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Novel Therapeutic Approaches for Treatment of Melasma

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Abstract: There are millions of people suffering from acquired hyperpigmentation diseases such as melasma all over the world. The appearance of melasma is indicated by symmetrical, hyperpigmented patches and macules that can take on several forms, such as blotchy, irregular, arcuate, and polycyclic. Hormonal treatments (including oral contraceptives), pregnancy, antiepileptic drugs, intense sun exposure, phototoxic substances, and genetic predisposition are common triggers of melasma. There are several treatments available for patients who are suffering from melasma. Typically, first-line treatments include medications that influence the route where pigment is produced, broad-spectrum photoprotection, and camouflage. Chemical peels are frequently included in second-line treatment, albeit patients with darker skin should use caution while using them. While carrying a high risk of making the disease worse, laser and light therapy are potentially viable options for people who have failed previous treatments. There is a need for an alternative strategy with fewer side effects and high success rates because of several shortcomings and consequences of existing treatments. Novel approaches, including microemulsions, nanoemulsions, solid lipid nanoparticles, nanostructured lipid carriers, liposomes, niosomes, transfersomes, aquasomes, ethosomes, penetration enhancer vesicles, chitosan nanoparticles, ethyl cellulose nanoparticle, and fullerene, lead to greater effectiveness, quicker recovery, and higher patient satisfaction.This review summarizes the novel approaches and clinical trials used for the management of melasma.

Keywords: Nanotechnology, melasma, hyperpigmentation, treatment, novel approaches, clinical trials.

Introduction

The word melasma originates from the Greek word melas, which means black. In addition, it is called chloasma and a pregnant mask [1-4]. It is described as an uneven hypermelanosis of the face and neck that ranges in color from light to dark brown, and occasionally ashen gray-

brown [1,4,5]. It is thought that the most common cause of pigmentation on the face is melasma. However, there are a variety of other types, including post-inflammatory and drug-induced hyperpigmentation, Riehl's melanosis, ashy dermatosis, poikiloderma of Civatte, and erythrosis peribuccale of Brock [1]. There is currently no known pathogenesis for melasma, although numerous etiologic variables have been linked to the disease's origin. Melasma's onset or worsening has been linked to pregnancy, the use of birth control pills, estrogen and progesterone hormones, genetics, cosmetics and medications, photosensitizing medications, thyroid abnormalities, psychosomatic factors, hepatic dysfunction and other systemic conditions, parasites, and sun exposure [1,6-13]. Men only account for 10% of all cases of the condition, which primarily affects women. All racial groups are affected, although those with darker skin tones (skin types IV to VI), particularly those of East Asian, Hispanic, and Southeast Asian descent who reside in regions with high UV radiation, are more likely to develop melasma [1,4,14-19]

Based on the physical examination, three clinical melasma patterns have been identified: Centro-facial, malar, and mandibular [5,7,13,20-22]. The cheeks, upper lip, nose, forehead, and chin are all included in the Centro-facial pattern. The cheeks and nose are the only parts of the body where the malar pattern is found. The mandibular pattern is the involvement of the mandibular ramus [13,21]. Melasma has been divided into four main categories based on visible light and Wood's light examination: epidermal, dermal, mixed, and indeterminant or inapparent. Epidermal melasma typically has a pale brown color. Wood's light inspection heightens its color contrast. By visible light, dermal melasma appears blue or ash grey. Wood's light analysis reveals little improvement and a less clear border. With Wood's light examination, the mixed type, which is often dark brown, is sometimes accentuated by either epidermal or dermal melasma. The indeterminate or inapparent melasma typically has dark brown skin, can be challenging to spot, and is most common in people with skin types V–VI (dark brown or black complexion). With Wood's mild study, the lack of contrast is not readily apparent [5,13,20,22]. The Melasma Area and Severity Index (MASI), Melasma Quality of Life Scale (MelasQoL), modified MASI (mMASI), mexametry and colorimetry are used to assess melasma [23,24].

