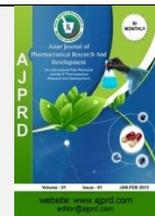


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Review Article

## A Concise Review on Contemporary and Novel Treatments Addressing the Prevention and Control of Hyperpigmentation

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### ABSTRACT

Hyperpigmentation is a common skin condition characterized by the darkening of certain areas of the skin due to an excess production of melanin. This condition can be caused by a variety of factors, including sun exposure, hormonal changes, inflammation, and skin injuries. Hyperpigmentation can have a significant impact on a person's self-esteem and quality of life. Hormonal changes, such as those experienced during pregnancy or menopause, can also lead to hyperpigmentation. Inflammation from conditions like acne or eczema can cause the skin to produce excess melanin, resulting in dark spots or patches. Additionally, skin injuries, such as cuts or burns, can trigger the body to produce more melanin as part of the healing process, leading to hyperpigmentation. Creams containing ingredients like hydroquinone, retinol, or vitamin C can help lighten dark spots and even out skin tone. Medications containing corticosteroids, may be recommended for more severe cases of hyperpigmentation. In addition, novel drug delivery systems such as liposomes, Transferosomes, Niosomes etc. have shown better penetration topically hence they can be used to treat pigmentation. Understanding the causes of hyperpigmentation and seeking appropriate treatment can help improve the overall health and appearance of the skin. By addressing the underlying factors contributing to hyperpigmentation and using targeted skincare products or treatments, individuals can achieve a more even complexion and feel more confident in their skin.

**Background:** The topic of hyperpigmentation is of significant interest in dermatology and cosmetology due to its widespread prevalence and impact on individuals' skin health and appearance. Several traditional treatments such as topical hydroquinone and retinoids have been utilized for managing hyperpigmentation, there is an increasing recognition of the need for more effective and targeted intervention.

**Keywords:** Hyperpigmentation, Melanin, Dark patches, Tyrosinase-inhibitor, Skin whitening agent.

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### INTRODUCTION

The pigment melanin is essential for shielding the skin from the damaging effects of ultraviolet (UV) light. The modulation of pigmentation involves both genetic and environmental factors. Disorders exhibiting aberrant skin pigmentation are caused by either insufficient or excessive levels of melanin<sup>(1)</sup>. Excessive secretion of melanin leads to hyperpigmentation whereas insufficient secretion of melanin leads to hypopigmentation. Hyperpigmentation is a prevalent dermatological condition

characterised by a typically darker skin tone. Despite recent breakthroughs, the regulation of skin pigmentation remains largely unknown, despite being a significant human phenotypic characteristic. Melanocytes engage in a complicated process known as melanogenesis to produce the pigment melanin in melanosomes. The melanocyte is influenced by extrinsic stimuli including medications and UV light, and it interacts with the endocrine, immunological, inflammatory, and central neurological systems<sup>(2)</sup>

**Pathophysiology of Pigmentation:**

Pathophysiology of Pigmentation due to UV radiations follows following mechanism,

