Melasma Adjuvant Therapy Using Edelweiss Callus Extract in Combination with Polydeoxyribonucleotide, Glutathione, and Cannula Injection Technique: A Case Report

Asoka Murascandrika[a*], Alamanda Murasmita[b], Ammarilis Murastami[b]

[a] *MM Clinic Skin Center and Aesthetic, Central Java, Indonesia*
[b] *Department of Dermatology dan Venereology Faculty of Medicine, Sebelas Maret University Hospital, Central Java, Indonesia*
**Corresponding Authors: amcandrika@gmail.com*

Abstract

Melasma is a long-lasting hyperpigmentation syndrome that is manifested by symmetrical brown macules on the face. Treatment choices are intended to enhance effectiveness while minimizing side effects. Recently, regenerative botanical compounds as anti-tyrosinase and antioxidant plants have been increasingly emphasized, especially the Edelweiss callus extract. Not just for its antioxidative and anti-inflammatory properties, this botanical also affects melanogenesis in a manner that provides excellent safety versus conventional depigmenting agents. The Edelweiss callus extract contains leontopodic acids, flavonoids and phenolic constituents which not only are advantageous in protecting against oxidative damage but also reduces tyrosinase activity and helps to restore epidermal barrier function. This report details a 38-year-old female patient with melasma that had been present in her skin for 5 years despite previous topical depigmenting agents and chemical peels; she underwent cannula-guided injection therapy. By methods recognized by the Directorate General of Intellectual Property in Indonesia, PDRN, glutathione and Edelweiss callus extract were included in the formulation. There was significant clinical improvement after six treatment sessions, resulting in the gradual lightening of hyperpigmented areas with improvements in texture of the skin after three treatment sessions (no significant adverse reactions reported). All of these findings indicate that phytoconstituent-based complementary therapies are effective in treating melasma when applied safely with Edelweiss callus extract.

***Keywords*:** *Melasma, Polydeoxyribonucleotides, Glutathione, Edelweiss callus extract, Herbal medicine*

Abstrak

Terapi Ajuvan Melasma Menggunakan Ekstrak Kalus Edelweiss yang Dikombinasikan dengan Polideoksiribonukleotida, Glutathione, dan Teknik Injeksi Kanula: Laporan Kasus. Melasma adalah sindrom hiperpigmentasi kronis yang ditandai dengan munculnya bercak (makula) berwarna cokelat secara simetris pada wajah. Pilihan terapi bertujuan untuk meningkatkan efektivitas sekaligus meminimalkan efek samping. Belakangan ini, penggunaan senyawa botani regeneratif yang memiliki sifat anti-tirosinase dan antioksidan, khususnya ekstrak kalus *Edelweiss* semakin mendapat perhatian. Selain memiliki sifat antioksidan dan anti-inflamasi, bahan botani ini juga memengaruhi proses melanogenesis dengan profil keamanan yang jauh lebih baik dibandingkan agen depigmentasi konvensional. Ekstrak kalus *Edelweiss* mengandung asam leontopodik, flavonoid, dan komponen fenolik yang tidak hanya bermanfaat dalam melindungi kulit dari kerusakan akibat stres oksidatif, tetapi juga mampu menghambat aktivitas tirosinase serta membantu memulihkan fungsi sawar epidermis. Laporan ini membahas kasus seorang pasien wanita berusia 38 tahun dengan melasma yang telah dideritanya selama 5 tahun, meskipun sebelumnya telah menjalani terapi menggunakan agen depigmentasi topikal dan prosedur *chemical peel*, pasien tersebut kemudian menjalani terapi injeksi dengan kanula. Menggunakan metode yang telah diakui oleh Direktorat Jenderal Kekayaan Intelektual Indonesia, formulasi yang digunakan mencakup PDRN, glutathione, dan ekstrak kalus *Edelweiss*. Perbaikan klinis yang signifikan diamati setelah enam sesi perawatan, yang ditandai

dengan memudarnya area hiperpigmentasi secara bertahap serta perbaikan tekstur kulit setelah tiga sesi perawatan (tidak dilaporkan adanya efek samping yang berarti). Seluruh temuan ini menunjukkan bahwa terapi komplementer berbasis fitokonstituen—khususnya yang menggunakan ekstrak kalus *Edelweiss*—merupakan pilihan yang efektif dan aman untuk menangani melasma.