Numerous treatment modalities, such as topical whitening creams (hydroquinone [HQ], azelaic acid, retinoids, vitamin C, kojic acid, and arbutin), chemical peels, mesotherapy, and energy-based tools (laser, light, microneedling, radiofrequency [RF], microdermabrasion, iontophoresis, and sonophoresis), have been tried till date with disappointing outcomes

[8,20,25-,30]. Monotherapy using chemical peels and topical whitening creams frequently necessitates a lengthy course of therapy and results in a high rate of recurrence after stopping the regimen [29-31]. Energy-based device application causes erythema, edema, post-inflammatory hyperpigmentation (PIH), guttate hypopigmentation, and rebound of pigmentation. These side effects come with many treatment options and significant expenses [32]. For an effective response rate when treating melasma, a multimodality approach is necessary due to the disease's multifaceted pathophysiology [30-33]. Novel approaches such as microemulsion, nanoemulsion, solid lipid nanoparticle, nanostructured lipid carrier, liposome, niosome, transfersome, aquasome, ethosome, penetration enhancer vesicle, chitosan nanoparticle, ethyl cellulose nanoparticle, fullerene result in greater effectiveness, quicker improvement, and higher patient satisfaction [34-36].

Novel Approaches for the Treatment of Melasma

There are various novel treatments available for melasma. Some of them are shown below in "Figure 1".