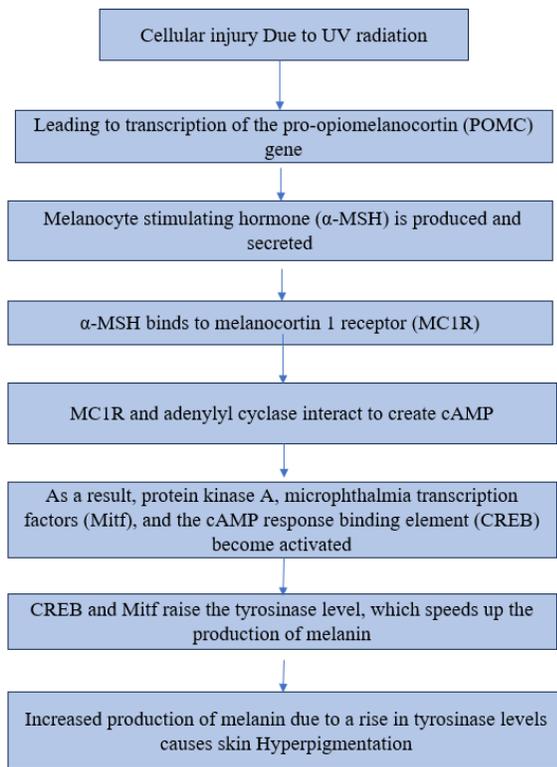


Figure 1: Pathophysiology of Pigmentation

**Causes of pigmentation:**

A frequent condition that can be brought on by a number of circumstances is skin pigmentation. Genetics, sun exposure, and some drugs are the three main factors that contribute to skin pigmentation. It will be easier to treat and prevent skin pigmentation if we are aware of its basic causes.(3)

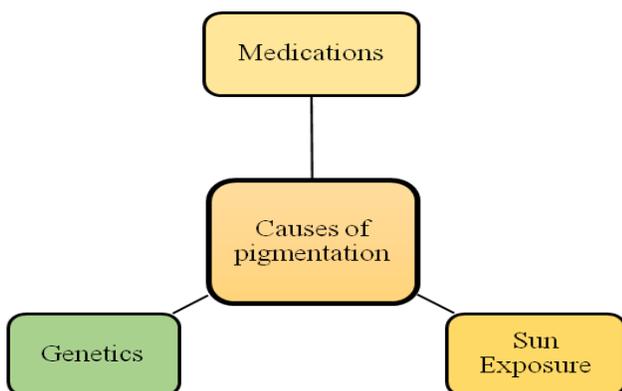


Figure 2: Causes of Pigmentation

**a) Medications:**

Antibiotics are a class of drugs that may boost the synthesis of melanin, which darkens the skin. Skin pigmentation may also worsen if certain drugs, such birth control pills, are taken concurrently. A patient should consult their physician

to determine if any medications could impact the tone of their skin.(4) Ten to twenty percent of cases of acquired hyperpigmentation are brought on by drugs, which is a very prevalent cause of skin pigmentation. Many medications have the potential to cause pigmentation, however the most popular ones include non-steroidal anti-inflammatory medications (NSAIDs), tetracyclines, phenytoin, amiodarone, antimalarials, antipsychotics, and heavy metals. Increased melanin synthesis, increased lipofuscin synthesis, or cutaneous deposition of drug-related material can all contribute to drug-induced skin pigmentation. certain heavy metals, including iron, can get up in the dermis leading damage to dermal vessels. If used in large enough amounts, a noticeable alteration in skin tone may be noted without a discernible rise in melanin. Drugs can react with melanin in a variety of ways, such as forming a drug-pigment complex, causing non-specific post-inflammatory changes in persons who are predisposed to them, or directly causing pigmentation by reacting and accumulating with other substances in the skin.(5)

**b) Sun Exposure:**

UV radiations emitted by the sun is the common cause for skin pigmentation. The body generates more melanin to safeguard itself from the sun's UV radiation, this could make the skin more pigmented. The mechanism of melanin synthesis involving UVradiationsinvolve following steps.

