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Research article

Anti-inflammatory Activity of Clove Oil and Mangosteen Peel Extract on Lipopolysaccharide/UVA+UVB-induced Inflammatory Mediators and Effect on Wound Healing of HaCaT Cells

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Abstract: This research examined the anti-inflammatory and wound-healing activity of clove oil and mangosteen peel extract. The clove oil, mangosteen peel, and a combination of clove oil with mangosteen peel extract (1:1) were assessed via modulation of the production of pro-inflammatory molecules by inhibition of the pro-inflammatory cytokines (tumor necrosis factor-α: TNF-α, prostaglandin E2: PGE2) production and the reduction of inflammatory cytokines such as interleukin 10 (IL-10) in the HaCaT cell model. Wound healing activity and cytotoxicity of clove oil and mangosteen peel extract on HaCaT cells were also evaluated. In addition, the combination of clove oil with mangosteen peel extract (1:1) inhibited the production of TNF-α (20.21 ± 0.47 pg/ml) and PGE2 (6.88 ± 0.01 pg/ml) and induced the production of IL-10 (218.44 ± 4.90 pg/ml). The percentage of wound healing (% wound closure) was evident at 48 hours. The combination of clove oil and mangosteen peel extract exhibited complete wound closure with no cytotoxicity. These results provided scientific evidence supporting the efficacy of the combined use of clove oil and mangosteen peel in reducing inflammatory processes.

Keywords: Clove oil; mangosteen peel extract; anti-inflammatory activity; wound healing activity; HaCaT cells

1. Introduction

The skin is the largest organ of the human body. The epidermis, the outermost layer of the skin, serves as the primary barrier protecting the body from the environment and prevents the loss of water and body fluids. When the skin barrier is disrupted by multiple internal or external factors, dry skin, itching, and skin inflammation occur. Notably, keratinocytes are the most abundant cells in the epidermis, and their main function is to produce keratin, induce cytokine secretion, and, in severe cases, participate in various skin inflammatory responses [1-5].

Inflammation is an essential innate immune response that is crucial for combating pathogens. Dysregulated and untimely inflammation contributes to various chronic inflammatory disorders such as psoriasis, atopic dermatitis, rheumatoid arthritis, coronary heart disease, Crohn's disease, and cancer [6-9]. The inflammatory response involves a complex network of interactions among

immune cells and pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF-α). TNF-α is a pro-inflammatory cytokine that is crucial for cell survival and apoptosis processes of normal and malignant cells [10-12]. TNF-α is a crucial pro-inflammatory mediator implicated in the pathogenesis of psoriasis, atopic dermatitis, and rheumatoid arthritis and is frequently observed to act as a risk factor for the occurrence of psoriasis skin lesions [13]. Prostaglandin 2 (PGE2) is one of the most predominant PGs produced in the body. Under physiological conditions, PGE2 is a key mediator of many biological functions. For inflammation, PGE2 is of particular interest due to its role in the occurrence of clinical signs of inflammation: redness, swelling, and pain [14-15]. Interleukin 10 (IL-10) has been found to regulate inflammation. This process includes the resolution of inflammation associated with acute infections or tissue injury at both local and systemic levels [16]. Consequently, reduced IL-10 levels can lead to increased immunopathology or the development of autoimmune disease by promoting excessive or persistent inflammatory responses [17]. The inflammatory response is indeed recognized as the essential first, active phase of wound healing [18-19]. In skin repair, the tissue-infiltrating leukocytes are widely considered the main cellular effectors of inflammation. However, IL-10 serves as a multifunctional immunosuppressive cytokine exhibiting strong anti-inflammatory effects, reducing inflammation mediated by innate immune cells and T lymphocytes. Across diverse cell types, including macrophages, neutrophils, dendritic cells, and T cells, IL-10 inhibits pro-inflammatory activity and suppresses the expression of pro-inflammatory mediators, resulting in beneficial outcomes of the local inflammatory response on the repair process [20].

Effective wound healing requires a timely transition from inflammation to tissue repair. While initial inflammation is necessary, an excessive response can cause tissue damage and delay recovery. Therefore, anti-inflammatory agents are essential to modulate inflammatory mediators and create a balanced microenvironment [21]. By resolving inflammation, these agents prevent cellular stress and establish a stable foundation for re-epithelialization and rapid tissue regeneration [22]. Building on this principle, multiple mechanisms of action have been proposed to describe the specific anti-inflammatory potential of plant-derived phytochemicals.

The present study explored the potential of clove oil, mangosteen peel extract, and a combination of clove oil with mangosteen peel extract in a ratio of 1:1 in the modulation of pro-inflammatory molecule production by inhibiting the production of TNF-α, PGE2, and the reduction of inflammatory cytokines such as IL-10, in the LPS-induced HaCaT cell model and the wound-healing benefits.

2. Materials and Methods

2.1 Materials

Human keratinocyte HaCaT cells were purchased from the CLS Cell Lines Service GmbH, Federal Republic of Germany. Chemicals for the determination of toxicity were purchased from Invitrogen™, USA. The commercial ELISA kits were used for measurement of TNF-α, IL-10 (Abcam, Cambridge, UK) and PGE2 (Cayman Chemicals, Ann Arbor, USA) according to the manufacturer's instructions.

