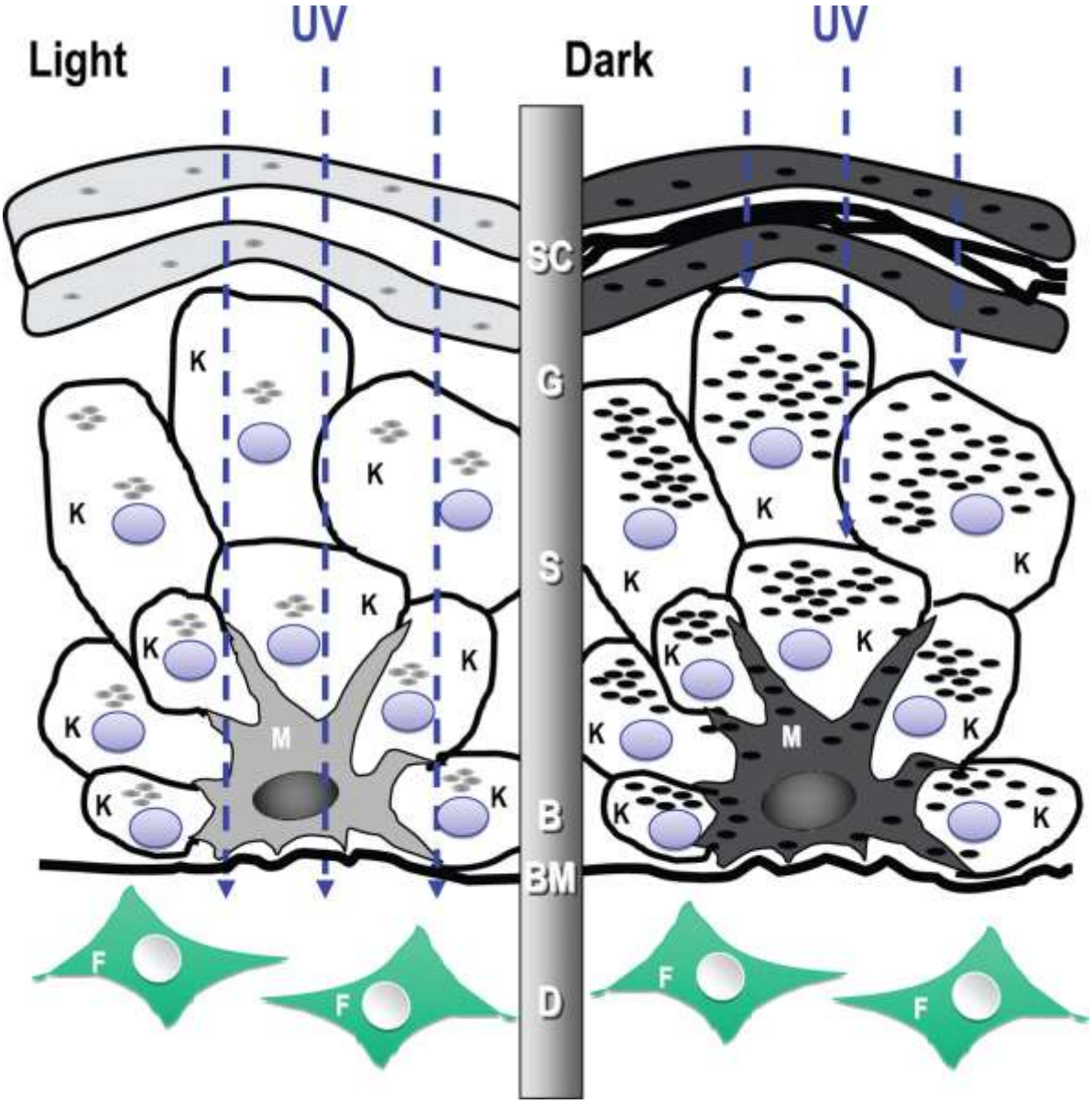


Figure 2. Schematic of human skin architecture from light- and dark-pigmented skin types [18]. From top to bottom: SC, stratum corneum; G, stratum granulosum; S, stratum spinosum; B, stratum basale; BM, basement membrane; D, dermis. Cell types: K, keratinocyte; M, melanocyte; F, fibroblast; shaded oval, melanin granule.

The first step of biosynthesis of both eumelanin and pheomelanin begins the same way. Tyrosine is converted into dihydroxyphenylalanine (DOPA), which requires tyrosine hydroxylase and tetrahydrobiopterin as a cofactor. The enzyme tyrosinase then converts dihydroxyphenylalanine into dopaquinone, which can follow a variety of pathways to form the eumelanin or pheomelanin. The primary stimulus for melanogenesis and subsequent melanosome production is UV radiation, which upregulates melanocyte production of pro-opiomelanocortin (POMC) and its downstream products, alpha-melanocyte-stimulating hormone (alpha-MSH) and adrenocorticotropic hormone (ACTH). The overall effect is to increase eumelanin production (**Figure 3**). (Interestingly, people

with pro-opiomelanocortin mutations have red hair and Fitzpatrick skin type 1 due to the relative increase in pheomelanin to eumelanin expression) [24,25].

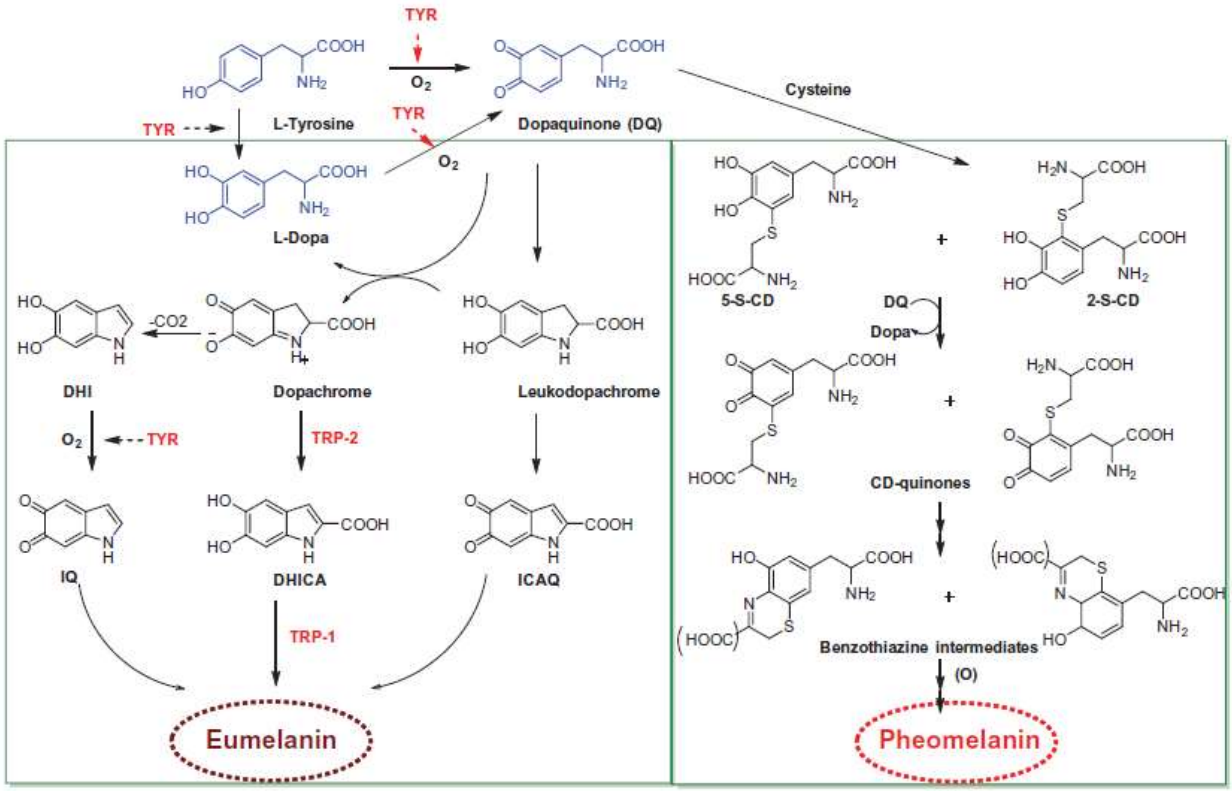


Figure 3. Melanogenesis pathway (production of eumelanin and pheomelanin) [1]. (Tyr: tyrosinase; DQ: dopaquinone; L-Dopa: L-3:4-dihydroxyphenylalanine; DHICA: 5,6-dihydroxyindole-2 carboxylic acid; DHI: 5,6-dihydroxyindole; ICAQ: indole-2-carboxylic acid-5,6-quinone; IQ: indole-5,6-quinone; HBTA: 5-hydroxy-1,4-benzothiazinylalanine).

7. Regulation of Skin Pigmentation

Given that melanocytes are present in a variety of tissues in the body, the initiation and extent of pigmentation or melanogenesis can be influenced by a number of intrinsic and extrinsic factors. In addition, melanogenesis can also be influenced by predetermined genetic factors such as age and ethnicity, and this process has evolved to provide protection and maintenance of homeostasis. Extrinsic factors include UVR and certain chemical compounds, while intrinsic factors include molecules secreted by surrounding keratinocytes, fibroblasts, inflammatory, neural or endocrine cells which are affected by conditions such as pregnancy and diabetes [18].

A. Intrinsic regulation of skin pigmentation

In human skin, melanogenesis is a tightly regulated process. Indeed, several extracellular signals are transduced via dedicated signaling pathways and mostly converge to MITF, a transcription factor integrating upstream signaling and regulating downstream genes involved in the various inherent mechanisms modulating melanogenesis. The synthesis of melanin pigments occurs in melanocytes inside melanosomes where melanogenic enzymes (tyrosinase and related proteins) are addressed with the help of specific protein complexes. The melanosomes loaded with melanin are then transferred to keratinocytes. Melanocytes produce Proopiomelanocortin (POMC)

peptides, cytokines, NO, prostaglandins, and leukotrienes, which act via an autocrine or paracrine way on keratinocytes, and are involved in immune and inflammatory responses. Keratinocytes also produce several factors in response to UVR exposure, with paracrine action on melanocytes, which may stimulate or inhibit melanogenesis. The increase in estrogen levels during pregnancy can cause hyperpigmentation (melasma, areolar hyperpigmentation and line nigricans). Catecholamines may be produced by keratinocytes from L-DOPA, the melanin precursor, and can bind to α1 and β2 adrenergic receptors in melanocytes, stimulating melanogenesis via the cAMP pathway and Protein kinase C-β (PKC-β). Besides this canonical regulation, melanogenesis can also be modulated by other non-specific intrinsic pathways (hormonal environment, inflammation) and by extrinsic factors (solar irradiation such as ultraviolet irradiation, environmental pollution) [26,27]. MITF has been investigated intensively among the many transcription factors known to regulate melanocyte function. MITF itself is regulated by many other transcription factors, including PAX3 (a neural-crest-associated transcription factor), SOX9, SOX10, LEF-1/TCF (a downstream regulator of Wnt signaling pathway), and CREB (cAMP responsive-element-binding protein, which is phosphorylated by signals via MC1R, melanocortin-1 receptor) [28].

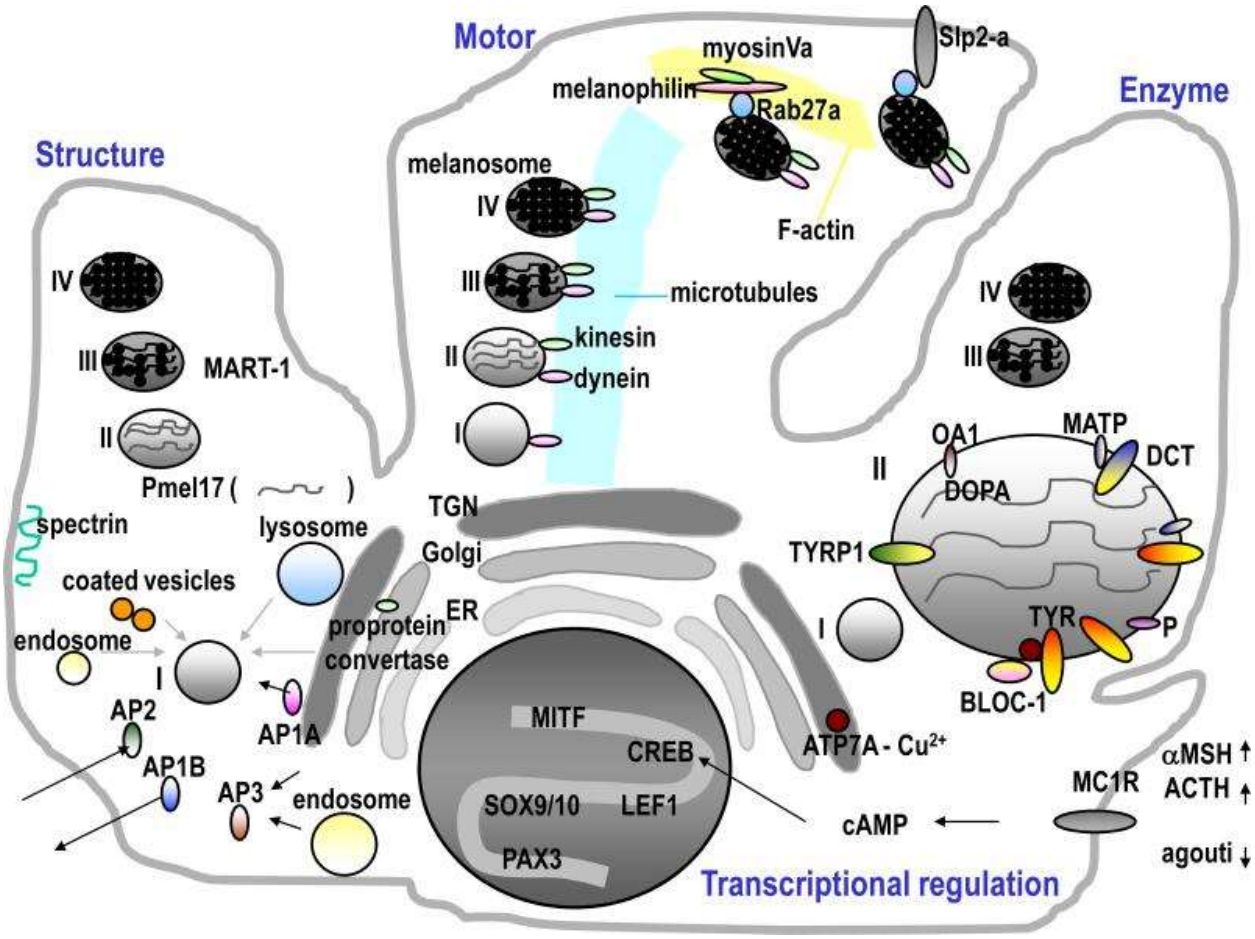


Figure 4. Factors that affect skin pigmentation within melanocytes [29]. Schemes show components involved in melanosome structure (left), transport (middle), enzyme (right) and transcriptional (bottom) related factors. Abbreviations: Microphthalmia-associated transcription factor (MITF); Adrenocorticotropic hormone (ACTH); α-Melanocyte-stimulating hormone (α-MSH); melanocortin type 1 receptor (MC1R).

B. Extrinsic regulation of skin pigmentation by ultraviolet radiation (UVR)

UVR increases proliferation and/or recruitment of melanocytes, the number of dendrites, and the transfer of melanosomes to a supranuclear location on the keratinocytes for DNA photoprotection. On the other hand, the expression of POMC peptides, MC1-R, and melanogenic enzymes increases in keratinocytes and melanocytes respectively. UVR has numerous effects on skin, including DNA damage, tanning, vitamin D synthesis, carcinogenesis, and immunomodulation. In keratinocytes, UV-mediated DNA damage activates p53, which then binds and activates the POMC gene. The POMC polypeptide is post-translationally cleaved, producing adrenocorticotropic hormone, α-MSH, and β-endorphin. Secreted keratinocyte-derived α-MSH then signals to melanocytes via the MC1R, a G protein-coupled receptor. The pigmentation (tanning) response is an adaptation that provides some delayed protection against further DNA damage and carcinogenesis, while the opioid response may be an evolutionary adaptation for promoting sun-seeking behavior to prevent vitamin D deficiency [27], [30,31].

Exhibit 1. Management of Hyperpigmented Disorders Linked to Sun Light [23]
The first line of treatment is to avoid the causative or aggravating factor, i.e., sun light exposure, by using sun blocking agents. Such protection has shown to reduce the incidence or relapse of melasma. In association with UV blocking agents, the second line of treatment may be physical therapies (cryotherapy, laser, IPD, dermoabrasion) or chemical peels which are quite efficient for the treatment of hyperpigmentation. However, they are usually not sustainable and associated with relapses. The risks of side effects such as hypo- or hyperpigmentation (PIH) specially in dark skins phototypes is also high with these procedures. Alternatively, less invasive and costly than physical modalities, topical or oral treatments, combining depigmenting agents with different modes of action may be useful. They may contain different molecules acting at different level of melanogenesis: (1) inhibitors of tyrosinase (e.g., hydroquinone, mequinol, rucinol, arbutin, kojic acid, azelaic acid or natural extracts such as pomegranate extract rich in ellagic acid); (2) inhibitors of tyrosinase maturation (e.g., N-acetyl glucosamine); (3) inhibitors of melanosome transfer (e.g., niacinamide, soybeans, lectins). Other agents can be used to complete the action of melanogenesis such as agents accelerating epidermal desquamation and melanin turn over (e.g., retinoids, salicylic acid, hydroxy acids) or agents acting by other modes such as anti-inflammatory and/or anti-vasculature agents (e.g., dexamethasone, fluocinolone acetate, and tranexamic acid) or antioxidants (e.g., vitamin C, resveratrol, vitamin E, ferulic acid, natural agents such as grapeseed extract, and gingko biloba).

8. Skin Whiteners

Pigmentation of the skin occurs as a result of increased melanin production or deposition due to various reasons including age, hormonal imbalances, endocrine disease, inflammation, and/or exposure to damaging radiation, resulting in dermatologic conditions such as lentigines, melasma, or post-inflammatory hyperpigmentation. The enzymatic breakdown of tyrosine into DOPA and then dopaquinone leads to the synthesis of two types of skin pigment (melanin), eumelanin and pheomelanin. These skin pigments (of which eumelanin is the more abundant and which regularly correlates with the visual phenotype) are produced by melanocytes, which use melanosomes to transport the pigments to keratinocytes. One melanocyte is typically attached to approximately 30 keratinocytes. Melanosomes are surrounded by keratinocytes, which absorb the melanin after activation of the protease-activated receptor (PAR)-2. Expressed in keratinocytes but not

melanocytes, PAR-2 is a seven transmembrane G-protein coupled trypsin/tryptase receptor activated by a serine protease cleavage. PAR-2 is believed to regulate pigmentation via exchanges between keratinocytes and melanocytes. Notably, melanogenesis can also be initiated by UV irradiation. Under these conditions, melanogenesis is a defensive manifestation to protect the skin and is characterized by accelerated melanin. synthesis and transfer to keratinocytes, leading to darkening of the skin in the exposed areas. Melanocytes synthesize more melanin in darker-skinned people, and their larger melanosomes accommodate this comparatively greater abundance of melanin and consequently break down more slowly than in lighter-skinned people. Inhibiting tyrosinase, thus preventing melanin formation, and blocking the transfer of melanin into keratinocytes represent the two main pathways through which the development of skin pigmentation can be hindered. Hydroquinone, vitamin C, kojic acid, arbutin, mulberry extract, and licorice extract are the most effective tyrosinase inhibitors. Skin pigmentation is also thought to be inhibited by two small proteins contained in soy—soybean trypsin inhibitor (STI) and Bowman–Birk inhibitor (BBI). Both STI and BBI have been shown in vitro and in vivo to exhibit depigmenting activity and to prevent UV-induced pigmentation by inhibiting the cleavage of PAR-2. Consequently, STI and BBI are thought to influence melanosome transfer into keratinocytes, thereby exerting an effect on pigmentation. Niacinamide, a vitamin B3 derivative, has also been demonstrated to hinder the melanosome transfer from melanocytes to keratinocytes. Soy and niacinamide, the most effective PAR-2 blockers, are the main agents for preventing this transfer. There are three classes of topical agents used within the two pathways of inhibiting melanin formation. In addition to the inhibitors of tyrosinase and PAR-2, exfoliating products (e.g., a-hydroxy acids, b-hydroxy acid, retinoids) have the capacity to increase cell turnover to outpace the rate of melanin production. Such exfoliation can also be achieved through microdermabrasion and the use of facial scrubs. Broad-spectrum sunscreens should also be employed in any skin care program intended to reduce or eliminate undesired pigmentation. The most effective way of preventing pigmentary alterations remains the avoidance of chronic sun exposure. Although numerous topical therapies exist for skin lightening, they are limited by efficacy and pigmentation recurrence after treatment cessation. The use of OTC lightening agents is widespread among those patients with hyperpigmentation disorders who reside in the United States. Those with melasma and PIH were more likely to use an OTC lightening cream. The majority of patients believed that OTC creams were safe to use without physician supervision. In those who had also tried prescription products, triple combination was deemed most effective compared to other lightening agents. Multiple systemic therapies for skin lightening exist including oral carotenoids, glutathione, melatonin, *Polypodium leucotomos* (tropical fern that has long been used for the treatment of inflammatory disorders by Native Americans) hydrophilic extract, procyanidin, and tranexamic acid. Preliminary data for the treatment of hyperpigmentation are promising, and currently, these oral treatments appear safe. Among the natural extracts, mulberry and licorice are popular components added to the skin whiteners. Also, lemon extract is used in the preparations like Skin Bright, Lucederm and Meladerm as a potent skin bleaching ingredient. However, it can only be used at low concentrations because it easily causes skin irritation [15], [32], [42], [56].

