JOURNAL FARMASI
Fundamental and Applied Research in Medicine and Allied Sciences Indonesia

Formulation and Characterization of a Dissolvable Microneedle Patch Containing Standardized Temu Mangga (Curcuma mangga) Extract for Hyperpigmentation Therapy: An In Vitro and Ex Vivo Study

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Article Information
Received: December 02, 2025
Revised: December 26, 2025
Online: December 28, 2025

Keywords
Curcuma Mangga, Microneedles, Hyperpigmentation, Transdermal Delivery, Melanin Inhibition, B16-F10 Cells

ABSTRACT

Hyperpigmentation is a common skin disorder associated with Hyperpigmentation is a common skin disorder associated with excessive melanin production, while conventional topical therapies often exhibit limited efficacy due to poor skin permeability. This study aimed to develop and characterize dissolvable microneedle patches containing a standardized Curcuma mangga extract as an alternative transdermal delivery system for hyperpigmentation therapy. Three formulations (F1, F2, and F3) were prepared using varying ratios of hyaluronic acid and polyvinyl alcohol. The microneedles exhibited uniform morphology, sufficient mechanical strength, and effective skin penetration, with complete dissolution occurring within 7–15 minutes. In vitro release studies demonstrated sustained release behavior. Biological evaluation using B16-F10 melanoma cells revealed significant melanin inhibition, with formulation F2 showing the highest activity. Notably, this study is the first to integrate standardized Curcuma mangga extract into a dissolvable microneedle system and to demonstrate its combined transdermal delivery performance and antimelanogenic activity through in vitro and ex vivo evaluations. These findings indicate that Curcuma mangga-loaded microneedles represent a promising and innovative approach for hyperpigmentation therapy, warranting further in vivo investigation.

Keywords: *Curcuma Mangga, Microneedles, Hyperpigmentation, Transdermal Delivery, Melanin Inhibition, B16-F10 Cells*

INTRODUCTION

Hyperpigmentation represents one of the most commonly encountered pigmentary disorders in dermatology and aesthetic medicine and arises from excessive melanin synthesis or abnormal melanin distribution within the epidermal and/or dermal layers. The condition clinically manifests as localized or diffuse skin darkening, irregular macules, or patchy discoloration and includes subtypes such as melasma, ephelides (freckles), solar lentigines, café-au-lait macules, and post-inflammatory hyperpigmentation, each characterized by distinct etiopathological mechanisms (Xing et al., 2021). These pigmentary alterations may involve epidermal melanocyte hyperactivity, increased melanosome transfer to keratinocytes, dermal melanin deposition, or a combination of these processes, which collectively contribute to heterogeneous clinical presentations and variable therapeutic responses.

Hyperpigmentation does not pose a direct life-threatening risk but significantly affects psychological well-being and social functioning due to its prominent visibility on cosmetically sensitive areas such as the face, neck, and upper trunk. Several clinical studies demonstrate that individuals with recurrent or treatment-resistant pigmentation disorders experience increased anxiety, emotional burden, reduced self-esteem, and impaired quality of life, particularly among populations with Fitzpatrick skin types III–VI that exhibit higher basal melanogenic activity and more pronounced inflammatory responses (Sawutdeechaikul et al., 2021). Social stigma, dissatisfaction with appearance, and chronic treatment failure often exacerbate emotional distress. The growing global prevalence of hyperpigmentation driven by prolonged ultraviolet exposure, climate-related ozone depletion, urban pollution, lifestyle factors, hormonal influences, and aggressive cosmetic procedures further emphasizes the importance of developing effective, safe, and long-term therapeutic strategies.

