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IDEAS AND INNOVATIONS

Cosmetic

Ethosome (ETHOSOMEPTT) Photothermal Therapy with Nd:YAG Laser (Pastelle Pro): A Novel Nanotechnology Approach for Treatment-resistant Melasma

Jee Soo Kook, MD*
Jovian Wan, MBChB†
Kyung Tae Bae, MD‡
Kyu-Ho Yi, MD, PhD§

Summary: Melasma poses considerable challenges in dermatologic management, particularly due to variable treatment responses and frequent recurrence following conventional interventions. We describe ethosome photothermal therapy (ETHOSOMEPTT, N-Finders Co., Ltd, Korea), an innovative 5-layer nanosystem that integrates transdermal delivery technology with targeted laser energy. The platform incorporates ethosomes, phospholipid vesicles containing ethanol, with plasmonic gold and platinum nanoparticles to provide dual therapeutic mechanisms: enhanced drug penetration and controlled hyperthermia. Upon activation by specific laser wavelengths, this system generates localized heat while facilitating the delivery of active ingredients to deeper tissue layers relative to conventional topical treatments. A clinical example demonstrates its utility: a 42-year-old woman with persistent malar melasma spanning 6 years, who had undergone treatment with hydroquinone, oral tranexamic acid, and neodymium-doped yttrium aluminum garnet laser with insufficient improvement, demonstrated a 68% reduction in Modified Melasma Area and Severity Index after 12 treatment sessions. Treatment was well tolerated, with transient erythema as the primary side effect. The mechanism underlying ethosome photothermal therapy encompasses ethanol-mediated enhancement of stratum corneum permeability, targeted delivery via plasmonic nanoparticles, and controlled thermal effects on tissue structure. This methodology represents a potential advancement in melasma management, particularly for cases demonstrating limited response to conventional therapies. *(Plast Reconstr Surg Glob Open 2025;13:e7318; doi: 10.1097/GOX.0000000000007318; Published online 9 December 2025.)*

INTRODUCTION

Managing melasma remains problematic for both clinicians and patients, with existing therapies frequently yielding inconsistent results and unacceptable side effects. As a chronic condition with relapsing tendencies affecting millions globally, particularly women of childbearing age, melasma creates significant psychosocial burdens that extend far beyond its clinical severity. Contemporary first-line treatments continue to rely on decades-old approaches, including topical hydroquinone, kojic acid, and retinoids, which collectively show 40%–60% improvement rates but entail risks of irritation, ochronosis, and rapid rebound pigmentation upon discontinuation. Interventional procedures, including chemical peels and laser therapies, frequently exacerbate the condition through postinflammatory hyperpigmentation, especially in darker skin types. Even more advanced photodynamic therapy, while theoretically promising, experiences limitations from impractical incubation periods and frequent paradoxical darkening that constrain real-world utility.

Three primary biological obstacles account for these therapeutic shortcomings. First, the skin's formidable barrier function prevents adequate delivery of active

*From the *It's Me Clinic, Ansan, Republic of Korea; †Medical Research Inc., Wonju, Republic of Korea; ‡It's Me Clinic, Sejong, Republic of Korea; and §Division in Anatomy and Developmental Biology, Department of Oral Biology, Human Identification Research Institute, BK21 FOUR Project, Yonsei University College of Dentistry, Seoul, Republic of Korea.*

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ingredients, with less than 5% of topical agents reaching the dermoepidermal junction where melanocytes reside.[1] Second, the lack of cellular specificity in energy-based treatments often leads to collateral damage, triggering further pigmentation. Third, emerging research confirms that melasma involves not just melanocyte hyperactivity but also underlying dermal changes, vascular proliferation, and solar elastosis, factors that many current therapies overlook.