Exhibit 2. Classification of depigmenting agents and their mechanism of action [193]		
Stage of melanin synthesis	**Deposition**	**Active molecules**
Before melanin synthesis	Tyrosinase transcription	Tretinoin, c-2 ceramide
	Tyrosinase glycosylation	$PaSSO_3Ca$
	Inhibition of plasmin	Tranexamic acid
During melanin synthesis	Tyrosinase inhibition	Hydroquinone, mequinol, azelaic acid, kojic acid, arbutin, deoxyarbutin, licorice extract, rucinol, 2,5-dimethyl-4-hydroxy-3(2H)-furanone, *N*-acetyl glucosamine, resveratrol, oxyresveratrol, ellagic acid, methyl gentisate, 4-hydroxyanisole
	Peroxidase inhibition	Phenolic compounds
	Reactive oxygen species scavengers	Ascorbic acid, ascorbic acid palmitate, thiotic acid, hydrocumarins
After melanin synthesis	Tyrosinase degradation	Linoleic acid, α-linoleic acid
	Inhibition of melanosome transfer	Niacinamide, serine protease inhibitors, retinoids, lecithins, neoglycoproteins, soybean trypsin inhibitor
	Skin turnover acceleration	Lactic acid, glycolic acid, linoleic acid, retinoic acid
	Regulation of melanocyte environment	Corticosteroids, glabiridin
	Interaction with copper	Kojic acid, ascorbic acid
	Inhibition of melanosome maturation	Arbutin and deoxyarbutin
	Inhibition of protease activated receptor 2	Soybean trypsin inhibitor

8.1.Tyrosinase Inhibition

Tyrosinase, a rate-limiting enzyme in melanogenesis, is a melanocyte-specific copper-containing glycoprotein located within specialized organelles called melanosomes [216]. Since tyrosinase is a crucial enzyme in synthesizing melanin through melanogenesis, it becomes the most prominent

and successful target for melanogenesis inhibitors that directly inhibit the tyrosinase catalytic activity. Most of cosmetics or skin lightening agents commercially available are tyrosinase inhibitors [1]. Depigmentation can be achieved by regulating (i) the transcription and activity of tyrosinase, tyrosinase related protein-1 (TRP-1), tyrosinase related protein-2 (TRP-2), and/or peroxidase, (ii) the uptake and distribution of melanosomes in recipient keratinocytes, and (iii) melanin and melanosome degradation and turnover of "pigmented keratinocytes". Tyrosinase is a copper enzyme, which catalyses both the hydroxylation of monophenols to o-diphenols and the oxidation of o-diquinones to o-quinones. Most whitening agents act specifically to reduce the function of this enzyme by means of the following mechanisms: (i) interference with its transcription and/or glycosylation, (ii) inhibition by different modalities, (iii) reduction of by-products, and (iv) post-transcriptional control [33].

A. Hydroquinone

Hydroquinone (HQ) is a dihydric phenol with two important derivatives viz. monobenzyl and monomethyl ether of hydroquinone. Hydroquinone competitively inhibits melanin synthesis by inhibiting sulfhydryl groups and acting as a substrate for tyrosinase. Melanosomes and melanocytes are damaged by the semiquinone free radicals released during the above reaction. The effectiveness of HQ is related directly to the concentration of the preparation [34]. Sun screens, sun avoidance and bleaching agents, such as 4% hydroquinone alone or in combination with retinoid and topical steroids are conventional treatments [52]. Clinically, it is used to treat areas of dyschromia, such as in: melasma, chloasma, solar lentigines, freckles, post-inflammatory hyperpigmentation [35]. Concentrations of HQ vary from 2% (over the counter) to as high as 10% that are prescribed extemporaneously for resistant cases. It was known that the higher concentrations of HQ were more effective, but the irritating and toxin for melanocytes sign were obvious. There was a reduction in the effectiveness of HQ preparation due to oxidation so that stabilizing agents like sodium bisulphate and ascorbic acid were used as antioxidants. The most suitable vehicle for the formulation is a hydroalcoholic solution (equal parts of propylene glycol and absolute ethanol) or an hydrophilic ointment, or a gel containing 10% alpha-hydroxy acids (AHAs), taking into consideration the desired 3% to 5% HQ concentration in ethanol and propylene glycol 1:1 (or in a cream base or an AHA 10% gel) [33]. The FDA has even proposed banning over-the counter skin bleaching agents containing hydroquinone in 2006 [36]. It is also banned in EU since 2001 [37]. Due to the side-effect and safety profile, hydroquinone is not used as a component of cosmeceuticals available in the market for the treatment of hyperpigmentation. Possible long-term effects such as carcinogenesis may be expected as well. Metabolites of hydroquinone formed in the liver, e.g., p-benzoquinone and glutathione conjugates of hydroquinone, are mainly responsible for this. In the bone marrow, hydroquinone is oxidized into p-benzoquinone because of the high myeloperoxidase activity. Topically applied hydroquinone-containing creams may give rise to accumulation of these compounds, which can cause DNA damage and mutations [38]. Although, HQs exhibits In Vitro and In Vivo Anti-Cancer Activity in Cancer Cells and Mice [39]. However, other chronic adverse effects include exogenous ochronosis, cataract, pigmented colloid milia, sclera, and nail pigmentation, loss of elasticity of the skin, impaired wound healing and exuding an offensive fish odor. Topical Silymarin cream might serve as an effective and safe treatment modality [40]. Shankar et.al, 2014 concluded that fluorinated steroid containing 2-4% HQ-based triple combination for first line, with additional selective peels if required in second line treatment for melasma. Lasers are a last resort [193].

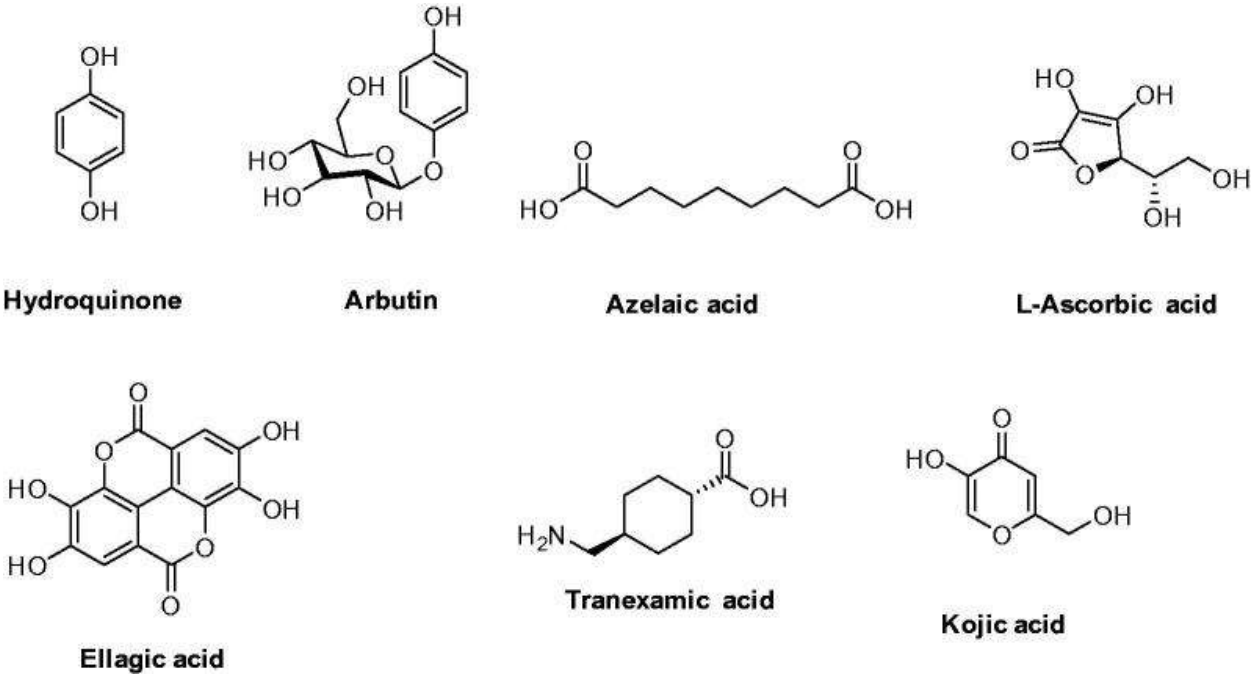


Figure 5. Chemical structure of well-known tyrosinase inhibitors as skin lightening agents [1].

Exhibit 3. Common lightening agents with brief M/A & S/E [41]		
Name	**Mechanism of action**	**Side effects**
Hydroquinone	Tyrosinase inhibition	Erythema, irritation, exogenous ochronosis
Azelaic acid	Tyrosinase inhibition	Stinging, burning, itching, dryness
Kojic acid	Tyrosinase inhibition	Irritation, contact dermatitis
Ascorbic acid	Inhibition of reactive oxygen species	No significant adverse event
Retinoids	Downregulation of Tyrosinase	Irritant reaction, dryness, hyperpigmentation
Corticosteroid treatments	Anti-inflammatory and nonselective inhibition of melanogenesis	Telangiectasias, epidermal atrophy, steroid-induced acne, striae, hypopigmentation
Niacinamide	Inhibition of melanasome transfer	Irritation
Licorice	Melanin dispersion, tyrosinase inhibition	No significant adverse event
Undecylenoyl phenylalanine	Antagonist of α-melanocyte-stimulating hormone, β-adrenergic, stem cell receptors	No significant adverse event

Exhibit 3. Common lightening agents with brief M/A & S/E [41]		
Name	**Mechanism of action**	**Side effects**
4-N-butylresorcinol	Tyrosinase inhibition, antioxidant, anti-inflammatory	Mild erythema and itching
Soybean	Inhibits melanosome transfer to keratinocytes	No significant adverse event
Arbutin	Inhibition of tyrosinase	Skin irritation
Glucosamine	Inhibition of tyrosinase activation	Skin rash
Mequinol	Inhibition of tyrosinase	Skin irritation, redness, peeling

B. Kojic Acid

Kojic acid (5-hydroxy-2 hydroxymethyl-4-pyrone), crystalline white powder, is increasingly being used as a skin-lightening agent in skin care products marketed in Japan since 1988. It is a naturally occurring hydrophilic fungal product derived from certain species of *Acetobacter*, *Aspergillus*, and *Penicillium*. It was first isolated from Aspergillus in 1907. Kojic acid (KA) suppresses free tyrosinase, mainly attributable to chelation of its copper, and it has been shown to be responsible for therapy and prevention of pigmentation, both in vitro and in vivo. In Japan, it is used in nonprescription skin care products up to a concentration of 1%. To increase percutaneous absorption and thus therapeutic activity, it is usually used at the highest concentration allowed. Since it is used intensively in foods (such as bean paste, soy, and sake) in some countries, particularly Japan, it was thought to be safe [42]. This has been used for a long time in Japan in the form of an alternative to hydroquinone. American Academy of Dermatologists have clinically proven that KA can be effective for the treatment of hyper-pigmentation. KA functions similar to Arbutin and inhibits the activity of the enzyme tyrosinase. Like mentioned earlier, tyrosinase is responsible for the production of melanin [43]. It reduces hyperpigmentation by inhibiting the production of free tyrosinase and is also a potent antioxidant. KA is used at concentrations ranging from 1% to 4% [34]. Montazeri et. al, 2019 detailed potent anti-Toxoplasma activity with direct and indirect effects on the parasite [44]. Kojic acid is most commonly used in cosmetic products, such as creams, lotions, and serums. It is also used in some soaps. Many products with kojic acid are intended for use on the hands or face [45]. The major applications of KA and its derivatives in medicine are based on their biocompatibility, antimicrobial and antiviral, antitumor, antidiabetic, anticancer, anti-speck, anti-parasitic, and pesticidal and insecticidal properties. In addition, KA and its derivatives are used as anti-oxidant, anti-proliferative, anti-inflammatory, radio protective and skin-lightening agent in skin creams, lotions, soaps, and dental care products [46]. Burnett et.al, 2010 stated that KA was not a toxicant in acute, chronic, reproductive, and genotoxicity studies [47]. Contact dermatitis is the most common side effect of topical KA use. Even if KA does not initially irritate the skin, there's a risk of developing allergic contact dermatitis with continued use. However, KA does not find a place in the cosmeceuticals available. This could be due to the side effect profile of this drug [34], [48].

C. Azelaic Acid

Azelaic Acid (AA) is derived from the fungus *Pityrosporum ovale* and can be found in rye, wheat, and barley. The effect of AA can be attributed to its ability to inhibit the energy production and/or DNA synthesis of hyperactive melanocytes, and partially to its anti-tyrosinase activity. This may

also account for the beneficial effect on post-inflammatory hyperpigmentation [49], [55]. It brightens the skin tone while visibly improving the evenness of skin texture and reducing the look of blemishes. It is a multi-functional support ingredient for all skin types and also acts as an effective antioxidant, antibacterial, keratolytic and comedolytic [50,51]. Faghihi et.al, 2017 demonstrates that triple-combination of 20% azelaic acid + 10% resorcinol + 6% phytic acid was found to be an effective and safe peeling agent in the treatment of melasma and it was as effective as 50% glycolic acid peel [52]. In a similar study, Dayal et.al, 2017 stated that Glycolic acid (GA) peel alone or in combination with topical hypopigmenting agents (GA peel every 3 weeks with twice daily 20% AA cream) has shown encouraging results for treatment of melasma, improvement in melasma quality of life (MELASQOL) scores without serious side effects [53]. AA-loaded nano-emulsion with hyaluronic acid as a double targeting strategy to increase drug retention and tyrosinase inhibition activity reached the deeper layers of the skin while improving in vitro tyrosinase inhibition; hence, it could be a promising treatment to dermic melasma [54]. This agent preferentially targets abnormal and highly active melanocytes with minimal effect on uninvolved skin [55]. Topical potent steroids and 20% AA cream combines the beneficial effects of both besides perhaps increasing the compliance of the patients. AA with tretinoin caused more skin lightening after three months than AA alone, and a higher proportion of excellent responders at the end of treatment. The combination of AA 20% cream and glycolic acid 15% or 20% lotion was as effective as HQ 4% cream in the treatment of hyperpigmentation in darker skinned patients, with only a slightly higher rate of mild local irritation. Particular advantages of AA therapy include its favorable safety and side effect profile. It is non-teratogenic, is not associated with systemic adverse events or photodynamic reactions and exhibits excellent local tolerability. Adverse effects from the AA included irritant contact dermatitis that was usually mild and transient, but occasionally was pronounced [33]. However, Tehranchinia et.al, 2018 demonstrates that common therapeutic approaches for melasma include topical HQ, AA, steroids, chemical peels, and lasers, most of which could not induce remarkable and constant satisfying outcomes [57].

D. Glutathione

Glutathione (GSH), being a strong antioxidant with additional anti-melanogenic properties, has recently become the most popular "systemic skin lightening molecule." In addition to be one of the richest antioxidants, it is being promoted as a skin-lightening agent, following the discovery of its anti-melanogenic properties. GSH is one of agents which is commonly used to lighten skin color in Asia as a dietary supplement. The most "popular" and controversial route of administration of glutathione for skin lightening has been intravenous (IV). GSH, an LMW thiol-tripeptide (component of cysteine, glutamate and glycine) is central to the maintenance of intracellular redox balance [58]. The proposed mechanisms of action include (a) direct inactivation of the enzyme tyrosinase by binding with the copper-containing active site of the enzyme, (b) mediating the switch mechanism from eumelanin to phaeomelanin production, (c) quenching of free radicals and peroxides that contribute to tyrosinase activation and melanin formation, and (d) modulation of depigmenting abilities of melanocytotoxic agents [33], [59]. Orally administered GSH, 500 mg per day for 4 weeks, resulted in a lightening of skin color in a small number of subjects [60] and 250 mg/d, in both reduced and oxidized forms effectively influences skin properties. Overall, glutathione in both forms are well tolerated [61]. In its reduced form, GSH is an antioxidant and also is involved in pheomelanin formation. Although glutathione is present in its both reduced (GSH) and oxidized (GSSG) states, the majority of it found in the body is in the reduced form. GSH conducts antioxidant activity by scavenging free-radicals during reductive detoxification of

hydrogen peroxide and lipid peroxide. Chung et.al, 2016 reported that GSH monoethyl ester (GSH-MEE) was effective for anti-melanogenesis, whereas GSH itself was not. Particularly GSH-MEE (but not GSH itself), was effective without affecting cellular viability for reducing melanin and tyrosinase activity and raising the suggested pheomelanin/eumelanin ratio. Taken together, this novel esterified GSH derivative could be developed as a safe and efficient agent for the treatment of hyperpigmentary skin disorders (Figure 6) [62].

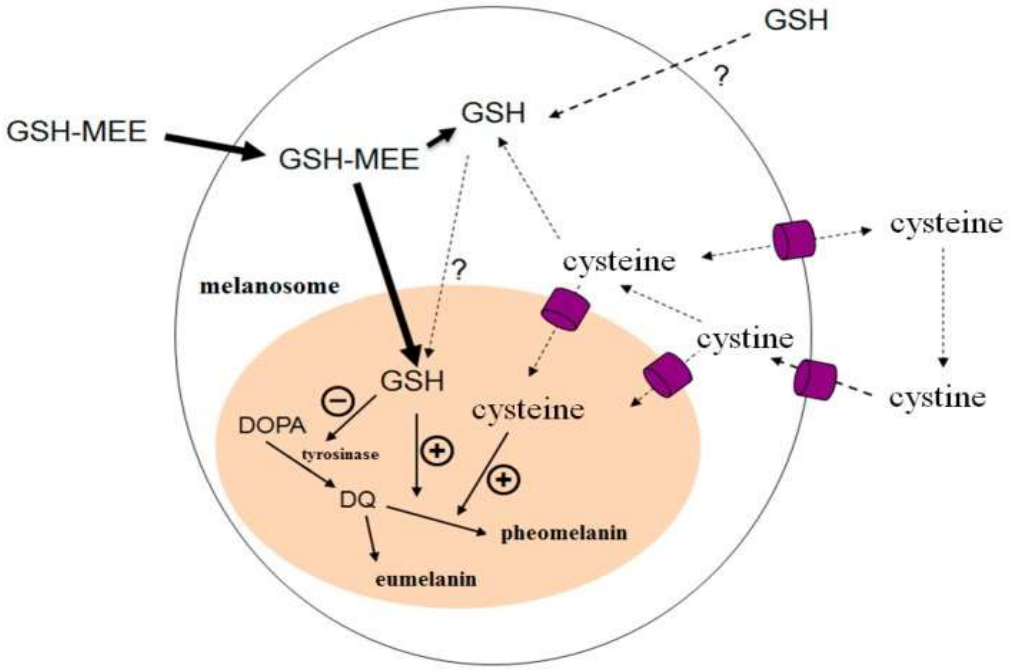


Figure 6. Possible effects of GSH-MEE, GSH, and cysteine on melanogenesis [62]. GSH synthesize intracellularly and exported to extracellular space. Cellular uptake of GSH itself is not probable. GSH-MEE cross the biological membranes by simple diffusion and metabolize intracellularly to generate GSH. Cysteine is readily transported across cell membranes but potentially toxic at high concentrations due to generation of reactive oxygen species and depletion of pyridoxal phosphate. GSH-MEE (but not GSH itself) could suppress the melanin production and tyrosinase activity and raise the suggested pheomelanin/eumelanin ratio. black arrows, melanin synthesis process flow; dotted black arrows, transport process flows of GSH, cysteine, and cysteine, bold black arrows, transport process flow of GSH-MEE; question marks, not yet confirmed; +, positive effects (activation); −, negative effects (suppression); purple shape, membrane channel. GSH, reduced glutathione; GSH-MEE, GSH monoethyl ester; DOPA, dihydroxyphenylalanine; DQ, dopaquinone.