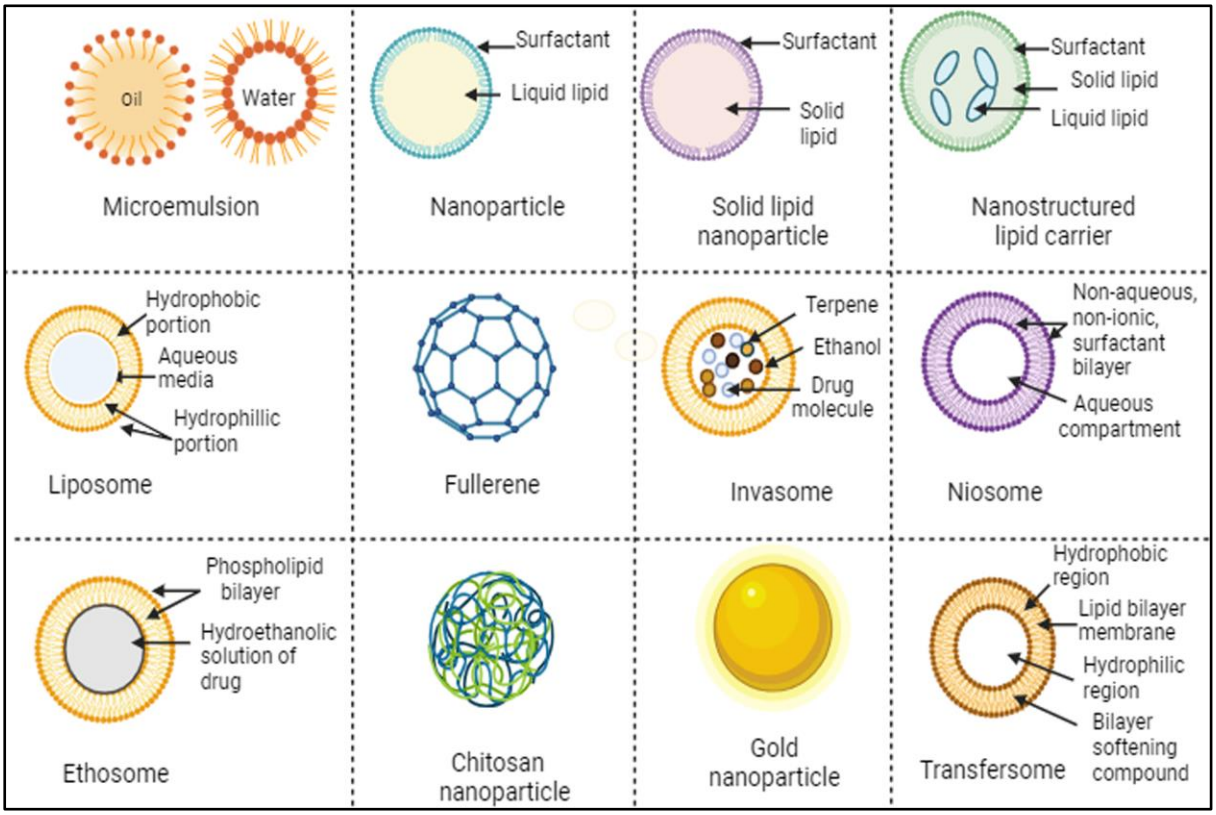

Figure 1. Novel Approaches for the Treatment of Melasma

Microemulsion

Microemulsions are made up of water, oil, and an amphiphile and are a single, thermodynamically stable, optically isotropic liquid solution [37,38]. They can be classified as bicontinuous systems, water-in-oil (w/o), or oil-in-water (o/w) systems depending on their structure. The main distinction between the oil and water phases is the extremely low interfacial tension. Due to the incorporation of both lipophilic and hydrophilic domains, these flexible systems, which can accept both hydrophilic and hydrophobic pharmacological substances, are now of enormous scientific and technological interest to researchers. These flexible delivery methods raise the bioavailability of lipophilic medications by improving their solubilization while safeguarding them from oxidation and enzymatic hydrolysis [38].

Nanoemulsion

Water, oil, surfactant, and co-surfactant mixtures which are transparent, isotropic, and thermodynamically stable are called nanoemulsions [39, 40]. Nanoemulsions are characterized by emulsions with droplet diameters between 20 and 300 nm. Nanoemulsions have improved bioavailability and can be applied to both hydrophilic and lipophilic compounds. Dispersions look opaque between 70 and 100 nm and transparent below that, whereas nanoemulsions with droplets larger than 100 nm appear white [41]. This strategy aims to address some of the problems that existing medication delivery systems have, including poor bioavailability and non-compliance. Nowadays, pharmacology, the design of dosage forms, and research have all focused heavily on nanoemulsions [40].

Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLN) were invented in the early 1990s as an alternate colloidal carrier approach for regulated drug delivery [42]. Compared to polymeric nanoparticles, SLN offers additional benefits for drug delivery, including a nontoxic and adaptable colloidal drug carrier system, because physiological lipids are used; the tolerability is good, and high-pressure homogenization is used for larger-scale production [42, 43].

Nanostructured Lipid Carriers

Both a liquid and a solid lipid matrix make up NLCs, the second generation of lipid nanocarriers. Because of the solid matrix, NLCs have a better ability than emulsions to immobilize drugs and avoid the particles from aggregating. The mobility of the drug molecules that have been added is also significantly decreased by the solid phase. Additionally, compared to SLNs, the solid matrix's liquid oil droplets enhance the drug loading capacity. NLCs have

additional advantages over polymeric nanoparticles, such as biodegradability, less toxicity, sustainable drug release because of a solidified lipid matrix, drug protection, controlled release, occlusive properties, improved skin permeation, which boost skin hydration, and abstaining using organic solvents while manufacturing [44, 45].

Liposome

Cholesterol and safe, organic phospholipids can be used to create liposomes, which are small synthetic vesicles with a spherical shape. The size, hydrophobic and hydrophilic properties, and biocompatibility of liposomes make them attractive drug delivery systems. As spherical vesicles with particle diameters ranging from 30 nm to several micrometers, liposomes are frequently recognized. They consist of aqueous units encased in one or more lipid bilayers, with the polar head groups, directed inward towards the inner and outward towards the aqueous phases, respectively. The traditional bilayer structures of polar lipids are dependent on molecule shape, temperature, environmental parameters, and preparation circumstances. However, polar lipids can also self-assemble into a range of colloidal particles [46, 47].

Transfersomes

Transfersomes, a novel form of liposomes, fall under the group of liposomes or vesicles that have been variously explained as elastic, highly deformable, or ultra-flexible. Unlike typical liposomes, which are thought to only penetrate the stratum corneum's outer layers where they have a drug- or cosmetic-localizing effect, transfersomes are supposed to penetrate the epidermal layers as full vesicles to arrive at the systemic circulation. Transfersomes or deformable vesicles have been shown to enhance the skin delivery of a variety of medications in vitro and the ability of these materials to penetrate the body in vivo to give therapeutic doses that are on par with subcutaneous injection[48, 49].