This therapeutic stalemate necessitates innovative solutions that transcend conventional paradigms. Recent advances in nanodermatology suggest that lipid-based carrier systems, particularly those incorporating penetration enhancers such as ethanol, could revolutionize transdermal delivery.[2] Similarly, the advent of plasmonic nanoparticles, materials that convert light to heat with extraordinary efficiency, offers new possibilities for targeted melanocyte modulation.[3]

INNOVATIVE IDEAS

Ethosome photothermal therapy (EPT) uses a 5-layer nanostructure designed to overcome limitations in transdermal drug delivery and thermal targeting. The system features an ethosome outer layer containing high-concentration ethanol that modifies stratum corneum lipid organization to facilitate penetration. These vesicles differ from conventional liposomes in their ability to interact with skin lipids and create channels for enhanced delivery.[4] The core component consists of 50-100-nm gold nanoparticles (ETHOSOMEPTT, N-Finders Co., Ltd, Korea) and platinum cores designed to respond to 1064-nm wavelength laser energy.

We applied this approach in a 42-year-old Southeast Asian woman with Fitzpatrick skin type IV who presented with bilateral malar hyperpigmentation refractory to multiple treatments during a 6-year period. Her prior interventions included 2 years of topical combination therapy with 4% hydroquinone and 0.05% tretinoin, 8 sessions of Q-switched neodymium-doped yttrium aluminum garnet laser, nonablative fractional laser, intense pulsed light, and a 6-month course of oral tranexamic acid. Although partial improvements were observed, the pigmentation consistently recurred. All topical agents and laser procedures had been discontinued for at least 6 months before initiating EPT, ensuring a sufficient washout period and minimizing confounding effects.

The treatment protocol involved ultrasound-assisted application using 1 MHz waves to facilitate nanoparticle penetration to depths of 300–500 μm, as measured by confocal microscopy. Subsequent 1064-nm laser (Pastelle Pro, Wontech Inc., Seoul) irradiation activated the plasmonic response, generating controlled thermal effects at melanocyte locations. Temperature monitoring confirmed maintenance of 42–45°C for 3–5 minutes during each session.

Reflectance confocal microscopy in our case demonstrated melanocyte clustering predominantly at the depth of 300–500 μm, corresponding to the upper to mid dermis. This anatomical localization informed the selection of laser parameters in our EPT protocol, ensuring that energy deposition aligned with the targeted cellular layer. By delivering controlled thermal energy to this depth, the approach aimed to modulate melanocyte activity effectively while minimizing collateral damage to surrounding structures. These findings highlight the importance of depth-specific imaging in guiding energy-based therapies for pigmentary disorders.

Twelve treatment sessions across 4 months resulted in measurable clinical changes (Fig. 1). Standardized photography and Modified Melasma Area and Severity Index evaluation documented progressive pigmentation reduction, with scores decreasing from 24.6 to 7.9, representing a 68% improvement.

High-frequency ultrasound assessment revealed structural changes in the dermis, with increased echogenicity suggesting collagen reorganization. Patient tolerance was good, with reported pain scores averaging 1 out of 10 and downtime limited to mild erythema resolving within hours.

The treatment approach incorporates 3 mechanisms: ethanol-mediated enhancement of stratum corneum permeability, plasmonic nanoparticle activation for localized thermal effects, and controlled temperature parameters designed to influence melanogenesis while avoiding cellular damage. This combination addresses both drug delivery limitations and the need for targeted thermal intervention in pigmentary disorders.

Takeaways

Question: Can a nanotechnology platform combining ethosomes with plasmonic nanoparticles overcome treatment resistance in melasma patients whose conventional therapies have failed?

Findings: This case study demonstrated that ethosome photothermal therapy achieved a 68% improvement in melasma severity scores in a patient with multiple failed previous treatments including hydroquinone, oral tranexamic acid, and laser therapy over 6 years.

Meaning: Nanotechnology-based combination therapy may offer hope for patients with treatment-resistant melasma when standard approaches have been exhausted.