Multiple articles have been published in the lay press on the use of GSH for a variety of diseases including melasma. IV use of GSH has been associated with severe life-threatening reactions including Stevens–Johnson syndrome and anaphylaxis [41]. According to Dilokthornsakul et.al, 2019 skin whitening effect of glutathione is still inconclusive due to the quality of included studies and inconsistent findings [63]. Cosmetic doctors have called on the UK government to warn consumers about the dangers of skin whitening antioxidant glutathione. However, concern is growing over the use of the antioxidant by unqualified or unlicensed practitioners, including in some salons, to lighten the color of the skin [64]. Finally, there is little convincing evidence in

favor of GSH as a therapy for hyperpigmentation at the present time, and there are many unresolved controversies that surround its use, as reported by Sonthalia et.al, 2018 [58]. FDA clarified that only glutathione tablets are approved by the agency, and not glutathione injectables. Antioxidant's main use is to counter the A/Es of cancer treatments, but is now being used by consumers seeking whiter skin. Its side effect is the whitening of skin as it deactivates tyrosinase, the enzyme that helps produce melanin, the pigment that determines skin color. Glutathione may cause kidney failure and blood poisoning [65,66].

E. Arbutin

Arbutin, the b-D-glucopyranoside derivative of hydroquinone, is a naturally occurring plant derived compound found in the dried leaves of a number of different plant species including, bearberry (*Arctostaphylos uva-ursi*), blueberry, cranberry, and pear trees [34], [67]. Hydroquinone occurs in nature as the b-glucopyranoside conjugate (arbutin). *Uva-ursi folium* (bearberry leaf) has been traditionally used in Japan (contained in the leaves of pear trees and certain herbs) to treat symptoms of lower urinary tract infections. The most representative constituent of this herbal drug is arbutin that is rapidly absorbed in the small intestine and undergoes hepatic conjugation to form HQ conjugates [68]. Arbutin is a mild agent for treating cutaneous hyperpigmentation, including melasma and UV-induced ephelides. Arbutin was first discovered in *Arctostapylos uva-ursi* (L.) Spreng and then in the leaves of *Vaccinicum vitis-idaca* L., *Pyrus pyrifolia* (Burm.f.) Kakai. and *Saxifraga stolonifera* (L.) Meerb. In both normal human melanocytes and melanoma, arbutin induces a decrease of tyrosinase activity without affecting mRNA expression, inhibits the 5,6-dihydroxyindole-2-carboxylic acid (DHICA) polymerase activity, and exerts an inhibitory effect on melanosome maturation. This phenotypic change was associated with the inhibition of tyrosinase and DHICA polymerase activities, and the degree of inhibition was dose dependent [67]. Higher concentrations are more efficacious than lower concentrations, but they may also result in a paradoxical hyperpigmentation [33]. The depigmentation effect of arbutin works through an inhibition of the melanosomal tyrosinase activity, rather than by suppression of the expression and synthesis of tyrosinase in human melanocytes [69]. It was found to inhibit the oxidation of l-tyrosine catalyzed by mushroom tyrosinase. The kinetics and mechanism for inhibition of tyrosinase confirms the reversibility of arbutin as a competitive inhibitor of this enzyme [33], [42]. The Scientific Committee on Consumer Safety (SCCS) assessed the use safety of alpha arbutin (for concentrations greater than 2% in facial creams and greater than 0.5% for body lotions) and of beta arbutin (for concentrations greater than 7% in facial creams) [70,71]. Treatment of the human skin model with 250 mcg of α-arbutin did not inhibit cell viability, while melanin synthesis was reduced to 40% of that in the control. These results indicate that alpha-arbutin is an effective and safe ingredient for skin-lightening [72]. Arbutin was less cytotoxic than hydroquinone to cultured human melanocytes [73,74]. Miao et.al, 2016 reported that deoxy-arbutin possesses a potent ability in skin lightening and antioxidation with less melanosome cytotoxicity [74]. Hamed et al, 2006 reported the efficacy and safety of deoxyarbutin, a new tyrosinase inhibiting agent both in vitro and in vivo on human skin. They demonstrated that deoxyarbutin has the potential to be as safe and effective as a depigmenting agent and suggested that it may act an as an alternative agent to hydroquinone [75].

F. Ellagic Acid

Ellagic acid (EA) is a phenolic compound related to flavonoids that is structurally a condensed dimer of gallic acid. It has been described as a tyrosinase inhibitor and is used in the cosmetic

industry as a whitening agent. It is present either in free form or as part of more complex molecules (ellagitannins), which can be metabolized to liberate ellagic acid and several of its metabolites, including urolithins. Only a small portion of EA is found in the free form. EA is usually conjugated with a glycoside moiety such as glucose, rhamnos, arabinose, or bound in the form of ellagitannins. Phenolic compounds possess benzene ring and hydroxyl group substituents and are able to quench free radicals and prevent cellular damage, thereby functioning as effective antioxidants. While EA 's antioxidant properties are doubtless responsible for many of its pharmacological activities, other mechanisms have also been implicated in its various effects, including its ability to reduce the lipidemic profile and lipid metabolism, alter pro-inflammatory mediators (tumor necrosis factor-α, IL-1β, IL-6), and decrease the activity of nuclear factor-κB while increasing nuclear factor erythroid 2-related factor 2 expression. Frozen apple, raspberry and blackberry are good sources of EA [76-78]. It is capable of preventing pigmentation caused by sunburn, found in trees, nuts, and fruit. It inhibits tyrosinase non-competitively in a dose-dependent manner, through its capacity to chelate copper, even if other mechanisms, such as a scavenger effect have been suggested [33], [55]. EA has been demonstrated to have melanogenic inhibitory activity both in vitro and in vivo. A topical product containing 0.5% ellagic acid and 0.1% salicylic acid appears to have better esthetics (texture, pleasantness to use, skin feel) than the 4% HQ product [79]. EA is oxidized by tyrosinase, producing reactive o-quinones. As an antioxidant it can inhibit the melanogenesis process. This first aspect should be taken into consideration in its application as a cosmetic ingredient due to the toxicity of o-quinones and its ability to modify the redox status of the cell [80]. Dietary and pharmacological interventions with berries rich in ellagic acid may be promising treatment strategies interrupting skin wrinkle and inflammation associated with chronic UV exposure leading to photoaging [81]. The antioxidant efficiency of EA is directly correlated with its degree of hydroxylation and decreases with the presence of a sugar moiety. Many health benefits of EA are attributed to its antioxidant properties because oxidative stress is involved in the pathogenesis of different diseases [78] EA is a plausible candidate used as a natural resource for manufacturing anti-photoaging cosmetics, which may have similar or enhanced activities with fewer side effects [82].

G. Aloesin

Aloesin, a natural hydroxymethylchromone derivative isolated from Aloe Vera, acts by two different mechanisms of action on tyrosinase activity, e.g., aloesin inhibits the formation of DOPA quinone by competitive inhibition at the DOPA oxidation site, reduction of copper ions at the hydroxylase site, and consequently tyrosine hydroxylation by noncompetitive inhibition. In comparison with other depigmenting agents, aloesin shows no cytotoxicity in cell-based assays, no skin irritation in preliminary human studies and any genotoxicity or mutagenicity in the Ames assay. Cultured cells used in tyrosinase activity assays show no morphologic abnormalities when treated with aloesin, and human melanocytes appear normal with multiple dendrites. Thus, aloesin is a potent inhibitor of human tyrosinase. However, because of the hydrophilic nature of the compound and moderately high molecular weight, penetration of human skin was poor. At non-cytotoxic concentration aloesin probably acting as a competitive inhibitor on DOPA oxidation and as a non-competitive on tyrosine hydroxylase activity [33]. Aloesin performed more inhibitory activity toward crude murine tyrosinase than mushroom tyrosinase and has been recently used in topically applied cosmetics due to its natural source and multifunctional activity in skin care. Aloesin treatment showed pigmentation suppression in a dose dependent manner; thus, aloesin might be used as an agent that inhibits melanin formation induced by UV radiation. In vivo, aloesin

and arbutin co-treatment inhibits UV induced melanogenesis in a synergistic manner [83-86]. The hydrophilic nature of the compound reduces the skin penetration of aloesin. Hence, combination treatment of aloesin with arbutin has been studied to assess the synergistic effects on tyrosinase activity. The two adhere to different mechanisms of action where aloesin exhibits noncompetitive inhibition while arbutin inhibits competitively. Studies of aloesin revealed no cytotoxicity, which makes it a good alternative to HQ [87]. The mixture of aloesin and arbutin can significantly inhibit the tyrosinase activity and melanogenesis of cultured human melanocytes. It showed the effects of aloesin and arbutin in a synergistic manner [88]. Even though aloesin appears to be an important component in the armamentarium against hyperpigmentation disorders, its hydrophilic nature renders it less able than hydroquinone to penetrate the skin [89]. However, some believe that its slower penetration of the skin endows aloesin with greater potential as a skin-lightening agent for cosmetic purposes [90].

H. Tranexamic Acid

Tranexamic acid (TXA) is commonly being used to reduce melanin synthesis in patients with melasma and also used as a raw material for functional whitening cosmetics. The mechanism of TXA, which is a lysine analog, in the treatment of UV-induced pigmentation includes interfering with the structure of plasminogen and preventing the binding of plasminogen to the lysine-binding sites of keratinocytes (**Figure 7**). The consequences of such event are less free arachidonic acid so a reduced ability to produce prostaglandins and thus decreased melanocyte tyrosinase activity and melanogenesis [91]. However, Cho et.al., 2017 reported that TXA can reduce melanin synthesis in melanoma B16-F1 cells by activating the extracellular signal-regulated kinase (ERK) signaling pathway and the autophagy system [92]. Histological and immunohistochemical evaluation following oral TXA has shown decrease in epidermal pigmentation as well as melasma-associated dermal changes such as number of vessels and mast cells, according to evidence-based review by Sharma et.al, 2017 [101]. Kim et.al, 2016 reported downregulation of Endothelin (ET)-1 by TXA for the same. The number of CD31-positive vessels and the expression of the vascular endothelial growth factor both tended to decrease. This immunohistochemical study found that suppression of ET-1 could be one of the mechanisms of action of TXA on melasma [100]. TXA 5%, topically twice a day for 12 weeks in the location of the melasma significantly reduced both melanin level and MASI score. Given its high efficiency and low drug side effects, this regimen results in high patient satisfaction compared with topical hydroquinone [93]. In a similar study with Asian population, Kanechorn et.al, 2012 reported topical TXA 5% produced erythema as side effects [98]. TXA has been found to lighten melasma by interfering with the interaction of melanocytes and keratinocytes by inhibiting the plasminogen/plasmin system. Tan et.al, 2017 reported (study results from a tertiary dermatological center in Singapore between 1 August 2009 and 31 March 2011) that low-dose oral TXA can serve as a safe and useful adjunct in the treatment of refractory melasma [94].

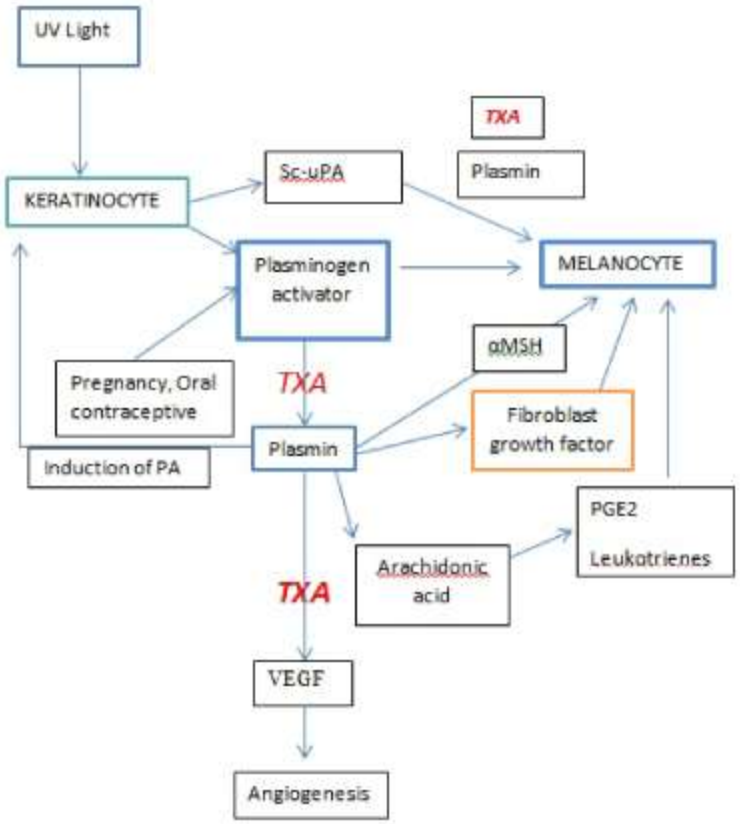


Figure 7. Pathogenesis of Melasma And Role of Tranexemic Acid [93]. TXA, a synthetic derivative of lysine, is a fibrinolytic agent that blocks the conversion of plasminogen to plasmin and thereby impedes the binding of plasminogen to keratinocytes. Human keratinocytes secrete the urokinase-type plasminogen activator, which increases the activity of melanocytes in vitro. The blockade of this effect may be due to the mechanism by which TXA reduces hyperpigmentation in melasma patients. The consequences of such event are less free arachidonic acid leading to a reduced ability to produce prostaglandins and thus decreased melanocyte tyrosinase activity and melanogenesis. Tranexamic acid has no effect on non-sun exposed healthy skin. Also, action of TXA on angiogenesis via plasmin could also play a contributory role in its action on melasma. Blocking of the Sc-uPA pathway may be another mechanism through which TXA reduces hyperpigmentation. TXA: Tranexemic acid, PA: Plasminogen activator, Sc-uPA: Single Chain urokinase Plasminogen Activator, VEGF: Vascular Endothelial Growth Factor.

TXA is easily available (5 mL ampoule containing 500 mg of the drug) and affordable. Better therapeutic response to treatment in the micro-needling group could be attributed to the deeper and uniform delivery of the medication through microchannels created by micro-needling. EMLA Cream (lidocaine 2.5% and prilocaine 2.5%) was used as anesthetic in this study. Budamakuntla et.al, 2013 reported more than 50% improvement without major adverse events observed in both the treatment groups. The MASI scores, physician global assessment (PGA) and patient global assessment (PtGA) score showed a significant decreasing trend from the baseline to the fourth, eighth, and twelfth week of treatment with TXA [95]. Melasma relapse was found to be 72% as reported by Tan et.al, 2017. TXA treatment should not be short-term, but needs to be maintained for an extended period of time. However, TXA is used as a haemostatic treatment, it is prescribed

at a dosage of 1,000 mg 3 times daily. For melasma, it is commonly used at a dosage of 250 mg twice daily, which is only one-sixth of the normal dosage of TA as a haemostatic agent. Kim et.al, 2017 reported that ADEs were minor, with a few cases reporting hypo-menorrhoea, mild abdominal discomfort, and transient skin irritation. These results support the efficacy and safety of TXA, either alone or as an adjuvant to routine treatment modalities for melasma [96]. Hair follicles are important reservoirs for co-drug delivery. Hsieh et.al, 2013 reported TXA to be a superior candidate as a co-drug. Daily administration of co-drugs (both TXA and HQ) to the skin did not generate irritation for up to 7 days [97]. An eight-week, prospective, randomized, double-blind, vehicle-controlled clinical study evaluated a combination of niacinamide and TXA as a topical moisturizer in the treatment of 42 Korean women with irregular facial hyperpigmentation. This formulation was significantly more effective in reducing the hyperpigmentation than the vehicle control, providing an effect beyond that achieved with sunscreen [99]. Role of oral TXA as adjuvant to other therapies such as fluocinolone based TC (fluocinolone acetonide 0.01%, HQ 4%, tretinoin 0.05%), HQ, and laser were assessed in RCTs. All these studies reported significantly enhanced efficacy with addition of TXA to TC (LOE 2), IPL and LASER treatment (LOE 2, 4) in melasma [101]. Zhang et.al, 2018 review shows that both single and adjuvant TA treatments showed a significant reduction of MASI and MI scores while incurring minimal side effects [102]. It can also be used when other topical treatments fail [103].

I. Ascorbic Acid

Ascorbic acid may inhibit melanin production by reducing o-quinones, so that melanin cannot be formed by the action of tyrosinase until all vitamin C is oxidized. It interferes with the different steps of melanization, by interacting with copper ions at the tyrosinase active site and reducing dopaquinone and DHICA oxidation. Melanin can be changed from jet black to light tan by the reduction of oxidized melanin. Because vitamin C is quickly oxidized and decomposes in aqueous solution, it is not generally useful as a depigmenting agent (**Figure 8**). Ascorbic acid is an effective reducing agent, which, at high concentrations, can momentarily retard the melanin-biosynthesis pathway, but never eliminate it. On the contrary, the resultant accumulation of diphenol produces an indirect activation on this pathway when the reductant is completely depleted. However, ascorbic acid is highly instable, being quickly oxidized and decomposed in aqueous solution and, because of its prevalent hydrophilic nature, has a low degree of penetration into the skin. Stable derivatives of vitamin C have been synthesized to minimize this problem. Magnesium-L-ascorbyl-2-phosphate (VC-PMG) is a vitamin C derivative that is stable in water, especially in neutral or alkaline solution containing boric acid or its salt. The more stable ascorbate ester VC-PMG (QD approval was obtained by the Takeda Pharmaceutical Company Limited in 1988) is more lipophilic and has a greater permeation through the stratum corneum. VC-PMG is hydrolyzed by phosphatases of the liver or skin to vitamin C and thus exhibits vitamin C– reducing activity. VC-PMG is hydrolyzed by phosphatases of liver or skin to ascorbic acid and thus exhibits vitamin C-reducing activity. It significantly suppressed melanin formation on purified tyrosinase or cultured cells and inhibited melanin formation without cell growth suppression on cultured human melanoma cells. Inhibition of melanogenesis was stronger when the activity of melanogenic enzymes was relatively high. VC-PMG is absorbed percutaneously, stays in the skin, and inhibits tyrosinase activity of melanocytes. The addition of 1% to 3% 1,1-methyleneglycol-bis increases the absorption of VC-PMG. In situ experiments demonstrated that 10% VC-PMG cream was absorbed into the epidermis and that 1.6% remained 48 hours after application [33], [42]. Al-Niaimi et.al, 2017 reported that a concentration above 20% does not increase its biological

significance and, conversely, might cause some irritation. Reputable products of vitamin C available today are, therefore, in the range of 10 to 20% [105]. A study compared 5% ascorbic acid and 4% HQ shows that situation improved more than 90% but ADEs were around 70% in melasma patients. Author concluded that vitamin C may play a role as it is devoid of any side-effects, can be used alone or in combination therapy [106].

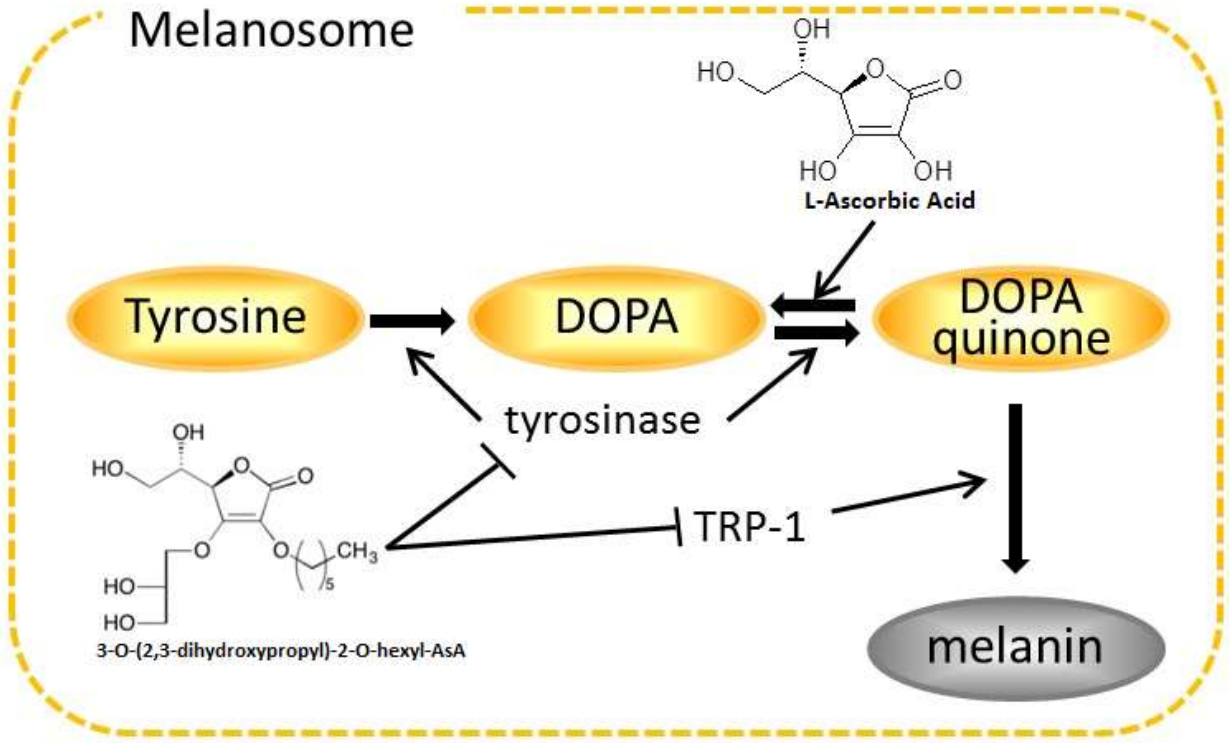
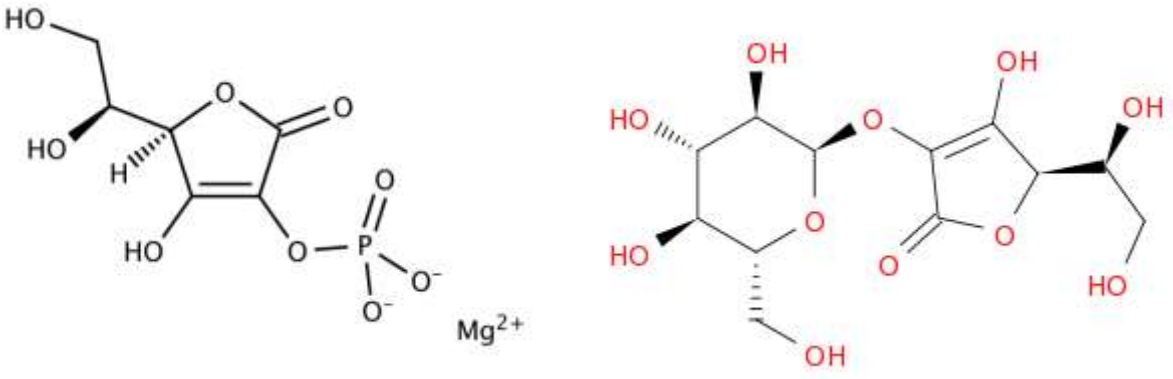


Figure 8. Plausible mechanisms of action of alkylglyceryl-Ascorbic acid derivatives on melanogenesis inhibitory activity [104].

