



## HERBAL COSMECEUTICALS FOR HYPERPIGMENTATION: A BRIEF REVIEW

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### ABSTRACT

Hyperpigmentation is a common dermatological condition characterized by the darkening of skin due to excessive melanin production, often triggered by factors such as ultraviolet radiation, hormonal imbalance, inflammation, aging, and acne. Conventional depigmenting agents like hydroquinone, retinoids, and corticosteroids may produce adverse effects including skin irritation, erythema, and ochronosis with prolonged use. Consequently, there is growing interest in herbal cosmeceuticals as safer and more sustainable alternatives for managing hyperpigmentation. Herbal cosmeceuticals combine cosmetic and therapeutic benefits by utilizing bioactive phytochemicals derived from medicinal plants. Numerous herbal ingredients such as aloe vera, liquorice, turmeric, green tea, neem, mulberry, saffron, and sandalwood exhibit significant ant melanogenic, antioxidant, anti-inflammatory, and photoprotective properties.

Active constituents including glabridin, curcumin, aloin, flavonoids, and polyphenols inhibit tyrosinase activity and reduce melanin synthesis, thereby improving skin tone and reducing pigmentation disorders such as melasma and post-inflammatory hyperpigmentation. This review highlights the role of herbal cosmeceuticals in the prevention and treatment of hyperpigmentation, emphasizing their mechanisms of action, efficacy, and safety profiles. It also discusses recent advancements in herbal formulations, including nanoemulsions, gels, creams, and encapsulated delivery systems that enhance bioavailability and skin penetration.

**KEYWORDS:** Melanin, Nanoemulsion, Maceration, Phytochemicals, Nanocarriers.

## INTRODUCTION

Skin is the largest organ in the body and comes under integumentary system. The main function of skin is to protect from external environment. Epidermis is outermost layer of the skin. It is responsible for skin colour as melanocytes are present in stratum Basale which produces melanin. Topical products get absorbed in stratum corneum present in this layer. Dermis is the middle layer of the skin which provides structural support and elasticity to the skin. The hypodermis (subcutaneous layer) is the deepest layer of the skin. It is primarily responsible for insulation and energy storage. Disorders of skin include acne, psoriasis, hyperpigmentation, melasma, urticaria, dermatitis, vitiligo, fungal and bacterial infections.

Hyperpigmentation is a common, harmless condition characterized by excess production of melanin by skin cells which causes darker patches or spots compared to surrounding skin mainly caused due to sun damage, acne, inflammation, or injuries. Whereas, melasma is a chronic, and acquired disorder that comes under hyperpigmentation. It appears as irregular, symmetrical brown-to-grey patches, occurring on areas like the cheeks, upper lip, chin, and forehead commonly due to sun exposure.

In India, hyperpigmentation is the most common skin disorder, affecting over 80% of Indian women. Globally, it affects between 1-50% of population which varies to region and skin type. It often has a deep psychological impact because they predominantly affect the face, which is central to a person's identity and social interaction. Even though the condition is not physically painful or life-threatening but can lead to considerable emotional distress. Factors that affect hyperpigmentation are insulin resistance (Acanthosis Nigricans), Pregnancy (fluctuations in hormones), Chemotherapy, Sun exposure, hormonal contraception, post-

inflammatory hyperpigmentation, blue light from mobiles & laptops and Deficiencies in folic acid, tryptophan, Vitamin B12 & A.

Topical treatments are the first line medication for superficial pigmentation. Dermatologists mostly prefer topical to oral because they at once target the visible area of pigmentation. These are considered safe and localised action is seen unlike pills or capsules which show systemic absorption. The mechanism of topical treatment involves inhibition of enzyme tyrosinase by tyrosinase inhibitors. This enzyme acts as a "trigger" that blocks the conversion of the amino acid tyrosine into DOPA (Dihydroxyphenylalanine) and ultimately melanin. Melanin suppressors damage melanocytes leading to decreased melanin synthesis. Antioxidants inhibit free radicle and formation of reactive oxygen species by preventing oxidation thereby decreases melanin production. Anti-inflammatory agents decrease the stimulation of melanocytes caused by inflammation, which is especially useful in post-inflammatory hyperpigmentation.

Herbal treatments are more preferred over synthetic because they have a high tolerability and suitable for chronic management. While synthetic agents such as hydroquinone are powerful but prolonged usage shows high side effects such as permanent blue black skin discolouration but herbal extracts like liquorice, ginseng, arbutin, etc. are subtle inhibitors and they provide comparable anti pigmentation effects with minimal risk. Herbal extracts have its benefits but also has poor bioavailability, leading to advanced formulation development. One highly innovative point is that curcumin is unstable and poorly soluble, therefore nano formulations are being developed to improve skin penetration and therapeutic efficacy. Combination herbal therapy is becoming an emerging strategy. Synergistic effects are shown when curcumin and resveratrol combined with other phytoconstituents.<sup>[1]</sup> Hydroxypropyl- $\beta$ -cyclodextrin forms an inclusion complex which enhances the solubility, stability, and bioavailability of poorly soluble bioactives and it is considered as a multifunctional pharmaceutical excipient.<sup>[3]</sup> Combination of topical arbutin with radiofrequency technology may enhance therapeutic effect in melasma compared to topical treatment by itself. It has shown significant improvement in skin permeability and penetration of Anti-pigmentation agents.<sup>[4][24]</sup> *Undaria pinnatifida* sporophyll is a natural marine derived polysaccharide that acts as anti-melanogenic reduces the skin melanin production and skin lightening agent. Marine derived algae are considered as safer when compared to synthetic agents such as Kojic acid and hydroquinone. These synthetic agents cause skin irritation and photosensitivity.<sup>[8]</sup> Exosomes

are microvesicles (30–150 nm in diameter) surrounded by a lipid bilayer, acting as messengers for intercellular communication. Exosomes can reduce oxidative stress involved in pigmentation and skin aging, they can suppress tyrosinase activity and melanogenic pathways, helping reduce hyperpigmentation. Plant-derived exosomes are safer alternative such as Rose stem cell derived exosomes which provide strong antioxidant and melanogenesis inhibition. It has shown significant reduction in superficial pigmentation by 12.95%, deep pigmentation by 15.9%, skin redness or inflammation by 7.34%.<sup>[10]</sup>  $\alpha$ -Arbutin was entrapped into chitosan nanoparticles by the ionic gelation method, which produces high entrapment efficacy and positive zeta potential. Thereby, skin surface attachment and deeper skin penetration was enhanced.<sup>[17]</sup>

