

Abietic Acid from Pine Rosin Extract Promotes Diabetic Wound Healing by Enhancing Angiogenesis and Activating Key Signaling Pathways

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ABSTRACT

Diabetes mellitus involves sustained high blood sugar levels that impair wound repair processes, including extended inflammation, diminished blood vessel formation, and hindered cell growth. These issues contribute to persistent, infection-prone wounds that heal slowly. Factors such as heightened oxidative stress and buildup of advanced glycation end-products further complicate recovery in diabetic patients. Consequently, there is a pressing demand for innovative, low-risk therapies to improve diabetic wound care. The present research assessed the ability of abietic acid—the primary constituent of pine rosin—to support wound healing in high-glucose environments. Experiments utilized human umbilical vein endothelial cells (HUVECs) and streptozotocin-induced diabetic mice. In vitro evaluations focused on cell survival, vessel formation, and activation of critical pathways involving protein kinase B (Akt), extracellular signal-regulated kinase (ERK), p38, and vascular endothelial growth factor (VEGF). In vivo assessments measured wound closure rates. Results showed that abietic acid enhanced angiogenesis and stimulated key signaling cascades in cell cultures. In the animal model, treatment with abietic acid markedly sped up healing, achieving a 93.3% reduction in wound area by day 10 versus only 46.5% in untreated controls. These outcomes indicate abietic acid holds promise as a supportive agent for diabetic wound repair and merits additional research. Subsequent work should refine dosage regimens, assess markers of inflammation and oxidative stress, and test effectiveness in type 2 diabetes models to facilitate clinical application.

Keywords: Wound healing, Angiogenesis, Abietic acid, VEGF, HUVECs

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Introduction

Diabetes mellitus represents a long-term metabolic condition marked by ongoing hyperglycemia, which severely disrupts normal wound repair mechanisms [1]. Wounds in diabetic individuals typically display extended inflammatory phases, decreased new vessel development, and weakened cell division, problems worsened by advanced glycation end-products and elevated oxidative stress [2, 3]. Such abnormalities hinder effective healing and underscore the necessity for improved treatment options. Existing therapies for diabetic ulcers often rely on growth factors like platelet-derived and epidermal variants [4]. While beneficial for tissue repair, these agents carry notable drawbacks, including allergic responses and heightened cancer risk [5]. Hence, the search continues for safer, more reliable interventions.

Natural compounds have drawn considerable interest for their capacity to address diabetic complications [6, 7]. Pine rosin, used historically in traditional medicine, exhibits anti-inflammatory, antioxidant, and vessel-promoting activities [8]. Recent evidence points to abietic acid as the key contributor to these benefits. Studies indicate that abietic acid can regulate inflammation, counteract oxidative damage, and foster angiogenesis by boosting

endothelial cell growth and movement via the VEGF signaling route [9–12]. Nevertheless, detailed knowledge of how abietic acid functions specifically in high-glucose (HG) settings that replicate diabetes remains incomplete, limiting its targeted therapeutic advancement.

Pine rosin (colophony) is a hardened resin derived from pine tree oleoresin (*Pinus* species). It is composed mainly of abietane diterpene resin acids—including abietic acid, levopimaric acid, neoabietic acid, and palustric acid—that make up 80–90% of its content. These acids feature a tricyclic hydrophenanthrene skeleton with different oxidation states that underlie their anti-inflammatory and antioxidant capabilities. Minor neutral fractions and volatile terpenes may also be present, varying by origin and refinement [8, 13]. Given its established protective and vessel-stimulating properties, abietic acid was selected as the focal bioactive element from pine rosin for evaluation in diabetic wound contexts.

Prior investigations have noted wound-healing benefits from pine rosin preparations, yet limited work has isolated abietic acid's actions in hyperglycemic milieus that mirror diabetic physiology. The current investigation integrates cell-based and animal models to explore abietic acid's pro-angiogenic and inflammation-modulating properties while clarifying its molecular basis, offering fresh perspectives on its therapeutic value.

With diabetes rates rising globally alongside associated healing deficits, new treatment strategies are critically needed [14, 15]. This study therefore sought to determine abietic acid's impact on wound recovery in diabetic-like conditions. Particular attention was given to its influence on cell survival and vessel formation in HUVECs exposed to high glucose. Activation of essential pathways—Akt, ERK, p38, and VEGF—central to cell persistence, division, and angiogenesis was also examined [16, 17]. In vivo testing in a streptozotocin (STZ)-induced diabetic mouse model further evaluated wound closure efficacy [18]. To the best of our knowledge, this represents the initial comprehensive analysis of abietic acid's mechanistic contributions to wound healing in diabetic settings, potentially guiding the creation of improved, lower-risk options for better patient results.