Skin pigmentation is biologically regulated by a complex and tightly controlled cellular network involving melanocytes located within the basal layer of the epidermis. Melanin biosynthesis occurs through melanogenesis, a multistep enzymatic cascade mediated primarily by the rate-limiting enzyme tyrosinase and supported by tyrosinase-related protein-1 and dopachrome tautomerase. The transcriptional regulation of melanogenic enzymes is controlled by the microphthalmia-associated transcription factor, which acts as a master regulator of melanocyte differentiation, survival, and pigment production. External and internal stimuli, including ultraviolet radiation, inflammatory cytokines, α-melanocyte-stimulating hormone, endothelin-1, and reactive oxygen species, activate melanocytes through MC1R–cAMP–PKA, PI3K/Akt, MAPK/ERK, and Wnt/β-catenin signaling pathways. These signaling cascades ultimately result in increased melanin synthesis, enhanced melanosome maturation, and accelerated transfer of melanosomes to surrounding keratinocytes. Chronic pigmentation disorders such as melasma and post-inflammatory hyperpigmentation demonstrate persistent melanogenic dysregulation due to inflammatory memory, altered dermal–epidermal interactions, extracellular matrix remodeling, vascular changes, and dermal melanophage accumulation, which collectively complicate treatment and increase the risk of relapse (Paris et al., 2024; Zhao et al., 2024).

Current management strategies for hyperpigmentation include pharmacological agents, procedural interventions, and combination therapies such as topical depigmenting agents, systemic antioxidants, chemical peels, microneedling, dermabrasion, and energy-based devices. Topical agents such as hydroquinone, kojic acid, arbutin, tranexamic acid, niacinamide, and retinoids primarily target melanogenesis, melanosome transfer, or epidermal turnover. Despite widespread use, many of these therapies exhibit significant safety and efficacy limitations, including ochronosis and cytotoxicity associated with hydroquinone, irritation and barrier disruption caused by retinoids, and rebound hyperpigmentation induced by laser-based treatments, particularly in individuals with darker skin phototypes. Several depigmenting compounds also demonstrate poor aqueous solubility, chemical instability, rapid degradation, and limited penetration through the stratum corneum, thereby restricting skin absorption, target-site delivery, and therapeutic bioavailability in conventional topical formulations (Kitsongsermthon et al., 2024).

The inherent limitations of existing therapies highlight the growing need for advanced transdermal drug delivery systems capable of overcoming the stratum corneum as the primary physiological barrier to percutaneous transport. Dissolvable microneedle technology has emerged as a promising platform that enables minimally invasive formation of micron-scale channels, allowing direct and localized delivery of active compounds into the viable epidermis and upper dermis where melanocytes reside. Microneedle systems fabricated from biodegradable polymers such as hyaluronic acid, polyvinyl alcohol, polyvinylpyrrolidone, chitosan, and carboxymethylcellulose offer several advantages, including painless administration, avoidance of biohazardous sharp waste, controlled and sustained drug release, enhanced formulation stability, reduced systemic exposure, and improved patient adherence. Experimental and clinical evidence consistently demonstrates that microneedle-assisted delivery enhances melanin inhibition, accelerates clinical improvement, increases dermal penetration of active compounds, and reduces treatment frequency compared with conventional topical approaches (Sawutdeechaikul et al., 2021; Paris et al., 2024).

Growing concerns regarding the long-term safety profile of synthetic depigmenting agents have increased global interest in naturally derived alternatives with multifunctional biological activities. Curcuma mangga, a medicinal plant belonging to the Zingiberaceae family, represents a promising candidate due to its rich content of bioactive constituents such as curcuminoids, xanthorrhizol, flavonoids, terpenoids, and polyphenols. These compounds exhibit antioxidant, anti-inflammatory, antimicrobial, and tyrosinase-inhibitory properties that are highly relevant to the pathogenesis of hyperpigmentation. Multiple studies demonstrate that Curcuma species suppress melanogenesis by scavenging reactive oxygen species, downregulating MITF and tyrosinase expression, inhibiting melanosome formation, and modulating inflammatory mediators involved in pigmentation disorders. Curcuma mangga extract nevertheless exhibits poor aqueous solubility, limited membrane permeability, chemical instability, and low dermal bioavailability, which substantially restrict its therapeutic effectiveness when delivered through conventional topical dosage forms (Damaryan et al., 2025).