Invasomes

Invasomes are liposomal vesicles that have terpene, ethanol, and phospholipids in their structures; these substances give the soft vesicles the necessary transdermal penetration capabilities [50, 51, 52]. These nanovesicles limit the action of many drugs by increasing drug permeability into the epidermis and reducing absorption into the systemic circulation [50]. Invasomes concentrate on offering many advantages, including improved drug effectiveness, higher compliance, and patient convenience [51].

Niosomes

One of the most promising drug carriers is the niosome, which is created when cholesterol and nonionic surfactants self-associate in an aqueous phase. Niosomes are composed of two layers. Niosomes are nonimmunogenic, biocompatible, and biodegradable. They offer controlled and/or continuous drug delivery at the target site and are very stable and long-lasting [53, 54]. Based on vesicle size, niosomes can be divided into three types. The three different forms of vesicles are small unilamellar vesicles (SUV, size=0.025-0.05 m), large unilamellar vesicles (LUV, size=0.10 m), and multilamellar vesicles (MLV, size=0.05 m) [54].

Ethosomes

Ethosomes are elastic nanovesicles made upof phospholipids, ethanol (up to 50%), and water [55,56]. To create elastic nanovesicles, ethanol, a well-known permeability booster, was introduced to the vesicular systems. To promote lipid fluidity and cell membrane permeability, the stratum corneum lipid and the polar head group area of the lipid molecules may interact to lower the lipid's melting point. Due to the injection of ethanol into the vesicular membranes, the elastic vesicles can pass through pores that are considerably smaller than their diameters[55]. Ethosomes are distinct vesicular carriers that stand apart from other lipid nanocarriers in a variety of significant ways. These include the lack of negative effects, simplicity of synthesis, and mechanism of permeation augmentation (which is linked to the fluidity of the entire system's bilayer) [56].

Penetration Enhancer Vesicles

The stratum corneum (SC), a barrier comprised of keratinized, dead epithelial cells ringed by a lipid-rich matrix, prevents the majority of actives from efficiently penetrating the skin. Within the last few decades, a diverse range of nanoparticles with various components and unique putative permeation mechanisms have been created to facilitate the penetration of weakly diffusing compounds into the SC [57].

Chitosan Nanoparticles

Chitosan is one of the natural polymers that are most frequently employed in the creation of nanomedicines because it has very desirable properties for drug delivery and has proven to be very successful when produced in a nanoparticulate form. Several characteristics of this polysaccharide, including its cationic nature and its solubility in aqueous medium, have been documented as determining its effectiveness. The capacity to stick to mucosal surfaces, which allows for a longer stay at drug absorption sites and more drug permeation, is, nevertheless,

what makes it so appealing. Chitosan has also shown that it can improve macromolecules' ability to pass past epithelial barriers by momentarily opening such barriers [58].

Ethyl Cellulose Nanoparticles

One of the cellulose's important derivatives is ethyl cellulose (EC). The most common natural polymer is known as cellulose. EC, a nontoxic and biodegradable polymer, has lately gained appeal due to its special ability to produce oleogels, spread active compounds, and form films in the pharmaceutical and food industries. Oleogels based on EC nanoparticles offer enormous promise as harmful hydrogenated oil replacements in food goods. In several food and drug applications, the EC emulgel can be utilized to replace fat and encapsulate active substances.EC generates micro- and nanoparticles with distinct features since it is a water-insoluble polymerandnon-digestible [59].

Fullerenes

Fullerene and its analogs, particularly water-soluble fullerene analogs, have been dubbed cutting-edge, potent antioxidants that are supposed to minimize intracellular ROS and avoid oxidative cell injury while exhibiting reduced cytotoxicity [60].

Gold Nanoparticles

Gold nanoparticles (AuNPs) offer non-toxic carriers for applications involving the transport of drugs and genes. In these systems, the gold core gives the assembly stability while the monolayer enables fine-tuning of surface characteristics like charge and hydrophobicity [61]. “Table 1” summarizes the various novel approaches and their applications.