High-frequency ultrasound radiation, when combined with skin lightening gel (ascorbyl glucoside with niacinamide) caused reduction in hyperpigmentation by causing enhanced transepidermal transport of the gel [107]. Tai et.al, 2009 stated that VC-PMG and ascorbic acid-2-glucoside (AA2G) (**Figure 9**) are very safe compounds for human use and also the most famous skin-whitening ingredients used in commercial cosmetics, compared to KA [108]. Vitamin C iontophoresis may be an effective treatment modality for melasma [109]. In this double-blind, placebo-controlled RCT, vitamin C solution was applied to one half of the face and distilled water (control) was applied to the other half. After 12 weeks of iontophoresis treatment, the colorimeter recorded a clinically significant reduction in luminance value on the treated side compared to the control side [55]. Both microphthalmia-associated transcription factor–siRNA (MITF-siR) cream and VC-PMG demonstrated significant improvement in the skin lesions compared to adjacent normal skin in melasma in a study. The total efficiency rate was 20% in the VC-PMG group, which was significantly lower than the MITF-siR group [110]. Taira et.al, 2018 reported that 3-O-Glyceryl-2-O-hexyl ascorbate (VC-HG), having an added glyceryl group and a hexyl group had an impact on skin lightening/whitening by inhibiting tyrosinase protein synthesis and interfering with intracellular melanosome transport [111]. Ascorbic acid and its QDs are the most popular

skin lightening quasi drugs that have ever been used in Japan. A 2% L-ascorbic acid 2-glucoside-containing cream was shown to accelerate the disappearance of ultraviolet light B (UVB) (280–320 nm)—induced hyperpigmentation of the skin [112]. However, Puvabanditsin et.al, 2006 reported that administration of topical 10% vitamin C derivative (VC-PMG) and topical 5% vitamin E had no bleaching effects observed after 2, 4, 6, 8, 10 and 12 weeks compared to the placebo [113].



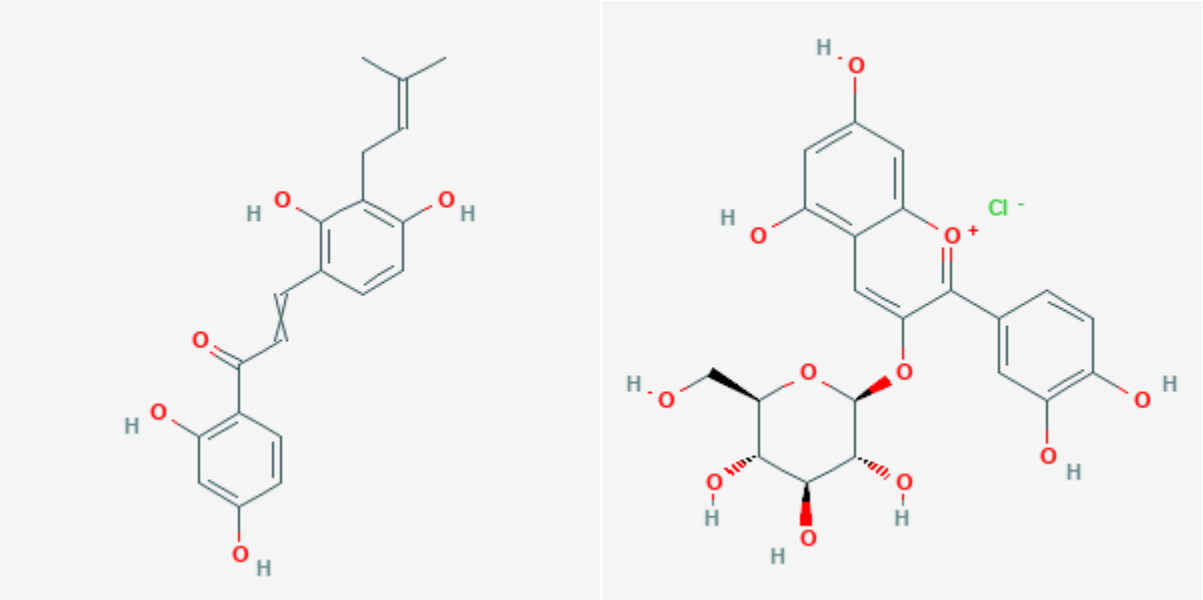
(a) Magnesium-L-ascorbyl-2-phosphate (VC-PMG) (b) ascorbic acid-2-glucoside (AA2G)

Figure 9. Ascorbic acid derivatives in hyperpigmentation management

J. Mulberry Extract

The leaves of the white mulberry (*Morus alba*, Moraceae) have been used for many years in traditional medicine in China, Korea, Japan, and Thailand. Fever-reducing, liver-protecting, and blood pressure-lowering properties are attributed to them [114]. Studies have shown that mulberry fruits possess several potential pharmacological health benefits including anti-cholesterol, anti-obesity and hepatoprotective effects which might be associated with the presence of some of these bioactive compounds. Volatile compounds found in mulberry fruits grown in Spain included acetic acid, 3-hydroxyl-2-butanone, ethyl butyrate, ethyl acetate, 3-methylbutanal, 2-methybutanal, heptanal, methional, hexanal, trans-2-hexanal, 2-octenone,hexanoic acid, benzaldehyde, methyl hexanoate, 2-ethylhexanal, octanal, limonene, 6-methyl-5-hepten-2on, ethyl hexanoate, 2,4-nonanadienal, phenylacetaldehyde, trans-2-octenal, cis-α-ocimene, terpinonene, 2-nonanone, nonanal, octanoic acid, cis-2-nonenal, dodecanoic acid, terpinen-4-ol, ethyl octanoate, ethyl dodecanoate, decanal, decanoic acid and ethyl decanoate [115]. Yuan et.al, 2017 also reported its antioxidant, neuroprotective, immunomodulative and antitumor activities [116]. An in vitro anti-tyrosinase activity study of the extracts from a hybrid Mulberry plant obtained from *Morus alba* L. and *Morus rotundiloba* Koidz, is shown to prove as new source of Thai whitening agent. The presence of betulinic acid, as an anti-inflammatory and anti-tyrosinase activity agent, is also reported [117]. Mulberry (*Morus alba* L.) leaves containing many nutritional components are the best food for silkworms. *Morus alba* L. also contains rutin, isoquercitrin, and astragalin. The root bark of *Morus alba* has been shown to have a skin whitening effect. But its activity was low and weaker than that of KA [33]. Yang et.al, 2014 reported the polyphenols contained in the leaves have depigmentation properties that have been demonstrated in vitro [114]. Lim et.al, 2019

reviewed anti-melanogenic property of all its stem, root, leaf, twig and fruit [118]. However, the anti-tyrosinase activity could be due to inhibition of DOPA oxidase activity of tyrosinase and superoxide scavenging activity. IC50 (concentration causing 50% inhibition of activity of tyrosinase) was very low (0.396%) as compared to 5.5% for hydroquinone and 10.0% for kojic acid. A patch test using 1% paper mulberry extract revealed no significant skin irritation at 24 h and 28 h [34]. 2,4,2',4'-tetrahydroxy-3-(3-methyl-2-butenyl)-chalcone (TMBC) (**Figure 10**) obtained from M. nigra significantly reduced the melanin content and cellular tyrosinase activity in B16 melanoma cells, although it increased mRNA levels of cellular tyrosinase [119]. Zheng et al, 2010 screened tyrosinase inhibitory properties of a total of 29 constituents isolated from roots of M. nigra (Black Mulberry). Among them, nine compounds (5'-geranyl-5,7,2',4'-tetrahydroxyflavone, steppogenin-7-O-β-d-glucoside, 2,4,2',4'-tetrahydroxychalcone, moracin N, kuwanon H, mulberrofuran G, morachalcone A, oxyresveratrol-3'-O-β-d-glucopyranoside and oxyresveratrol-2-O-β-d-glucopyranoside) showed better tyrosinase inhibitory activities than kojic acid (IC50 value 46.95 ± 1.72 μM, with 2,4,2',4'-tetrahydroxychalcone having the highest activity (IC50 value 0.062 ± 0.002 μM, 757-fold lower IC50 than kojic acid) [120]. Fresh fruits of M. nigra microwave assisted extractions were investigated by Koyu et.al, 2017. The highest tyrosinase inhibitory activity (IC50 value 1.44 mg/mL) was observed in the optimum microwave extraction system yielding the highest amount of anthocyanin content (13.28 mg/g cyanidin-3-glucoside equivalent) (**Figure 10**), suggesting the important potential of anthocyanins on tyrosinase inhibition [121].



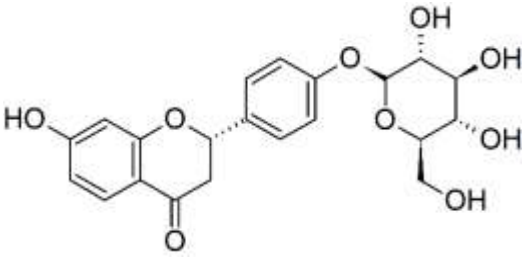
(a) TMBC **(b) Cyanidin-3-glucoside**

Figure 10. Important tyrosinase inhibitors from Mulberry extract

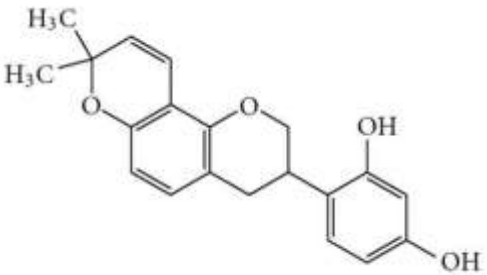
K. Licorice

Licorice extract is obtained from the root of Glycyrrhia Glabra L, legume native to Europe and Asia. It is cultivated extensively in India. Liquorice root offers skin depigmenting, lightening, emollient, anti-acne, photo protection, antiaging, antimicrobial and antioxidant properties, all helpful for a healthy skin. Role of G. glabra on skin is mainly attributed to its antioxidant activity

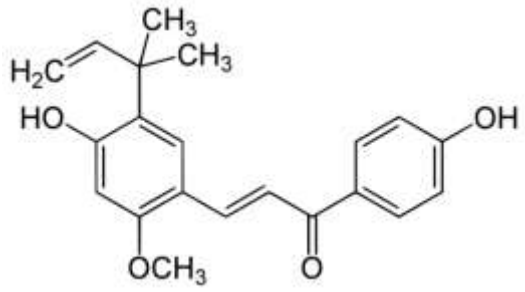
of phytochemicals namely triterpene, saponins (Glycyrrhizin-salts of glycyrrhizic acid) and flavonoids. Glycyrrhizetic acid controls the secretion of melanin in skin and it has the effect of reducing dark pigmentation and making the complexion fairer. Methanolic extract of its rhizome has been reported to be a potent tyrosinase inhibitor in human skin with more than 75% inhibition. The IC50 value was found to be within range when compared to well-known skin whitening agent i.e. Kojic acid. Therefore, it is likely to be useful for cosmetic applications [125]. The licorice extract includes liquiritin, isoliquertin (a chalcone) that occurs as a glycoside and during drying is partly converted into liquiritin (**Figure 11**), liquiritigenin, isoliquiritigenin, and other compounds [33], [87]. Liquiritin causes depigmentation by two mechanism: (i) via melanin dispersibility by means of the pyran ring of the color dispersing flavonoidal nucleus of liquiritin, and (ii) via amelanodermic and epidermal stain removing property. Acute and chronic toxicity studies have been carried out with no adverse effects. Glabrene and isoliquiritigenin (20, 40, 4-trihydroxychalcone) in the licorice extract can inhibit both mono- and diphenolase tyrosinase activities. The IC50 values for glabrene and isoliquiritigenin were 3.5 and 8.1 mM, respectively, when tyrosine was used as substrate. The effects of glabrene (**Figure 11**) and isoliquiritigenin on tyrosinase activity were dose-dependent and correlated to their ability to inhibit melanin formation in melanocytes [33]. Glabrene and isoliquiritigenin exert varying degrees of inhibition on tyrosinase-dependent melanin biosynthesis, suggesting that isoflavenes and chalcones may serve as candidates for skin-lightening agents [122]. Glabridin (**Figure 11**), a polyphenolic flavonoid is the main component of licorice extract [87], [123]. This ingredient has been shown to scavenge ROS, inhibit UVB-induced pigmentation and tyrosinase without affecting DNA synthesis, and possess anti-inflammatory properties [127]. Glabridin has been shown in vitro to have a skin lightening effect 16 times greater than that of hydroquinone and might reduce UVB pigmentation [34]. Licorice extracts also influence pigmentation by removing epidermal melanin, inhibiting the biosynthesis of melanin and inhibiting the activity of tyrosinase in a dose-dependent manner. Licorice extract has been tested in the treatment of melasma with good results and very mild irritation [87]. Costa et.al, 2010 stated that the association of Emblica, Licorice and Belides is a safe and efficient alternative for the treatment of melasma [124]. Licochalcone A, an active ingredient in licorice extract, was shown in vitro to decrease prostaglandin E2, leukotriene B4, interleukin-6, and tumor necrosis factor- alpha in human keratinocytes. Licochalcone A (**Figure 11**) may also effectively reduce sunburn erythema. Patients treated with 0.05% of the Licochalcone A -rich licorice extract and vehicle immediately and 5 hours after exposure to UVB irradiation had significantly less erythema where the Licochalcone A was applied [126].

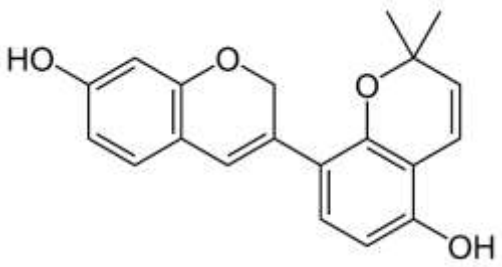


(a) Liquiritin



(b) Glabridin





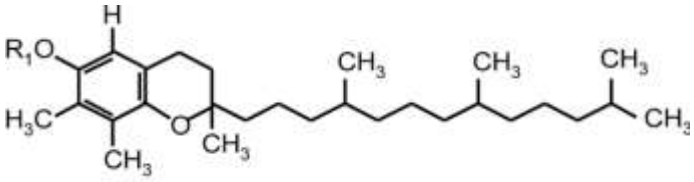
(c) Licochalcone A **(d) Glabrene**

Figure 11. Important Licorice ingredients for skin depigmenting, lightening

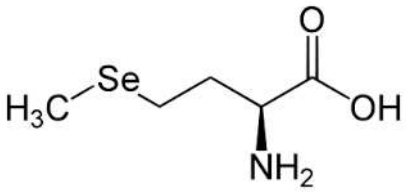
L. Alpha-Tocopherol

Vitamin E is the major lipophilic antioxidant in plasma, membranes, and tissues. The term "vitamin E" includes eight naturally occurring molecules (four tocopherols and four tocotrienols) that have vitamin E activity. In humans, alpha tocopherol (α-Toc) is the most abundant vitamin E derivative, followed by gamma tocopherol [128]. There is a large body of experimental evidence proving its photo-protective effects. It has been shown to cause depigmentation by interference with lipid peroxidation of melanocyte membranes, increase in intracellular glutathione content, and inhibition of tyrosinase [129]. Antioxidants such as vitamin B, vitamin C or vitamin E can also reduce the photooxidation of pre-existing melanin particles. Hence, these vitamins with antioxidant activity are common applied in skin-whitening cosmetic formulations [87]. The antioxidant properties of α-Toc, which interferes with lipid peroxidation of melanocyte membranes and increases the intracellular glutathione content, could explain its depigmenting effect. α-Toc has a more effective and long-lasting antioxidant response. Topical application of α-Toc and ascorbic acid, in vivo, decreases the tanning response inhibiting the UV-induced melanogenesis and proliferation of melanocytes. An alternative compound is alpha-Tocopherol ferulate (α -Toc-F), a derivative of α-Toc linked by an ester bond to ferulic acid, an antioxidant, which provides stabilization to α-Toc, similar to ascorbic acid. α-Toc inhibited melanogenesis in cultured normal human melanocytes, although it did not influence melanin synthesis in enzyme solution prepared as cell homogenates. In addition, α-Toc stimulated intracellular GSH synthesis [33]. Although, topical alpha-tocopherol is mostly used at concentration of 5% or less, products with varying concentrations have been marketed. Side-effects such as allergic or irritant reactions are rare with topical vitamin E and hence, it is a component of cosmeceuticals preparations. Kamei et.al, 2009 reported that both d-β-tocopherol and d-γ-tocopherol might be useful as effective ingredients in whitening cosmetics with lower skin toxicity to prevent or improve skin pigmentation such as skin spots and freckles caused by UV exposure. Analysis by reverse transcription-polymerase chain reaction showed that the mechanism of melanogenesis inhibition by d-beta- and d-gamma-tocopherols in cells might be attributed to reduced expression of tyrosinase and tyrosinase related protein-2 mRNA in addition to direct inhibition of the tyrosinase [130]. Kuwabara et.al, 2006 reported that gamma-tocopheryl-N,N-dimethylglycinate hydrochloride (gamma-TDMG) or KA (250 microM) were added to homogenates of B16 melanoma cells, their tyrosinase activity was significantly inhibited by approximately 40% and 75%, respectively [131]. However, Keen et.al, 2016 commented that Vitamin E alone has shown minimal efficacy in the treatment of melasma [132]. Oral procyanidin + vitamins A, C, E proved to be safe and effective among Filipino women

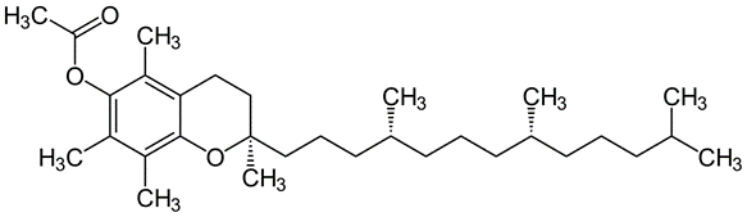
with epidermal melasma, after 8-week trial period. There was a significant reduction in MASI scores and pigmentation by mexametry in malar regions [133]. Daily use of a facial lotion containing niacinamide, panthenol, and tocopheryl acetate improved skin tone and texture and was well tolerated in Indian women with facial signs of aging [134]. Experimental evidence suggests that topical and oral vitamin E has anticarcinogenic, photoprotective, and skin barrier-stabilizing properties [135]. Mice treated with each form of vitamin E showed no signs of toxicity and had significantly less acute and chronic skin damage induced by UV irradiation, as indicated by reduced inflammation and pigmentation and by later onset and lesser incidence of skin cancer [136]. Topical L-selenomethionine alone and combined with vitamin E gave the best protection against UV-induced blistering and pigmentation. In protecting against skin cancer, topical RRR-alpha-tocopherol (Oral) and topical L-selenomethionine (Lotion) plus oral RRR-alpha-tocopheryl acetate were (Lotion) best. Significant synergy of L-selenomethionine with vitamin E was not observed [137]. Appreciable photoprotection can be obtained from the combination of topical stable aqueous solution of 15% L-ascorbic acid (vitamin C) and 1% alpha-tocopherol (vitamin E) to pig skin daily for 4 days [138].