2.2 Methods

2.2.1 Extraction of *Garcinia mangstana* peels and clove bud

To obtain the crude *G. mangostana* extract, dried peels were mixed with ethanol at a solid-to-solvent ratio of 1:10 g/mL and subjected to three 30-minute cycles of ultrasonic-assisted extraction (UAE) at room temperature, 40 kHz, 500 W. The extract was filtered, and the solvent was removed under reduced pressure to obtain crude *G. mangostana* extract. Furthermore, the clove bud was extracted by steam distillation for 6 h. The distillate was partitioned with dichloromethane and dried over Na_2SO_4 to provide clove oil as a brown liquid.

2.2.2 *Preparation of extract samples*

Due to the hydrophobic nature of clove oil and mangosteen peel extract, both samples were initially dissolved in dimethyl sulfoxide (DMSO) to prepare concentrated stock solutions. The stock solutions were then diluted with Dulbecco's Modified Eagle Medium (DMEM) to obtain the desired working concentrations, while maintaining the final DMSO concentration at 0.1% (v/v) in all cell culture experiments to minimize vehicle-induced cytotoxicity. The final concentrations tested in the cell culture experiments were 0.078, 0.156, 0.313, 0.625, 1.250, 2.500, 5.000, and 10.000% (v/v) for clove oil and 0.078, 0.156, 0.313, 0.625, 1.250, 2.500, 5.000,

and 10.000 mg/ml for mangosteen peel extract. Additionally, a combination of clove oil and mangosteen peel extract was prepared by mixing the concentrations exhibiting >80% cell viability of clove oil and mangosteen peel extract at a ratio of 1:1 v/w.

2.2.3 Cell cultures

The HaCaT cells were maintained in 75 cm^2 culture flasks using DMEM supplemented with 10% (v/v) fetal bovine serum (FBS) and 1% (v/v) penicillin-streptomycin. The cultures were incubated in an incubator at 37°C and 5% CO_2. The cells were grown the day before being used in the experiment. The cells with 75-80% confluence were harvested from the flasks via trypsinization (0.25% v/v trypsin-EDTA).

2.2.4 Cell viability assays

HaCaT cells were seeded in 96-well plates at a density of 2×10^4 cells/well, and their viability was subsequently assessed using the WST-1 assay. WST-1 reagent (diluted 1:10 in serum-free medium) was added to each well at a volume of 100 μL, and the wells were incubated at 37°C for 45 min. Post-incubation, the plate was gently shaken for 10 min to ensure uniform dye distribution before measuring the absorbance at 450 nm. Only samples exhibiting at least 80% cell viability were selected for further study [23]. Selection was based on the non-toxicity criteria of ISO 10993-5. Cell viability was calculated as follows:

$$\% \text{ Cell viability} = (OD_{sample}/OD_{control}) \times 100$$

2.2.5 TNF-α assays

TNF-α secretion in HaCaT cells was quantified using ELISA kits in accordance with the manufacturer's instructions. Briefly, $2x10^4$ cells per well were cultured and pre-stimulated with lipopolysaccharide (LPS, 20 μg/ml). Sample supernatants were obtained at the indicated time points and subjected to ELISA. Colorimetric changes were measured at 450 nm, and concentrations were expressed as pg/ml [24].

2.2.6 PGE2 assays

HaCaT cells in DMEM were seeded in 96-well plates at a density of 2×10^4 cells per well and cultured for 24 h. Then the medium was replaced with PBS, and the cells were irradiated with UVA+UVB (6 mJ/cm^2) to stimulate inflammatory cytokines. Post-irradiation, the cells were maintained in fresh DMEM for another 24 h. Subsequently, the supernatant was collected, and the PGE2 production was determined using a PGE2 EIA monoclonal colorimetric assay kit according to the manufacturer's instructions [25].

2.2.7 IL-10 assay

The IL-10 production in the HaCaT cells was measured using ELISA kits in accordance with the manufacturer's instructions. To stimulate IL-10 secretion, LPS (5 μg/ml) from *Escherichia coli* 0111:B4 (purified by trichloroacetic acid extraction; Sigma, Australia) was used to stimulate IL-10 production. HaCaT cells (density $2x10^4$ cells per well) were seeded in a 96-well cell culture plate (Corning Costar, Sigma, Australia) and incubated for 24 h at 37°C and 5% CO_2, followed by pretreatment with individual test compounds [26].

2.2.8 Wound healing

To simulate wound healing, the central scratch model was performed on confluent HaCaT monolayers using a sterile pipette approximately 1 mm in diameter. Following the initial scratch, all media were discarded from the culture dish to eliminate unattached HaCaT cells. The media were immediately replaced with the sample in DMEM that was modified to contain low fetal bovine serum and incubated for 48 h. The wound area can be calculated by manually tracing the cell-free area in captured images using the ZEN software of a ZEISS Fluorescence Microscope. Under normal conditions, the wound area will decrease over time. The migration rate can be expressed as the change in the wound area over time. The scratch wound assay can be used to assess the migration capacity of keratinocytes under different experimental conditions. Alternatively, the migration rate can be expressed as the percentage of area reduction or wound closure. The closure percentage will increase as cells migrate over time:

$$\text{Wound Closure \%} = \left[\frac{A_{t=0h} - A_{t=dh}}{A_{t=0h}}\right] \times 100\%$$

- $A_{t=0h}$= area of the wound measured immediately after scratching ($t = 0h$)
- $A_{t=dh}$= area of the wound measured $h$hours after the scratch is performed

ZEN software of ZEISS Fluorescence Microscope was used to trace and quantify the cell-free wound area from captured images. Three fields of view per well (n = 3 fields/well) were captured and measured. Wound closure (%) values were averaged across all three fields before final calculation to ensure representative and reproducible results [27].