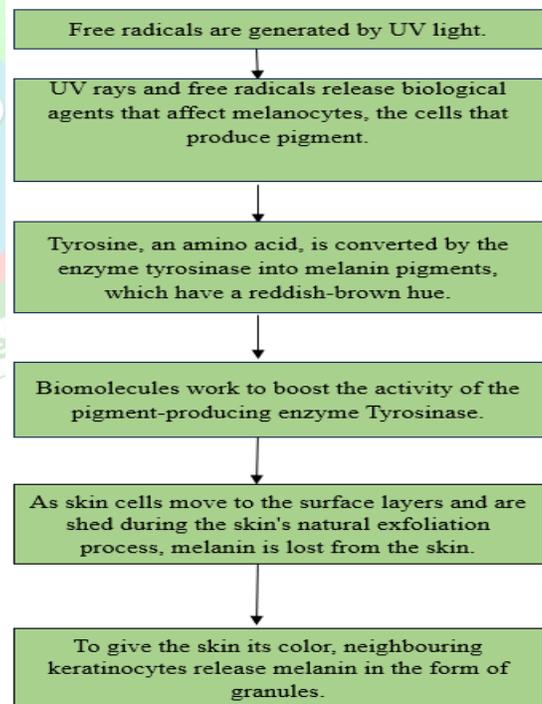


Figure 3: Mechanism of melanin synthesis due to UV

**c) Genetics:**

Unexpectedly, skin tone can be influenced by 125 genes. It may be possible to anticipate an individual's melanocyte count through genetics. Skin cells called melanocytes are responsible for producing melanin. Melanosomes, on the other hand, must be transported and increased during hyperpigmentation and tanning, while they shrink during hypopigmentation. People with darker skin tones are more likely to have higher quantities of melanin, the pigment that gives skin its colour. For instance, those with darker skin

tones typically have higher melanin levels compared to people with paler skin tones(4)

Although hyperpigmentation can be caused by any inflammatory skin condition, acne vulgaris, atopic dermatitis, and impetigo are the most common causes of hyperpigmentation in patients with darker skin tones. Some aetiologies consist of (6)

**Etiology of Hyperpigmentation:**

**Table 1:** Etiology of Pigmentation

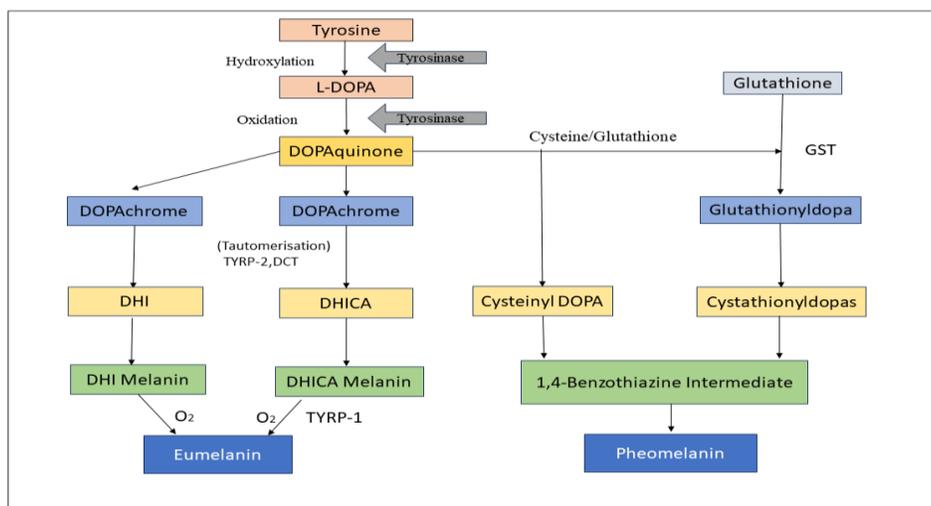
1.	Infections	<ul style="list-style-type: none"> <li>• Viral exanthems</li> <li>• Fungal infections</li> <li>• Impetigo</li> </ul>
2.	Allergic/ Immunologic	<ul style="list-style-type: none"> <li>• Contact dermatitis</li> <li>• Atopic dermatitis</li> <li>• Scleroderma</li> <li>• Sarcoidosis</li> <li>• Systemic lupus erythematosus</li> <li>• Dermatomyositis</li> <li>• Insects bite reaction</li> </ul>
3.	Papulosaquamous Disorders	<ul style="list-style-type: none"> <li>• Psoriasis</li> <li>• Lichen planus</li> <li>• Pityriasis rosea</li> <li>• Lichen simplex chronicus</li> </ul>
4.	Cutaneous Injury	<ul style="list-style-type: none"> <li>• Laser/light therapy</li> <li>• Burns</li> <li>• Cryotherapy</li> <li>• Chemical peels</li> <li>• Radiation therapy</li> </ul>