(a) γ- TDMG



(b) L-selenomethionine



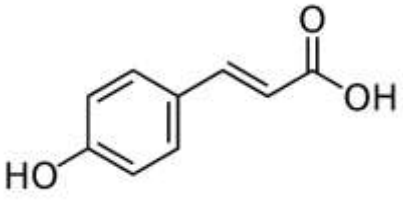
(c) Tocopheryl acetate

Figure 12. Vitamin E associated compounds for hyperpigmentation management.

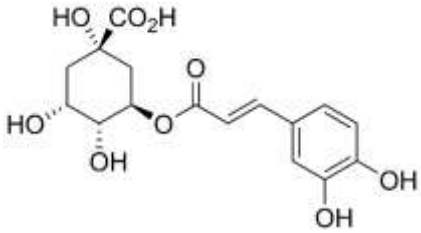
M. *Polypodium leucotomos*

Polypodium leucotomos (PL) is used as an adjunct photoprotective agent in melasma. Polypodium is a fern of the Polypodiaceae family that is unique to Central and South America. PL's mechanisms of action include the promotion of the p53 suppressor gene expression, modulation of inflammatory cytokines, upregulation of endogenous antioxidant systems, and blockade of UV radiation-induced cyclooxygenase–2 expression [41]. Various extracts of PL applied topically or taken orally have been shown to have several beneficial antioxidants, photo-protectant, antimutagenic, and immunoregulatory effects [140]. The most significant differences between this extract and conventional anti-oxidants refer to its capacity as a superoxide anion scavenger. The majority of traditional anti-oxidants such as vitamin C, E, carotenoids are good quenchers of singlet oxygen; however, PL also exhibits excellent anti-oxidant properties against superoxide anion. In addition to its anti-oxidant activity, PL shows promise in the prevention of photodamage

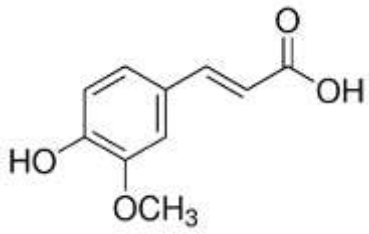
and photo-carcinogenesis because it enhances DNA repair and modulates the inflammatory and immune responses [149]. Fernblock® (IFC, Madrid, Spain), an aqueous extract of PL, is a potent antioxidant ingredient with demonstrated photo- and immune-protective activities against UVA and UVB radiations. It is available in over-the-counter formulations in topical and oral sunscreens and has been used since the 1970s for the treatment or adjunctive treatment of various skin conditions [142]. For many years, extracts of this fern have been used for treating a variety of skin conditions, including psoriasis, atopic dermatitis, vitiligo, polymorphic light eruption, and melasma. Growing evidence indicates the oral administration of oral PL extract can provide effective protection against solar UV radiation. PL extract 240mg taken twice daily for 60 days was a safe and effective means for reducing the damaging effects of UV radiation [139]. Phenolic components of PL extract include chlorogenic acid, coumaric acid, vanillic acid, caffeic acid and ferulic acid (**Figure 13**), the latter two being the most potent inhibitors of oxidation in vitro [145]. Coumaric, ferulic and vanillic acids were metabolized by CYP450-dependent mono-oxygenases and partially conjugated to glucuronic acid and sulfate. These phenolic compounds may contribute to the health benefits afforded by this oral photo-protectant [146]. Winkelmann et.al, 2015 concluded that PL is well tolerated at all doses administered and associated with a negligible risk of side effects [140]. Extracts of PL, topically applied or orally taken, have been shown to have a variety of potentially beneficial properties. Administration of PL leads to a significant reduction of sensitivity to UVR ($p<0.05$) in all patients. Dark-eye patients and patients with higher UVR sensibility (lower basal MED) would be the most benefited from oral PL treatment [141]. PL appears to be a useful adjunctive treatment for melasma [142] and may have the potential to help with post-inflammatory hyperpigmentation [143], even with just once-daily application during summer months, results in mild improvement of melasma [144]. PL is an effective chemo-photoprotector against PUVA-induced skin phototoxicity and leads to substantial benefits of skin protection against damaging effects of PUVA as evidenced by histology [147]. PL suppressive effects on UVB-induced erythema within 2 hours of administration which demonstrates the potential correlation between non-invasive colorimetry outcomes and UVB induced molecular damage [148]. Wistar rats using doses of 0, 2000, 3500, and 5000 mg/kg bw/day Fernblock® by gavage for 28 consecutive days. No mortality or toxic effects were observed and no target organs were identified. The no observed adverse effect level was determined to be 5000 mg/kg bw/day, the highest dose tested [150].

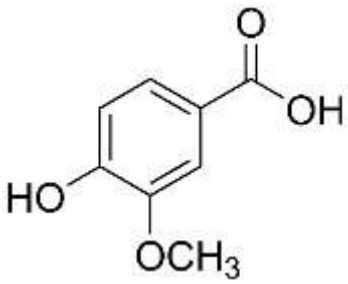


(a) Coumaric acid

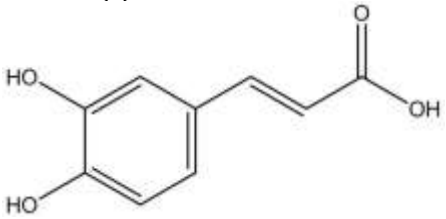


(b) chlorogenic acid





(c) Ferulic acid **(d) Vanillic acid**



(e) Caffeic acid

Figure 14. Phenolic components of *Polypodium leucotomos*

8.2.Blocking of Melanosome Transfer

The activation of protease-activated receptor-2 (PAR-2), a seven trans-membrane G-protein coupled receptor, which is expressed in keratinocytes and not in melanocytes, was found to activate keratinocyte phagocytosis, enhancing the melanosome transfer. Inhibition of PAR-2 cleavage by serine protease inhibitor, such as RWJ-50353, completely avoids the UVB-induced pigmentation of epidermal analogs [33].

A. Niacinamide

Given a sufficient bioavailability, niacinamide has antipruritic, antimicrobial, vasoactive, photo-protective, sebostatic and lightening effects depending on its concentration [155]. Niacinamide is an effective skin lightening compound that works by inhibiting melanosome transfer from melanocytes to keratinocytes [152]. Niacinamide or nicotinamide is a biologically active form of niacin (vitamin B3) involved in over 200 enzyme reactions in the form of nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate [33]. Topical application of niacinamide at concentrations that do not affect cell viability are reversible inhibitors of melanosome transfer, resulted in a dose-dependent and reversible reduction in hyperpigmented lesions [151]. Niacinamide had no effect on the catalytic activity of mushroom tyrosinase or on melanogenesis in cultured melanocytes. Hakozaki et al.,2002 found that niacinamide decreased melanocyte transfer by 35-68% in a keratinocyte/melanocyte coculture method [152]. Clinical trials using 2% niacinamide have shown that it significantly reduces the total area of hyperpigmentation and increases skin lightness after 4 weeks of treatment. The study also showed that the daily use of niacinamide with sunscreen was effective in reducing hyperpigmentation and in increasing lightness of basal skin color compared with sunscreen alone [34]. Niacinamide interferes in melanosome transfer to keratinocytes is used in the formulations of Meladerm and Lucederm [15]. The lightening effect of Niacinamide 4% versus HQ 4% was apparent at 4 weeks of treatment, whereas it was more evident at 8 weeks in melasma patients. HQ had the disadvantage of moderate adverse effects in 18% of patients, compared to milder in 7% with niacinamide. Treatment with niacinamide showed no significant side effects and was well tolerated; therefore, it could be used for longer periods, as part of the initial hyperpigmentation treatment and as maintenance drug [153]. There is a strong need for the improvement of hyperpigmentation especially among Asian women. Ultrasound radiation enhanced the absorption of skin-lightening agents in the stratum corneum in a radiation-time-dependent manner. In the facial clinical trial, use of ultrasound radiation together with the skin-lightening gel (coupling gel of ascorbyl glucoside and niacinamide) significantly reduced facial hyperpigmented spots compared with both no treatment and skin-lightening gel alone after 4 weeks [154]. A formulation containing the

combination of niacinamide + TXA reduced the appearance of irregular pigmentation, providing an effect beyond that achieved with sunscreen [99]. Bissett et.al, 2009 reported that combination of 5% niacinamide and 1% N-undecylenoyl phenylalanine is an effective anti-aging technology for use on facial skin. The combination formulation was significantly more effective than the vehicle and the 5% niacinamide formulation alone in reducing the appearance of hyperpigmentation after 8 weeks [156]. Bissett et.al, 2007 reported that topical combination of 2% N-acetyl glucosamine with 4% niacinamide ensured greater effect on facial hyperpigmentation that N-acetyl glucosamine alone [157]. A similar study by Kimball et.al, 2010 detailed that a formulation containing the combination of niacinamide + NAG reduced the appearance of irregular pigmentation including hypermelaninization, providing an effect beyond that achieved with SPF 15 sunscreen [158]. Bissett et.al, 2004 reported that 5% niacinamide was well tolerated by the skin and provided significant improvements in fine lines/wrinkles, hyperpigmentation spots, texture, skin yellowing (sallowness) and red blotchiness. In addition, skin yellowing (sallowness) versus control was significantly improved [159]. In addition to previously observed benefits for topical niacinamide, additional effects were identified by Bissett et.al, 2005, which was improved appearance of skin wrinkles and yellowing and improved elasticity [160].

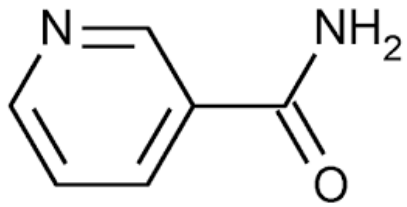


Figure 15. Niacinamide

B. Soy

Glycine max/Soybean, a legume commonly grown in East Asia, consists of many biologically active substances, including isoflavones and serine protease inhibitors. Glycine max, known as the soybean or soya bean, is a species of legume native to East Asia. Soybean (*Glycine max* L. Merrill) is one of the major crops containing antioxidant components such as phenolic acids, tocopherols, phytic acids, trypsin inhibitor, amino acid and isoflavones containing quercetin, genistein, daidzein and glycitein; small proteins (Bowman-Birk inhibitor, soybean trypsin inhibitor) tannins, and proanthocyanidins [161,162]. Daidzein and genistein are two major components of soy isoflavones [168]. The aglycone group (daidzein, genistein and glycitein) and acetylglucoside group (acetyldaidzin, acetylgenistin and acetylglycitin) of soy isoflavones, could inhibit UVB-induced death of human keratinocytes and reduce the level of desquamation, transepidermal water loss (TEWL), erythema and epidermal thickness in mouse skin [169]. Supplementation with 160 mgs/day of soybean isoflavone can reduce total AV lesion as a result of decreased DHT level [170]. The Supplement to Compendium of Materia Medica states that black beans can be beneficial to sperm and bone marrow production, muscle strength, hair growth, and the immune system. Modern scientific research shows that black beans have hypolipidemic and antioxidant properties and can be used to beautify the skin [163]. In-vitro studies have unleashed the anti-aging, antioxidant, pigment-reducing, photoprotective, and melanosome transfer inhibiting properties of soybean extract [55]. It has been reported that these nutritional components in soybean were associated with human health benefits such as decreased risks of various cancers, heart disease,

cardiovascular disease, and increased antioxidative effects [161]. The fatty acids in soy inhibit trypsin which is a known activator of PAR-2, may be used as a natural alternative to skin lightening [165]. Furthermore, the isoflavones inhibit the DOPA oxidase activity thus inhibiting melanogenesis [34]. Soybean trypsin inhibitor (STI) inhibited PAR-2 cleavage, and completely inhibited the UVB-induced pigmentation of the epidermal equivalents containing melanocytes [33]. Although, Lai et.al, 2012 reported that black bean extracts have good antioxidant and tyrosinase-inhibitor properties, particularly in the bud rather than the dry seeds, where the budding process can improve the antioxidant and whitening properties of black soybean [163]. The major components of soy are phospholipids (45-60%), and essential fatty oils (30-35%). It also contains active ingredients like isoflavones, vitamin E and serine protease inhibitors-soybean trypsin inhibitor (STI) and Bowman-Birk protease inhibitor (BBI). The protease inhibitors inhibit PAR-2 activation, thereby inhibiting melanosome transfer. Soy has proven to be both efficacious and safe. Several skin care products containing soy are available to improve hyperpigmentation. Skin lightening benefit can be seen after 12 weeks of twice daily application. The de-pigmenting effect of soymilk is reversible and daily topical treatments for 7 months result in no adverse effects [34]. Zhao et.al, 2009 reported that non-denatured *Glycine max* extracts induced elastin promoter activity, inhibited elastase activity and protected elastic fibers from degradation by exogenous elastases in vitro, may be used as skin care agents to reduce the signs of skin ageing [164]. Evaluation through clinical observation, self-assessment, colorimetry, and photography over a 12-week period demonstrated the soy-containing moisturizer to have a more favorable outcome in terms of improving mottled pigmentation, blotchiness, dullness, fine lines, overall texture, overall skin tone, and overall appearance than the vehicle alone. Another study involving Caucasian and Hispanic women found that application of soy extract to melasma lesions once daily for three months led to an average reduction of hyperpigmentation of 12% [55]. Soy isoflavone is an attractive source of functional cosmetic materials with anti-wrinkle, whitening and skin hydration effects. After consumption, the majority of soy isoflavones are converted to their metabolites in the human gastrointestinal tract. Lim et.al, 2014 reported that isoflavone daidzein metabolite 6,7,4'-Trihydroxyisoflavone pretreatment significantly reduced UV induced matrix metalloproteinases (MMPs) in normal human dermal fibroblasts that are responsible for akin aging [166]. Liu-Smith et.al, 2016 reported that genistein and quercetin targeted tyrosinase directly or indirectly (**Figure 16**).

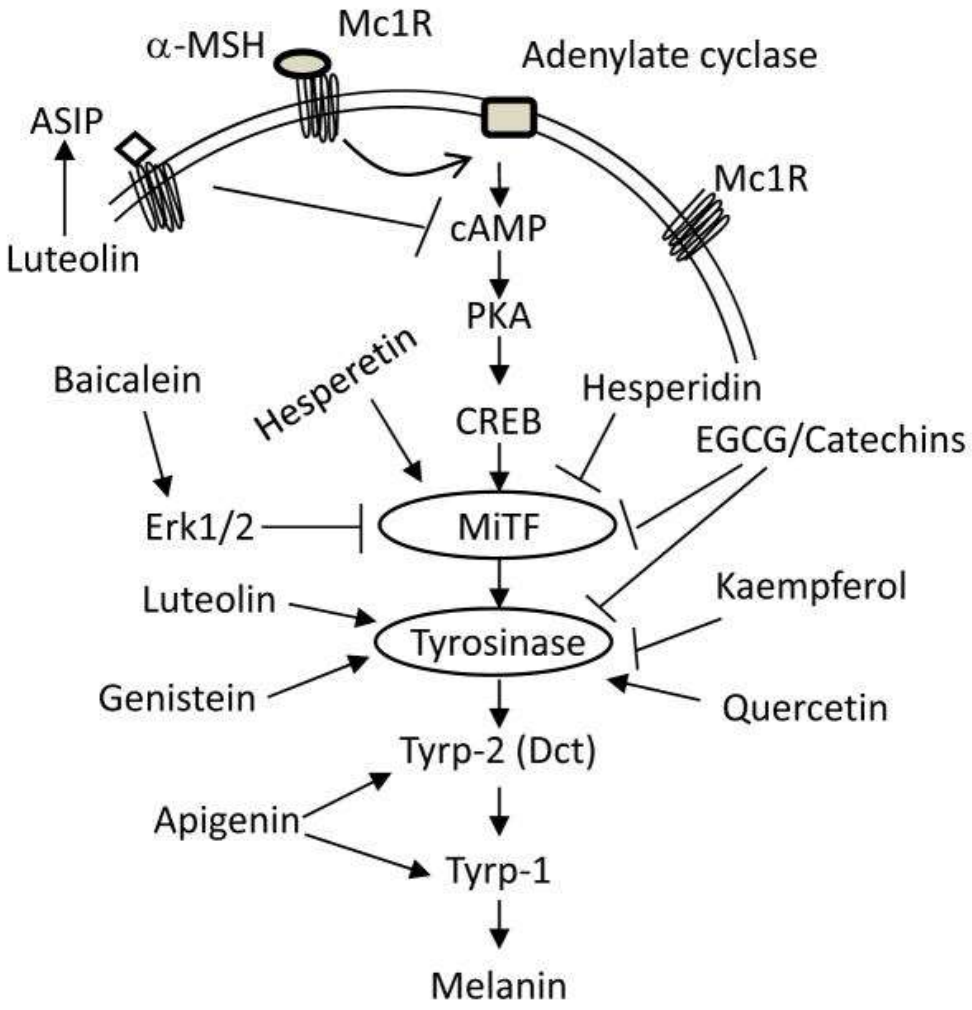
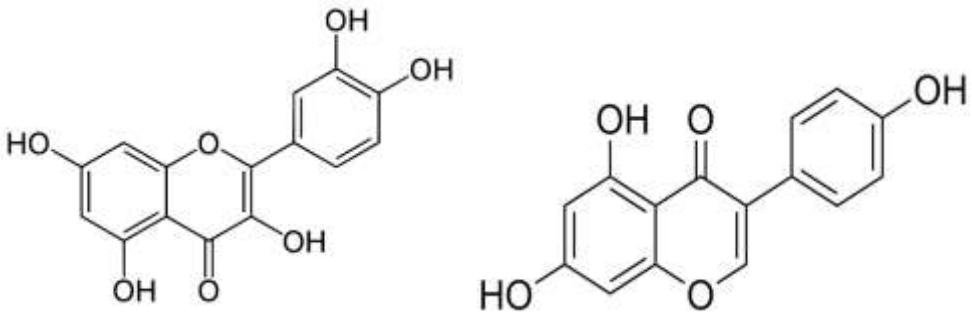
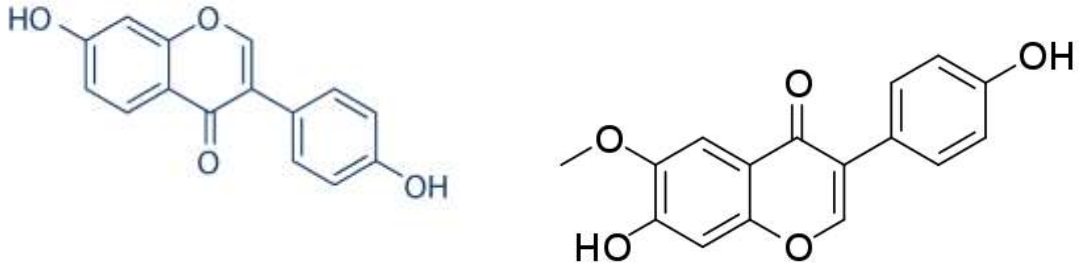


Figure 16. Molecular mechanisms of flavonoids on melanin synthesis [167]. Mushroom tyrosinase has been widely used as a substitute for mammalian tyrosinase to screen for tyrosinase inhibitors as it is inexpensive and commercially available in a purified form. Soy isoflavones are attractive source of functional cosmetic materials with anti-wrinkle, whitening and skin hydration effects. For quercetin, two studies showed stimulatory effect and one showed an inhibitory effect for melanogenesis. Genistein also exhibited melanogenic effect. So, the skin whitening of soya bean may be explained by some other mechanism(s).



(a) Quercetin **(b) Genistein**



(c) Daidzein **(d) Glycitein**

Figure 17. Soy isoflavones (aglycones) of skin care prospect

C. Lectins and Neoglycoproteins

Lectins are proteins found in certain foods such as wholegrains, beans and some vegetables. Potatoes, eggplant, soybeans, lentils, capsicum, wheat germ, red kidney beans, peas, tomatoes, peanuts are rich in lectins. Oral consumptions may cause problems like inflammation, leaky gut, blocking absorption of some minerals, immune response and toxicity and digestive complaints [171]. Lectins and neoglycoproteins have been explored as candidates that are involved in this phenomenon, because of their influence in cellular processes including intracellular trafficking, endocytosis and cell-cell recognition. Lectins and neoglycoproteins interrupt melanocyte and keratinocyte contact and interaction, by binding their specific plasma membrane receptors, inhibiting melanosome transfer. This inhibition is reversible and is shown to be enhanced by the presence of niacinamide [87]. Minwalla et.al, 2001 reported fusion of keratinocyte and melanocyte plasma membranes with formation of tunneling nanotubes. Molecules involved in transfer are being identified. Transfer is influenced by the interactions of lectins and glycoproteins and, probably, by the action of E-cadherin, SNAREs, Rab and Rho GTPases [172].

8.3.Accelerating epidermal desquamation and melanin turn over

The capacity of several compounds to disperse melanin pigment and/or accelerate epidermal turnover can result in skin lightening. Chemical substances used as exfoliates, such Alpha Hydroxy Acids (AHAs), free fatty acids, and retinoic acid, stimulate cell renewal facilitating the removal of melanized keratinocyte, leading to melanin granules loss. Topical application has been shown to reduce the visibility of age spots without reducing their size or number, and can be useful in the treatment of melasma. Unsaturated fatty acid, such as oleic acid, linoleic acid, or alpha-linolenic acid, suppress pigmentation, in vitro, whereas saturated fatty acids, such as palmitic acid, increase the rate of melanogenesis. Alpha hydroxy acid (AHA) and beta hydroxy acid (BHA) are two main classes of hydroxy acids.