2.2.9 Statistical analysis

All data are expressed as the mean ± standard deviation (S.D.) of three independent biological replicates (n=3). Statistical differences between groups were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test for multiple comparisons. A p-value of < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS Statistics version 25.

3. Results and Discussion

3.1 Anti-inflammatory activity

The cytotoxicity of clove oil and mangosteen peel extract was tested on HaCaT cells using WST-1 assays, based on an inhibitory concentration at 50% growth (IC_{50}). The IC_{50} values of clove oil and mangosteen peel extract were 9.05 ± 0.28 % v/v and 7.67±0.42 mg/ml, respectively. Cells with 80% cell viability were selected for the combination experiment. The results showed no significant difference in cell viability (>80%) between treatment with clove oil (0.078-1.25% v/v) and mangosteen peel extract (0.078 mg/ml) (Figure 1A and B). Notably, the combination of clove oil (0.078 %v/v) and mangosteen peel extract (0.078 mg/ml) at a 1:1 v/w ratio yielded high cell viability (86.70 ± 4.12 %) (Figure 1C). Based on these results, these concentrations were selected for further study.

Clove oil, mangosteen peel extract, and the clove oil-mangosteen peel extract combination suppressed the production of inflammation-related cytokines. When LPS was administered to HaCaT cells, TNF-α and PGE2 production showed a significant increase. The effects of clove oil, mangosteen peel extract, and their combination treatments on TNF-α and PGE2 production in LPS-stimulated cells were examined, and the results were shown in Figure 2A-C. The stimulation of HaCaT cells with LPS for 24 h led to a dramatic increase in these inflammatory markers. Subsequently, the levels of TNF-α production were measured following treatment with clove oil, mangosteen peel extract, and the combination extract. The combination sample (0.078% v/w) significantly stimulated TNF- α production in the HaCaT cells. The treatment of HaCaT cells with the clove oil-mangosteen peel extract (0.078%) combination showed a 20.21 ± 0.47 pg/ml cytokine secretion level of TNF-α activity. In comparison, the cytokine secretion level for clove oil alone (0.078% v/v) and mangosteen peel extract alone (0.078 mg/ml) were 22.65 ± 3.36 pg/ml and 32.46 ± 0.61 pg/ml, respectively. (Figure 2A).

The PGE2 levels in HaCaT cells were treated with clove oil, mangosteen peel extract, and the clove oil-mangosteen peel extract combination and then incubated with UVA+UVB. The PGE2 levels were significantly inhibited by treatment with the combination of clove oil-mangosteen peel extract (0.078 %v/w) in the ratio of 1:1 when compared to each extract. The UVA+UVB treatment of HaCaT cells induced the production of PGE2 up to a level of 34.73 ± 0.00 pg/ml, while the unstimulated cells produced only 2.35 ± 2.33 pg/ml. The clove oil (0.078% v/v), mangosteen peel extract (0.078 mg/ml), and the combination of clove oil-mangosteen peel extract (1:1) treatment showed cytokine secretion levels of 6.80±0.02 pg/ml, 8.89 ± 0.04 pg/ml, and 5.88 pg/ml, respectively (Figure 2B). The anti-inflammatory cytokine IL-10 (% production) of the tested samples on human keratinocyte skin cells (HaCaT) after exposure to the samples for 24 h was measured. There was no significant inhibition of IL-10 production in the treatment of clove oil (0.078% v/v), mangosteen peel extract (0.078 mg/ml) and the combination of clove oil-mangosteen peel extract (ratio 1:1). The percentage production of IL-10 in clove oil treated sample (0.078% v/v) and the sample treated with the combination of clove oil with mangosteen peel extract (0.078%v/w) were 209.80 ± 6.54 pg/ml, 92.10 ± 1.41 pg/ml and 218.44 ± 4.90 pg/ml, respectively (Figure 2C).