Materials and Methods

Reagents

The EZ-Cytox Cell Viability Assay Kit was sourced from DoGenBio (Seoul, Korea). Antibodies targeting ERK, phosphorylated ERK (p-ERK), p38, phosphorylated p38 (p-p38), Akt, and phosphorylated Akt (p-Akt) came from Cell Signaling Technology, Inc. (Danvers, MA, USA). Fetal bovine serum was acquired from Invitrogen (Grand Island, NY, USA). Abietic acid ($\geq 98\%$ purity) was obtained from Sigma-Aldrich (St. Louis, MO, USA) and served as the primary test substance across experiments. Deoxyshikonin ($\geq 95\%$ purity) from Sigma-Aldrich acted as the positive control. Other chemicals, including DMSO and MTT, were analytical-grade products from standard vendors.

Cell culture

HUVECs were acquired from ATCC (Manassas, VA, USA) and employed between passages 3 and 6. Cells were maintained in Endothelial Cell Growth Medium-2 (EGM-2; Lonza, Walkersville, MD, USA) containing 10% FBS, penicillin/streptomycin, L-glutamine, and sodium pyruvate. Cultures were kept at 37 °C in a 5% CO₂ humidified incubator. Cells were pelleted by centrifugation, resuspended in fresh medium, and dissociated into single-cell suspensions.

Cell viability assay

Viability of HUVECs exposed to deoxyshikonin, rosin, and abietic acid was determined via the EZ-Cytox method. Cells received varying doses: deoxyshikonin (1.6–100 μ M), rosin (3.125–100 μ g/mL), and abietic acid (0.4–12.5 μ M). Seeding occurred at 1×10^4 cells/well in 96-well plates (100 μ L volume) followed by 24 h attachment. Compounds were then added for another 24 h incubation. Vehicle controls contained 0.5% (v/v) DMSO. After treatment, 10 μ L EZ-Cytox reagent was introduced per well for 30 min, and absorbance was read at 450 nm on a PowerWave XS microplate reader (Bio-Tek Instruments, Winooski, VT, USA). Blank wells consisted of medium plus reagent only.

Tube formation assay

Tube formation was evaluated in HUVECs according to established protocols [19]. Cells were plated on Matrigel-coated surfaces and exposed to non-toxic levels of deoxyshikonin, rosin, abietic acid, and high glucose (30 mM),

alone or in combination. All agents were prepared in culture medium. Angiogenic capacity was quantified via ImageJ software (NIH, Bethesda, USA) by assessing total tube length, junction (branch) count, and mesh area—standard metrics of endothelial vessel-forming potential.

Western blotting analysis

HUVECs (2×10^5 cells/mL) in 60-mm dishes were treated for 24 h with abietic acid (6.25 and 12.5 μ M), rosin (25 and 50 μ g/mL), or deoxyshikonin (3 and 6 μ M). Lysates were generated using RIPA buffer (Cell Signaling Technology) supplemented with protease inhibitors and 1 mM PMSF. Equal protein amounts (30 μ g/lane) underwent SDS-PAGE, transfer to PVDF membranes, and probing with specific primary and secondary antibodies. Phosphorylated forms were normalized to total proteins, with GAPDH as the loading control. Signals were detected with ECL Advance reagents (GE Healthcare, Buckinghamshire, UK) and imaged on a LAS 4000 system (Fujifilm, Tokyo, Japan).

Wound healing effect in a mouse model of cutaneous wounds

All procedures adhered to Gachon University animal care guidelines (approval GU1-2024-IA0027-00). Male ICR mice (4–5 weeks) were supplied by Orient Bio Co., Ltd. (Seongnam, Korea). Wound healing was tested in a full-thickness excisional model as outlined previously [17, 20]. A 5-mm circular skin wound was created on the dorsal surface. Animals were divided randomly into two groups ($n = 6$ each) and received daily applications of either distilled water (control) or abietic acid (1.6 μ M). Wound photographs were taken on days 0, 2, 4, 6, 8, and 10 with a 10-megapixel camera. Wound areas were measured using ImageJ, and closure percentage calculated as: [(initial area – current area)/initial area] $\times$ 100.