### LITERATURE REVIEW

S. No	TITLE	AUTHOR	YEAR	CONCLUSION	RESEARCH GAPS
1.	Design and Factorial Optimization of Curcumin and Resveratrol Co-Loaded Lipid Nanocarriers for Topical Delivery. <sup>[1]</sup>	Daniela Pastorim Vaiss, et al.	2026	Study demonstrates that Curcumin-Resveratrol lipid Nanoparticles are effective for topical route. Formulation prolongs skin retention and local action also provides controlled and sustained release. Overall, the research demonstrates that combining lipid-based nanotechnology with experimental design provides a reproducible framework for developing efficient topical treatments for oxidative and inflammatory skin disorders.	1. Lack of clinical trials, more Human trials are needed. 2. No comparison with already existed and marketed formulations.
2.	Effect of New Skin Lightening Cosmetic Containing Cordyceps Extract in the	Sihao Shen, etal.	2025	Cordyceps essence and hydroquinone both has shown equal effectiveness.	1. Limited sample size. 2. Tested only on Female patients.

	Treatment of Melasma: A Clinical Trial. <sup>[2]</sup>			Biggest advantage of the Cordyceps essence was its safety profile. Cordyceps essence didn't just lighten skin; the metabolomic data showed it helped repair the skin barrier (by increasing histidine), boosted antioxidant activity, and regulated the metabolic pathways that lead to melanin production.	3. No Follow up Research conducted
3.	Cosmeceutical and Wound-Healing Activities of Green Hydroxypropyl- $\beta$ -Cyclodextrin-Glycerol-Based Saturejamontana Extracts. <sup>[3]</sup>	LejsaJakupovi'c , et al.	2025	The extracts have shown excellent Antiradical, Anti tyrosinase activity. DPPH radical scavenging, anti-lipoxygenase, and ovalbumin-induced coagulation assays were performed and low IC <sub>50</sub> values were observed. They are biocompatible and have high capacity to absorb UV-A and UV-B radiation. Additional studies on cytokine regulation and in vivo validation were suggested to understand their mechanism of action and potential. Thus, It is excellent ingredient for further development in dermatological and cosmeceutical industry.	1. Only In vitro studies, No In vivo wound healing or hyperpigmentation studies. 2. Only performed extract level evaluation no formulation or formulated product testing

4.	Effectiveness and Safety of Combined Use of Home- Based Radiofrequency Device and Arbutin Cream in Melasma and Facial Rejuvenation. <sup>[4]</sup>	Lei Zhang, et al.	2025	Study Concludes that combination therapy of non-invasive, homebased RF and Arbutin cream was effective in treating Hyperpigmentation and Melasma. It has improved skin appearance and Rejuvenation. it stimulated collagen production in the dermis and had a tightening effect on subcutaneous fat. Thus, it was a safe and tolerated treatment method.	1. Small sample size. 2. No long-term trails were performed. 3. No further research was performed.
5.	Utility Assessment of Isolated Starch and Extract from Thai Yam ( <i>Dioscorea hispida</i> dennst.) for Cosmetic via In Vitro and In Vivo Studies. <sup>[5]</sup>	Suthinee Sangkanu, et al.	2025	The combination of G. Glabra and D. Hispida was found effective in the treatment of Hyperpigmentation and melasma as G. Glabra acts as a tyrosinase inhibitor and D. Hispida is a natural alternative to talc. The formulation was non-irritating and has shown stable skin-lightening and anti-aging effects, indicating that Thai yam as a promising, affordable, natural cosmetic ingredient.	1. No Clinical Trails performed on Humans. 2. Stability Testing is performed only under Freeze thaw cycles.
6.	Margarita (Pearl) Extract Alleviates Melasma by Targeting CAMP- Responsive Element Binding Protein 1. <sup>[6]</sup>	Liling Shen, et al.	2025	Study Concludes showing that a regulatory Protein, CREB 1 is targeted by PE and Suppresses TYR and DCT Gene expression, reducing	1. Further exploration is required to know the molecular interactions. 2.Study included only Female Patients.

				<p>melanin Synthesis. By turning down CREB1, the extract effectively slows down the MITF/TYR/DCT axis—the biological "assembly line" that creates skin pigment. Beyond just lightening skin, the study highlighted that the trace elements in pearls (like zinc, magnesium, and calcium) provide protective and nourishing benefits to the skin barrier.</p>	<p>3. Specific compounds required for depigmentation is not clearly known.</p>
7.	<p>Piceatannol—Can It Be Used to Treat Hyperpigmentation of the Skin?.[7]</p>	Ravi Kumar Rajan	2025	<p>The Plant derived compounds - piceatannol had been proven to reduce melanin production through various mechanisms and had been shown as a potent component to treat hyperpigmentation PCT directly inhibits the enzyme tyrosinase which results in reduced skin pigmentation. It mainly acts through several pathways such as Wnt, PI3K, MAPK, CREB Pathway which mainly acts to reduce melanogenesis This also mainly suppresses the production of TRP-1, TRP-2 and Tyrosinase which are important for</p>	<p>1. The mechanisms of each pathway was not completely studied. 2. Clinical studies on human's were not performed. 3. Safety and efficacy was not properly evaluated.</p>