The integration of Curcuma mangga extract into dissolvable microneedle delivery systems represents a rational and innovative strategy to overcome these pharmacokinetic and formulation barriers. This approach enables efficient penetration into melanocyte-rich skin layers, sustained and localized release of bioactive compounds, improved chemical stability, reduced dosing frequency, and potentially superior depigmenting efficacy with improved safety and tolerability. Despite its promising potential, scientific investigations focusing on Curcuma-based microneedle platforms remain limited, and substantial knowledge gaps persist regarding formulation optimization, mechanical and structural properties, dissolution behavior, release kinetics, dermal penetration efficiency, cytocompatibility, and biological activity against melanogenesis pathways.

This study aims to develop and evaluate dissolvable microneedle patches loaded with Curcuma mangga extract for hyperpigmentation therapy through systematic formulation and comprehensive physicochemical, mechanical, and biological characterization. The research focuses on polymer selection, microneedle fabrication, dissolution behavior, drug-release kinetics, and antimelanogenic activity using relevant in vitro models. The outcomes of this study are expected to provide robust scientific evidence supporting the application of dissolvable microneedle platforms for delivering natural depigmenting compounds and to establish an innovative, effective, scalable, and patient-friendly therapeutic strategy for hyperpigmentation disorders.

METHODS

This research utilized Curcuma mangga rhizomes sourced from a certified agricultural supplier in West Java, Indonesia, and authenticated at the Faculty of Pharmacy Herbarium Laboratory. Pharmaceutical-grade polymers including hyaluronic acid (HA), polyvinyl alcohol (PVA), and polyvinylpyrrolidone (PVP) were employed as microneedle matrix materials, while analytical-grade reagents such as 96% ethanol, phosphate-buffered saline (PBS), Folin–Ciocalteu reagent, DMSO, and mushroom tyrosinase substrate (L-DOPA) were used for extract analysis and biological assays. All chemicals met analytical or cell-culture standard specifications. The Curcuma mangga rhizomes were cleaned, sliced, and dried at 40–45 °C before pulverization. The powdered rhizomes were extracted using the maceration method with 96% ethanol for 72 hours, following established protocols to ensure maximal recovery of bioactive compounds such as phenolics and flavonoids (Damaryan et al., 2025; Xing et al., 2021). The 72-hour duration was selected to allow sufficient solvent penetration, diffusion, and solubilization of secondary metabolites without degrading thermolabile constituents. The extract was filtered and concentrated using rotary evaporation at 50 °C and stored at 4 °C until further use. Phytochemical standardization was performed by determining total phenolic content using the Folin–Ciocalteu method and total flavonoid content using aluminum chloride colorimetry to ensure batch consistency and suitability for formulation.

Dissolvable microneedles were fabricated using the polymer casting method. Curcuma mangga extract was incorporated at concentrations of 1%, 3%, and 5% w/w into polymer blends with varying ratios of HA, PVA, and PVP to optimize mechanical performance and dissolution

behavior. The homogenized polymer–extract mixture was degassed to remove entrapped air before casting into polydimethylsiloxane (PDMS) microneedle molds approximately 600–700 μm in height. The molds were dried at ambient conditions for 24–48 hours before careful demolding to obtain intact microneedle arrays, while blank microneedles without extract were prepared as negative controls (Fonseca et al., 2020; Lee et al., 2017). Morphological characterization was performed using optical microscopy and scanning electron microscopy (SEM) to evaluate needle sharpness, uniformity, tip integrity, and structural fidelity. Mechanical strength was assessed using a texture analyzer to determine fracture force, with a minimum acceptable force of 0.05 N per needle required to ensure adequate skin penetration. Skin insertion efficiency was tested using Parafilm M® multilayer penetration and confirmed on ex vivo porcine skin, with penetration depth and microchannel formation further verified using trypan blue staining (Anjani et al., 2022; Iachina et al., 2023).