Table 1: Various Novel Approaches and their Applications

Novel Carriers	**Herbs/Drugs**	**Therapeutic Activity**	**Outcomes**	**Applications**	**Ref.**
Microemulsion	Ascorbic acid (AA)	It has key defence against skin damage caused by Reactive oxygen species.	Increased stability, improved penetration, preservation of AA from degradation	Skin lightening agent	[37] [62]

	Hesperetin	It has protective effect on skin damage due to its anti-tyrosinase and anti-oxidant activity	Increased permeation and reduced skin irritation	Antioxidant, anti-inflammatory, UV protection ability	[63]
	Hydroquinone (HQ)	It acts as tyrosinase inhibitor	Improved stability and increased penetration	Anti tyrosinase activity	[64]
	Arbutin, Lactic acid, Niacinamide	Arbutin: Tyrosinase's function in melanogenesis is inhibited by arbutin. Lactic acid quickens removal of pigmented cells from epidermis. Niacinamide stops melanosomes from passing from keratinocytes to melanocytes.	Improved stability	Skin whitening agent	[65]
	Punica Granatum	It contains ellagic acid, which chelates copper at tyrosinase active site and is thought to have skin lightening qualities.	Reduced skin erythema and melanin, increased stability	Skin whitening, sun protecting, moisturizing, anti-wrinkle, anti-stain anti-acne, anti-stain and anti-freckles effects	[66]
Nanoemulsion	Kojic monooleate	It works as a tyrosinase inhibitor to cure excessive melanin synthesis in human skin	Improved stability, high conductivity, less toxic	Anti tyrosinase activity	[67] [68]

	Deoxyarbutin	It inhibits tyrosinase more potently than HQ while being less hazardous to melanocytes and other cells.	Improved penetration	Anti tyrosinase activity	[69]
	Azelaic acid with hyaluronic acid	Azelaic acid has anti- tyrosinase activity while hyaluronic acid acted as adjuvant in the formulation	Enhanced penetration, improved stability and greater spreadability, decreased tyrosinase activity	Anti-inflammatory, anti-bacterial, anti keratinizing, antioxidant and depigmentation properties	[70]
Solid Lipid Nanoparticles	JSH18	It acts as tyrosinase inhibitor which is involved in melanin production.	Higher drug content and entrapment efficiency	Skin whitening agent	[71]
	N-Acetyl-D-Glucosamine	It inhibits tyrosinase enzymes in melanocytes	More stable and more permeable	Anti-inflammatory and depigmenting agent	[72]
	Trans-reserveratrol	It reduces tyrosinase activity	Enhanced permeability, tyrosinase inhibitory action	Anti-aging, anti-hyperpigmentation agent	[73]
	Curcumin	It exhibits antioxidant property	Increased solubility and permeability	Antioxidant and anti-inflammatory agent	[74]
	Green tea leaves	It contains polyphenols with potent antioxidant activity and also have ability to inhibit anti-	Enhanced penetration, greater entrapment efficacy, improved stability	Antioxidant and anti-tyrosinase activity	[75]

		tyrosinase activity.			
Nanostructured lipid carriers	N-Acetyl-D-Glucosamine	It inhibits production of melanin and changes expression of multiple pigment-related genes.	Reduction in melanin distribution pattern, increased drug release, enhanced permeation	Anti-tyrosinase agent	[76]
	Trans-reserveratrol	It has capacity to suppress tyrosinase enzyme.	Increased tyrosinase inhibitory activity and boosted encapsulation efficacy	Skin-lightening agent	[77]
	Tranexamic acid	It is plasmin inhibitor	Safe and effective	Anti-tyrosinase activity	[78]
	Anthocyanin	It neutralizes excessive amount of free radicals which in turn reduce inflammation in body.	Enhanced DPPH scavenging activity, increased stabilization and inhibition of melanogenesis	Photoprotecti-ve agent	[79]
	4-N-Butylresorcinol	It works by inhibition of tyrosinase and the tyrosinase-related protein-1	Effective, increased permeation and enhanced stability	Anti-tyrosinase activity	[80]
	Asparagus racemous root extract	It has tyrosinase inhibitory activity	Higher entrapment efficacy and tyrosinase inhibitory activity	Antioxidant, anti-inflammatory and skin whitening activity	[81]
	Phenylethyl resorcinol	It possesses potent tyrosinase inhibitory activity	Increased stability	Anti tyrosinase activity	[82]