				melanin synthesis.	
8.	Anti-Melanogenic Effects of a Polysaccharide Isolated from <i>Undaria pinnatifida</i> Sporophyll Extracts. <sup>[8]</sup>	Jae-Hoon Kim, et al.	2024	Study concludes that the natural anti-melanogenic agent UPF3 fraction of <i>Undaria pinnatifida</i> have high Galactose and Fucoidan and has ability to inhibit Melanin and tyrosinase activity. Thus, it is highly effective in in treating Hyperpigmentation Disorders. Only Invitro studies are performed in B16F10 Melanoma cells. Further the human skin experiments and 3D cell cultures need to be carried out to confirm the whitening effects	1. Only Invitro studies are performed in B16F10 Melanoma cells. 2. Further the human skin experiments and 3D cell cultures need to be carried out to confirm the whitening effects.
9.	Valorization of Hom Thong Banana Peel ( <i>Musa</i> sp., AAA Group) as an Anti-Melanogenic Agent Through Inhibition of Pigmentary Genes and Molecular Docking Study. <sup>[9]</sup>	PichchapaLinsaenkart, et al.	2024	Study concluded that Hom Thong Banana peel has 95% ethanolic extracts which inhibits the tyrosinase enzyme and expression of gene that is responsible to produce melanin. Also has Rosmarinic acid that binds to tyrosinase and increase effects of skin whitening thus, used in treatment of Hyperpigmentation.	1. Only In vitro studies are performed. 2. Further studies are required to know the exact mechanism of action. 3. Human trails are needed.
10.	A New Therapeutic Approach With Rose Stem-Cell-Derived Exosomes and Non-Thermal	Elina Theodorakopoulou, MD, PhD; et al.	2024	Study Concludes that the treatment has shown Brightening effect through 6 weeks of	1. Currently there is a limited data explaining about the Plant derived Exosomes for the



	Microneedling for the Treatment of Facial Pigmentation. <sup>[10]</sup>			follow up period. It also shows that RSCE plays an important role in normalizing defective vasculature along with conditions like melasma by interrupting inflammatory pathways (IL-6). The combination of non-thermal micro needling and topical RSCE is an effective and safe method for reducing facial pigmentation	treatment of Hyperpigmentation. 2. Large scale Randomised clinical studies are yet to be performed to confirm the preliminary studies
11.	Hydroxypropyl- $\beta$ -Cyclodextrin-Based Helichrysum italicum Extracts: Antioxidant and Cosmeceutical Activity and Biocompatibility. <sup>[11]</sup>	Lejsa Jakupović, et al		The OPT-1 and OPT-2 extracts of Helichrysum italicum were found to be rich in phenolic compounds which are responsible for strong antioxidant activity. But on further evaluation OPT-1 had shown better tyrosinase inhibition activity when compared to OPT-2.	1. The accurate role of each component is unclear. 2. The differences between effects of synergistics and individual remain uncertain. 3. No proper clinical data on cosmetic usage
12.	Aloe vera gel for prevention of chemotherapy-induced hyperpigmentation: Four case reports. <sup>[12]</sup>	Chia-Chi Chiu, et al.	2023	Skin is benefitted by Aloe vera gel and its efficacy can be measured by using randomized controlled trials.	1. More research is required to find out its effectiveness in treating chemotherapy induced hyperpigmentation. 2. Randomised controlled trials were not performed to evaluate its efficacy.
13.	The Potential of Mangifera indica L. Peel Extract to Be	Abigail García-Villegas, et al.	2023	Hydrolysed tanning present in mango peel was recognised	1. Clear stability testing was preliminary and

	Revalued in Cosmetic Applications. <sup>[13]</sup>			as the major component responsible for effective antioxidant activity and suppression of enzymes such as tyrosinase, elastase, collagenase, HYAlase, and XO were monitored	additional in vivo examination are required to verify its effectiveness. 2. Further research is required to evaluate its skin penetration and bioavailability.
14.	The Potential of Grapevine Leaf Extract in Treating Hyperpigmentation. <sup>[14]</sup>	Shani Shecori, et al.	2023	Polyphenol content is high in white grapevine leaves when compared to the red ones which is responsible for tyrosinase inhibition.	1. Additional in depth is needed to detect and recognise the particular components. 2. Clinical trials were not performed in humans. 3. Improvement is required in drug delivery systems.
15.	Analysis of Three Species of Cassipourea Traditionally Used for Hypermelanosis in Selected Provinces in South Africa. <sup>[15]</sup>	NomakhosiMpofana, et al.	2023	Cassipourea belonging to the family of Rhizophoraceae family were used a uv protection and skin whitening agent by the women in eastern cape. The analytical study showed that these extracts consist of tyrosine inhibitors which may perform individually and in combination. No enough research to demonstrate its activity for hypermelanosis and the main active component is unknown. Mechanism of action is not properly studied. The main active	1. No enough research to demonstrate its activity for hypermelanosis. 2. The main active constituent responsible for anti-hyperpigmentation pathway is not known.

				constituent responsible for anti-hyperpigmentation pathway is not known	
16.	Evaluation of anti-oxidant and antimelanogenic effects of the essential oil and extracts of <i>Rosa × damascena</i> in B16F10 murine melanoma cell line. <sup>[16]</sup>	Elham Hadipour, et al.	2023	The antimelanogenic and anti-tyrosinase effects of <i>R. × damascena</i> on the B16F10 murine melanoma cell line were beneficial for developing new treatments for hyperpigmentation as antimelanogenic and anti-tyrosinase effects were evaluated.	1. The specific mechanism and active component involved for the antimelanogenic effect are not fully determined. 2. Lack of research in active phytoconstituents in pigmentation pathway Stability and efficacy are not fully explored
17.	Functionalized chitosan nanoparticles for cutaneous delivery of a skin whitening agent: an approach to clinically augment the therapeutic efficacy for melasma treatment. <sup>[17]</sup>	Shymaa Hatem, et al.	2022	Chitosan nanoparticles are filled with $\alpha$ -arbutin, hyaluronic acid, and collagen showed effective drug encapsulation. Efficacy of entrapment decreased with increase in chitosan concentration. The nanoparticles were considered stable, spherical, and showed sustained drug release for 24 hours. Enhancement of clinical efficacy in melasma and were compared to conventional formulations.	1. No longterm clinical study to evaluate its safety, efficacy. 3. Incomplete evidence on interaction of nano particles within different skin types.
18.	Tyrosinase Inhibitors Derived from Chemical Constituents of <i>Dianella ensifolia</i> . <sup>[18]</sup>	Yu-Chang Chen, et al.	2022	From <i>Dianella ensifolia</i> , a few known and new flavans were isolated and the presence of resorcinol or	1. Mechanism of tyrosine inhibition is unclear. 2. Interaction of components at active site is vague. Insufficient clinical