In silico molecular docking and structural analysis

Docking studies explored abietic acid's interaction with VEGF. The ligand's 3D structure was built and minimized with the MMFF94 force field. The human VEGF-A crystal structure (PDB ID: 3V2A) was obtained from the RCSB Protein Data Bank, stripped of waters, supplemented with polar hydrogens, and assigned Kollman charges via AutoDock Tools 1.5.6. Blind docking was executed with AutoDock Vina 1.2.5 using a grid encompassing the full protein. Twenty poses were produced (exhaustiveness = 8), and the lowest-energy conformation was chosen. The complex was visualized in PyMOL 2.5, with hydrophobic and hydrogen-bond interactions analyzed. 2D diagrams were created in BIOVIA Discovery Studio to highlight key binding residues.

Statistical analysis

Data were analyzed by ANOVA with Bonferroni post-hoc correction. Differences were deemed significant at $P < 0.05$.

Results and Discussion

This investigation examined abietic acid, the predominant resin acid in pine rosin, for its capacity to promote diabetic wound healing in high-glucose settings. Multiple *in vitro* and *in vivo* experiments evaluated impacts on endothelial viability, angiogenesis, pathway activation, and wound closure in diabetic mice.

Prior to testing under high-glucose stress, non-cytotoxic concentration ranges for HUVECs were established with the Ez-Cytox assay (**Figure 1**). Rosin, abietic acid, and deoxyshikonin (positive angiogenesis control) were screened across concentration gradients: deoxyshikonin from 1.6–100 μ M, rosin from 3.125–100 μ g/mL, and abietic acid from 0.4–12.5 μ M. Deoxyshikonin exhibited notable toxicity (20.8–76.9% reduction) starting at 6.25 μ M, while abietic acid showed moderate toxicity (15.4–33.5%) beginning at 12.5 μ M. Rosin displayed strong toxicity (84.6–86.5%) at 50–100 μ g/mL. Safe concentrations identified in these viability tests were subsequently applied in tube formation studies.

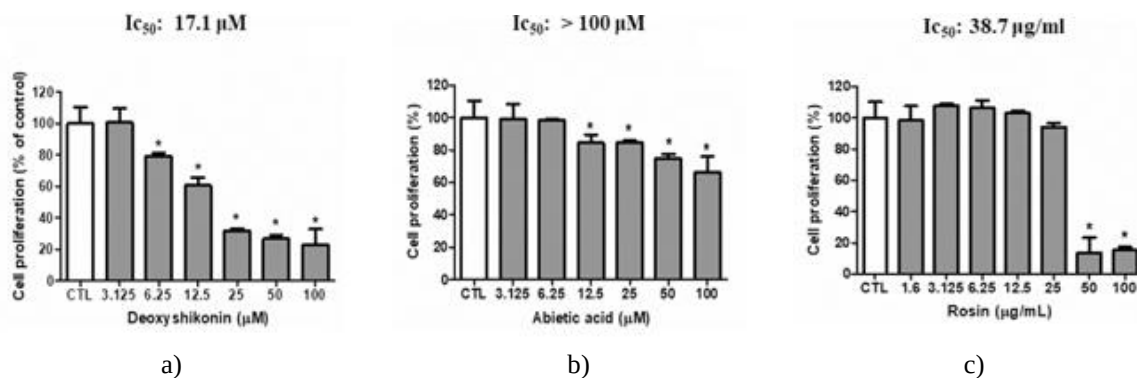


Figure 1. Influence of deoxyshikonin, abietic acid, and rosin on the viability of HUVECs. Cells were exposed to varying concentrations of deoxyshikonin, rosin, or abietic acid for 24 hours. Viability was measured with the EZ-Cytox assay. a) Deoxyshikonin (1.6, 3.125, 6.25, 12.5, 25, 50, and 100 μM) b) Rosin (3.125, 6.25, 12.5, 25, 50, and 100 μg/mL) c) Abietic acid (0.4, 0.8, 1.6, 3.2, 6.25, and 12.5 μM). *p < 0.05 versus the control group.