Kata Kunci: *Melasma, Polideoksiribonukleotida, Glutathione, Ekstrak Kalus Edelweiss, Obat Herbal*

Introduction

Melasma is a chronic acquired hyperpigmentation disorder characterized by symmetrical light-to-dark brown macules and patches that are mostly distributed on sun-exposed facial areas. It usually occurs in the centrofacial, malar, and mandibular regions and is more common in women (Fitzpatrick skin phototypes III-V) who live in tropical and subtropical areas with high UV exposure.[1] Melasma is relatively harmless, but is a major cosmetic and psychosocial issue for many people because facial pigmentation is known to affect self-esteem, emotional well-being, social interaction, and quality of life.[2] Melasma is a chronic and persistent disease that causes embarrassment, frustration, anxiety, and social isolation. Melasma has gradually been recognized as more than just a pigmentary disorder, but also a therapeutic challenge with enormous psychosocial burden and a poor quality of life.

Melasma varies between ethnicity, location, hormonal status, and environmental exposure. Melasma is more common in Asian, Middle Eastern, and Latin American regions, as people with darker skin phototypes and cumulative sun exposure are more common.[3] Women are most vulnerable in most cases, especially for females at reproductive age. Many endogenous and external factors impact the onset of the disease and its course, including ultraviolet radiation, visible light exposure, hormonal effects, pregnancy, oral contraceptive use, thyroid dysfunction, genetic risk factors, chronic inflammation, and skin aging.[4] Recent studies have also revealed that blue light exposure is associated with long-term melanocyte activation and oxidative damage in people with darker skin phototypes.[2] These findings support the notion that melasma is a multi-modality disorder in which environmental triggers are interlinked to the biological mechanisms.

Melasma is still difficult to treat clinically because it comes back often after it has appeared to be in a better state. And it is most common after discontinuing treatment or failing photoprotection.[4] Melasma, in general, is recurrent and we know that it is not just a pale epidermal pigmentation. Melasma is associated with hyperactivity of melanocytes and oxidative stress, vascular deterioration, chronic inflammation, basement membrane dysfunction, and photoaging.[2,4] Therefore, only treatment for epidermal melanin loss may only produce temporary and partial improvement. The focus has also been shifted towards multimodal therapeutics that can treat multiple pathogenic mechanisms which contribute to the persistence of melasma.

Melanogenesis plays a major role in melasma pathogenesis. Melanin is produced in melanocytes in physiologic conditions through the enzymatic conversion of tyrosine into melanin pigments. Tyrosinase is the main rate-limiting enzyme involved and determines the conversion of tyrosine to dihydroxyphenylalanine and dopaquinone to eumelanin and pheomelanin production.[5] Melanocytes are more active by the metabolic mechanism and thicker dendricity, and thus generate more melanin to be transferred to surrounding keratinocytes. Melanocyte size increases in melasma and tyrosinase expression is increased in the skin, and epidermal and dermal melanin deposition is increased.[2] So, dysregulated melanogenesis is one of the major therapeutic targets in melasma treatment.