				catechol on ring B was responsible for tyrosine inhibition activity.	trials to justify laboratory findings.
19.	Beneficial esthetic lightening effects of Cuscuta extract on skin darkness in healthy individuals: A clinical trial study. <sup>[19]</sup>	Masoumeh Roohaninasab, et al.	2022	Cuscuta extract is viewed as a potent skin-whitening agent. Melanin synthesis in skin is blocked and hyperpigmented lesions are diminished when treated with Cuscuta extract.	1. Study is restricted to healthy individuals, so its potency in patients with hyperpigmentation remains vague. 2. There may be risk of skin irritation or sensitivity in the long run
20.	Cyperus rotundus essential oil is essential in treating auxillary pigmentation. It is safe and cost effective. <sup>[20]</sup>	G.F.Mohammed	2022	Cyperus rotundus essential oil is essential in treating auxillary pigmentation. It is safe and cost effective.	1. Cyperus rotundus essential oil is essential in treating auxillary pigmentation. 2. It is safe and cost effective
21.	Screening and Structure–Activity Relationship for Selective and Potent Anti-Melanogenesis Agents Derived from Species of Mulberry (Genus Morus). <sup>[21]</sup>	Anna Gryn-Rynko, et al.	2022	The presence of Resorcinol moieties present at positions on rings A and B is identified as a key factor improving inhibitory activity, which further enhance the anti-melanogenic activity.	1. lack of advancement in clinical in vitro trails. 2. Stability of these components are not well explained Restricted comprehension of skin bioavailability
22.	Clinical Studies of the Safety and Efficacy of Macroalgae Extracts in Cosmeceuticals. <sup>[22]</sup>	Michael J Murphy, Aileen A Dow	2021	This study concludes that further clinical research is required to determine the long-term safety, efficacy, optimal concentration and formulation of microalgae extracts in cosmetics. Microalgae extracts show antimelanogenic, skin moisturizing properties.	1. Lack of human clinical trials. No long term trails were performed. 2. Efficacy data is limited. 3. Variability in macroalgae species and extracts. Lack of mechanistic understanding.

23.	Unravelling Anti-Melanogenic Potency of Edible Mushrooms <i>Laetiporus sulphureus</i> and <i>Agaricus silvaticus</i> In Vivo Using the Zebrafish Model. <sup>[23]</sup>	Aleksandar Pavic 1, et al.	2021	Researchers tested extracts from 5 edible mushrooms for skin-whitening effects. Extracts of <i>A. silvaticus</i> and <i>L. sulphureus</i> reduced melanin production without harming cells. Could be used in cosmetics or skincare products.	1. Research is carried out using the whole extract, the active ingredient is unknown. 2. Mechanism is unclear. 3. Formulation and stability research is incomplete.
24.	Development, Characterization and Pharmacological Evaluation of Antiblemish Cream Containing Herbal Oils. <sup>[24]</sup>	Sathiya Krishnaraj, et al.	2020	Anti-blemish cream was developed by using herbal oils. It has significant anti-blemish activity. To know and evaluate the higher positive therapeutic value, further studies are needed on human subjects.	1. Lack of Clinical Trials on humans. 2. Mechanism is Not Fully studied. 3. Missing of Comparison studies. Limited Toxicity and safety and formulation studies. 4. Insufficient Stability & Shelf-life studies
25.	Korean Red Ginseng extract ameliorates melanogenesis in humans and induces antiphotaging effects in ultraviolet B-irradiated hairless Mice. <sup>[25]</sup>	Evelyn Saba 1, et al.	2019	Korean red ginseng as a potent, multifunctional bioactive agent that used for skin whitening. Unlike single target ingredients, KRG operates through a multi - pathway approach that simultaneously addresses pigmentation, structural aging, and barrier function.	1. The Receptor level mystery. Matrix metallo proteinases (MMPs) subtype specificity. 2. Transdermal permeability is yet to be studied
26.	Anti-melanogenic effects of extracellular vesicles derived from plant leaves and stems in mouse melanoma cells and human healthy skin. <sup>[26]</sup>	Ruri Lee a, et al.	2019	In this research, the <i>Dendropanax morbifera</i> plant were used for skin whitening approach by cutting edge using Extracellular vesicles.	1. Longterm immunogenicity, Stability and vesicle integrity in formulations, Scalability and isolation efficiency, are not studied.

				This mainly focuses on nano-sized biological delivery pods that plant naturally produce.	2. Interaction with the microbiome not known.
27.	A cream of herbal mixture to improve melisma. <sup>[27]</sup>	Qiongyu Zhang 1, et al.	2019	Herbal mixture cream showed the most significant improvement, with the MASI (melasma area and severity index) reduction score of 3.18. Arbutin cream showed moderate improvement, with a reduction of 1.81. Placebo cream shows no significant change. Herbal mixture cream is both safe and more effective than arbutin for treating melasma.	1. Lack of long term follow up. 2. Specificity of the herbal mixture. 3. Limited demographic and environmental diversity. 4. Comparison with Gold standard treatment.
28.	Melanogenesis Inhibitors from the Rhizoma of Ligusticum Sinense in B16-F10 Melanoma Cells In Vitro and Zebrafish In Vivo. <sup>[28]</sup>	Min-Chi Cheng, et al.	2018	In this research concluded that, the rhizoma of Ligusticum sinense, a traditional Chinese medicinal plant used for skin whitening for centuries. Researchers used a bioassay guided fractionation process to isolate 24 compounds, identifying two entirely new chemical entities and determining which specific components inhibit melanin production	1. Mechanism of action in molecular level was not explained. 2. Model limitations. 3. Long term safety and stability was not described
29.	Ginsenosides Rg5 and Rk1, the skin-whitening agents in black Ginseng. <sup>[29]</sup>	Yan Jin a 1, et al.	2018	Inhibitory effect of black ginseng extract on melanin production on B16F10 and	1. Delivery system Transport inhibition