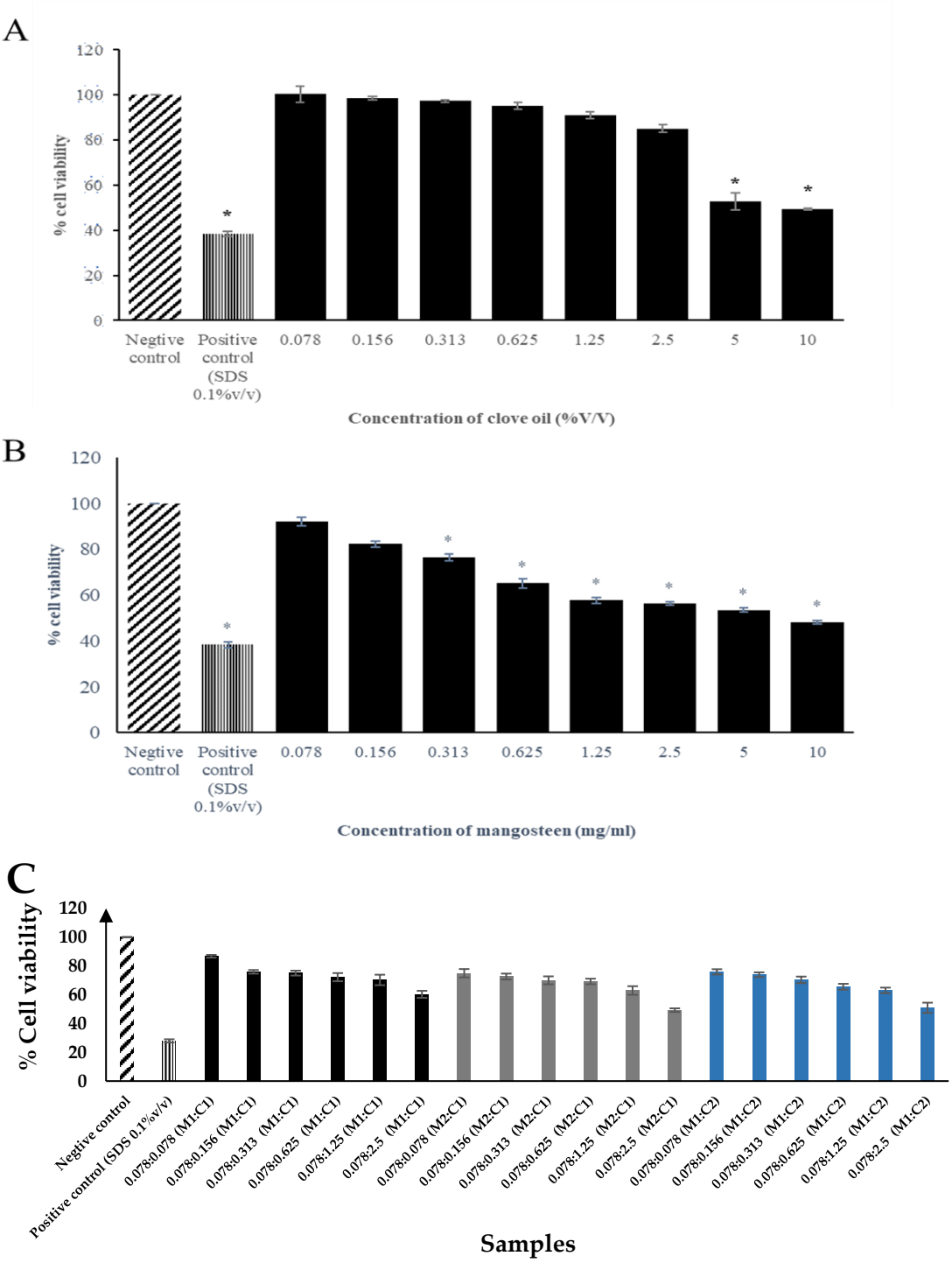


Figure 1. Effects of clove oil (C, v/v) (A), mangosteen peel extract (M, w/v) (B) and clove oil and mangosteen peel extract at different ratios (M1:C1, M2:C1 and M1:C2) (C) on the viability of HaCaT cells. After culturing the cells with clove oil (0.078-10.000% v/v) or mangosteen peel extract (0.078-10.000 mg/ml), cell viability was measured using WST-1 assays after 24 h. Results are expressed as mean ± SD (n=3, * $P < 0.05$) compared with the negative control.