The effect of UV radiation is the main trigger for melanogenesis. UV exposure induces oxidative stress and the generation of reactive oxygen species (ROS) such as hydroxyl radicals, hydrogen peroxide, and superoxide anions.[2] Oxidative stress promotes melanocytes to multiply and upregulates the melanogenic pathway by increasing tyrosinase and microphthalmia-associated transcription factors. ROS also contribute to lipid peroxidation and mitochondrial dysfunction, DNA injury, and inflammatory mediator release, which

lead to pigmentation problems.[2] Since melasma lesions are more susceptible to oxidative signatures and less protective antioxidant defense mechanisms due to the imbalance in redox, this implies that redox imbalance is a major factor in the progression of the disease. Visible light and blue light exposure may also play a role in pigmentation persistence through oxidative processes. As compared to ultraviolet radiation alone, visible light exposure can induce more prolonged hyperpigmentation in darker skin phototypes.[2] Melanocytes exposed to visible light have increased ROS production and melanogenic activity. Environmental pollutants and photoexposure may further exacerbate oxidative injury and prolong disease life.

Besides oxidative stress, vascular problems are more and more recognized as the cause of melasma. In melasma lesions, vascularization and vascular endothelial growth factor expression are also well documented from microbiological and histological studies.[4] Ultraviolet light stimulates keratinocytes and fibroblasts to release proangiogenic mediators to promote dermal vascular proliferation. The vascular permeability may increase inflammatory cell infiltration and melanocyte activation. Dermoscopic studies show telangiectasia and erythematous features in melasma lesions to support the vascular aspect of the disease. These findings suggest that vascular dysregulation may cause resistance to treatment and recurrence of chronic melasma.

Dermal and structural alterations also contribute to disease persistence. Basement membrane dysfunction, solar elastosis, fibroblast activation, and extracellular matrix degradation were observed in melasma skin.[4] The chronic ultraviolet exposure is associated with photoaging and dermal integrity loss that can lead to abnormal interactions among melanocytes, keratinocytes, fibroblasts, and inflammatory cells. Activated fibroblasts may release melanogenic cytokines and growth factors that perpetuate pigmentation abnormalities. Basement membrane dysfunction also enables melanin to enter the dermis, and thus pigmentation is not cured by conventional treatments. This explains why epidermal depigmentation alone may not be enough to address the complex pathology of melasma.

Chronic inflammation is another important factor in melasma development. A high mast cell infiltration and increased inflammatory mediators have been observed in the skin affected by the disease, and increased levels of melanocytes were observed.[2,4] UV radiation and oxidative stress activate inflammatory pathways that increase melanogenesis. Mast cells contribute to dermal remodeling and vascular growth through the release of histamine, tryptase, and cytokines. Proinflammatory mediators such as interleukin-1, interleukin-6, tumor necrosis factor-alpha, and endothelin-1 may directly enhance melanocyte activity and melanin production. Therefore, chronic low-grade inflammation can lead to resistance and recurrence of the treatment. In addition, the multifactorial pathogenesis of melasma is the main reason for the low effectiveness and high recurrence rates of monotherapy. The current melasma management approaches are for suppressing melanogenesis and decreasing pigmentation. Hydroquinone is still the gold-standard depigmenting agent, as it inhibits tyrosinase activity and melanin synthesis.[4] Triple combination creams containing hydroquinone, tretinoin, and corticosteroids are generally used for their synergy in epidermal turnover and inflammation control. Other topical agents are azelaic acid, kojic acid, niacinamide, cysteamine, retinoids, and botanical extracts.[5] Long-term hydroquinone and corticosteroids use may result in irritation, erythema, steroid-induced skin atrophy, exogenous ochronosis, and rebound hyperpigmentation. These adverse effects result in decreased patient compliance and less long-term use.