**Pathway of Melanogenesis:**

Melanosomes are intracellular organelles that resemble lysosomes and are responsible for producing and storing skin colours such as melanin. The colour of skin is determined by the distribution of these pigments among nearby keratinocytes. The Raper Mason pathway, which is also known as the precursor for melanin production, is the result of a series of spontaneous enzymatic events that start with the amino acid L-tyrosine. The melanogenesis pathway takes place inside a melanosome and produces either yellow-red pheomelanin or black-brown eumelanin. Tyrosinase activity is elevated by L-Dopachrome, while melanosome synthesis is enhanced by L-Tyrosine. Therefore, controlling

the amounts of L-Tyrosine and L-DOPA is essential for maintaining the homeostasis of melanogenic systems.

Tyrosinase is a glycoprotein that is thought to be a possible target for a number of therapeutic treatments since it is the rate-limiting enzyme in the process leading to the creation of melanin and contains copper. The microphthalmia transcription factor (MITF) is a master transcription factor that controls the tyrosinase, TYRP-1, and TYRP-2 enzymes involved in melanogenesis. Both the adrenocorticotrophic hormone (ACTH) and the melanocyte-stimulating hormone ( $\alpha$ -MSH), which are found in the dermis and epidermis, are important regulators of the melanogenesis pathway.<sup>(7)</sup>