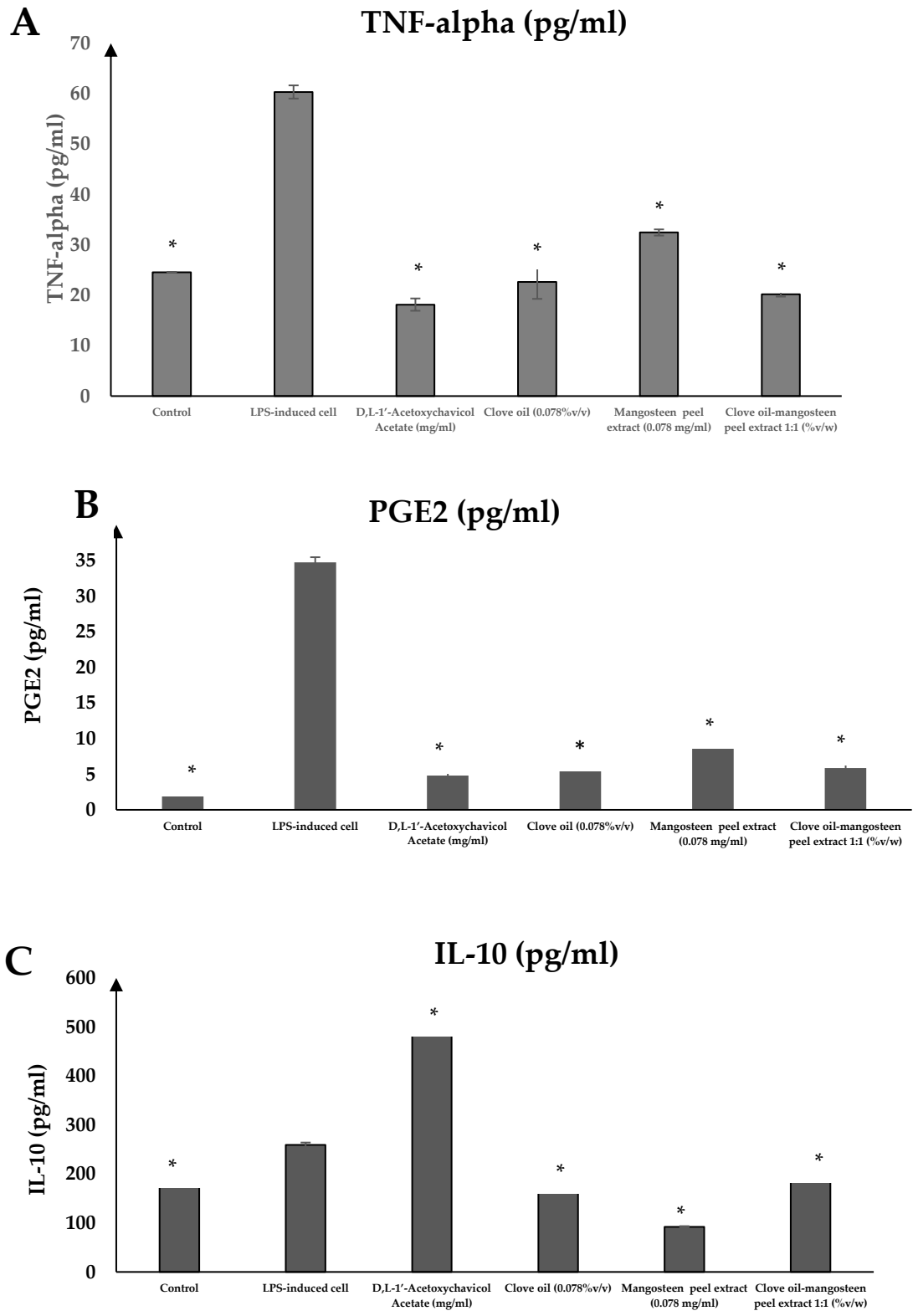


Figure 2. Effect of clove oil, mangosteen peel extract, and their combination on TNF-α (A), PGE2 (B), and IL-10 (C) production in LPS-induced cells. Results are shown as MEAN ± SD, n = 3. * P<0.05 for difference from the LPS-stimulated group.

The biological properties of clove have been described, but its influence on the immune system. The essential oil of clove inhibited the production of these cytokines in vitro. Eugenol was also found to be the major component of the clove extract, making up 71- 90% of the oil, and probably is the causative agent of cytokine inhibition. Clove oil exhibits significant *in vitro* cytotoxicity toward human skin cells, a property primarily attributed to its eugenol content (54–73%). While eugenol remains highly toxic at concentrations as low as 0.06%, it conversely demonstrates protective effects against skin photoaging when diluted to 0.001% [28]. Furthermore, clove oil has been well reported as an anti-inflammatory, antioxidant, antibacterial, and antibiofilm agent [29-31]. Because of its many properties, the presence of clove oil in the formulation could have led to quicker wound healing [32]. Clove constituents demonstrate immunomodulatory effects by suppressing T-cell proliferation and enhancing B-cell expansion, consistent with previous reports of attenuated cellular immunity and augmented humoral responses. Cytokine profiling further supports this shift, revealing a reduction in Th1-associated pro-inflammatory mediators like IFN-γ, alongside an upregulation of Th2-related cytokines, including IL-4, IL-10, and TGF-β [33-35]. Several studies demonstrated the antinociceptive actions of crude extracts of the pericarp of *Garcinia mangostana* L. and of some of its isolates. *G. mangostana* L. peel extract, α-mangostin, and γ-mangostin exhibited anti-inflammatory effects by reducing inflammatory mediators' production in LPS-induced RAW 264.7 cells [36]. Mangosteen extract and α-mangostin attenuated the severity of dextran sulfate sodium (DSS)-induced ulcerative colitis in mice [37]. Furthermore, a recent study demonstrated that this protective effect is mediated by the suppression of nuclear factor-kappa B (NF-κB) activation, driven by the potent anti-inflammatory and antioxidant properties of mangosteen [38-40]. *G. mangostana* pericarp ethanolic extract *(*GME*)* significantly reduced pro-inflammatory cytokine expression (TNF-α, IL-6, and IL-1β) through modulation of the TLR-2 pathway using α-, β-, and γ-mangostin and garcinone B components [41]. Another study presented that the combination of *G. mangostana*, *Curcuma comosa*, and *Acanthus ebracteatus* was highly effective as an anti-inflammatory [42].