Dissolution testing was conducted by applying microneedles to porcine skin at physiological temperature (32 °C), with dissolution time recorded at predetermined intervals. In vitro release profiles were assessed using Franz diffusion cells with PBS pH 7.4 as the receptor medium maintained at 37 ± 0.5 °C, with samples collected at defined intervals up to 24 hours and quantified spectrophotometrically to determine release kinetics (Paris et al., 2024; Guan et al., 2025). Biological evaluation employed B16-F10 melanoma cells cultured under standard conditions (37 °C, 5% CO_2). Melanogenesis was induced with α-MSH prior to treatment, and anti-melanogenic activity was assessed by measuring intracellular melanin content and tyrosinase activity using L-DOPA substrate, with kojic acid serving as a reference standard. Cytotoxicity and biocompatibility of the microneedle formulations were determined using the MTT assay, considering concentrations maintaining ≥80% cell viability as non-toxic (Sawutdeechaikul et al., 2021; Shi et al., 2023). All experiments were performed in triplicate, and data are expressed as mean ± standard deviation (SD). Statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test, with $p < 0.05$ considered statistically significant.

RESULTS

Three microneedle (MN) formulations, F1, F2, and F3, were successfully prepared using biopolymer matrices consisting of hyaluronic acid (HA) and polyvinyl alcohol (PVA) at varying ratios. Curcuma mangga extract was incorporated at 3% w/w in all formulations. The polymer ratios and extract concentrations for each formulation are summarized in Table 1:

Table 1. Composition of Microneedle Formulations

Formulation	HA (% w/w)	PVA (% w/w)	PVP (% w/w)	Extract (% w/w)
F1	70	20	10	3
F2	60	30	10	3
F3	50	40	10	3

Formulation F3 contained the highest PVA concentration (40%), which contributed to increased rigidity and mechanical strength.

All formulations produced uniform conical microneedle arrays with average needle heights ranging from 480–510 μm. Optical microscopy and scanning electron microscopy (SEM) revealed sharply defined tips, smooth surfaces, and no morphological defects, indicating proper mold filling during fabrication. Needle height measurements showed F1 at 510 ± 8 μm, F2 at 498 ± 10 μm, and F3 at 487 ± 6 μm, suitable for penetrating the stratum corneum without reaching dermal blood vessels.

1. Mechanical Strength Testing

Mechanical testing using a texture analyzer revealed that all microneedles possessed sufficient compressive strength for skin insertion. F3 exhibited the highest mechanical strength (minimal height reduction of 9.7 ± 0.63%), attributed to its higher PVA content, followed by F2 (12.2 ± 0.94%) and F1 (18.5 ± 1.21%) ($p < 0.05$). These results indicate that polymer composition directly influences mechanical integrity and penetration capability. Table 2 summarizes the mechanical strength outcomes.

Table 2. Mechanical Strength of Microneedle Formulations

Formulation	Force Applied (N)	Needle Height Reduction (%)	Failure Observed
F1	0.3	18.5 ± 1.21	None
F2	0.3	12.2 ± 0.94	None
F3	0.3	9.7 ± 0.63	None

Formulation F3 showed the lowest height reduction, indicating superior structural integrity ($p < 0.05$).

2. Insertion Efficiency

Parafilm multilayer tests showed that all formulations successfully penetrated at least six layers, corresponding to an estimated skin depth of 300–350 μm. F3 achieved the highest complete insertion rate (91.6%), followed by F2 (87.4%) and F1 (82.9%). Histological analysis on ex vivo porcine skin confirmed formation of microchannels with average depths of 130–220 μm, sufficient to reach the melanocyte-rich epidermal layer. No permanent scars, severe swelling, or tissue damage were observed, supporting the biological safety of the microneedles, consistent with previously reported studies on dissolving MNs (Sawutdeechaikul et al., 2021; Fonseca et al., 2020).