**Figure 4:** Pathway of Melanogenesis

## Novel Carrier systems used in management of Pigmentation

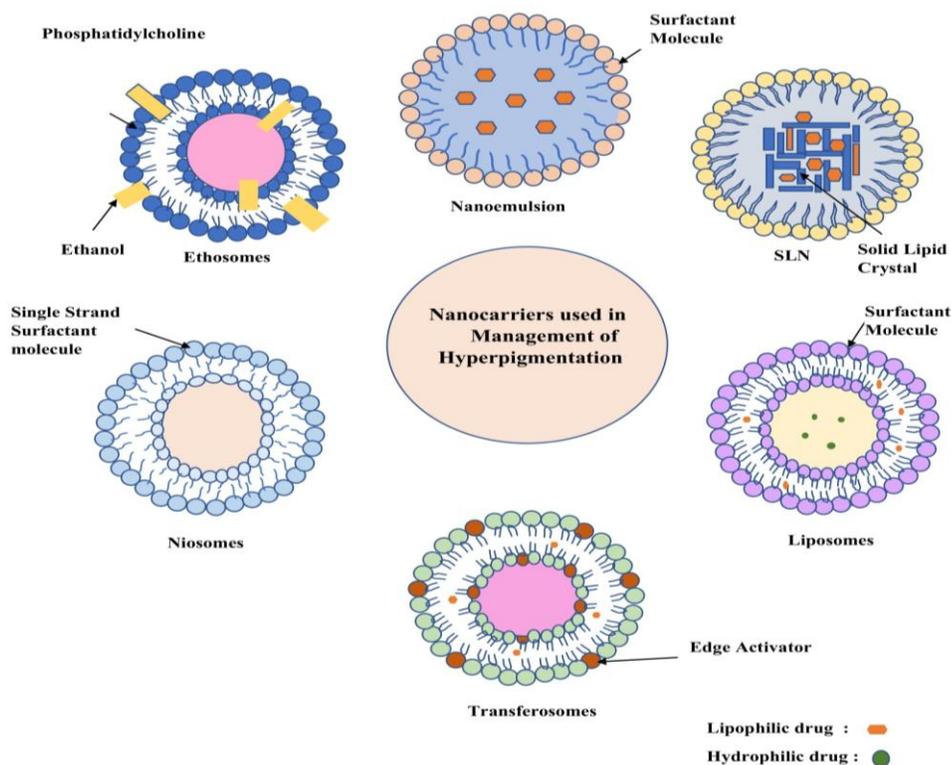


Figure 5: Novel Carrier Systems used in management of Hyperpigmentation

### a) Nano/Micro emulsions:

The two immiscible phases of nanoemulsions and microemulsions are the aqueous phase combined with the oil phase with the aid of surfactants. Because of their small size and ability to boost the solubility of both hydrophilic and lipophilic medicines, these carriers have prospective use in cosmeceuticals and topical drug delivery. Histopathology demonstrated that this microemulsion did not cause any skin irritation or disturb epidermal layers. Consequently, the use of nanoemulsions and microemulsions in the management of hyperpigmentation and melasma could be investigated. The incorporation of kojic monooleate, a tyrosinase inhibitor, into nanomulsion resulted in a 54.76% survival rate for 3T3 cells. Similarly, tyrosinase inhibition and enhanced drug retention were investigated in relation to azelaic acid and hyaluronic acid nanoemulsion. The formulation demonstrated strong skin penetration in vitro and a considerable reduction in tyrosinase activity, according to the in vitro mushroom tyrosinase inhibition experiment.<sup>(9)</sup>

### b) Solid lipid nanoparticles:

After forming an occlusive layer on the skin's surface, solid lipid nanoparticles were investigated as appealing options for topical distribution because they improve medication penetration and hydrate the stratum corneum. They also have a lot of benefits, like increased stability, bioavailability, and drug entrapment. Hence Tyrosinase inhibitors in particular have been developed as lipid nanocarrier. Better drug

localization and skin targeting were achieved by Ghanbarzadeh et al. (2015) when they developed hydroquinone solid lipid nanoparticles gel, which demonstrated higher hydroquinone deposition in the skin epidermis ( $46.5\% \pm 2.6\%$ ) than hydroquinone gel ( $15.1\% \pm 1.8\%$ ).<sup>(10)</sup>

### c) Liposomes/Nanosomes:

British haematologist Alec Douglas Bangham made the initial discovery of liposomes in 1961 at the Babraham Institute in Cambridge, England<sup>(11)</sup>. Hydrophobic and hydrophilic drugs can be incorporated into liposomes, which are small, spherical vesicles composed of a concentric phospholipid and cholesterol bilayer. To efficiently administer the medication and improve stratum corneum penetration, they may readily integrate with the cell membrane and change the fluidity of the membrane. Melasma patients were investigated using liposomal serum containing azelaic acid, 4-n-butylresorcinol, and retinol. Following treatment, the melasma severity scale (MSS) improved and the Melasma area and severity index (MASI) score increased from 41.7% to 85%.<sup>(12)</sup>

Nanosomes possess similar characteristics to liposomes but are monolayered which means contain single lipid layer. A patient with melasma participated in a single-blind clinical trial that assessed the safety and effectiveness of topical vitamin C nanosome with iontophoresis and contrasted it with a 70% glycolic acid peel. Using baseline comparison and photos to assess the results, it was discovered that the

nanosome was superior than glycolic acid peel in terms of reducing hyperpigmentation.<sup>(13)</sup>

#### d) Transferosomes:

Vesicular carrier systems known as transferosomes are specifically engineered to have an edge activator and at least one interior aqueous compartment surrounded by a lipid bilayer. These lipid bilayer-enclosed aqueous cores generate ultra-deformable vesicles with self-optimizing and self-regulating properties. Because transferosomes are elastic by nature, they can squeeze and reshape themselves into complete vesicles through skin constrictions or tiny pores that are much smaller than the vesicle size without causing a measurable loss. Phospholipid and a single-chain surfactant acting as an edge activator make up transferosomes. Edge activators perform exceptionally well as membrane stabilizing agents to enhance the deformability of vesicle membranes. When mixed in the right proportion with the right lipid, the resultant mixture allows the transferosomes to become both ultra-flexible and deformable.<sup>(14)</sup>