3.2 Wound healing activity

The percentage of wound healing (as measured by % wound closure) was evident at 48 h. The combination of clove oil and mangosteen peel extract at a 1:1 ratio showed a higher percentage of wound healing compared to both clove oil and mangosteen peel extract treated individually. Specifically, at 48 h, the wound healing values were 83.36 ± 7.62% for clove oil (0.078% v/v), 92.09 ± 3.41% for mangosteen peel extract (0.078 mg/mL), and 100.00 ± 0.00% for the 1:1 combination formulation, respectively (Figure 3). The morphology of HaCaT cells also showed wound healing with clove oil and mangosteen peel extract on the cells at 0, 24, and 48 h (Table 1). This study demonstrates that the 1:1 combination significantly enhances wound healing, achieving closure within 48 hours, which outperforms individual clove oil treatment (83.36±7.62%). These results align with the dual functionality of eugenol in clove oil, which simultaneously exerts anti-inflammatory effects and promotes collagen formation [43]. The superior migration of HaCaT cells is attributed to eugenol-induced cytoskeletal remodeling, facilitating efficient cell transition across the wound [44]. Additionally, clove oil promotes migration through cytoskeletal remodeling, and mangosteen extract further supports the proliferation phase by enhancing skin cell migration and proliferation [45]. Notably, the finding that the 1:1 combination resulted in a significantly higher percentage of wound healing compared to the individual treatments is a critical observation. This suggests a promising combined effect within the 2D culture model. In addition to the complementary anti-inflammatory properties, the cumulative phytochemical load in the combination appears to have reached an optimal balance that promoted the rapid migratory stimulus, while finely tuning the initial inflammatory signals required to trigger the proliferative phase effectively. Several researchers previously demonstrated anti-inflammatory and wound healing activities of various medicinal plants. *Dorema aucheri* is a plant that has shown significant capacity to inhibit the production of TNF-α, a key mediator in the inflammatory process. Decreasing TNF-α levels may contribute to the reduction of inflammation and accelerate the skin wound healing process [46]. *D. aucheri* polysaccharides played a role in inflammation modulation. They can interact with immune cells and affect the production of cytokines, including TNF-α. In this way, polysaccharides help relieve inflammation and support the healing process. In addition, *Curcuma mangga*, with its primary component curcuminoids, demonstrated excellent anti-inflammatory activity. A cream with 10% *C. mangga* extract proved more effective than diclofenac gel, a

standard anti-inflammatory drug. In wound healing, this cream accelerated fibroblast migration by 80% within 36 hours, promoting faster tissue regeneration and recovery [47]. *Solanum diploconos* contained active compounds such as caffeic acid and lutein. It effectively reduced inflammatory mediators such as TNF-α. In a wound healing assay, a 1% *S. diploconos* cream accelerated skin wound healing by approximately 35%, promoting fibroblast migration and faster wound closure [48]. Overall, the anti-inflammatory and wound healing activities of Clove oil and mangosteen peel extract were evaluated using only one cell model. Further research is needed to explore the therapeutic potential of these compounds in vivo studies and their specific mechanisms of action.

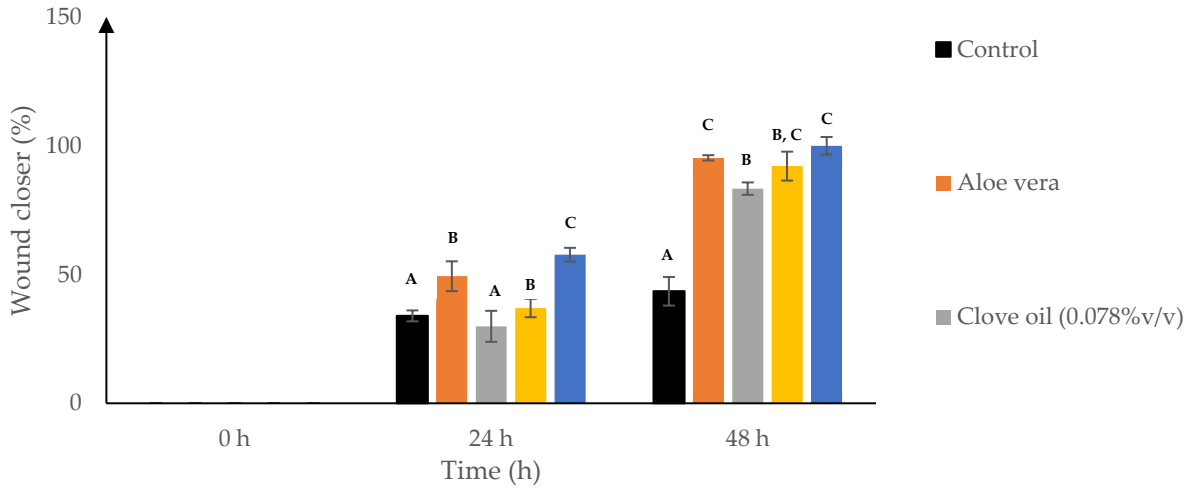


Figure 3. Preconcerted of Wound healing closure comparing HaCaT cells exposed to growth medium (DMEM low serum), media with aloe vera as a positive control of the assay, and media with samples. $^{A-C}$: $P < 0.05$ for differences from the untreated control group at the same time (n=3).

4. Conclusions

The clove oil and mangosteen peel extract combined at the ratio of 1:1 v/w enhanced the reduction of the LPS-induced TNF, PGE2, and IL-10 production in HaCaT cells. Interestingly, this combination also displayed a high inhibitory effect against pro-inflammatory mediators and cytokines, which may promote anti-inflammatory activity. The mechanism was also found in this study to be at least partially related to interactions among the key bioactive compounds. However, future research should focus on formulating these extracts into realistic delivery systems, such as nanoemulsions or topical gels, and evaluating their stability and efficacy in clinical settings.