A. Alpha Hydroxy Acids

Hydroxy acids, also called fruit acids, are among non-organic acids which have been used in the treatment of skin disorders since about 40 years ago. The driving force behind the increase in HAs use in cosmetic dermatology and skin care systems has been their antiaging effects [195]. They

are some of the most widely used and studied anti-aging skincare compounds. Clinical trials have shown the effectiveness of these ingredients in reversing the effects of photoaging and improving wrinkles, skin elasticity, tone and hydration. The benefits of AHAs have long been recognized. AHAs including glycolic acid, lactic acid, malic acid, tartaric acid, and citric acid (**Figure 18**) are often used extensively in cosmetic formulations. AHAs have been used as superficial peeling agents as well as to ameliorate the appearance of keratoses and acne in dermatology. However, caution should be exercised in relation to certain adverse reactions among patients using products with AHAs, including swelling, burning, and pruritus [174]. AHA is used in the treatment of several skin conditions such as acne, scar, pigmentation, skin dryness and wrinkles. They involve in metabolic pathways and essential cell cycles, including Krebs cycle, glycolysis and biosynthesis of serin. AHAs act on both the epidermal and the dermal levels. When applied to the skin, AHAs stimulate the exfoliation of epidermal cells in the stratum corneum by interfering with the ionic bonding between these cells. This results in the sloughing off dull and rough skin and promotes cellular renewal. Initially used for treatment of hyperkeratosis and other skin conditions affecting subcutaneous turnover, AHAs were found to promote softer, smoother skin, faded wrinkles, lightened age spots, and decreased blemishes. AHAs also improve the subcutaneous barrier function, increase epidermal proliferation and thickness, and restore hydration and pursiness through an increase in hyaluronic acid. The well-known benefits of AHA's include exfoliation, moisturization, reduction of fine lines and wrinkles, collagen synthesis, firming and skin lightening. Glycolic acid is the smallest at AHA compounds, extracted from sugar. Formulations containing 10-15% GA are currently used topically, vaginally and rectally or as ophthalmic preparations for treatment at skin aging and hyper pigmentation due to sunlight. A negative side effect of AHAs may be a sensation of stinging or burning immediately after application, particularly on people with sensitive skin. New more lipophilic AHAs will be utilized more in the future, especially when targeting oily skins [173]. Sour milk (LA) and sugarcane juice (GA) were applied to the face. In low concentrations, AHAs decreased corneocyte cohesion, leading to sloughing of dead cells and stimulation of new cell growth in the basal layer. In higher concentrations, they cause epidermilysis. AHAs have been reported to be effective in treating pigmentary lesions such as melasma, solar lentigines, and post-inflammatory hyperpigmentation. The mechanism of this effect might be due to epidermal remodeling and accelerated desquamation, which would result in quick pigment dispersion. GA and LA might work on pigmentary lesions not only by accelerating the turnover of the epidermis but also by directly inhibiting melanin formation by inhibiting tyrosinase in melanocytes. GA or LA (at doses of 300 or 500 mg/ml) inhibited melanin formation in similar dose-dependent manner, without affecting cell growth. The bioavailability of AHAs increases as the pH decreases (desirable pH 2.8–4.8), and they are the only peels that are time-dependent and can be neutralized easily [33]. The most common indications for chemical peeling are chronic photoaging and hyperpigmentation. Chemical peels are the third most commonly performed noninvasive cosmetic procedure in the US, with over 1,300,000 procedures performed in 2016 alone. There has been a paradigm shift in recent years, with lasers largely supplanting deep peels. Despite this shift, superficial peels have proliferated in both popularity and product diversity [190].

Glycolic acid peels are commercially available as free acids, partially neutralized (higher pH), buffered, or esterified solutions. They are available in various concentrations ranging from 20%–70%. The higher the concentration and lower the pH, the more intense the peeling will be. In general, gel formulations have a slower penetration time and are easier to control. Fabbrocini et.al,

2009, classified glycolic peels as: very superficial (30%–50% GA, applied for 1–2 minutes); superficial (50%–70% GA, applied for 2–5 minutes); and medium depth (70% GA, applied for 3–15 minutes) [175]. GA peels have antiinflammatory, keratolytic, and antioxidant effects. GA targets the corneosome by enhancing breakdown and decreasing cohesiveness, causing desquamation. The intensity of GA peel is determined by the concentration of the acid. GA peels need to be properly neutralized in order to stop acidification of the skin. Priming the skin with hydroquinone, or topical retinoids, before performing a peel has been found to increase peel efficacy and reduce the risk of post-inflammatory hyperpigmentation. After the skin has been cleansed and degreased, GA solution is applied using cotton buds or a brush in a sequential manner starting from the forehead to the left cheek, chin, right cheek to cover the entire face [176]. When properly used, superficial exfoliation with glycolic acid at concentrations of 30 to 50% has demonstrated excellent clinical efficacy in the treatment of superficial hyperpigmentation, mild-to-moderate chrono- and photoaging, and fine rhytides [190]

Exhibit 4. Glycolic Acid in Melasma Management

Study	Result	Reference
Concentrations of 20%–70% GA were administered every 3 weeks, either alone or in combination with a topical regimen of 2% hydroquinone plus 10% GA	There was significant improvement in melasma and fine facial wrinkling in patients who received the combination of creams and peeling.	Lim et.al, 1997[177]
55%–75% GA versus 10%–15% trichloroacetic acid (TCA) peels in 100 patients with recalcitrant melasma. The peels were conducted at 15-day intervals in both groups.	Response to TCA was rapid, and produced better results than GA. However, relapse was more common in the TCA group (25%) than in the GA group	Kella et.al, 2001 [178]
Using 50% GA, once-monthly for 3 months, peeling was performed upon 15 Indian females with melasma	An improvement in MASI score was observed in 91% of patients. A better response was seen in patients with epidermal melasma, compared to those with mixed melasma	Javaheri et.al, 2001 [178]
20 Indian patients received serial GA peels (30% GA for the first three sittings; 40% GA for the next three sittings), combined with the modified Kligman's formula (2% hydroquinone, 0.025% tretinoin, and 1% mometasone). A further 20 Indian patients received only the modified Kligman's formula, with no peeling.	In both groups, a significant decrease in the MASI score was observed from baseline to 21 weeks. However, the GA peel group showed more rapid and greater improvement.	Sarkar et.al, 2002 [180]*
21 Hispanic women with bilateral, epidermal, and mixed melasma to assess the efficacy of 4% hydroquinone cream versus 4% hydroquinone cream combined with GA peels. Patients received GA peels (20%–30% GA) every 2 weeks to one side of the face only, in	Pigmentation was measured objectively using a Mexameter® (Courage + Khazaka electronic GmbH, Cologne, Germany) and the MASI, and measured subjectively using a linear analog scale and physician and patient global	Hurley et.al, 2002 [181]*

addition to twice-daily application of 4% hydroquinone cream to the other side of the face	evaluation. Both sides of the face showed a reduction of pigmentation, and there was no significant difference.	
Patients with melasma were treated with a 70% GA peel on one half of the face, while the other half was treated with a 1% tretinoin peel.	A significant decrease in the modified MASI score was observed on both facial sides from baseline to 6 weeks, and then from 6 to 12 weeks.	Khunger et.al, 2004 [182]
Same as above, melasma patients were treated with a 70% GA peel on one half of the face, and with a 1% tretinoin peel on the other one.	Two peels to be equally effective and well tolerated.	Kligman et.al, 2004 [183]
In 15 cases of melasma (epidermal: 80%; dermal: 13.3%; and mixed: 6.6%), 52.5% GA concentration was applied for 3 minutes.	There was good to fair response in patients with epidermal and mixed melasma, while no significant improvement was seen in dermal melasma.	Grover et.al, 2003 [184]
Serial GA peels (from 35%–50%, and 70% every second peel) plus combination topical therapy (azelaic acid and adapalene) in 28 women with melasma	Better results in the group receiving chemical peel plus topical therapy, but only when the GA concentration was 50% or higher.	Ebril et.al, 2007 [185]
A triple combination cream consisting of fluocinolone acetonide 0.01%, hydroquinone 4%, and tretinoin 0.05% was used in an alternating sequential treatment pattern, cycling with a series of GA peels, for the treatment of moderate to severe melasma.	Hyperpigmentation was significantly reduced at 6 and 12 weeks, compared with baseline, with evaluations showing improvement of 90% or more by week 12.	Rendon et.al, 2008 [186]
In a comparative study of 10%–20% TCA versus 20%–35% GA peels for the treatment of melasma, similar improvement was seen with both peels.	GA peel was seen to be associated with fewer side effects than the TCA peel, and gave the added benefit of facial rejuvenation.	Kumari et.al, 2010 [187]
A similar study as above, 15% TCA peel versus 35% GA peel for the treatment of melasma, there was no statistically significant difference in efficacy.	Both peels significantly reduced MASI scores, and both were found to be equally effective in the treatment of melasma. It was also seen that adverse effects were more common with TCA than with GA peels.	Puri et.al, 2012 [188]

***** The concentration of GA used by Hurley et.al, 2002 was low (20%–30%), compared to the 30%–40% GA used by Sarkar et.al, 2002. This could be a reason for the difference in the results they observed.

Lactic acid, especially the L isomer, increases ceramide biosynthesis in vitro and in vivo. Presumably lactic acid achieves this by acting as a general lipid precursor by providing acetate and providing more reducing power in the form of NADH or NADPH [33]. Glycolic acid and lactic acid suppress melanin synthesis by inhibiting tyrosinase activity, the critical enzyme involved in

melanin synthesis, in human and in mouse melanoma cells. Both the transcription and translation of tyrosinase were decreased significantly, which resulted in the reduced enzyme function but with no significant effect on cell growth. Based on that in vitro analysis, increased epidermal turnover and inhibition of melanin formation were surmised to be the effects of glycolic acid and lactic acid treatment [195]. Lactic acid peels being relatively inexpensive and having shown equally good results in a few studies. Pure lactic acid, full strength (92%; pH 3.5), was used 3 weeks until the desired response was achieved, but not more than six sessions. Follow-up was carried out for 6 months after the last session. All patients had skin type IV. Patients showed marked improvement, as calculated by the MASI score before and after treatment, and the response was highly statistically significant. No side effect was recorded in all treated patients [189]. Clinically, lactic acid has demonstrated comparable efficacy in the treatment of photodamage, superficial hyperpigmentation, and fine rhytides compared to standard glycolic acid peels. Because lactic acid has a lower pH than glycolic acid, a lower concentration is often used to achieve an equivalent depth of keratocoagulation compared to glycolic acid, which allows a favorable side effect profile and recovery time [190]. Further, lactic acid was compared with a well-established peeling agent, Jessner's solution in a split-face design, and similar improvement was seen on both the sides with no relapse at a follow-up after six months [191]. Puri et.al, 2015 reported that Jessner’s solution (comprising 14g resorcinol, 14g salicylic acid, 14mL lactic acid in ethanol constituted to 100mL) can be an adjuvant treatment with TCA in the treatment of acne scars, improving the results and minimizing post inflammatory hyperpigmentation [192]. Histological differences in skin treated with glycolic, lactic, citric and acetic acids once daily for 6 weeks were investigated by Yamamoto et.al, 2006. The melanin pigments in the basal layer were less prominent in the glycolic and lactic acid-treated skin than in the citric and acetic acid-treated skin. The melanin deposits in the horny layers were equal for all AHA. However, the melanin deposits in the squamous layers were less prominent in the glycolic and lactic acid-treated skins than in the citric and acetic acid-treated skins [194].

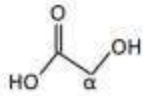
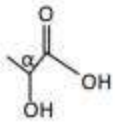
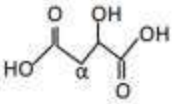
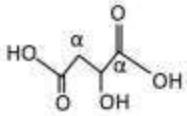
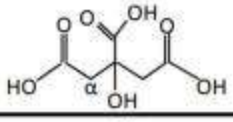
AHAs		structure	Molecular weight
Glycolic acid	C_2H4O3		72
Lactic acid	$C_3H_6O_3$		90
Malic acid	$C_4H_6O_5$		134
Tartaric acid	$C_4H_6O_6$		150
Citric acid	$C_6H_8O_7$		192

Figure 18. The structures of AHAs commonly used in dermatology [174].

B. Beta Hydroxy Acid

Salicylic acid (SA) peels have been shown useful in PIH, including for patients with darker skin types [196]. It is also a phytohormone, a plant product that acts similar to a hormone and regulates cell growth and differentiation. SA functions as a desquamating agent that penetrates and dissolves the intercellular matrix of the stratum corneum [87]. Being a lipophilic agent and having an ability to concentrate in the pilosebaceous apparatus, SA peels are a good therapeutic option for comedonal acne and hyperpigmentation. Pre-peel regimens differ between acne vulgaris, photodamage, and hyperpigmentation, including melasma and post-inflammatory hyperpigmentation. The combination of pre-peel application of 4% hydroquinone twice daily with peeling produces substantial decreases in the intensity of hyperpigmentation in both post-inflammatory hyperpigmentation and melasma [197]. Superficial SA peels are both safe and efficacious for treatment of acne vulgaris, oily skin, textural changes, melasma, and post-inflammatory hyperpigmentation in patients with skin types V and VI. In an open label trial, 25 patients were treated with five salicylic acid peels (20-30% concentration) provided at two-week intervals. Patients underwent two weeks of pretreatment with hydroquinone 4%. Four out of five patients with Fitzpatrick type V or VI had greater than 75% improvement in pigmentation [198]. Fifty patients attending the outpatient clinic of Dermatology Department, with clinically evident periorbital hyperpigmentation were included. All patients were divided randomly into two groups of 25 each and one group was treated with 4% HQ and another group with 30% SA for 12 weeks. Separately, both the treatments significantly improved the dermatological life quality index of the patients although there was no significant difference found between the two groups [199]. Combination of SA peel 20-30% and topical tretinoin 0.1% treatment showed significant clinical improvement of PIH than each treatment alone with no complications [200]. SA peels are beneficial in whitening the face of Asian patients with acne. The whitening effect would be an important factor in choosing the superficial peeling agent for them [201]. Clinical efficacy of SA

33% peeling once in a month, for a total of 4 times in patients with melasma reveals statistically significant values comparing MASI score obtained by digital photo and MASI score obtained clinically [202].

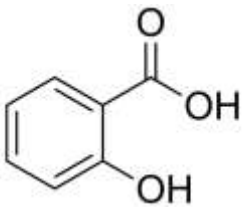


Figure 19. Salicylic Acid

C. Linolenic Acid

Unsaturated fatty acids including oleic acid (C18:1), linoleic acid (C18:2) or α-linolenic acid (C18:3) suppresses melanogenesis and tyrosinase activity, while saturated fatty acids such as palmitic acid (C16:0) or stearic acid (C18:0) increases it. Omega-3 polyunsaturated fatty acids (PUFAs) like *Linoleic acid* (LnA) reduces the activity of tyrosinase in melanocytes, while mRNA levels remain unchanged. α-LnA and LnA were reported to reveal skin-whitening capability through the mechanism of tyrosinase inhibition by Anso et.al, 1999 [205]. This may influence the enzyme's degradation via a physiologic proteasome-dependent mechanism, altering the tyrosinase protein content in hyperactive melanocytes [87]. LnA is known to have a whitening effect on hyperpigmented skin, and is encapsulated in liposomes for topical application because of its low solubility in aqueous solution. Topical application of alpha-linolenic acid to UV-stimulated hyperpigmented dorsal skin of brownish guinea pigs. The number of melanocytes in the treated skin was similar to the number in the skin of the pigmented control, indicating that the pigment-lightening effect was not due to depletion of melanocytes. Linoleic acid also influences skin pigmentation by stimulating epidermal turnover and increased desquamation of melanin pigment from the epidermis [203]. Liposomal LnA (0.1%) showed a whitening effect comparable to 10.0% non-liposomal LA and was far more effective than 3.0% non-liposomal LnA [204]. Ko et.al, 2018 reported LnA ester, ethyl linoleate decreased melanin production and tyrosinase activity through the reduction of tyrosinase and TRP1 expression. Ethyl linoleate may be used as a non-cytotoxic and skin-whitening agent as a cosmetic and medicine [206]. In a 6-week, double-blind, RCT among 60 patients, LnA in combination with lincomycin and betamethasone valerate was found to result in higher improvement than a combination of the latter two or vehicle [101].

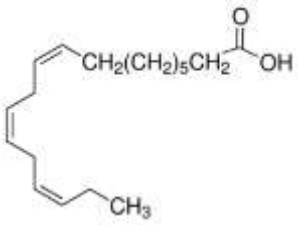
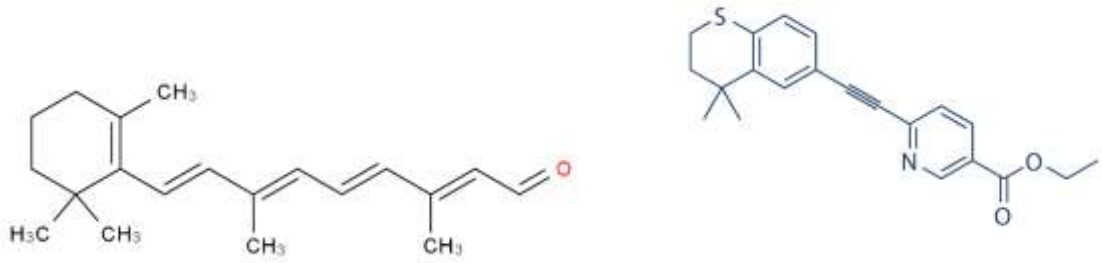


Figure 20. Linolenic Acid

D. Retinoids

Topical retinoids such as all-trans-retinoic acid (RA), 13-cis-retinoic acid (isotretinoin), retinol, retinaldehyde, tazarotene, and adapalene have been shown to improve dyspigmentation of photodamaged skin including mottling and actinic lentigines. RA monotherapy has also been

demonstrated to improve melasma and post-inflammatory hypermelanosis [208]. Irritant reactions can result from long-term daily use of 4% or higher HQ, particularly when used in combination with irritants such as retinoids. An early formulation, Kligman's formula containing 5% HQ, 0.1% tretinoin, and 0.1% dexamethasone, is one such combination that was effective yet problematic due to its use of high concentrations of tretinoin and a potent fluorinated steroid. 4% HQ, 0.05% tretinoin, and 0.01% fluocinolone acetonide triple combination agent has been shown to be both safe and effective in the treatment of melasma and photoaging in skin of color and is used successfully in clinical practice to treat PIH. Topical tretinoin, all-trans-retinoic acid, is a naturally occurring metabolite of retinol and first-generation retinoid. Concentrations range from 0.01 to 0.1% and tretinoin can be formulated in creams, gels, and microsphere gels, which allows for the controlled release of tretinoin leading to less irritation. Tretinoin was significantly more effective than vehicle in lightening PIH lesions when assessed by clinical and colorimetric analysis after a 40-week trial with 54 black patients to determine the safety and efficacy of 0.1% tretinoin in the treatment of PIH. However, 50% of patients developed retinoid dermatitis, which is the concern with using retinoids in skin of color. Third-generation retinoids, adapalene and tazarotene, are synthetic topical agents that are also effective in the treatment of PIH. Adapalene is formulated in creams or gels in 0.1 to 0.3% concentrations; whereas, formulations of tazarotene include 0.05 and 0.1% creams or gels. Both agents have been shown in clinical studies to safely and effectively treat PIH, particularly acne-induced PIH, in darker skinned individuals. Isotretinoin (13-cis-retinoic acid) is a naturally occurring, first-generation retinoid that is available in both oral and topical formulations [209]. These cosmetic products are suspected to contain illegal active substances (in particular hydroquinone, tretinoin and corticosteroids) that may provoke as well local as systemic toxic effects, being the reason for their banning from the EU market [210].



(a) Retinaldehyde **(b) Tazarotene**

Figure 21. Topical retinoids

8.4.Antioxidants

Oxidative stress is an integral element that influences a variety of biochemical reactions throughout the body and is known to play a notable role in melanogenesis. Exogenous triggers of oxidative stress, such as UVR and VL, lead to pigment formation through somewhat different pathways, but both share a common endpoint-the potential to generate cosmetically undesirable hyperpigmentation [211]. There is evidence that situations of mild stress, such as caloric restriction or physical activity, can modulate the aging process, since they increase mitochondrial activity, also increasing the generation of ROS - which would provoke an adaptive response, with improvement of defense mechanisms and consequent better response and resistance to stress. Antioxidant molecules employed that have proven utility also have whitening action by inhibition

of tyrosinase (for example, ascorbic acid and ellagic acid) or anti-inflammatory (for example, pycnogenol) (Figure 22) [212]. Schalka et.al, 2017 concluded that UV, VL and IR light induce pigmentation. To prevent hyperpigmentation, protection using adequate sunscreens on exposed areas is needed. To date, no efficient protection from IR light exists, but topical antioxidants may be able to provide some protection [213]. Antioxidants neutralize free radicals produced by various environmental insults such as ultraviolet radiation, cigarette smoke and air pollutants, thereby preventing cellular damage [214]. For example, grape seed extract rich in monomers of flavanols, vitamin C, and zinc, has a beneficial effect on skin radiance (improvement of luminosity, reduction of imperfections, and improvement of skin firmness) in women [222]. Snail slime (SS) is currently revolutionizing the world of cosmetics and human skin care. The efficacy of SS in wounds healing has been proven both in vitro and by clinical studies. SS reduced melanin content and tyrosinase activity on B16F10 cells with IC50 values of 288 μg/mL and 286 μg/mL, respectively, without altering cell viability [223].