#### e) Niosomes:

Nonionic surfactant vesicles, or Niosomes, form closed bilayer structures in aqueous conditions and can be employed as drug carriers for both lipophilic and amphiphilic substances. Niosomes are microscopic lamellar structures that are created when cholesterol and a non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class are mixed together. A buffer solution with the proper pH is often included within the enclosed interior of niosomes. Cholesterol plus a tiny quantity of an anionic surfactant, such as diacetyl phosphate, stabilise the non-ionic surfactant vesicles that form the amphiphile in niosomes. Non-ionic surfactants have a few advantages over phospholipids, including being more cost-effective and having a higher

chemical stability due to their resistance to easy hydrolysis or oxidation during storage. It is possible to alter the vesicular structure to enable controlled or sustained drug distribution, which will increase the system's effectiveness over extended periods of time. They increase the oral bioavailability of poorly absorbed medications and increase the drugs' penetration via the skin.<sup>(15)</sup>

#### f) Ethosomes:

One of the unique lipid vesicular systems that has a comparatively high concentration of ethanol is the ethosomes. Touitou created this ethanolic vesicular system. Ethosomes are mainly composed of ethanol, water, phospholipid and drug. The structural components of ethosomal vesicles include an inner aqueous core carrying medication and a phospholipid bilayer. In comparison to other lipid nanocarriers, ethosomes have a higher percentage of ethanol, have a more fluid vesicular bilayer, have a different mechanism of skin penetration, are easier to prepare, and have less adverse effects. Compared to liposomal formulations, which have an ethanol content of up to 10%, ethosomes have a high ethanol concentration of 20–45%. Because of its great penetration enhancer properties, ethanol facilitates the easy and efficient distribution of medicinal substances into the deeper layers of the skin and the systemic circulation. Numerous molecules, including hydrophilic, lipophilic, and high molecular weight substances, can be entrapped by ethosomes. Both transcellular and intercellular mechanisms allow drugs to penetrate through intact stratum corneum. Ethosomal size is influenced by concentration of phospholipid and ethanol. As the concentration of ethanol increases the vesicle size decreases whereas increase in concentration of phospholipid leads to increase in vesicle size of Ethosomes.<sup>(16)</sup>

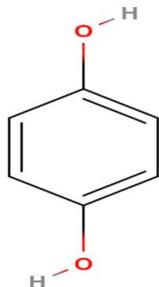
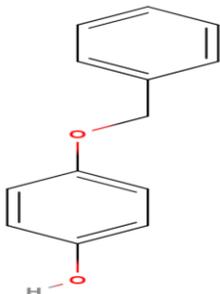
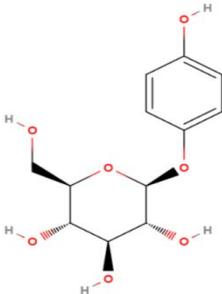
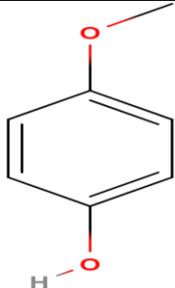
### Novel Formulations to treat Pigmentation:

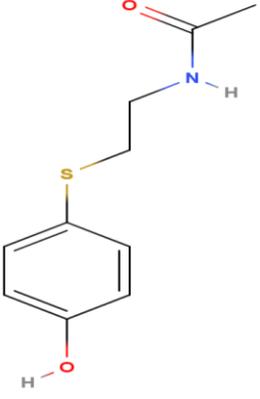
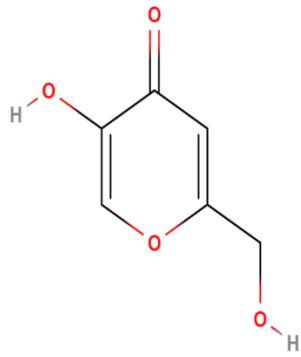
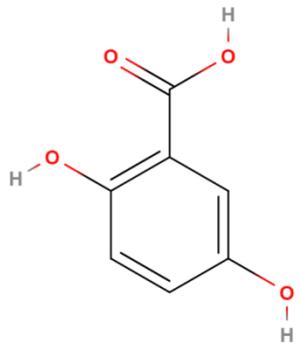
Table: 2 Novel Formulations to treat Pigmentation