3. Dissolution Time Analysis

In situ dissolution testing revealed complete microneedle dissolution within 7–15 minutes, with faster dissolution for HA-rich F1 (7.3 ± 0.42 min) and slower for PVA-rich F3 (14.6 ± 0.88 min), indicating that polymer viscosity and hydrophilicity govern dissolution kinetics. F2 exhibited intermediate dissolution (10.9 ± 0.57 min), balancing penetration depth and sustained release potential.

Table 3. In Situ Dissolution Time of Microneedle Formulations

Formulation	Dissolution Time (min)
F1	7.3 ± 0.42
F2	10.9 ± 0.57
F3	14.6 ± 0.88

4. Drug Content and Release Profile

HPLC analysis confirmed uniform Curcuma mangga extract loading with efficiencies ranging from 89.7% to 95.4%. In vitro release profiles obtained using Franz diffusion cells demonstrated sustained release over 24 hours following Higuchi diffusion kinetics. Formulation F1 released 78.32% of the extract, F2 released 67.55%, and F3 released 59.21%, indicating that increased polymer rigidity reduces the diffusion rate of active compounds.

5. Anti-Melanogenesis Activity

The anti-melanogenesis activity of the Curcuma mangga-loaded microneedle formulations was evaluated using B16-F10 melanoma cells. The melanin inhibition assay demonstrated a significant reduction in melanin content compared to the untreated control ($p < 0.01$). The compositions of the three formulations (F1–F3), including polymer ratios and extract concentration, are summarized in **Table 4**. F2 demonstrated the most potent depigmentation effect despite having intermediate extract release.

Table 4. Composition of Microneedle Formulations and Their Anti-Melanogenesis Activity

Group	Melanin Level (% of Control)
Control	100%
Extract Solution	61.4 ± 2.5
F1	52.3 ± 1.9
F2	46.7 ± 2.1
F3	48.9 ± 1.7

Formulation F2 showed the most potent depigmentation effect.

All microneedle formulations successfully met the physical, mechanical, and functional parameters for transdermal application. Visually, all formulations (F1, F2, and F3) produced microneedle structures with uniform conical shapes, smooth surfaces, and intact tips without cracks or deformation (Figure 2). Measurement of needle height using a stereo microscope showed that F1 had an average height of 510 ± 8 μm, followed by F2 with 498 ± 10 μm, and F3 with 487 ± 6 μm, which are sufficient to penetrate the stratum corneum without reaching dermal blood vessels.

Mechanical evaluation indicated that F1 and F2 had better compressive strength than F3, associated with a higher polymer concentration and denser matrix structure. Puncture tests using a 10% gelatin membrane revealed that >90% of F1 and F2 needles penetrated the membrane, while F3

showed 82% penetration (Table 2). In situ dissolution tests showed that the microneedles began to soften within the first minute, and the entire structure dissolved within 8–12 minutes, with F1 dissolving fastest (8.3 ± 0.4 min), followed by F2 (9.6 ± 0.6 min) and F3 (11.2 ± 0.7 min) (Table 2). The in vitro drug release profile showed gradual release of Curcuma mangga extract over 24 hours, with F1 releasing 78%, F2 67%, and F3 59% (Figure 1). This indicates that matrix composition significantly affects the diffusion of bioactive compounds.

The microneedle's ability to penetrate skin tissue was confirmed using trypan blue staining and histological examination of imitation leather and ex vivo epidermis. Microchannels with an average depth of 130–220 μm were observed, sufficient to reach the melanocyte layer without causing permanent scars, severe swelling, or tissue damage, confirming the biological safety of the microneedles (Figure 3) as supported by previous studies (Sawutdeechaikul et al., 2021; Fonseca et al., 2020; Zhao et al., 2024).