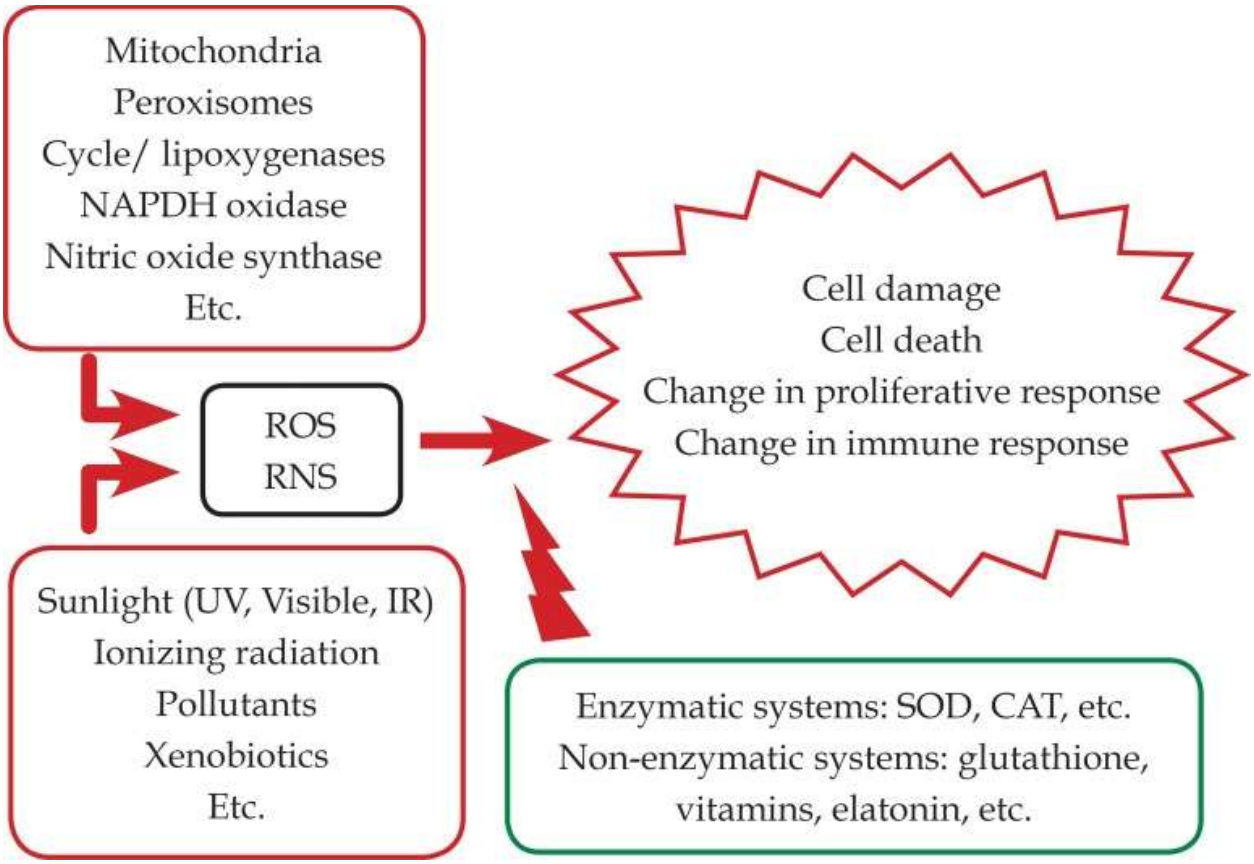


Figure 22. Diagram of the redox balance in the skin [212].

A. Tea

Green tea has long been studied for its antioxidant and anti-inflammatory properties. Fresh tea leaves contain polyphenols, primarily the catechins epigallocatechin (EGC), epicatechin (EC), epigallo-catechin-3-gallate (ECGC), and epicatechin gallate (ECG) [217,218]. These four catechins, of which EGCG is the most abundant, account for up to 30% of tea leaf dry weight [215]. The irradiation of green tea polyphenol did not change and even increased its anti-wrinkle,

skin-whitening and anticancer effects on the human skin [221]. According to the abstract of a single RCT, green tea has shown clinical efficacy in treating melasma [55]. Tea and its components have been shown to inhibit intracellular and cell-extracted tyrosinase activities. EGCG causes such inhibition in mushrooms, and oolong tea reduces tyrosinase activity in B16 mouse melanoma cells. Tea flavonoids have metal chelation abilities. For example, proanthocyanidins, which are flavonoids from grape seeds, inhibit tyrosinase by chelating tyrosinase-bound copper. Black tea theaflavins and Green Tea flavonols are also known to exert antioxidant effects by radical scavenging and metal chelation. White tea was also reported to have higher levels of antioxidant activity than green tea [34], [215]. EGCG significantly inhibits cell growth as well as the migration and invasion of melanoma cells [220]. EGCG reduced melanin secretion and production in melanoma cells [217].

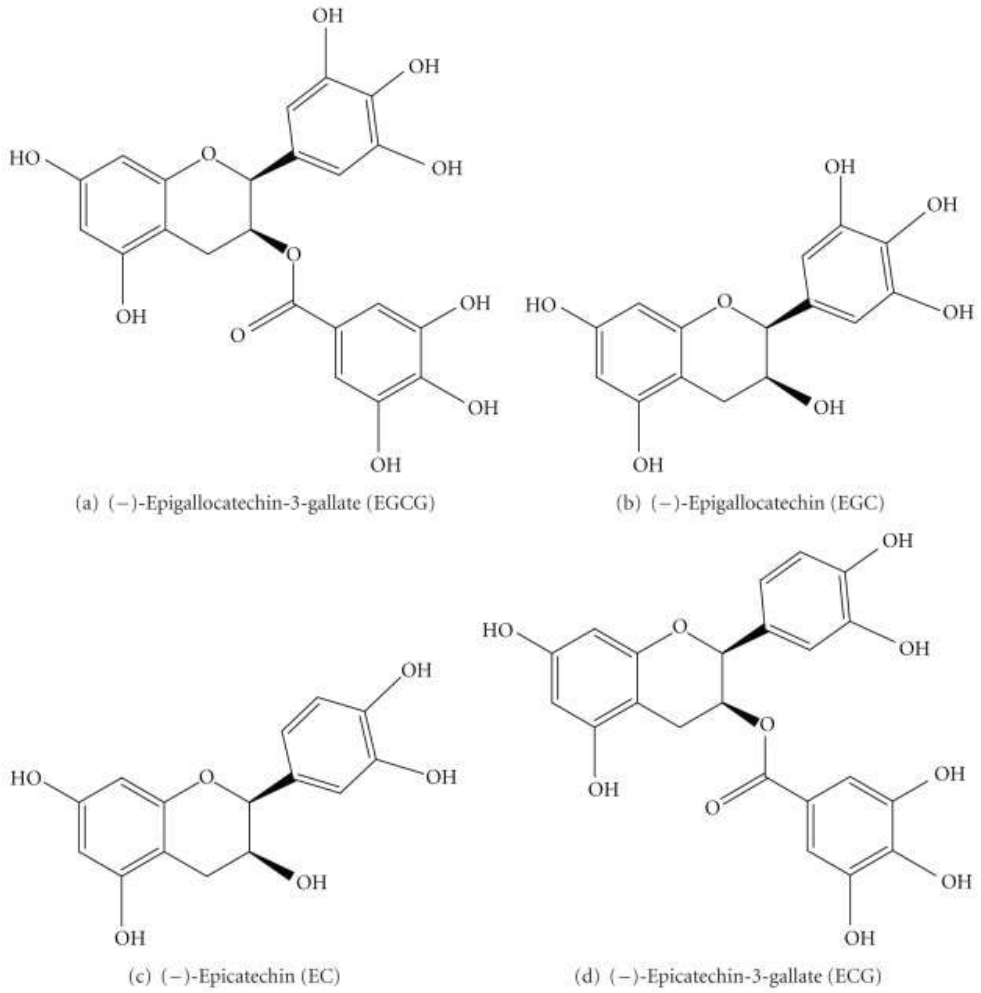


Figure 23. Structure of green tea polyphenols [219].

B. Ginseng

Panax ginseng has been used traditionally in eastern Asia to treat various diseases, due to its immunomodulatory, neuroprotective, antioxidative, and antitumor activities. Recently, several reports have shown that extract, powder, or some constituents of ginseng could inhibit melanogenesis in vivo or in vitro. The underlying mechanisms of antimelanogenic properties in

ginseng or its components include the direct inhibition of key enzymes of melanogenesis, inhibition of transcription factors or signaling pathways involved in melanogenesis, decreasing production of inducers of melanogenesis, and enhancing production of antimelanogenic factor. Cinnamic acid, one of the major components of *Cinnamomum cassia* Blume, is found in the root and seed of P. ginseng. Cinnamic acid is reported to have inhibitory activity on mushroom tyrosinase. Cinnamic acid significantly reduced melanin production, tyrosinase activity, and tyrosinase expression in the melan-a cells. In addition, cinnamic acid showed depigmenting activity on the UVB-tanned skin of brown guinea pigs [224].

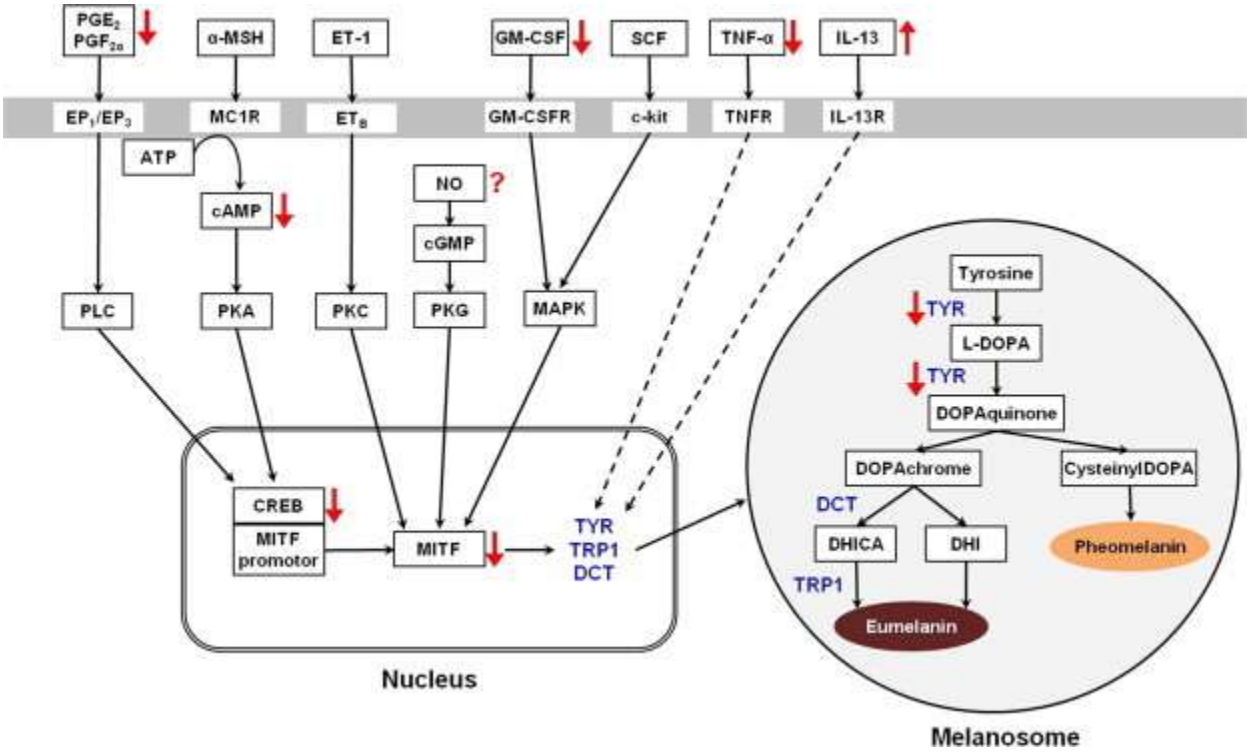


Figure 24. Schematic view of the effects of ginseng on melanogenesis [224]. Black solid arrow indicates activation, black dashed arrow indicates inhibition, red upward arrow indicates increase by ginseng components, and red downward arrow indicates decrease by ginseng components. α-MSH, α-melanocyte stimulating factor; CREB, cAMP response element-binding protein; DCT, dopachrome tautomerase; DHI, 5,6-dihydroxyindole; DHICA, 5,6-dihydroxyindole-2-carboxylic acid; DOPA, 3,4-dihydroxyphenylalanine; EP1, prostaglandin E receptor 1; ET-1, endothelin-1; ETB , endothelin receptor type B; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-13, interleukin 13; MAPK, mitogen-activated protein kinases; MC1R, melanocortin 1 receptor; MITF, micropthalmia-associated transcription factor; NO, nitric oxide; PGE2, prostaglandin E2; PGF2α, prostaglandin F2α; PKA, protein kinase A; PKG, protein kinase G; PLC, phospholipase C; SCF, stem cell factor; TNF-α, tumor necrosis factor-α; TRP1, tyrosinase-related protein-1; TYR, tyrosinase.

Exhibit 5. Direct effects of ginseng and its components on melanogenesis in vivo and in vitro [224]

Reagent	Experimental model	Dose	Effects on melanogenesis
Powder of KRG	Melasma lesion of female patients	3 g/d oral 24 wk	MASI: decreased MELASQoL: improved Patient- and investigator-rated global improvement scale: improved
Ethanol extract of ginseng seed	Melan-a cells cultured with phorbol-12 myristate 13-acetate	100 ppm 3 d	Melanin content: decreased tyrosinase activity: decreased
Extract of KRG and FKRG	Mushroom tyrosinase		Tyrosinase activity: decreased
Aglycone of ginsenoside Rh4	B16 cells stimulated by a-MSH	20e50mM 5 d	Melanin content: decreased Tyrosinase activity: decreased MITF expression: decreased
p-Coumaric acid	Mushroom tyrosinase		Tyrosinase activity: decreased
Ginsenoside Rb1	B16 cells stimulated by a-MSH	125e500mM 2 d	Melanin content: decreased Tyrosinase activity: decreased
Ginsenoside F1	Human skin artificially tanned by UV irradiation	0.1% cream topical 8 wk	Luminosity values: increased

*α-MSH, α-melanocyte stimulating factor; FKRG, fermented Korean Red Ginseng; KRG, Korean Red Ginseng; MASI, melasma area and severity index; MELASQoL, melasma quality of life scale; MITF, micropthalmia-associated transcription factor

Lee et.al, 2019 reported that Ginsenoside Rg1 increases melanogenesis and tyrosinase activity in human melanocytes. In contrast, ginsenoside F1 (GF1), a metabolite produced by the hydrolysis of Rg1, is reported to inhibit visible pigmentation. GF1 has potential for development as an effective whitening reagent for the treatment of pigmentary disorders and lightening of darkened skin color as a cosmetic ingredient [225]. Ginsenoside Rb2 (Gin-Rb2) decreased potent melanogenesis in melan-a cells, with 23.4% at 80 μM without cytotoxicity. Gin-Rb2 also decreased tyrosinase and MITF protein expression in melan-a cells. Furthermore, Gin-Rb2 presented inhibition of the body pigmentation in the zebrafish in vivo system and reduced melanin contents and tyrosinase activity [230]. The ethanol extract of ginseng seed showed an excellent inhibitory effect on melanin production (due to presence of arbutin) and demonstrated low cytotoxicity when applied to melanocytes, compared to the ethanol extracts of ginseng root and ginseng leaf [226]. Jiménez et.al, 2018 reported that P. ginseng berry mediated gold nanoparticles,

significantly reduced melanin content and suppress tyrosinase activity in α-MSH-stimulated B16BL6 cells. In addition, P. ginseng berry mediated gold nanoparticles exhibited moisture retention capacity [227]. Lee et.al, 2018 reported that P. ginseng berry calyx (Pg-C-EE) exerted skin-protective effects through antimelanogenesis activity in α-MSH–induced B16F10 cells (a murine melanoma cell line from the C57BL/6J mouse), antiphotoaging activity in UVB-irradiated HaCaT cells (immortalized human keratinocytes and have been extensively used to study the epidermal homeostasis and its pathophysiology), and antioxidant activity in hydrogen peroxide–induced HaCaT cells. In addition, Pg-C-EE inhibited Activator Protein-1 (AP-1) and cAMP response element binding (CREB) transcription factors and their upstream activation pathway (mitogen-activated protein kinases, MAPK and CREB) **(Figure 25**) [228]. Yang et.al, 2017 reported that fermented red ginseng is believed to be more effective in reducing wrinkles and enhance whitening compared to unfermented red ginseng [229]. Song et.al, 2011 reported 3 g of Korean red ginseng powder was orally administered for a 24-week period in 25 women resulted improvement in 74% of the patients and it was tolerated by most of the patients [231].

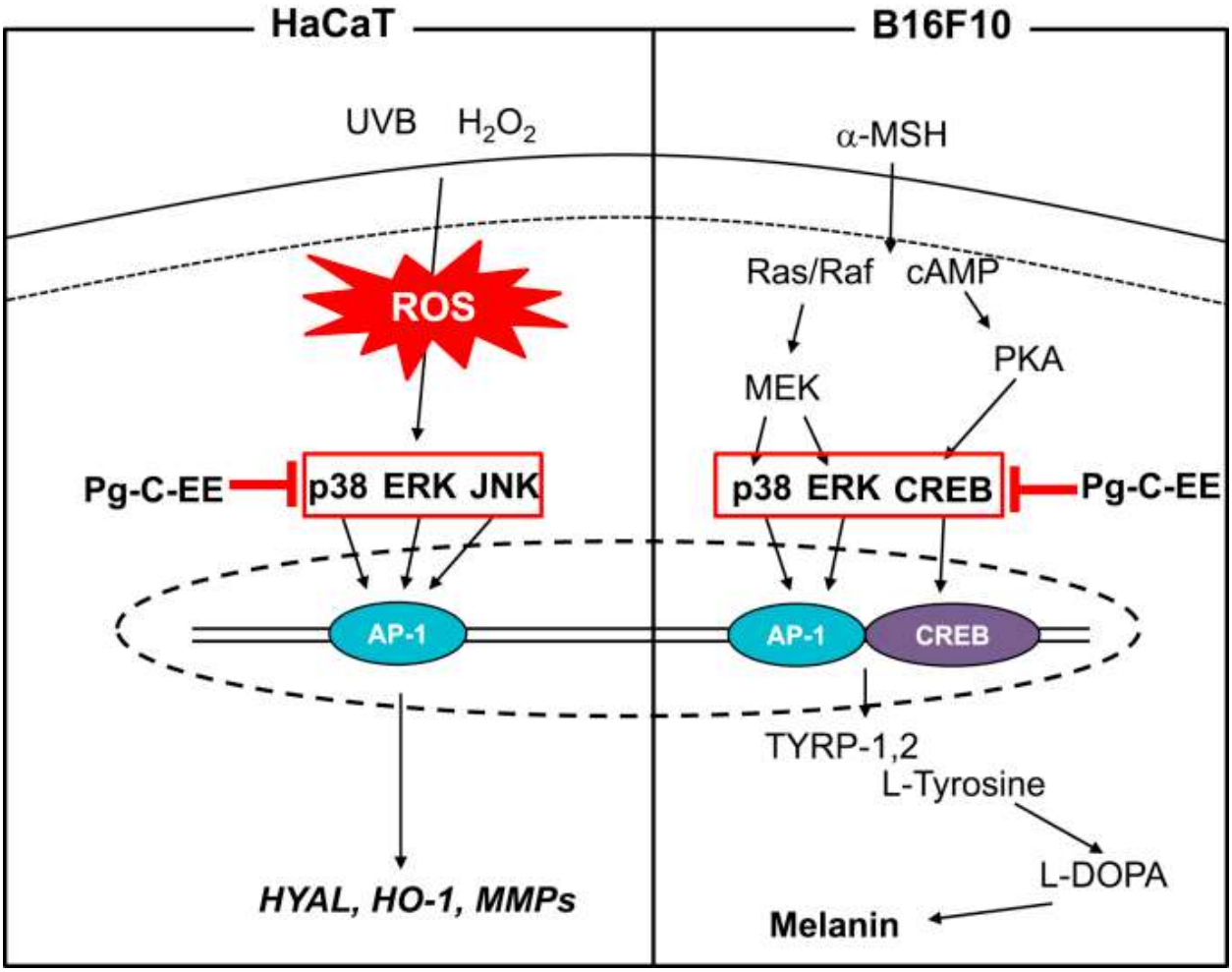


Figure 25. Pathway by which Pg-C-EE inhibits melanogenesis and ROS generation [228]. α-MSH, α-melanocyte–stimulating hormone; AP-1, activator protein 1; cAMP, cyclic adenosine monophosphate; CREB, cAMP response element binding; ERK, extracellular signal-regulated kinase; HO-1, heme oxygenase-1; HYAL, hyaluronidase; JNK, c-Jun N-terminal kinase; L-

DOPA, L-dopamine; MMP, matrix metalloproteinase; Pg-C-EE, Panax ginseng calyx ethanol extract; PKA, Protein kinase A; ROS, reactive oxygen species; TYRP, tyrosinase-related protein; UVB, ultraviolet B.