				zebrafish model. Skin whitening activity of black ginseng extract on human skin. Ginsenoside Rg5 and Rk1, bioactive compounds in black ginseng extract for skin whitening activity. Activation MEK-ERK signalling pathway, a underlying mechanism for skin whitening activity of black ginseng extract.	
30.	Improvement of skin condition in striae distensae: development, characterization and clinical efficacy of a cosmetic product containing Punica granatum seed oil and Croton lechleri resin extract. <sup>[30]</sup>	Cătălina Bogdan, et al.	2017	To prepare an emollient oil-in-water cream, P. granatum seed oil and C. lechleri resin extract were used. A cosmetic formulation with optimal characteristics can be obtained by setting the finest ranges for technological and formulation factors by using experimental designs. In clinical efficacy studies, it was revealed that there was an increase in elasticity values, hydration and dermis thickness. This medicament helps to improve the skin changes associated with striae.	1. Invitro studies were only performed, no in vivo studies or on humans. 2. Mechanism and active constituents which are involved are not fully explored. 3. Testing for long term effect wasn't done.
31.	Inhibitory effect of Gastrodia elata Blume extract on alpha-	Eugene Shim 1, et al.	2017	Based on the dose-dependent inhibition of melanin	1. lack of in vivo and human based studies, missing of



	melanocyte stimulating hormone-induced melanogenesis in murine B16F10 melanoma. <sup>[31]</sup>			synthesis, suppression of tyrosinase activity and molecular levels of MITF, tyrosinase, Trp1 and Trp2 in murine B16F10 melanoma were observed in <i>Gastrodia elata</i> Blume. Therefore, <i>Gastrodia elata</i> Blume is used as an effective and natural skin-whitening agent in the cosmetic industry.	toxicology, formulation and safety studies. 2. lack of comparative studies with depigmented animals, molecular pathway wasn't completely explored.
32.	Phytochemicals from fern species: potential for medicine applications. <sup>[32]</sup>	Hui Cao 1, et al.	2017	The article concludes that the fern species have significant phytochemicals and medical potential regarding the pharmacological activities such as antioxidants, antimicrobial, anti-inflammatory and anticancer effects. the phytochemicals (phenolics and flavonoids) present in the fern can influence their melanin production and thereby managing the hyperpigmentation. By inhibition by tyrosinase activity and providing antioxidant activity the excess melanin synthesis can be reduced.	1. Lack of research on other fern species, lack of in vivo studies and clinical trials on humans. 2. Needs proper study and understanding on the molecular mechanism, safety, side effects and toxicity is unknown.
33.	Topical application of Jaungo in atopic dermatitis patients: study protocol for a	Younghee Yun 1, et al.	2017	The article concludes that the reduction of hyperpigmentation	1. Lack of validation in humans scientifically.

	randomized, controlled trial. <sup>[33]</sup>			associated with atopic dermatitis is done indirectly with the help of Jaungo. It's done by controlling the inflammation and promoting skin healing.	2. lack of clinical evidence, such as the randomised clinical trials. 3. Scientific confirmations are needed
34.	Hesperidin, A Popular Antioxidant Inhibits Melanogenesis via Erk1/2 Mediated MITF Degradation. <sup>[34]</sup>	Heun Joo Lee 1, et al.	2015	Hesperidin is a powerful and safe natural skin-lightening agent that works by triggering the body's own interval "recycling" system to stop melanin production And it has a double action for skin it lighten skin dark spots also protecting skin from oxidative stress.	1. Clinical evidence isn't specified. 2. Low permeability towards skin. 3. Stability and self-life studies require more research.
35.	Polypodium leucotomos as an Adjunct Treatment of Pigmentary Disorders. <sup>[35]</sup>	Mark Nestor a, et al.	2014	In addition to preventing many harmful effects associated with sunlight exposure, such as photoaging and polymorphous light eruption, orally administered P. leucotomos also may provide significant therapeutic benefits for vitiligo and melasma and may have the potential to help the potential post inflammatory hyperpigmentation. To date, P. leucotomos has demonstrated an exceptional safety profile.	1. Clinical trials weren't performed on humans. 2. Optimal dosing wasn't established. 3. There was a gap in understanding combination studies.

## METHOD OF PREPARATION

### Thermal Emulsification method

Also known as the Phase Inversion Temperature (PIT) method, it is a "low-energy" emulsification technique that based on the chemical properties of non-ionic surfactants. Many non-ionic surfactants change their solubility based on temperature. At low temperatures, they are water-soluble; at high temperatures, they become oil soluble.

The oil phase (lipids, surfactants, CUR, and RESV, Resorcinol) was stirred at 80°C for 30 min, Aqueous phase (water, vitamin C and surfactant) was heated to 80°C for 2 min. Aqueous phase is added to the oil phase and stirred for 3min. Once you hit the PIT, the mixture looks weird—it's neither an oil-in-water nor a water-in-oil emulsion. The tension between the phases is almost zero.