Chemical peeling, laser therapy, microneedling, and mesotherapy have also been used as adjunctive treatments.[4] Chemical peels with glycolic acid, salicylic acid, or trichloroacetic acid can speed up epidermal turnover and remove pigment from the skin. However, post-inflammatory hyperpigmentation still presents a severe problem in darker skin phototypes. Laser and light-based therapies like Q-switched Nd:YAG lasers and fractional lasers have been shown to be effective but also very variable in long-term results. In the short term, they may improve, but long-term recovery remains uncertain. If the skin is too hot and their skin continues to be damaged for too long, it may cause more pigmentation due to inflammation. Tranexamic acid has recently received more attention because it inhibits plasmin-mediated melanogenesis and vascular activation. Oral, topical, and intradermal applications have shown promising results in several studies, but their recurrence after discontinuation is still frequent and no uniform protocols exist yet.[4]

Although melanogenesis is still the main therapeutic target in melasma, there is increasing evidence that vascular imbalances, dermal photoaging, oxidative stress, and chronic inflammation also contribute to disease persistence and recurrence.[2,4] However, the relative contribution of each pathogenic pathway is still controversial. Some studies emphasize epidermal melanocyte hyperactivity as the dominant mechanism, whereas others suggest that dermal dysregulation and vascular dysfunction may be equally important in refractory melasma. The different views may contribute to the inconsistent therapeutic responses of present monotherapy-based medicine.

Oxidative stress is the most important therapeutic target of melasma management. Reactive oxygen species from ultraviolet and visible light exposure stimulate melanogenesis and inflammatory signaling pathways.[2] Therefore, antioxidant therapy can help to control oxidative damage and restore redox balance in the skin microenvironment. Vitamin C, niacinamide, cysteamine, glutathione, and botanical extracts have all been shown to have potential benefits for pigmentation disorders.[5,6] Unlike the long-term use of conventional bleaching agents, antioxidant therapies may be more tolerable and less prone to irritation or rebound hyperpigmentation.

Glutathione is a naturally occurring tripeptide composed of glutamate, cysteine, and glycine which is one of the most important intracellular antioxidants in the body. Glutathione serves as a neutralizer of free radicals, reduces oxidative stress, and controls inflammatory reactions in melanogenesis. Glutathione inhibits tyrosinase activity and shifts melanin production from eumelanin to pheomelanin for lighter pigmentation.[7] Previous studies have tested oral, topical, and injectable glutathione formulations for skin lightening. Watanabe et al. also showed that topical oxidized glutathione enhanced skin brightness and overall skin health in healthy women.[8] In addition to depigmentation, glutathione may also improve skin texture and reduce oxidative damage associated with photoaging. This makes glutathione a promising adjunctive agent for melasma.

The use of herbal and plant-based products for hyperpigmentation is also increasing recently. Medicinal plant extracts have antioxidant, anti-inflammatory, anti-tyrosinase, and photoprotective properties that can be useful in pigmentary disorders.[1,5,6] Herbal therapies are also being considered as complementary treatments for long-term use and have fewer serious side effects compared with other pharmaceuticals to treat depigmenting disorders. A systematic review by Tang et al. reported that oral herbal drugs used as adjunctive therapy for melasma showed good efficacy and safety in terms of antioxidant and anti-inflammatory activity.[1]

Among new botanical compounds, the callus extract of Leontopodium alpinum (Edelweiss) has recently attracted much attention in aesthetic dermatology due to its antioxidant and photoprotective properties.[3] Edelweiss is a perennial alpine plant that is well adapted to harsh conditions such as high ultraviolet exposure, cold temperatures, dehydration, and oxidative stress. In order to survive in that environment, it can create a large amount of protective phytochemicals with strong cytoprotective activity.

Edelweiss contains a variety of biologically active compounds relevant to pigmentation disorders, including leontopodic acids, flavonoids, chlorogenic acid, tannins, and phenolic compounds.[3,9] Leontopodic acid A and B are major active metabolites and have strong antioxidant and free radical scavenging properties.[3] They can neutralize reactive oxygen species, reduce oxidative cellular injury, and suppress inflammatory pathways involved in melanogenesis. Flavonoids and phenolic derivatives also exhibit anti-tyrosinase effects and may contribute to melanin reduction.