Exhibit 2. Summary of clinical studies evaluating the efficacy of natural ingredients as hypo pigmenting agents [55]

Natural Ingredients	Hypo pigmenting Mechanism	Comparison	Pigmentation Disorder	Conclusion
Azelaic Acid (AA)	Mitochondrial oxidoreductase inhibition, DNA synthesis inhibition, Tyrosinase inhibition	20% AA vs. 4% HQ cream	Melasma	Melasma responded better to AA during second treatment month
		None	PIH	15% AA gel applied twice daily reduced PIH over 16 week period
		GA peel with twice daily 20% AA cream vs. 20% AA cream	Melasma	At 12 weeks, AA/GA combination has a statistically significant decrease in MASI score compared with AA alone
		None	PIH	Dermocosmetics containing AA showed improvement in pigmentation
Aloesin	Tyrosinase inhibition, tyrosine hydroxylase, DOPA oxidase	Aloesin vs. Arbutin vs. Aloesin/Arbutin	UVR-induced hyperpigmentation	Dose-dependent suppression in pigmentation with application of aloesin; synergism between arbutin and aloesin
Mulberry	Tyrosinase inhibition, melanogenesis inhibition, ROS Scavenger	75% mulberry extract	Melasma	Compared to placebo, 75% mulberry extract showed significant improvement in MASI score, average Mexamater measurements, and MelasQoL scores
Licorice Extracts	Tyrosinase inhibition (glabridin)	None	Melasma	Sixteen out of 20 patients had an “excellent response” to 20% liquitin cream applied BID for four weeks Glabridin was more efficacious compared to HQ

Exhibit 2. Summary of clinical studies evaluating the efficacy of natural ingredients as hypo pigmenting agents [55]

Natural Ingredients	Hypo pigmenting Mechanism	Comparison	Pigmentation Disorder	Conclusion
	ROS cavenger (glabridin)	None	UVR-induced hyperpigmentation	Skin brightener containing glabridin was shown to be clinically efficacious
	Disperses melanin (liquiritin)	Cream with belides, emblica, and licorice vs. 2% HQ	Melasma	Although depigmentation was seen in both groups, no statistical difference in efficacy
	Disperses melanin (liquiritin)	4% liquiritin vs. 2% liquiritin and HQ	Melasma	4% liquiritin significantly more effective than combination group
Lignin Peroxidase	Oxidizes and breaks down melanin	Lignin peroxidase cream vs. placebo or 2% HQ	Mottled hyperpigmentation	According to Mexameter evaluation, lignin peroxidase had more rapid and observable skin-lightening effect compared to placebo or HQ
		Lignin peroxidase cream vs. none, lignin peroxidase cream vs. 4% HQ	Facial dyspigmentation	Lignin peroxidase was more effective than applying nothing at all based on dermatospectrophotometer. Lignin peroxidase was superior to 4% HQ in aesthetics when including skin texture, lack of clarity and radiance, roughness, and overall appearance. Parity was demonstrated between both agents when evaluating skin lightening efficacy.
Kojic Acid (Ka)	ROS scavenger, tyrosinase inhibition	0.75% KA with 2.5% Vitamin C vs. 4% HQ	Melasma	Patients responded faster and better to HQ
		Compound (KA, emblica extract, glycolic	Facial dyschromia	Both treatments equally efficacious

Exhibit 2. Summary of clinical studies evaluating the efficacy of natural ingredients as hypo pigmenting agents [55]

Natural Ingredients	Hypo pigmenting Mechanism	Comparison	Pigmentation Disorder	Conclusion
		acid) vs. 4% HQ		
		1% KA vs. KA with 2% HQ vs, KA with 0.1% betamethasone vs. combination of products	Melasma	KA with HQ was most effective combination
Niacinamide	Inhibits melanosome transfer to keratinocytes	Cream containing 2% niacinamide with 2% tranexamic acid vs. vehicle control	Irregular facial hyperpigmentation	Niacinamide with TXA combination product showed efficacy
		Niacinamide 4% vs. desonide 0.05% vs. control	Axillary hyperpigmentation	4% Niacinamide with 0.05% desonide emulsion showed significant colorimetric improvement, though desonide alone was more effective
		None	PIH	Skin brightening compound containing retinol 0.5%, niacinamide 4.4%, resveratrol 1%, and hexylresorcinol 1.1% improved hyperpigmentation
Ellagic Acid	Tyrosinase inhibition	1% arbutin vs. synthetic 1% ellagic acid vs. synthetic 1% ellagic acid with plant extracts containing natural ellagic acid	Melasma	All three treatments show efficacy

Exhibit 2. Summary of clinical studies evaluating the efficacy of natural ingredients as hypo pigmenting agents [55]

Natural Ingredients	Hypo pigmenting Mechanism	Comparison	Pigmentation Disorder	Conclusion
		0.5% ellagic acid combined with 0.1% salicylic acid vs. 4% HQ	Hyperpigmentation and dark spots	Based on clinical grading, physical measurement of spot size by Chroma Meter, and patient questionnaire analysis, the compound had comparable efficacy to HQ but better aesthetics
Arbutin	Tyrosinase inhibition	1% arbutin vs. synthetic 1% ellagic acid vs. synthetic 1% ellagic acid with plant extracts	Melasma	All three treatments show efficacy
		None	Melasma	7% alpha arbutin in conjunction with the MedLite C6 Q-switched Nd:YAG laser showed favorable results
Green Tea	Antioxidant	2% analogue of green tea extract vs. placebo control	Melasma	2% analogue of green tea extract in hydrophilic cream shows clinical efficacy
Turmeric	Antioxidant	Turmeric extract cream formulation vs. unknown control	Facial hyperpigmentation	Formulation improved areas of hyperpigmentation by 14.16% (P<.0001) at four weeks
Soy	Anticarcinogenic (Isoflavones), inhibits melanosome transfer to keratinocytes (serine protease inhibitors)	Azelaic acid vs. glycolic acid vs. soy extract	Facial hypermelanosis	Soybean extract showed clinical efficacy based on video camera analysis
		None; authors compared affected vs. unaffected areas	Melasma	Application of soy extract to melasma lesions once daily for 3 months led to an average reduction of hyperpigmentation of 12%

Exhibit 2. Summary of clinical studies evaluating the efficacy of natural ingredients as hypo pigmenting agents [55]

Natural Ingredients	Hypo pigmenting Mechanism	Comparison	Pigmentation Disorder	Conclusion
		Soy moisturizer vs. vehicle control	Facial photodamage	Application of soy-containing moisturizer improved mottled pigmentation, blotchiness, dullness, fine lines, overall texture, overall skin tone, and overall appearance
Ascorbic Acid	UVA-mediated catalase inactivation	Topical AA with trichloroacetic acid peel vs. trichloroacetic acid peel	Severe melasma	Melasma peel (alpha-hydroxy acid, AA, and oxygen) showed improvement in 95 percent of patients at eight weeks
	Glutathione depletion, oxidant formation	Combined trichloroacetic acid peel and topical ascorbic acid vs. trichloroacetic acid peel	Bilateral epidermal melasma	According to digital photography and MASI score, combination product showed greater improvement
	Nitrous oxide production	Vitamin C vs. distilled water	Melasma	After 12 weeks of vitamin C iontophoresis treatment, the colorimeter recorded a clinically significant reduction in luminance value on the treated side
	ROS scavenger, tyrosinase inhibition	None	Melasma and post-inflammatory hyperpigmentation	Novel full-face iontophoresis mask and ascorbyl glucoside preparation over a 1 to 2 months period showed clinical efficacy. *In conjunction to the treatment, patients adhered to a regimen of mandelic/malic acid skin care regimen, broad-spectrum UVA/UVB

Exhibit 2. Summary of clinical studies evaluating the efficacy of natural ingredients as hypo pigmenting agents [55]

Natural Ingredients	Hypo pigmenting Mechanism	Comparison	Pigmentation Disorder	Conclusion
				sunblock, and basic sun protection.

9. Dark side of whiteners

Hydroquinone, mercury, and bleaching agents such as hydrogen peroxide are considered high risk ingredients used in cosmetics. These agents act in different ways to lighten skin, but generally work by suppressing the production of melanin, the pigment which gives human skin its color. Lartey et.al, 2017 reported the practice of skin lightening has been reported from North America, Europe, Asia, and Africa. In literature, some prevalence rates exceed 50%, and both sexes are involved. Common agents used include hydroquinone, mercury, corticosteroids, and caustic agents. The agents are easily accessible and affordable with very little regulation. Cutaneous and systemic side effects occur but do not appear to be a deterrent, as the notion of light skin as a surrogate for beauty is strong [238]. While effective in lightening skin color, the products are also associated with health risks, such as dermatitis, impaired wound healing and adrenal suppression. Mercury is associated with adverse neurological, psychological and renal effects and organic mercury compounds also have the ability to cross the placenta with toxic effects for the fetus. Cosmetic use of hydroquinone and corticosteroids were extensively prevalent among pregnant women and with negative impact on birth and placenta weights [5]. Among the toxic components, heavy metals are one of the major ingredients, which are used in them intentionally. Among the heavy metal impurities, mercury, arsenic, lead, cobalt, antimony, cadmium, nickel and chromium are highly toxic and are banned in cosmetics to be added intentionally as ingredients in European Union and United States [243]. However, Shroff et.al, 2018 reported side effects of skin fairness products containing hydroquinone, steroids, or mercury can include irritation, inflammation, thinning of skin, scarring, abnormalities among newborn babies if used during pregnancy and breast-feeding, and kidney, liver, or nerve damage. Skin-bleaching agents also increase susceptibility to infections including bacteria, fungus, parasites, and viruses. Some countries (e.g., Ghana, Ivory Coast, Nigeria, South Africa, and Zimbabwe) have banned the import of fairness products that contain hydroquinone and mercury. Nevertheless, many countries, including the two biggest markets, India and China, do not have regulations on ingredients contained within these products. The widespread use of skin fairness products presents a growing public health concern, particularly in Asia [2]. Many skin lightening creams also contain steroids in doses up to 1,000 times higher than in creams used to treat eczema and other skin conditions. Steroid use can cause all sorts of complications such as thinning of the skin, acne, red stretch marks and discoloration. Worse still, the steroids in these creams can act like cortisol, a hormone made by the body to deal with stress. Too much cortisol can cause a myriad of problems, including swelling of the face and abdomen, weight gain, thin skin that bruises easily, stretch marks, weak muscles, high blood pressure, diabetes, osteoporosis and depression [232]. Sharma et.al, 2017 detailed about new entity known as "Topical Steroid Damaged/Dependent face (TSDF)", that has been coined to encompass the various symptoms aggravated such as erythema or burning sensation on attempted cessation of topical steroid application [233]. In the Indian market, topical corticosteroids are easily

available; pharmacists are using it as OTC medicine, bypassing the need of a prescription [235]. Hence, misuse and prolonged use of the medicine without medical supervision particularly on the face produce different adverse effects such as steroid rosacea, acneiform eruption, hypertrichosis, demodicidosis, steroid addiction, dermatitis rosaceaformis steroidica, and red face syndrome. Red face syndrome is a condition where any attempted cessation of the application of topical corticosteroids on the face after prolonged use, leads to rebound erythema, burning, and scaling on the face [234]. Coondoo et.al, 2014 commented on use of topical steroids as "double edged sword". The end-users of topical corticosteroids are hapless patients. They tend to overuse topical corticosteroids beyond the time limit set by clinicians by repeating prescriptions. Of more concern is the mass use of topical corticosteroids as fairness creams. Vast sections of the Indian society have willingly or unknowingly become victims to the craze of beautification [236]. A Senegalese cohort study of 147 women showed a statistically significant increase in the risk of hypertension and diabetes linked to the use of skin-lightening agents. Other systemic adverse effects attributed to skin-lightening cosmetics include Cushing's syndrome, adrenal insufficiency, nephrotic syndrome, neurological disorders, and ocular disorders. Hypersensitivity reactions, including anaphylaxis, have also been attributed to these products. Many skin-lightening cosmetics contain substances that can harm the unborn child. For example, tretinoin is teratogenic while salicylic acid is feto-toxic. In practice, users are often unaware of the risk of severe adverse effects associated with skin-lightening cosmetics. Users should be informed of these adverse effects and encouraged to stop using these products, especially when skin disorders appear [237]. Mistry et.al, 2011 reported that cultural practice of skin bleaching is highly prevalent in Africa. Most reported cases of toxic effects of skin-lightening products occur in this region [239]. Legally, bleaching products might be drugs that are misused; however, more often, their presentations are those of true cosmetic brands, which are numerous. The active ingredients might be indicated on the packages, which could give the true information or not, but are often withheld. These products appear to be available in every country where they are used, including Northern countries, through well-organized networks of distribution. Despite these reports, surprisingly sparse epidemiological studies are available regarding the health impacts of skin-bleaching practices on Afro-Caribbean immigrant groups in the US [241]. All products are used as milks, creams or gel creams, or soaps. Caustic compounds (lemon juice, high concentration acid salicylic preparations, etc.) are sometimes used on certain areas that are more difficult to lighten (such as hands and feet).The compounds are commonly applied on the entire surface of the body, once or twice daily, often for decades because of the rapid reversibility of the lightening after stopping the use of the product [240]. Skin-lightening products are used by a third of African and Indian women in South Africa Cultural and historical perceptions equating a fairer skin with social advantage are pervasive and strongly reinforced by the media. There is a poor understanding of the risks associated with the use of these products. Public education campaigns are required to teach consumers about these risks and the importance of concomitant use of sunscreens with these products [242].

Figure 26. An Indian film star posing for a "Men Fairness Cream" [2], [244]. The trend seems to be changing with many new-age celebrities saying no to endorsing problematic products like alcohol, tobacco, fairness creams, aerated drinks etc. A recent survey showed that 80% of Indian men use fairness creams and the number of consumer's are growing 18% annually. There were no differences between women and men currently using products in their desire to look as fair as media celebrities.

Epilogue

Disorders of hyperpigmentation (including melasma, post-inflammatory hyperpigmentation, lentigo, etc.) are commonly seen in office-based dermatology practices worldwide. Their management is challenging and requires a long-term treatment plan. Facial and neck pigmentations are the most cosmetically important. They are common in middle-aged women, and are related to endogenous (hormones) and exogenous factors (such as use of cosmetics and perfumes, and exposure to sun radiation). The results are often unsatisfactory and topical agents may sometimes cause significant adverse reactions. An improved understanding of melanogenesis has also led to new pathways as targets for topical therapy. Multiple topical agents available act upon different steps of the pigmentation pathway. Cosmeceuticals for hyperpigmentation are in great demand and most of them target the key regulatory steps in melanin synthesis. Successful treatment typically involves a combination of topical agents with or without in-office procedures, exploiting the different mechanisms of action of each agent or treatment modality. Sunscreen use and minimizing sun exposure are crucial in all cases. Treatment of melasma and other facial pigmentations has

always been challenging and discouraging. It is important to avoid exposure to the sun or to ultraviolet lamps, and to use broad-spectrum sunscreens. Topical applications are the mainstay of treatment and include phenols, retinoids, corticosteroids, and their combinations. Additionally, many studies have addressed the safety and efficacy of chemical peels and laser/light sources for pigment reduction in melasma. Such procedures are most often considered second- and third-line therapeutic approaches. In order to identify any underlying causes of hyperpigmentation or identify any factors that may hinder treatment, it is essential to obtain a detailed medication history for all patients. It is also important to assess any family history and/or personal history of melasma. If the patient has been treated for melasma in the past, ascertain what therapies were used and how the patient responded. Allergic reactions to cosmetics and/or fragrance-based products may contribute to PIH. Serial photography is essential in the clinical management of hyperpigmentation. With the advent of laser technology, the treatment options have increased especially for dermal or mixed melasma. Lasers have been tried in the treatment of various pigmentary disorders with variable success. In contrast, laser therapies have not produced completely satisfactory results, because they can induce hyperpigmentation and recurrences can occur. Combining topical therapy with procedures such as chemical peels, intense pulsed light (IPL), fractional non-ablative lasers or radiofrequency, pigment lasers (microsecond, picosecond, Q-switched), and micro-needling, enhances results. Patients are savvy consumers who often present to physicians asking about the latest treatments and breakthroughs. With proper treatment, melasma can be controlled, improved, and maintained. With the patient population seeking effective systemic treatments for skin pigmentation, it is important for dermatologists to understand the properties, the efficacy, and the adverse events profile of each compound, thus ensuring proper use by patients, and that patients are appropriately counseled regarding treatment expectation and safety.

Article Summary

Hyperpigmentation is one of the most common skin disorders that affects both men and women of all ethnic groups, caused by several factors, such as UV exposure and skin inflammation. Topical whitening agents were found to be the best and the least aggressive therapy for treating hyperpigmentation compared to instrumental approaches. However, topical treatment faces several obstacles due to the low stability of the whitening agents. The number of patients that visit dermatologists with pigmentary disorders is significant. Patients are often overwhelmed with numerous OTC skin lightening agents, many without clinical evidence of efficacy. However, evidence-based studies on many of these agents is still lacking. The treatment of melasma should include a multimodality approach that incorporates photoprotective agents, antioxidant treatments, skin lighteners, exfoliants, and resurfacing procedures, as needed. Evidence-based studies suggest that first line therapies for melasma encompass intense photoprotection and topical lightening agents. Second-line treatments, such as chemical peels and lasers, are efficacious in some patients, but these approaches can be associated with acute and long-term complications, particularly in individuals with darker skin types. Given the global negative impact of melasma on the quality of life, a quest to find more efficacious treatments that offer sustained long-term remission for patients with this frustrating and therapeutically challenging disorder is ongoing.

Article Highlights

1. Elizabeth (1st) was known to take arsenic complexion wafers, which were essentially little bits of poison to give her that ghostly look.
2. Skin whitening is one of the most fastest growing industry, with marketing forecasters predicting it will be worth an estimated $US 31.2 billion by 2024.
3. Hyperpigmentation-related diseases include melasma, lentigines, nevus, ephelis, freckles, post-inflammatory hyperpigmentation, and age spots. Post-inflammatory hyperpigmentation appears in many skin conditions, including acne, eczema, and contact dermatitis.
4. Approximately $13 billion spent on skin care products and cosmetics in Asia Pacific's.
5. The regular and sustained use of skin bleaching products has been practiced in African and Asian contexts for decades, with prevalence estimates from 25% to 96%.
6. China accounts for about 40% of sales in Asia, Japan 21% and Korea approximately 18%.
7. While effective in lightening skin color, the products (hydroquinone, mercury, corticosteroids) are also associated with health risks, such as dermatitis, impaired wound healing and adrenal suppression.
8. . Among the heavy metal impurities, mercury, arsenic, lead, cobalt, antimony, cadmium, nickel and chromium are highly toxic and are banned in cosmetics to be added intentionally as ingredients in EU and US.
9. Ghana, Ivory Coast, Nigeria, South Africa, and Zimbabwe have banned the import of fairness products that contain hydroquinone and mercury.
10. 50% of patients developed retinoid dermatitis, which is the concern with using retinoids in skin of color.

Abbreviations: Tyrosinase related protein-1 (TRP-1); Global industry analysts (GIA); Proopiomelanocortin (POMC); Microphthalmia-associated transcription factor (MITF); Adrenocorticotropic hormone (ACTH); α-Melanocyte-stimulating hormone (α-MSH); melanocortin type 1 receptor (MC1R); alpha-hydroxy acids (AHAs); melasma quality of life (MELASQOL); 5,6-dihydroxyindole-2-carboxylic acid (DHICA); Scientific Committee on Consumer Safety (SCCS); Melasma Area and Severity Index (MASI); physician global assessment (PGA); patient global assessment (PtGA); Level of evidence (LOE); protease-activated receptor (PAR); soybean trypsin inhibitor (STI); Bowman–Birk inhibitor (BBI); quasi-drugs (QDs); Soybean trypsin inhibitor (STI); post-inflammatory hyperpigmentation (PIH); omega-3 polyunsaturated fatty acids (PUFAs)

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