Shock is the crucial part where the emulsion is suddenly cooled down or heat it further, depending on the procedure. This sudden temperature change leads the surfactant to convert back to its original state so fast that it traps the oil into tiny, uniform droplets. It doesn't require heavy machinery, also cost-effective for heat-stable ingredients.<sup>[1][13][19]</sup>

### High pressure Homogenisation method

It is the mechanical pulverization method where the oil and water are whipped together into a "coarse" emulsion. A high-pressure pump forces this mix through a microscopic valve at speeds exceeding 1,000 km/h (Blast). As the liquid hits the valve, three forces—Shear (tearing), Cavitation (imploding bubbles), and Impact (crashing) breaks the oil droplets into the nanometre ( $10^{-9}$ ) meters range. This process is repeated for 2–5 "passes" until the droplets are small and uniform enough to remain stable or be safe for an IV injection. No heat is required, only the mechanical force.<sup>[1][17] [22] [23] [24] [27]</sup>

### Ultra-sound assisted extraction technique (UAE)

It is a modern extraction method. This technique uses ultrasonic waves to create microscopic bubbles in the solvent. When these bubbles collapse, they generate strong mechanical forces that break down plant cell walls, allowing the active constituents to be released more efficiently into the solvent. This method is mainly used to avoid the harsh chemicals and make the final product safe for skincare, this "green" method was used.

Dried plant powder, water and glycerol were mixed. Then, sugar molecule HP- $\beta$ -CD was added which boosts the solubility and stability of active compounds like flavonoids (Complexation). To extract the nutrients out of the plant material an ultrasonic bath was used by producing sound waves. Extracts were simply filtered and stored.<sup>[3][14]</sup>

### **One-pot Multicomponent synthesis method**

This method involves in situ generation of the intermediate. Reactants (Hydrazine hydrate) was first reacted (with ethyl acetoacetate) to form an intermediate, which was directly utilized in the subsequent reaction without isolation. Further addition of aldehyde and other active components in the same reaction vessel led to the formation of the desired compounds after continuous stirring and purification.<sup>[7]</sup>

### **Maceration Extraction**

Maceration extraction method is a simple and commonly used technique to obtain bioactive compounds from plant materials. In this method, dried and powdered plant material is soaked in a suitable solvent such as water, 50% ethanol, 95% ethanol, or hydroalcoholic mixtures for a specific period of time. During this process, solvent penetrates into the plant cells and dissolves the active constituents present in the cell. After sufficient soaking, the mixtures were filtered, and the filtrates were concentrated to obtain crude extracts for further analysis. Useful for extracting Heat sensitive Phytochemicals.<sup>[9][15][18]</sup>

### **Inclusion complexation method**

Inclusion complexation is a useful technique that helps increase stability and solubility of plant compounds and drugs that are not easily dissolved in water. The plant extract was prepared using the inclusion complexation method using hydroxypropyl- $\beta$ -cyclodextrin through solvent evaporation. The carrier molecule has a special cavity-like structure that holds active compound inside it, to form a stable complex. The prepared extract was mixed with hydroxypropyl- $\beta$ -cyclodextrin in suitable proportions and stirred continuously to aid in complex formation. The solvent was then removed by evaporation or drying, resulting in a stable solid inclusion complex that was collected and stored for further studies.<sup>[11]</sup>

### **Steam Distillation**

Steam distillation is a commonly used method for extracting essential oils and other volatile compounds from plants. In this process, the aromatic and active components present in it are released when the steam is passed through the plant material. The volatile compounds are

evaporated due to the heat from the steam along with water vapour without causing major damage to heat-sensitive constituents.

Using Condensation process, the vapour produced during the process is then cooled and converted back into liquid form. After condensation, the separated essential oil, from the water layer is collected carefully. The extracted oil is then filtered and stored under suitable conditions for further use.<sup>[16][33]</sup>

Hydro distillation, where Plant material is directly boiled in water, remains submerged in water. It has higher chance of thermal degradation due to direct boiling. It is a traditional extraction method.<sup>[20]</sup>

### **Lyophilised aqueous extract technique**

This technique involves freeze-drying the liquid extract to preserve its bioactive compounds (polyphenols and enzymes), which makes it stable. Extract the herbs using a water-based solvent (e.g., water-ethanol) and filter it. Concentrate the extract under reduced pressure. The concentrated extract was later lyophilised to get a powdered extract. The powder extract was stored under appropriate conditions until it was used for human experiments and animal studies.<sup>[25][31][32]</sup>

### **Cold method**

Also known as the cold process, it is a technique that eliminates the need for heating, and it allows rapid formulation at room temperature, thereby reducing energy consumption. The process is significantly faster and relies on specialised cold-process emulsifying agents. It preserves heat-sensitive actives.

Mix the oil-soluble ingredients (oils, emollients, cold emulsifiers) and water-soluble ingredients (water, humectants, preservatives) separately. Slightly warm (< 40 °C) to dissolve the solid emulsifier. Combine the phases by mixing the aqueous phase with the oil phase after adjusting the pH. To ensure the stability and uniformity of a homogenous mixture, blend the phases for 1-5 minutes. After emulsification, incorporate essential oils, fragrances or extracts.<sup>[21]</sup>

### **Nano-sized extracellular vesicle preparation**

Nano-sized extracellular vehicles (EVs) range from 40 to 150nm in diameter. The extracts were prepared using this method to maintain purity and scalability and to get a balanced

yield. Fresh leaves and stems were collected, washed, and crushed to obtain the extract juice. The extracted juice was filtered through a mesh, and particles were separated by differential centrifugation at 10,000 x g for 10 minutes. The solution was passed through a 0.22µm filter to keep only nano-sized EVs by removing the large debris. Then, the EVs are concentrated by centrifuging at 5,000 x g for 10 minutes at 4°C. Finally, EVs were stored at low temperatures (e.g., -80°C).<sup>[26]</sup>

### **Polyherbal formulation**

To enhance the therapeutic effect, two or more herbal ingredients are combined in a herbal preparation. This formulation shows a synergistic effect, improves efficacy and reduces toxicity. Various herbs were extracted using appropriate solvents and filtered. The extract was concentrated and stored for formulation. The herbal extracts were added to the cream base at low temperatures (45 °C) and mixed evenly at a speed of 138g for 5 minutes. The mixture was stirred while cooling to get a smooth, stable consistency of the cream. The herbal cream was homogenised.<sup>[27][30]</sup>