As shown in experimental studies, Edelweiss extract may protect keratinocytes and fibroblasts from ultraviolet-induced oxidative damage and maintain extracellular matrix integrity.[3] Edelweiss-derived compounds may also suppress matrix metalloproteinases involved in photoaging and collagen degradation. Transcriptome profiling studies showed that Edelweiss callus culture extract regulates genes involved in antioxidative defense, collagen synthesis, skin barrier repair, and cellular regeneration[4], suggesting that Edelweiss may not only have depigmenting effects but also help with dermal restorative and anti-aging properties. The anti-inflammatory properties of Edelweiss are of great importance for melasma pathogenesis since chronic inflammation causes melanocytes to be activated and persistent pigmentation.

In modern plant biotechnology, Edelweiss has been further developed as a dermatological candidate through callus culture.[4,9] Plant callus or stem cell cultures can produce highly stable bioactive compounds in controlled laboratory conditions. Callus-based extractions can offer better consistency, purity, and preservation of active phytochemicals in addition to helping in reducing the environmental impact of overharvesting of alpine plants. Recent studies of secondary metabolites of Leontopodium taxa have shown their antioxidant, anti-inflammatory, antimicrobial, regenerative, and photoprotective properties in dermatology as well.[9] However, evidence of the use of Edelweiss callus extract for melasma treatment is limited and underreported.

Another emerging component in regenerative dermatology is polydeoxyribonucleotide (PDRN). PDRN consists of low-molecular-weight DNA fragments derived primarily from salmon or trout sperm cells.[10] Initially utilized in wound healing and regenerative medicine, PDRN is now being used in aesthetic dermatology because of its regenerative and anti-inflammatory properties. The biologic effects of PDRN are mainly mediated through activation of adenosine A2A receptors, leading to increased fibroblast proliferation, collagen synthesis, angiogenesis, tissue repair, and extracellular matrix remodeling.[10] PDRN can also help in reducing inflammatory cytokine release and assist in wound healing.

In aesthetic medicine, PDRN is utilized for skin rejuvenation, scar remodeling, hydration improvement, and barrier restoration.[10] Because melasma has been associated with chronic dermal inflammation, photoaging, and basement membrane disruption, regenerative therapies targeting tissue repair may improve treatment outcomes and reduce recurrence risk. Restoring dermal homeostasis may also improve skin resilience against ultraviolet-induced oxidative damage and chronic inflammatory stimulation.

Injection-based delivery systems are now becoming very popular in aesthetic dermatology because they allow direct intradermal deposition of active compounds. Mesotherapy and intradermal injection techniques may improve local bioavailability while overcoming limitations associated with epidermal barrier penetration.[10] Direct dermal delivery may therefore enhance the therapeutic efficacy of antioxidant and regenerative compounds in pigmentation disorders. Among injection techniques, blunt-tip cannula is an easier method to use and one that has more than one use. Cannula can minimize tissue trauma, bruising, vascular injury and patient discomfort and give more evenly distributed injected material. Achieving minimization of procedural inflammation is particularly important in melasma, as trauma can cause post-inflammatory hyperpigmentation and pigment instability. Cannula-assisted delivery may be safer and more tolerable for repeated pigment-prone skin treatment. There is also recent evidence that combination therapy may have more synergistic biologic effects than single-agent treatment alone. Antioxidants may also decrease UV-induced reactive oxygen species and regenerate the extracellular matrix which can help to reduce chronic inflammation.[2,6,10] Botanical extracts rich in phenolic compounds and flavonoids may also suppress tyrosinase activity and protect keratinocytes and fibroblasts from oxidative damage.[3,6] In this case, Edelweiss callus extract is a particularly attractive candidate because of its antioxidant, anti-inflammatory, photoprotective and anti-aging activity.[3,4,9]

The combination of Edelweiss callus extract with glutathione and polydeoxyribonucleotide may be a viable, multi-modal treatment approach for melasma. Glutathione has depigmenting and antioxidant potential as it inhibits tyrosinase and modulates melanogenesis pathways.[7,8] PDRN is involved in tissue regeneration, anti-inflammatory activity, extracellular matrix remodeling and dermal restoration.[10] Presenting these agents in cannula-assisted intradermal injection may enhance local bioavailability and minimize tissue trauma and procedure-related inflammation. Such a combination of anti-oxidative, melanogenesis dysregulation, chronic inflammation and dermal repair can be beneficial in a more effective manner than traditional monotherapy-based therapy.