DISCUSSION

The clinical response observed in this treatment-resistant melasma case suggests that EPT may address both epidermal and dermal components of pigmentary disorders. Recent histological studies have identified dermal changes in melasma lesions, including fibroblast alterations and vascular modifications, which may contribute to treatment resistance when only superficial approaches are used.[5]

In comparison with photodynamic therapy, EPT offers certain procedural differences. Photodynamic therapy typically requires incubation periods of 60–180 minutes and has reported posttreatment hyperpigmentation rates of 15%–30%.[6] In contrast, the ethosome system achieved

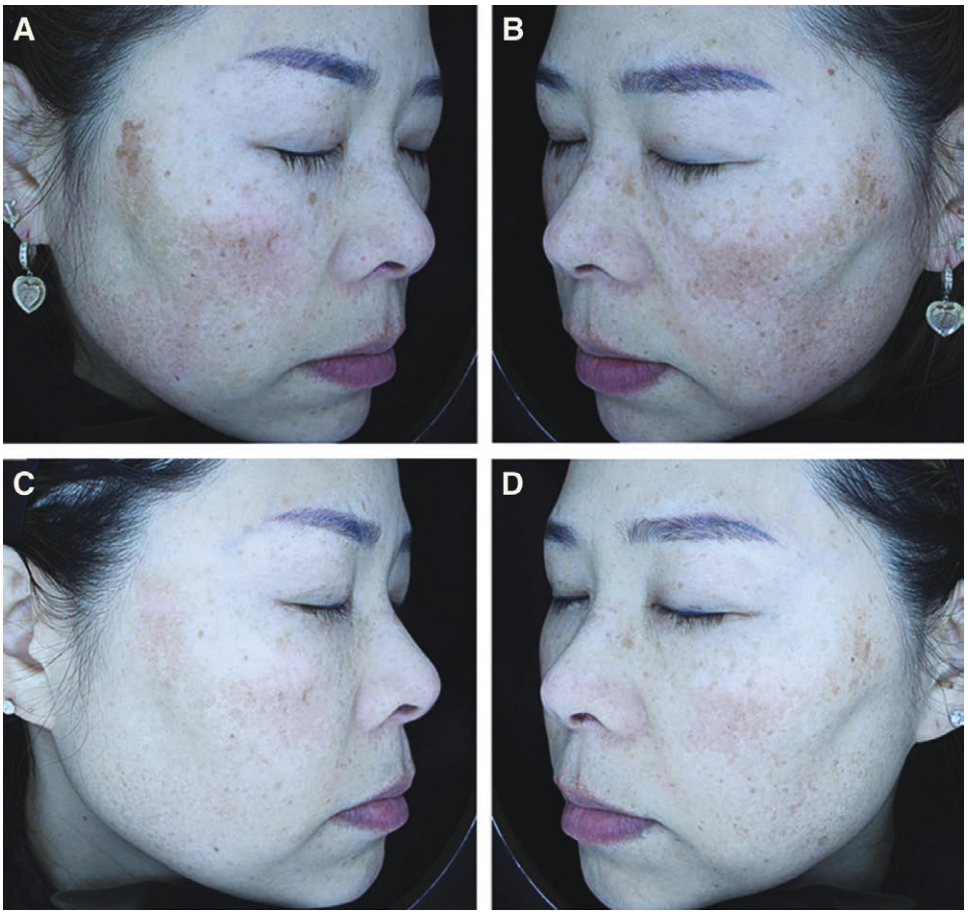

Fig. 1. Clinical photographs of a treatment-resistant melasma case showing bilateral malar hyperpigmentation before treatment (A and B) and after 12 sessions of EPT (C and D), demonstrating a 68% reduction in Modified Melasma Area and Severity Index score from 24.6 to 7.9.

penetration within 15 minutes in our case, with minimal postinflammatory changes observed. The ethanol component may contribute to this efficiency by enhancing permeability and providing antimicrobial effects.

The plasmonic properties of the gold nanoparticles allow for energy conversion at specific wavelengths, potentially enabling treatment at lower laser fluences compared with conventional approaches.[7] This may explain the clinical improvement observed in our patient who had previously received higher energy laser treatments without sustained benefit.

The dermal structural changes observed on high-frequency ultrasound warrant further investigation. The proposed mechanisms include increased transdermal absorption of active compounds via ethosomal carriers and photothermal-induced collagen remodeling, contributing to pigment reduction and dermal rejuvenation. The treatment approach may find applications beyond melasma. Solar lentigines, postinflammatory hyperpigmentation, and other recalcitrant pigmentary disorders share common pathophysiological features that could potentially respond to enhanced delivery systems combined with controlled thermal effects. The ability to target specific cellular populations while maintaining tissue integrity suggests that broader dermatologic applications may be achievable.