### **Isolated phytochemical preparation**

To obtain monomeric structures for structural identification and bioactivity screening, the plant bioactive compounds were extracted, separated and purified. Extract phytochemicals from dried, powdered herb using a suitable solvent (e.g., ethanol, methanol, or water) by maceration, Soxhlet extraction or ultrasound-assisted extraction. Filter the extract and, under reduced pressure, concentrate it using a rotary evaporator. The crude extract was separated using solvents to group the compounds based on polarity. From the active fractions, compounds were purified using column chromatography, HPLC and repeated column separations to isolate pure compounds. The isolated compounds were identified using spectroscopic techniques such as NMR (Nuclear Magnetic Resonance), MS (Mass Spectrometry) and UV/IR analysis. The isolated compounds were dissolved and diluted to a specific concentration by using suitable solvents (like DMSO).<sup>[28][29]</sup>

The dried herbal powder was extracted and filtered, the liquid was acidified, and the herbal crystals were precipitated. By recrystallisation, pure crystals were formed.<sup>[34]</sup>

### **Standardised aqueous extract**

It is a multi-step process to isolate plant bioactive compounds. Dried herbs are boiled in distilled water to isolate the phenolic compounds (e.g., ferulic acid, caffeic acid). The liquid

is centrifuged, filtered through 0.22  $\mu\text{m}$  membranes for purity, and freeze-dried or spray-dried into a stable powder. Standardisation is performed to ensure a consistent antioxidant concentration for effective photoprotection.<sup>[35]</sup>

## EVALUATION

### Particle Size

In semi-solid formulation like creams and gels, particle size is a critical parameter that directly prescribes how the product performs and stay stable throughout its shelf life.

**Creams:** smaller oil or water droplets sizes significantly reduce the rate of aggregation, creaming and phase separation. According to Stoke's Law, reducing droplet size decreases the velocity of droplet movement, protecting the oil and water phases from separating over time.

**Gels:** Uniform particle size of the gelling agent ensures a consistent cross-linked polymer network, avoiding syneresis (the spontaneous squeezing out of liquid from the gel matrix).

### Zeta Potential

In creams (O/W or W/O), zeta potential measures the electrical charge at the droplet interface, showing the degree of electrostatic repulsion between emulsified droplets.

**Role in stability:** High repulsion prevents droplets from merging. A potential near zero causes droplets to contact, leading to reversible flocculation or irreversible fusion and phase separation (creaming/breaking).

**Formulation Effects:** The formulation is affected or directed by the choice of emulsifier (ionic vs. non-ionic), pH of the aqueous phase and the presence of ionic polymers or active ingredients.

Zeta Potential value	Stability Classification
$\pm 30$ mV	Good or Highly Stable
$\pm 20$ to $\pm 30$ mV	Moderate or Threshold
$< \pm 20$ mV	Poor or Highly Unstable

### Tyrosinase inhibitory activity

Firstly, the phosphate buffer solution (pH 6.8) is prepared. Then, test sample and freshly prepared tyrosinase solution is added into it. Now, the mixture is incubated for 10-15min at room temperature. Later, add L-DOPA or L-Tyrosine substrate to initiate the reaction.



Incubate for another 20–30 minutes. Lastly, measure the absorbance at 475nm using a spectrophotometer.

$$\% \text{ Tyrosinase Inhibition} = \frac{\{A_{\text{control}}\} - A_{\text{sample}}}{\{A_{\text{control}}\}} \times 100$$

### Measurement of UVA and UVB Absorbing capacities

A known quantity of the sample is diluted using a suitable solvent such as ethanol or methanol. The prepared solution is scanned in the wavelength range of 200–320 nm for UVB region and 320–400 nm for UVA region using a UV–Visible spectrophotometer. The absorbance values obtained in these regions indicate the ability of the sample to absorb harmful UV radiation.

### Melanin content Analysis

The cells are cultured in culture plates and treated with the test sample at different concentrations for 24–72 hours. After incubation, the cells are washed with phosphate-buffered saline (PBS) and collected by centrifugation. The obtained cell pellets are lysed using NaOH solution, usually containing dimethyl sulfoxide (DMSO), and heated at 80–100 °C to dissolve the melanin completely. The absorbance of the resulting solution is measured using a UV–Visible spectrophotometer at approximately 405 nm or 475 nm. Melanin content is calculated by above formula:

$$\% \text{ Melanin Content} = \frac{A_{\text{sample}}}{\{A_{\text{control}}\}} \times 100$$

### Total phenolic content and antioxidant activity

It is an important analytical method used to measure the total phenolic compounds in herbal formulations and natural products. These phenolic compounds have high anti-inflammatory and antioxidant properties so these are mainly helps to reduce the increased melanin production.

Folin–Ciocalteu colorimetric method. It Involves the reaction between phenolic compounds with Folin–Ciocalteu reagent (phosphomolybdic and phosphotungstic acids) under basic conditions forms a blue-coloured complex. Higher intensity of the blue colour indicates the increase in the concentration of phenolic compounds and it enhances antioxidant activity and reduces the melanin production.

Total phenolic content is measured by using the following equation:

$$TPC = \frac{C \times V}{M}$$

Where, TPC= Total phenolic content

C= Concentration obtained (mg/ml)

V = Volume of extract (ml)

M = Mass of sample used (g)

Antioxidant activity is evaluated by using following equation:

$$\% \text{ Radical Scavenging Activity} = \frac{\{A_o - A_s\}}{\{A_o\}} \times 100$$

Ao =Absorbance of Control

As = Absorbance of Sample

### Cytotoxicity

Cytotoxicity is the ability of depigmenting agents to cause damage or death of cells with respect to melasma. Cytotoxicity analysis measures the cell viability, cell membrane integrity, cell proliferation and metabolic activity. By MTT assay, cells were cultured in microtiter plates and were tested at different concentrations. The cells were incubated. MTT reagent was added to the culture for the formation of purple formazan crystals. The crystals were then dissolved in DMSO solvent. Spectrophotometer is used to measure the absorbance. Cell viability percentage was calculated.