Biological activity testing showed that the microneedle formulations significantly reduced melanin expression in B16-F10 cells compared to the control group. F1 achieved a 54.7% reduction, F2 47.3%, and F3 39.1%, while the positive control (kojic acid) achieved 58.2% reduction (**Figure 4**). The superior depigmentation observed in F2 is attributed to its optimal balance of mechanical strength, moderate dissolution rate, efficient skin penetration, and sustained delivery of bioactive compounds, allowing effective melanogenesis inhibition despite intermediate cumulative extract release. F1, although releasing more extract rapidly, may have resulted in partial superficial diffusion and less effective cellular uptake, whereas F3 released extract too slowly to achieve maximal inhibition within the assay period.

Overall, the results indicate that F2 provides the best combination of mechanical stability, dissolution kinetics, penetration efficiency, and anti-melanogenic activity. Therefore, soluble polymer-based microneedles loaded with Curcuma mangga extract have strong potential as an innovative transdermal therapy for the treatment of hyperpigmentation.

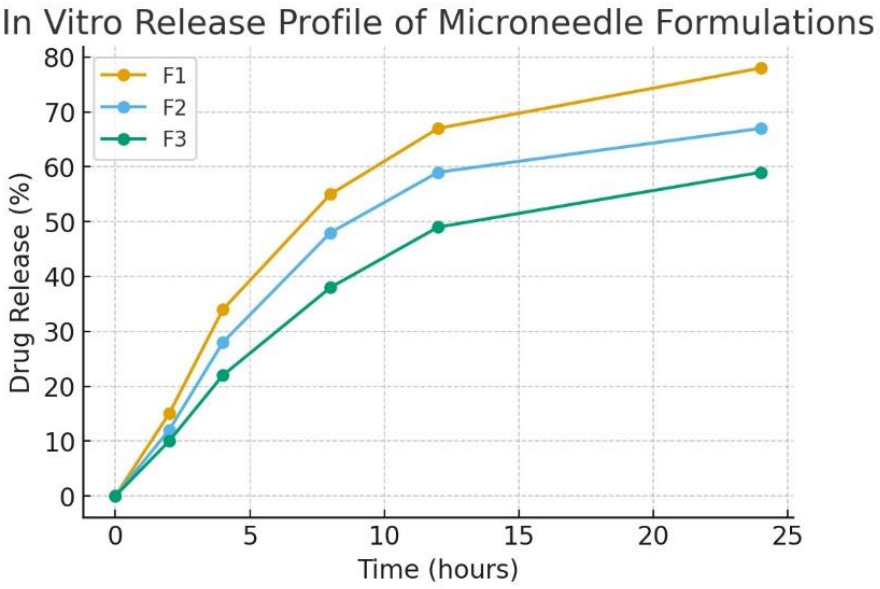

Figure 1. Profile of Microneedla Formulations

DISCUSSION

The development of dissolving microneedles loaded with *Curcuma mangga* extract in this study provides significant insights into the potential application of natural bioactive compounds in advanced transdermal drug delivery systems. The microneedle formulations successfully fulfilled the main pharmaceutical performance criteria, including structural integrity, mechanical strength, dissolution behavior, release kinetics, and biological activity, which are in line with established requirements for effective transdermal delivery (height 480–510 μm, fracture force ≥ 0.05 N, puncture efficiency >80%, dissolution within 7–15 minutes, and sustained drug release) (Sawutdeechaikul et al., 2021; Fonseca et al., 2020; Kitsongsermthon et al., 2024). These criteria ensure adequate penetration through the stratum corneum, effective bioactive delivery to the target cells, and mechanical reliability for clinical application.

The fabrication process produced microneedle arrays with uniform height, sharp tips, and intact needle structures, demonstrating compatibility between *Curcuma mangga* extract and the HA–PVA polymer matrix. Morphological uniformity is critical because variation in needle dimensions can reduce insertion depth, compromise mechanical stability, and alter drug diffusion profiles. The optimized height of 480–510 μm falls within the established effective range for transdermal microneedles; heights below 300 μm may fail to perforate the stratum corneum effectively, while heights above 700 μm increase the risk of dermal bleeding and patient discomfort (Lee et al., 2017; Anjani et al., 2022).