5. Acknowledgments

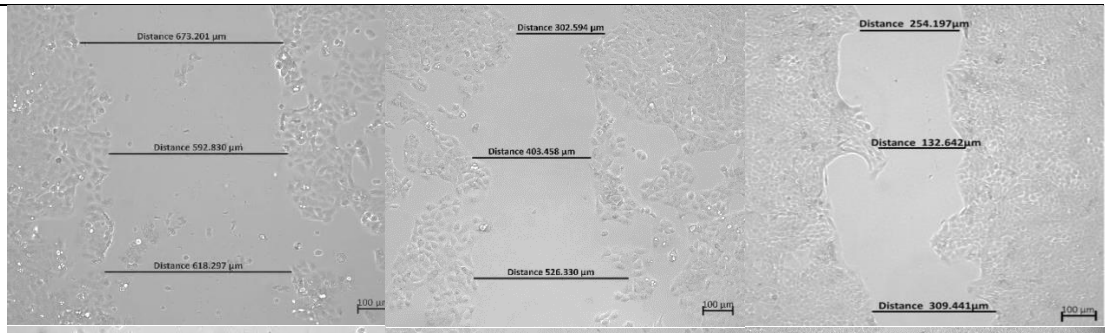
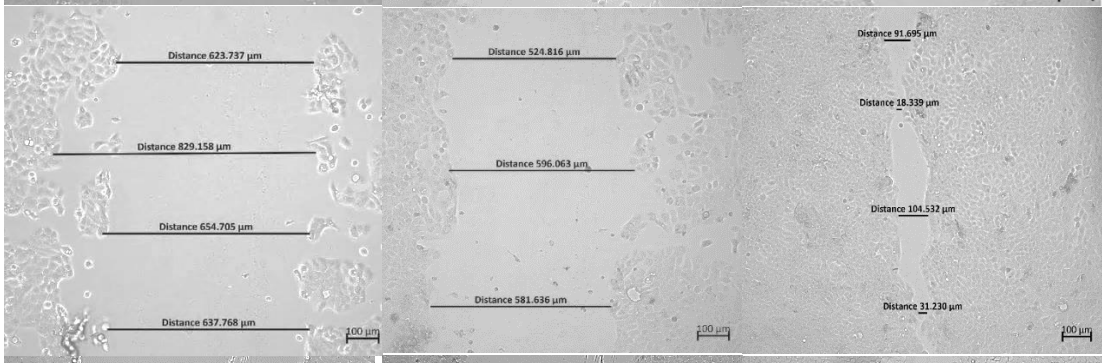
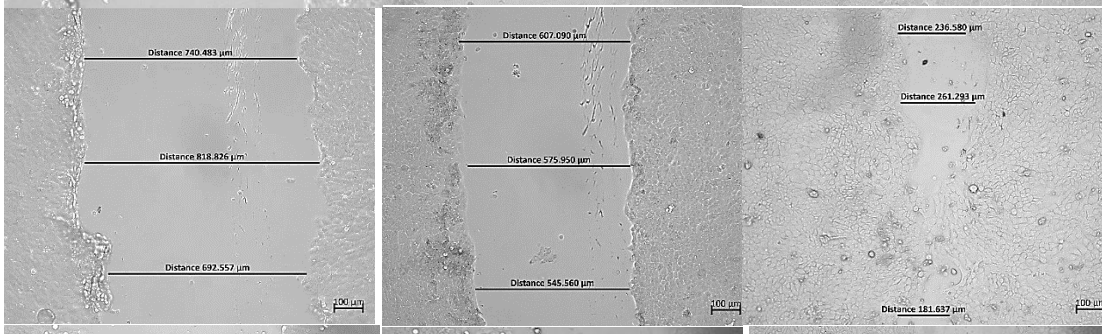
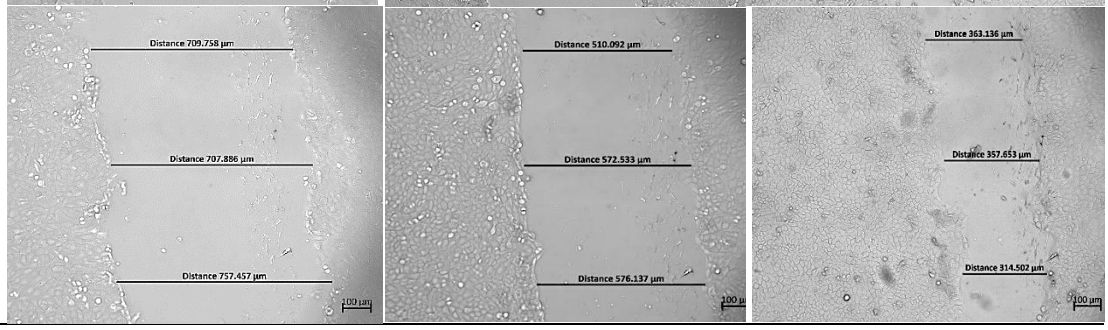
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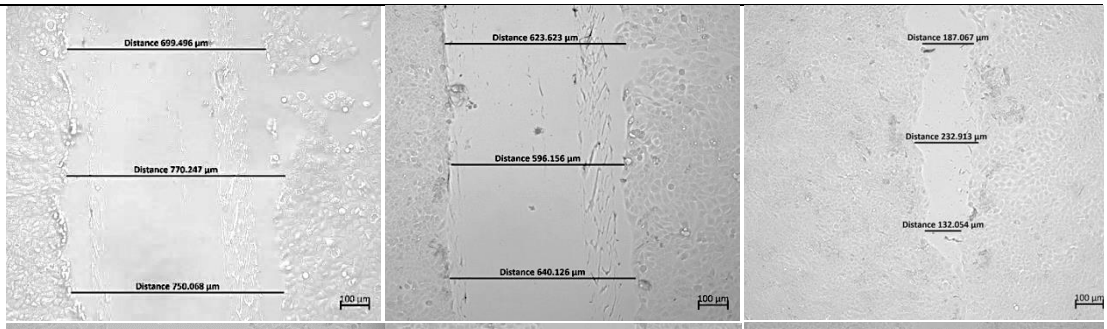
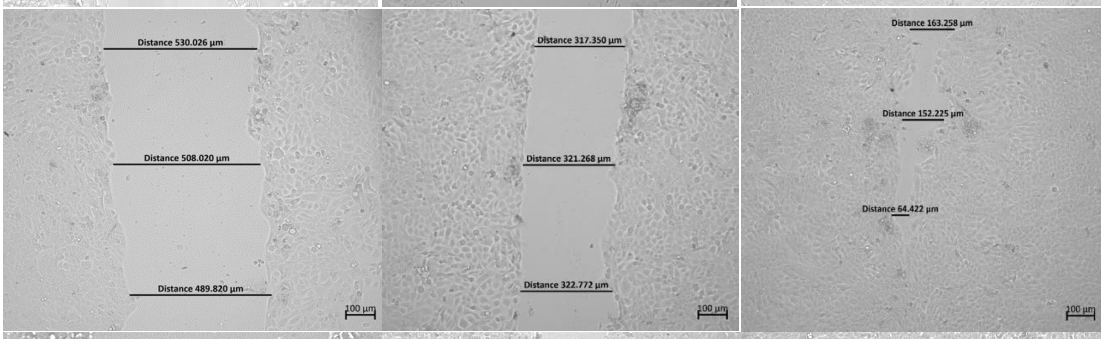
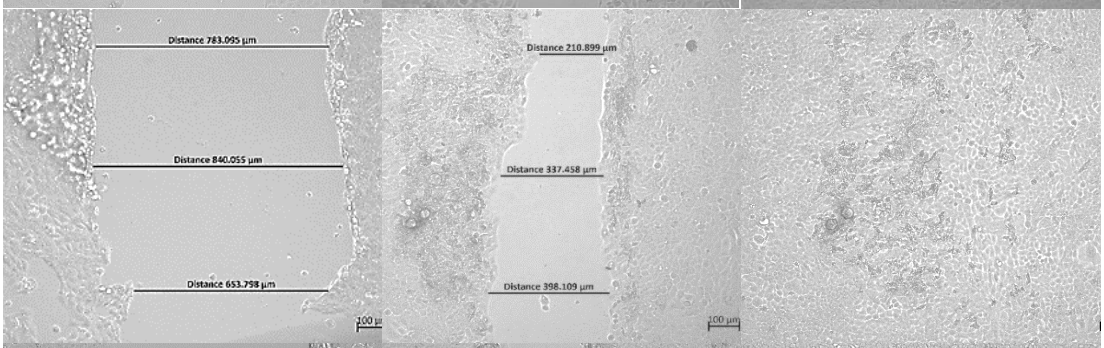
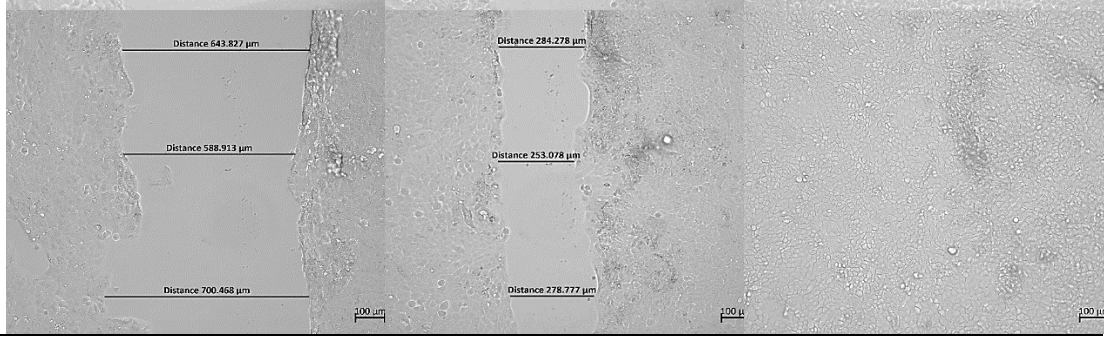
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Conflicts of Interest: The authors declare no conflict of interest.

Table 1. The morphology of HaCaT cells showed wound healing with clove oil and mangosteen peel extract on the cells at 0, 24, and 48 h. (scale bar = 100 μm)

Treatment	Time (h)		
	0	24	48
Negative control			
Positive control (10 μg/ml of Aloe vera)			
Clove oil (0.039%v/v)			
Clove oil (0.078%v/v)			

Treatment	Time (h)		
	0	24	48
Mangosteen peel extract (0.039 mg/ml)			
Mangosteen peel extract (0.078 mg/ml)			
Clove oil-Mangosteen peel extract (0.039%v/w ratio 1:1)			
Clove oil-Mangosteen peel extract (0.078%v/w ratio 1:1)			

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