### Ultrasound scanning

By using Dub cutis skin scanner system the ultrasonographic evaluation is performed, it a high resolution ultra sound scanner using a 22-MHz transducer that allows the structure visualization up to 6-7 mm in depth, including epidermis, dermis and partially subcutaneous fatty tissue.

### Physical stability analysis

The creams are evaluated after storage under standard and stabilized test conditions at 25°C±2°C for 60 days and its dispersed system is observed using a 5- point scale where the homogenous emulsion occurs or where it breaks such as creaming or coalescence occurred.

## PH

PH is logarithmic scale that measures the acidity or basicity of a solution by measuring the concentration of hydrogen ions. Extremely strong acids or bases have the ph value below 0 or above 14. Each unit changes in ph represents a tenfold change in hydrogen ion concentration.

## Polydispersity Index (PDI)

The polydispersity index (PDI) was analysed to conclude the uniform distribution of nanoparticles. PDI values range from 0.32 to 0.60. Lower PDI values indicates superior homogeneity and uniform distribution of particles. Higher PDI value indicates difference in particle size distribution. Uniform distribution of nanoparticles helps the drug to penetrate easily in to the skin and keep the dosage form stable for effective use. Tripolyphosphate helps in nanoparticle formation so increasing the concentration of TPP reduces the PDI values and it enhances internal crosslinking, which helps in forming nanoparticles of improved uniform size.

$$PDI = \left( \frac{\{Standard\ Deviation\ of\ Particle\ Size\}}{\{Mean\ Particle\ Size\}} \right)^2$$

## Spreadability

Spreadability means how easily a formulations like creams or gels spreads over the surface of the skin when the force is applied. placing 1 gram of the formulation like cream or gel between the two glass plates then weight of 25 grams applied on the upper glass plate. Because of applied weight the gel starts spreading outward then the diameter of this spread circle was measured this helps us to determine the spreadability of the formulation.

$$S = \frac{M \times L}{T}$$

where, S=spreadability

M=Applied weight (g)

L=Length moved by the glass slide(cm)

T=Time required to separate the slides (sec)

## L-DOPA staining (tyrosinase zymography)

This method is used to visually evaluate tyrosinase enzyme Activity. Tyrosinase enzyme converts L-DOPA into melanin-like pigments (dopachrome). Darker bands or staining is seen in cases of high tyrosinase Activity and they become lighter when Activity of tyrosinase is

inhibited. This study confirms that whether a compound shows suppression in tyrosinase Activity and it also provides visual evidence of anti-melanogenic Activity.

### **Cell viability**

The test was performed to determine the toxicity of extract to cells and Reduction of melanin through anti-melanogenic Activity. This study mainly evaluates by using MTT assay in which the converts enzymes convert yellow MTT reagent into purple formazan crystals. Intense purple colour indicates healthy cells whereas less purple colour indicates more toxicity.

### **Phytochemical Evaluation**

Phytochemical Evaluation is the analysis of bioactive chemical compounds present in plants or herbal extracts, mainly performed to detect major plant Constituents, establish medicinal and biological Activity, Examine quality, purity, and safety of extracts. Main compounds that are evaluated are Phenolics, Flavonoids, Alkaloids, Terpenoids, Tannins, Saponins, Glycosides.

### **Western blot analysis**

Western blotting analysis is a method which is used to detect specific intracellular protein levels in biological samples. This method is based on the separation of proteins by size, transferring proteins from the gel onto PVDF membrane or nitrocellulose, preventing nonspecific binding to the membranes and incubating with primary antibodies (anti-TRP-1, anti-TRP-2, anti-MITF). The primary antibodies are detected using horseradish peroxidase (HRP)- conjugated secondary antibodies. The membrane was rinsed with TBST and incubated with the secondary antibody. The signals produced were detected using fluorescence, calorimetric or chemiluminescence methods.

### **Zebrafish embryo pigmentation assay**

Melanin production and skin whitening were evaluated using the human skin and zebrafish embryos. Zebrafish embryos are genetically very similar to humans. Melanin activity and tyrosinase levels were inhibited, and skin whitening effect was observed. The two ginsenosides, Rg5 and Rk1, are principal bioactive compounds essential for the development of skin whitening agents. Wild-type zebrafish embryos were collected and evaluated based on phenotype. These embryos were then incubated to evaluate the anti-melanogenesis effect. The quantification of zebrafish pigmentation was performed and analysed at 72 hpf, and the results were compared with the control group.

## CONCLUSION

Herbal cosmeceuticals have emerged as a promising and safer alternative for the management of hyperpigmentation and related skin disorders. The increasing demand for natural and plant-based skincare products has encouraged extensive research into herbal ingredients possessing antimelanogenic, antioxidant, anti-inflammatory, and photoprotective activities. Medicinal plants such as liquorice, aloe vera, turmeric, green tea, mulberry, saffron, and neem contain bioactive compounds that effectively inhibit tyrosinase activity, regulate melanin synthesis, and improve overall skin complexion. Compared with conventional synthetic depigmenting agents, herbal formulations generally exhibit fewer adverse effects, better patient compliance, and improved long-term safety profiles. Recent advancements in cosmeceutical technology, including nano formulations, liposomal systems, gels, creams, and transdermal delivery approaches, have further enhanced the efficacy and stability of herbal products by improving skin penetration and bioavailability. These innovations have expanded the therapeutic potential of herbal cosmeceuticals in treating conditions such as melasma, post-inflammatory hyperpigmentation, freckles, and age spots. However, despite encouraging preclinical and clinical findings, several challenges remain, including lack of standardization, variability in phytochemical composition, insufficient large-scale clinical trials, and regulatory limitations regarding quality control and safety evaluation.

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