	Niacinamide	It blocks the transfer of melanosomes from surrounding keratinocytes to melanocytes, which lowers skin melanogenesis.	Enhanced permeability and stability	Skin whitening property	[83]
Liposome, Transfersome, Invasome	Phenylethyl resorcinol	It interferes with the conversion of tyrosine to 1-3,4-dihydroxyphenylalanine (L-DOPA), which in turn inhibits the activity of tyrosinase.	Higher tyrosinase inhibitory activity, decreased melanin concentration, and greater permeability were seen in transfersomes and invasomes.	Anti tyrosinase activity	[84]
Niosome	Alpha arbutin	It protects the skin from reactive oxygen species	Increased permeability, improved entrapment efficacy	Antioxidant properties	[85]
Transfersome and Ethosome	Linoleic acid	It is able to decrease melanin synthesis and tyrosinase activity	Increased permeation in both carriers	Anti tyrosinase activity	[86]
Ethosomes	Phenylethyl resorcinol	It inhibits tyrosinase activity	Higher entrapment, stability, tyrosinase inhibitory activity and reduced melanin content	Skin lightening activity	[87]
Penetration enhancer vesicles	3-Hydroxy Coumarin	It has potent inhibitory effect on recombinant human tyrosinase	Increased penetration	Anti tyrosinase activity	[57]

Chitosan nanoparticle	Glabridin	Glabridin retards melanogenesis in skin though the inhibition of tyrosinase activity	Increased stability	Antioxidant and skin lightening property	[88]
	Arbutin	Inhibits tyrosinase enzyme activity in skin	Higher stability and percentage release	Skin whitening agent	[89]
Ethyl cellulose nanoparticle	L-Ascorbic acid	It prevents oxidative damage to skin	Increased stability and permeability, non-toxic	Antioxidant	[90]
Fullerenes	Polyvinyl pyrrolidone	It protects skin cells against oxidative stress	Reduced UVA promoted melanogenesis and greater melanogenic potential	Antioxidant	[91]
Gold nanoparticle	Panax Ginseng	It has antioxidant and tyrosinase inhibitory action	Reduced tyrosinase expression, tyrosinase activity, melanin content and cellular melanin concentration	Antioxidant and anti-tyrosinase property	[92]

Clinical Trials Done on Melasma

The creation of new, secure, and effective molecules for the treatment of human disease is the ultimate goal of drug research. The component of this study involving human patients involves clinical trials. Though the risks and restrictions are substantially higher in scientific inquiry, preclinical research, and, they have the same fundamental ideas. The four phases of a clinical study are conducted. In phase I trials, new drugs are first given to healthy volunteers to gauge their safety and determine the best dosage for later studies. To assess the initial efficacy of a disease-fighting agent, phase II studies are conducted. Phase III investigations, which are sizable randomized studies, are usually utilized to demonstrate meaningful treatment action in a specific clinical situation. After a drug has received marketing approval, phase IV studies

also referred to as pharmacoepidemiologic studies are conducted. Some clinical trials are complete, as shown in "Table 2", while others are still in the beginning stages [93].