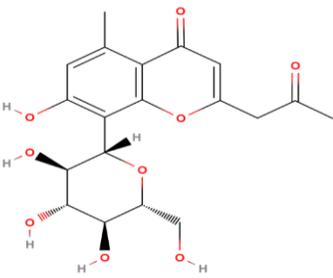
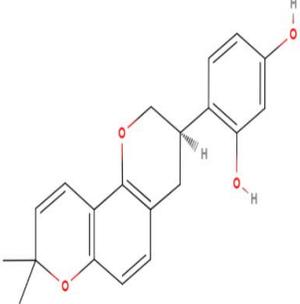
Sr.no	Author	Novel carrier	Drug	Reference
1	Farhad Mohammadi et.al 2020	Solid lipid Nanoparticles	Kojic Acid Dipalmitate	17
2	Julia cappzilles et.al 2023	Nanoemulsion	Kojic Acid Dipalmitate	18
3	Nishma Tanveer et.al 2022	Ethosomes	Kojic Acid Dipalmitate	19
4	Nur Illiyyin Akib et.al 2020	Ethosomes	Kojic Acid	20
5	Haji Muhammad Shoaib Khan et.al 2023	Ethosomes	alpha arbutin	21
6	Ai Hua Wen et.al 2006	liposome	Arbutin	22
7	Aryana Radmard et.al 2021	Niosomes	Arbutin	23
8	Paurnima Talele et.al 2020	Solid lipid Nanoparticles	Hydroquinone	24
9	Faezeh Taghawi et.al 2019	liposome	Hydroquinone	25
10	Amal A. Ammar et.al 2020	Niosomes	Hydroquinone	26
11	Simone Jacobus Berlitz et.al 2019	Nanoemulsion	Azelaic acid	27
12	Avni Nautiyal et.al 2023	Solid lipid Nanoparticles	Azelaic acid	28
13	Paula Melania Pasca et. Al 2022	Liposomes	Azelaic acid	29
14	Aulai Dwi Rahmi et.al 2018	Transferosomes	Azelaic acid	30

15	Ankita Mistry et.al 2016	Ethosomes	Azelaic acid	31
16	Chijian Zhang et.al 2021	Liposomes	Glabridin	32

### Marketed Drugs used to treat pigmentation:

Sr.No.	Agents	Chemical Structure	Description	Reference
1.	Hydroquinone		Tyrosinase is the enzyme that makes melanin, and HQ's (Hydroquinone) primary mode of action for treating hypopigmentation is to suppress it. Tyrosine is converted by the enzyme tyrosinase into precursors of melanin, including dopaquinone and dopachrome. Tyrosinase preferentially oxidises HQ over tyrosine when it is present, thus that no melanin is produced. Despite being a less efficient substrate for tyrosinase than tyrosine, HQ is efficiently oxidised because catalytic levels of dopa are produced, which serves as a cofactor for tyrosinase.	33,34
2.	Monobenzylether		A related substance called mono benzyl ether of hydroquinone (MBEH) interacts and causes permanent depigmentation even in regions far from the application site. It is metabolised inside the cell to produce a quinone species. Melasma or post-inflammatory hyperpigmentation should not be treated with MBEH due to its ability to kill melanocytes.	35,36
3.	Arbutin		Arbutin is a hydroquinone derivative that is present in pears, wheat, blueberries, and cranberries. Arbutin is used as an effective treatment of hyper pigmentary disorders, and displays less melanocyte cytotoxicity than hydroquinone. By competitively and reversibly binding tyrosinase without altering tyrosinase's mRNA transcription, arbutin inhibits melanogenesis. Arbutin works better at higher doses than at lower ones, but paradoxical hyperpigmentation may result from using higher quantities.	37,38,39
4.	Mequinol		Tyrosinase catalytically oxidises mequinol, another hydroquinone derivative, to create melanocytotoxic quinones. Skin depigmentation and pigment cell death are the outcomes of quinones' production. Melanin production has been reported to be inhibited by the combination of 0.01% tretinoin and mequinol, which has been demonstrated to be safe and effective in treating sun lesionens and accompanying hyperpigmentation.	35,40,41,42,43