In line with recent trends in plastic and reconstructive surgery, there is increasing emphasis on the integration of technology-driven prognostic tools to enhance treatment planning and postoperative monitoring. For instance, Guarro et al[8] demonstrated that smartphone-based digital measurement tools can reliably assess wound morphology, offering a reproducible and practical alternative to traditional methods for clinical documentation and follow-up in surgical patients. Similarly, the modified TIME-H (tissue, inflammation/infection, moisture, edge/epithelialisation) scoring system has shown value in predicting healing trajectories in complex wounds, particularly surgical site injuries, and may inform early intervention strategies in high-risk cases.[9] In parallel, Winter et al[10] validated the use of the LACE+ index—a composite metric incorporating length of stay, comorbidity burden, and emergency visits—as a predictive tool for 30-day outcomes in plastic surgery populations. These advances underscore the importance of integrating objective assessment tools in aesthetic and reconstructive contexts. Within this framework, EPT holds potential not only as a treatment modality for pigmentary disorders but

also as a programmable, image-guided strategy to manage postprocedural pigmentation such as postinflammatory hyperpigmentation, particularly in higher risk skin types. Future research should focus on standardizing treatment parameters, evaluating long-term safety profiles of nanoparticle delivery systems, and conducting controlled studies to establish efficacy across different pigmentary conditions and skin types.

Kyu-Ho Yi, MD, PhD
Division in Anatomy and Developmental Biology
Department of Oral Biology
Human Identification Research Institute, BK21 FOUR
Project, Yonsei University College of Dentistry
50-1 Yonsei-ro, Seodaemun-gu
Seoul 03722, Republic of Korea
E-mail: kyuho90@daum.net

DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

PATIENT CONSENT

Informed consent was obtained from all participants, with full disclosure of the study's purpose, risks, and confidentiality.

DECLARATION OF HELSINKI

This study was conducted in compliance with the principles set forth in the Declaration of Helsinki.

REFERENCES

1. Sguizzato M, Esposito E, Cortesi R. Lipid-based nanosystems as a tool to overcome skin barrier. *Int J Mol Sci*. 2021;22:8319.
2. Hallan SS, Sguizzato M, Mariani P, et al. Design and characterization of ethosomes for transdermal delivery of caffeic acid. *Pharmaceutics*. 2020;12:740.
3. Badir A, Refki S, Sekkat Z. Utilizing gold nanoparticles in plasmonic photothermal therapy for cancer treatment. *Heliyon*. 2025;11:e42738.
4. Esposito E, Calderan L, Galvan A, et al. Ex vivo evaluation of ethosomes and transethosomes applied on human skin: a comparative study. *Int J Mol Sci*. 2022;23:15112.
5. Kim M, Kim SM, Kwon S, et al. Senescent fibroblasts in melasma pathophysiology. *Exp Dermatol*. 2019;28:719–722.
6. Hatem S, El Hoffy NM, Elezaby RS, et al. Background and different treatment modalities for melasma: conventional and nanotechnology-based approaches. *J Drug Delivery Sci Technol*. 2020;60:101984.
7. Paithankar D, Hwang BH, Munavalli G, et al. Ultrasonic delivery of silica-gold nanoshells for photothermolysis of sebaceous glands in humans: nanotechnology from the bench to clinic. *J Control Release*. 2015;206:30–36.
8. Guarro G, Cozzani F, Rossini M, et al. Wounds morphologic assessment: application and reproducibility of a virtual measuring system, pilot study. *Acta Biomed*. 2021;92:e2021227.
9. Guarro G, Cozzani F, Rossini M, et al. The modified TIME-H scoring system, a versatile tool in wound management practice: a preliminary report. *Acta Biomed*. 2021;92:e2021226.
10. Winter E, Glauser G, Caplan IF, et al. The LACE+ index as a predictor of 30-day patient outcomes in a plastic surgery population: a coarsened exact match study. *Plast Reconstr Surg*. 2020;146:296e–305e.