Table 2: Clinical Trials of Drug Delivery for Melasma

Study Status and Status	**Study Title**	**Phase**	**Enrolled Participants**	**Treatment**	**Ref.**
June 30, 2021 Completed	Green banana peel extract for melasma treatment	Phase 1	72	Study Squad A pharmaceutical formulation comprising green banana peel extract will be used in addition to the SPF 30 sunscreen.	[94]
February 1, 2021 Completed	Effectiveness and safety of intradermal tranexamic acid injection as an adjunctive treatment for melasma in skin type IV – V	Not applicable	34	The treatment consisted of an intradermal injection of 1 ml of a 10 mg/ml tranexamic acid solution.	[95]
February 1, 2022 Completed	Comparison of 30% metformin and 2% nicotinamide lotion with Kligman formula in the treatment of melasma	Phase 2	88	Comparison of the Kligman method for the treatment of melasma with 30% Metformin and 2% Nicotinamide lotion.	[96]
July 2, 2018 Completed	Efficacy and Safety of PiQo4 Device for Treatment of Melasma	Not applicable	20	PiQo4 Laser System for treatment of Melasma.	[97]
March 16, 2016 Completed	Oral tranexamic acid and topical hydroquinone in the treatment of melasma	Phase 3	50	Tranexamic acid 250mg PO twice for 12 weeks, 4% Hydroquinone lotion for 12 weeks, and SPF 30 qam sunscreen for 24 weeks.	[98]

July 1, 2021 Completed	Tissue-resident memory T cells expression in melasma	_	20	_	[99]
November 1, 2022 Completed	Comparison of intralesional tranexamic Acid and platelet-rich plasma in the treatment of melasma	Phase 1	60	30 patients in Group A received intradermal tranexamic acid injections (4 mg/ml), while 30 patients in Group B received intradermal platelet-rich plasma injections (1 ml).	[100]
November 30, 2021 Completed	Comparison of a new masterful preparation to Kligman's trio in the treatment of melasma	Phase 2	40	Once daily application in addition to the same sunscreen	[101]
May 1, 2017 Completed	Efficacy of platelet-rich plasma in the treatment of melasma	Phase 2	20	PRP was applied at a quantity of 1 ml to the papillary dermis of the face, and the procedure was repeated after 15 and 30 days.	[102]
September 6, 2021 Completed	A clinical study to evaluate the effect of facial serum Q69 in moderating the appearance of mild to moderate melasma	Not applicable	96	Cosmetic facial serum, for 12 weeks, applies twice daily to lesional parts of the face. According to the dermatologist's instructions, 2% hydroquinone cream should be used twice daily for no more than 8 weeks on lesional areas of the face.	[103]
May 15, 2016 Completed	Topical Composition Therapy (2013-MCN-333) for the Treatment of Melasma	Phase 2	19	For 20 weeks, 0.5 grams should be topically administered to the skin's problem regions per day.	[104]
June 1, 2021 Complete	Comparison of a chemical peeling agent with transamine for the treatment of melasma	Phase 1	54	The 27 patients in Group A received 70% glycolic acid treatments every two weeks for 12 weeks, while the 27 patients in Group B received weekly injections of 0.05 mL of tranexamic acid solution in	[105]

				normal saline (4 mg/mL) into the melasma lesion at a distance of 1 cm using a sterile insulin syringe.	
October 28, 2022 Recruiting	Combination topical cysteamine and fractional 1927nm low-powered diode laser for treatment of facial melasma	Not applicable	20	In addition to daily use of the topical cysteamine cream for the duration of the trial (12 weeks), there are a total of three laser treatments.	[106]
April 1, 2019 Complete	Oral Superoxide Dismutase (GLISODin) to Decrease Melasma Severity.	Not applicable	40	500 mg/day between 12 weeks	[107]
March 22, 2023 Recruiting	A study to assess the effect of two facial sunscreens in improving wrinkles, fine lines, and melasma in adult participants	Not applicable	40	Face sunscreen should be liberally applied twice daily.	[108]

Conclusion

Melasma, predominantly a dermatological facial illness, manifests as having extreme psychosocial significance. Melasma has been treated using several chemical and instrumental methods.Researchers are turning to nanotechnology, which they consider a very promising approach, to boost the physicochemical stability and penetration of various hypopigmenting agents into deeper skin layers to cure melasma of both epidermal and dermal origin.Due to their greater skin permeation, oral routes may occasionally be used as a supplemental therapy option, but nanotechnology-based approaches for topical delivery of hypopigmenting medications will be the first line of treatment.

Conflict of Interest

We have no competing interests to declare.

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