Targeting multiple pathogenic pathways simultaneously can also improve therapeutic outcomes in refractory melasma. Combination therapy can reduce the reliance on aggressive depigmenting agents associated with irritation and rebound hyperpigmentation. Antioxidant and regenerative strategies may also help to address the underlying photoaging and dermal dysfunction that led to disease recurrence.

There is growing interest in regenerative and antioxidant-based therapies but clinical evidence on the utilization of Edelweiss callus extract for melasma is limited.[3,4,9] Most existing studies are mainly focused on photoprotection, anti-aging activities, and oxidative stress reduction as opposed to pigmentary disorders. In addition, standardized protocols combining Edelweiss extract, glutathione, PDRN and cannula-assisted delivery techniques have not yet been established in the literature. This lack of evidence highlights the importance of further clinical investigation regarding the efficacy, safety and potential complementary role of this multimodal regenerative approach in treatment-resistant melasma.

This case report aims to describe the clinical outcomes of adjuvant melasma therapy using Edelweiss callus extract, glutathione, PDRN, and cannula-assisted intradermal injection technique. The report also seeks to shed light on antioxidant and regenerative multimodal therapy as a complementary therapy for treatment-resistant melasma.

Case Report

A 38-year-old female was seen in a dermatology outpatient clinic with five years of continuous brownish facial patches. The hyperpigmented lesions initially showed up on each of the malar regions, then progressed to the perinasal area and chin. Prior treatments — including topical depigmenting agents and numerous chemical peels — resulted in little improvement. She had reported irregular use of sunscreen, denied hormonal treatment or other systemic drugs, and had no known allergies. Her mother and sister also had a family history of similar pigmentation. On examination, the patient was unremarkable, alert, and cooperative, and vital signs were normal. Her Fitzpatrick skin type was IV–V. On dermatology, there were multiple hyperpigmented macules and patches ranging from light to dark brown appearing symmetrically in the centre of the facial area (Figure 1a). Pigmentation was greatest on the right cheek and most prominent on the malar areas. Other lesions were found on the chin, but mild involvement on the forehead. The clinical diagnosis of melasma with a baseline Melasma Area and Severity Index (MASI) score of 13.1 was made.

The patient was treated using a regimen of mild facial cleanser, overnight cream including depigmenting agents, and daily use of SPF 30 sunscreen. Injection therapy was commenced using a special cannula-assisted technique and a commercial injectable product (Glushine, Indonesia) containing three active agents (polydeoxyribonucleotide (PDRN), glutathione, and Edelweiss callus extract). The formulation was given without dilution or modification. This was a copyrighted practice published with a copyright registration through the Directorate General of Intellectual Property (DGIP), Indonesia (No. EC00202457372). For 6 sessions in total, 9 cc solution was given every two weeks. Informed consent writing was acquired after an explanation of the procedure and possible risks. Ethical approval was obtained through the clinic's ethics board with the given reference number 001/MM-EC/XI/2025. Significant improvement was observed with gradual lightening of hyperpigmented area and general texture after the third session (Figure 1b). A significant decrease in pigmentation severity and distribution indicated that the MASI score had been downgraded from 13.1 to 3.8 at the conclusion of six sessions. Over the entire course of treatment, no adverse events including erythema, edema, bruising, or post-inflammatory hyperpigmentation were reported.