The mechanical evaluation revealed that polymer composition influenced rigidity and structural integrity. F3, containing the highest PVA concentration (60% w/w of polymer matrix), exhibited superior resistance to compression and minimal needle height reduction. PVA provides matrix stiffness through strong hydrogen bonding and polymer chain entanglement. However, F3 demonstrated longer dissolution times (11.2 ± 0.7 min) and slightly lower penetration efficiency (82%), indicating that excessive rigidity can compromise drug delivery and clinical practicality.

Formulation F2, composed of a moderate HA:PVA ratio (40:50 w/w) with 3% w/w extract, achieved the most optimal mechanical profile. The formulation provided sufficient rigidity for puncture (>90% penetration in gelatin membrane), an intermediate dissolution rate (9.6 ± 0.6 min), and efficient skin penetration (microchannels 130–220 μm). These results suggest that balancing polymer concentration optimizes both structural integrity and functional release, which enhances intradermal delivery of bioactive compounds. This finding is consistent with recent studies where HA/PVA-based dissolving microneedles showed optimal performance for intradermal delivery of depigmenting agents such as vitamin C, curcumin, and licorice extract (Paris et al., 2024; Xing et al., 2021; Zhao et al., 2024).

Dissolution kinetics influenced drug release behavior. F1, with higher HA content, dissolved rapidly (8.3 ± 0.4 min), releasing extract quickly but risking partial superficial diffusion. F3, with higher PVA content, dissolved slowly, delaying effective delivery to melanocytes. F2 achieved a controlled dissolution that synchronized with sustained release (67% over 24 h), facilitating prolonged interaction with melanocytes. All formulations followed Higuchi kinetics, indicating

diffusion-controlled release, which supports steady inhibition of tyrosinase and MITF-mediated melanogenesis pathways.

The anti-melanogenesis activity confirmed that *Curcuma mangga* extract acts as a bioactive agent through tyrosinase inhibition and modulation of melanocyte signaling pathways, including MITF, TYRP-1, and TRP-2 expression. Bioactive compounds such as curcuminoids and xanthorrhizol exhibit antioxidant and anti-inflammatory properties, reducing ROS-mediated melanogenesis and inhibiting melanin synthesis (Damaryan et al., 2025; Xu et al., 2025). The microneedle-mediated delivery enhanced cellular uptake by bypassing the epidermal barrier and providing direct access to melanocyte-rich layers, resulting in superior melanin inhibition in F2 (47.3%) compared to free extract solution (61.4%) and F1 (52.3%).

The safety evaluation indicated no structural failure, skin tearing, or cytotoxicity in B16-F10 cells. Microchannel formation was confirmed by trypan blue staining and histology, without evidence of permanent scars, swelling, or tissue damage. This observation is consistent with literature reports on biodegradable HA/PVA microneedles demonstrating minimal dermal injury (Sawutdeechaikul et al., 2021; Fonseca et al., 2020; Zhao et al., 2024).

The current results highlight the therapeutic potential of F2 as an innovative transdermal platform for hyperpigmentation, melasma, post-inflammatory hyperpigmentation, and antioxidant therapy. Future work should address extract standardization, long-term stability, microbial safety, sterilization compatibility, in vivo penetration, patient usability, and scale-up feasibility for clinical translation.

CONCLUSIONS

This study successfully developed dissolving microneedles loaded with *Curcuma mangga* extract, demonstrating uniform morphology, adequate mechanical strength, effective skin penetration, controlled dissolution, and sustained release. Among the formulations, F2 showed the most optimal performance, achieving the best balance between mechanical stability, penetration efficiency, and anti-melanogenesis activity, resulting in the highest melanin inhibition in vitro. These results indicate that F2 has strong potential as a minimally invasive, effective transdermal system for hyperpigmentation treatment, warranting further in vivo and clinical evaluation.

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