5.	N-Acetyl-4-S-Cysteaminylphenol		N-Acetyl-4-S-cysteaminylphenol, or NCAP, is a phenolic thioether that has been used in anti-melanoma research as well as the treatment of epidermal hyperpigmentation conditions like melasma. NCAP functions as a substitute substrate for tyrosinase in melanin-producing cells and shares structural similarities with tyrosine.	40
6.	Kojic Acid		Kojic acid is derived by <i>Penicillium</i> , <i>Aspergillus</i> , and <i>Acetobacter</i> species. In addition to being a tyrosinase inhibitor and a free radical scavenger, kojic acid chelates divalent ions. It functions by chelating copper (Cu <sup>3+</sup> ) at the tyrosinase enzyme's active site. Tyrosinase, sometimes referred to as polyphenol oxidase, is the enzyme that converts L-tyrosine to L-3,4-dihydroxyphenylalanine and sets a limit on the pace at which melanin is synthesised.	44,45,46,47
7.	Azelaic Acid		<i>Pityrosporum</i> is the source of azelaic acid, a straight-chain, saturated dicarboxylic acid that occurs naturally and is non-toxic. Azelaic acid appears to have a little effect on normal skin pigmentation, freckles, nevi, and senile lentigenes, but a selective effect on the mechanism of hyperactive and aberrant melanocytes. The suppression of DNA synthesis and mitochondrial oxidoreductase activity may be the mechanism by which Azelaic acid exerts its cytotoxic and antiproliferative effects.	35,48,49
8.	Gentisic Acid		A natural substance derived from the root of the <i>Gentiana</i> plant, gentisic acid is well-known for being a gentle and safe treatment for conditions causing cutaneous hyperpigmentation, such as melasma and UV-induced ephelides. Among the methyl gentisate was identified as a potential contender as a skin-lightening agent. The alkyl esters of gentisic acid were shown to be good inhibitors of melanogenesis, demonstrating tyrosinase inhibitory activities and mutagenicity to some extent.	50

9.	Aloesin		Aloe vera is the source of aloesin, a chromone derivative. By blocking the hydroxylation of tyrosine to DOPA and the oxidation of DOPA to dopaquinone, it competitively inhibits the activity of tyrosinase. Tyrosinase activity in normal human melanocytes treated with aloesin decreased in a dose-dependent manner, according to studies conducted by Jones et al.	38,50
10.	Glabridin		An isoflavonoid called glabiridin was first identified from the roots of Glycyrrhiza glabra. In addition to inhibiting tyrosinase activity, superoxide anion generation, and cyclooxygenase activity, glabridin has been demonstrated to reduce UVB-induced pigmentation. According to this, glabridin extract may have an impact on skin inflammation and melanogenesis.	51

## CONCLUSION:

Hyperpigmentation can be influenced by the UV radiations of sun, hormonal changes, and particular medications. Darker skin tones are often associated with hyperpigmentation, a common dermatological disorder. Hyperpigmentation is caused by an excess of melanin secretion, while hypopigmentation is caused by an insufficient amount. Several plants and phytoconstituents that are utilised as tyrosinase inhibitors and skin-whitening agents were covered in this review. The cosmeceutical sector is expanding exponentially in response to the growing demand for cosmeceutical goods. The cutting-edge technologies of the twenty-first century are represented by nanotechnology, which promises remarkable prospects for research platforms and the marketplace. The unique properties of liposomes, Niosomes, transferosomes, and other similar materials have drawn particular attention because of their capacity for increased permeability and higher bioavailability. Thus, liposome-based cosmetics may be a blessing in the treatment of skin conditions.

## Abbreviations:

UV= Ultra violet

DHICA= Dihydroxy indole Carboxylic acid

DHI= Dihydroxy indole

MITF= Microphthalmia transcription factor

MSH= Melanocyte stimulating factor

ACTH= Adrenocorticotrophic Hormone

CREB= cAMP response element binding protein

ROS= Reactive oxygen species

HQ= Hydroquinone

DOPA= Dihydroxyphenylalanine

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