Discussion

Melasma is an all-encompassing pigmentative disorder mediated by a wide range of hereditary, hormonal, and environmental factors, particularly ultraviolet (UV) radiation. Existing treatments (hydroquinone, chemical peeling, laser procedures) give only temporary gains, usually coupled with irritation and relapse. Based on this, botanicals and adjunctive treatment modalities that focus on antioxidant, anti-inflammatory, and anti-tyrosinase pathways to modulate melanogenesis have been increasingly recognized.[1,2] Callus extract of Edelweiss (Leontopodium alpinum) contains robust leontopodic acids, flavonoids and phenolic elements with powerful antioxidant and anti-inflammatory effects. These substances are also reactive

oxygen scavengers and down-regulate tyrosinase, the main enzyme responsible for melanin production. Excessive pigmentation is reduced by controlling tyrosinase expression.[3,4] Topical formulations prepared with Edelweiss extract have a notable ability to counteract oxidative stress and reduce the deposition of melanin in UV-exposed skin models suggesting that Edelweiss-based treatment serves as a naturally depigmenting agent.[6,9] It has been reported that we observed a difference in pigmentation and overall skin quality, using Edelweiss callus extract, PDRN and glutathione as co-supplements of the extracts. PDRN possesses tissue repair actions through adenosine A2A receptor-dependent pathways. By stimulating the proliferation of fibroblast and collagen reorganization, PDRN may promote neovascularization and anti-inflammatory action. Through such regenerative action, PDRN improves skin structure reconstruction mechanism and provides a more favorable environment for pigment regulation.

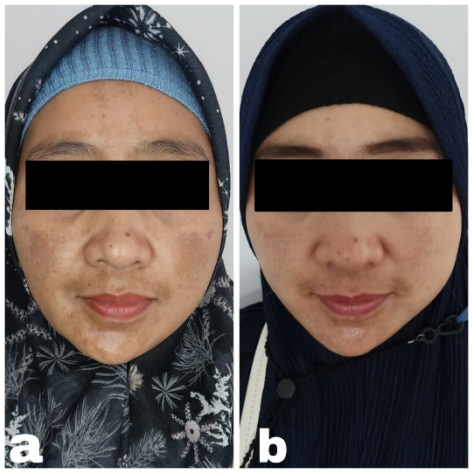

Figure 1. (a) Multiple hyperpigmented macules from light to dark brown, symmetrically distributed. **(b)** Follow-up after six treatment sessions showing significant lightening of hyperpigmented patches and improved overall skin texture.

Glutathione reduces tyrosinase activity and shifts melanin production toward pheomelanin and away from eumelanin, which gives brighter skin appearance. The excellent clinical effect observed in this patient corresponds to the synergistic actions of these three substances: Edelweiss extract exerts protective antioxidant activity and suppresses melanogenesis, whereas PDRN and glutathione promote cellular repair and pigment modulation. Together, these mechanisms offer two health advantages for those with anti-hyperpigmentation, skin-barrier support, and a good safety profile. Consistent with results of recent researches, the multimodal approach has favourable tolerability and efficacy for blending plant and regenerative extracts in patients with skin pigmentation disorders.[5]

Conclusions

The present article studied the medicinal effect of melasma and the combined intervention of Edelweiss (Leontopodium alpinum) callus extract, PDRN, and glutathione integrated as an intradermal therapy. The treatment reduced pigment changes and increased the radiance of the skin and no negative findings were described; implying synergistic action of phytochemicals and regenerative processes. These data indicate the possible involvement of herbal adjuvants in pigmentary diseases. For confirmation of these results, however, more clinical and mechanistic studies are needed to expand and further confirm their inclusion in evidence-based complementary dermatology level.

Conflict of Interest

AM declares no conflicts of interest. MND declares no conflicts of interest. AMM declares no conflicts of interest. No author has any personal or financial relationships that could influence the work presented in this manuscript.

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