In the tube formation assay performed under high-glucose conditions (**Figure 2**), angiogenesis in the HG control group was suppressed by 48.5% relative to the normal glucose group. Treatment with deoxyshikonin (3 μM) and rosin (25 μg/mL) notably enhanced tube formation, increasing it by 22.6 percent and 11.3 percent, respectively, compared with HG treatment alone. Abietic acid also produced significant, concentration-dependent improvements in tube formation (19.1% and 26% increases) over the HG-only group. Notably, abietic acid outperformed rosin in promoting vessel formation and achieved effects comparable to the positive control deoxyshikonin. These findings indicate that abietic acid helps preserve endothelial cell function critical for wound repair by mitigating the anti-angiogenic impact of elevated glucose levels.

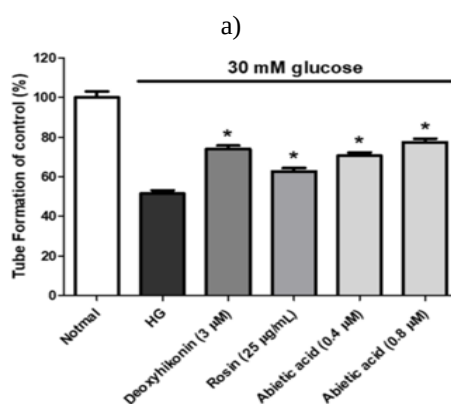
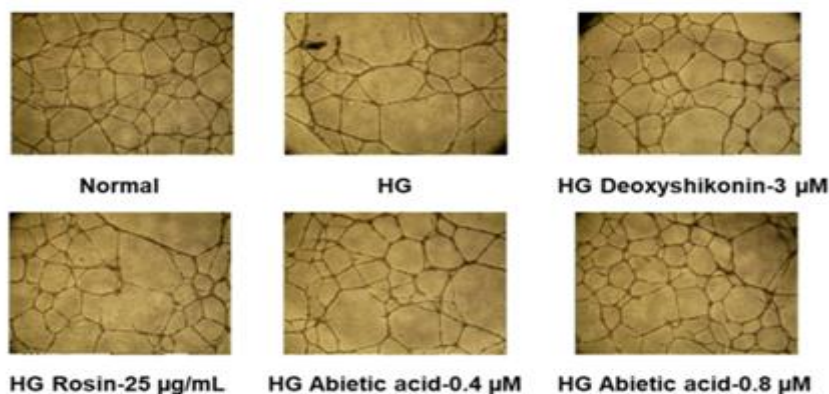


Figure 2. Influence of rosin, abietic acid, and deoxyshikonin on the formation of tubular structures by HUVECs. a) Representative microscopic images showing tube networks in HUVECs incubated for 24 hours

in the presence or absence of rosin, abietic acid, or deoxyshikonin. b) Quantitative assessment of angiogenic tube parameters determined with ImageJ software. * $p < 0.05$ versus the high-glucose group.

Western blot experiments were conducted to determine how rosin, abietic acid, and deoxyshikonin affect key signaling molecules in HUVECs (**Figure 3**). The analysis focused on phosphorylation status of Akt, ERK, and p38, along with VEGF protein abundance, under both standard and high-glucose environments.

Exposure to high glucose alone caused substantial downregulation of these proteins compared with normal conditions. p-Akt expression fell by 44%. When cells received HG plus rosin (25 $\mu\text{g/mL}$), p-Akt rose by 5% above the HG baseline. Addition of abietic acid at 0.4 μM increased p-Akt by 17%, while 0.8 μM raised it by 26%. The positive control deoxyshikonin (3 μM) under HG conditions elevated p-Akt by 33%.

p-ERK levels decreased markedly by 65% in HG. Co-treatment with rosin (25 $\mu\text{g/mL}$) restored p-ERK by 48%. Abietic acid at 0.4 μM enhanced p-ERK by 60%, 0.8 μM by 58%, and deoxyshikonin (3 μM) by 54% relative to HG alone.

HG suppressed p-p38 expression by 59%. Rosin (25 $\mu\text{g/mL}$) increased p-p38 by 32% over HG. Abietic acid produced further recovery: 40% at 0.4 μM and 51% at 0.8 μM . Deoxyshikonin (3 μM) improved p-p38 levels by 56%.

VEGF protein was reduced by 65% under HG conditions. Rosin (25 $\mu\text{g/mL}$) elevated VEGF by 44%. Abietic acid treatment yielded increases of 59% (0.4 μM) and 57% (0.8 μM), whereas deoxyshikonin (3 μM) produced the strongest upregulation at 86% compared with the HG control group.

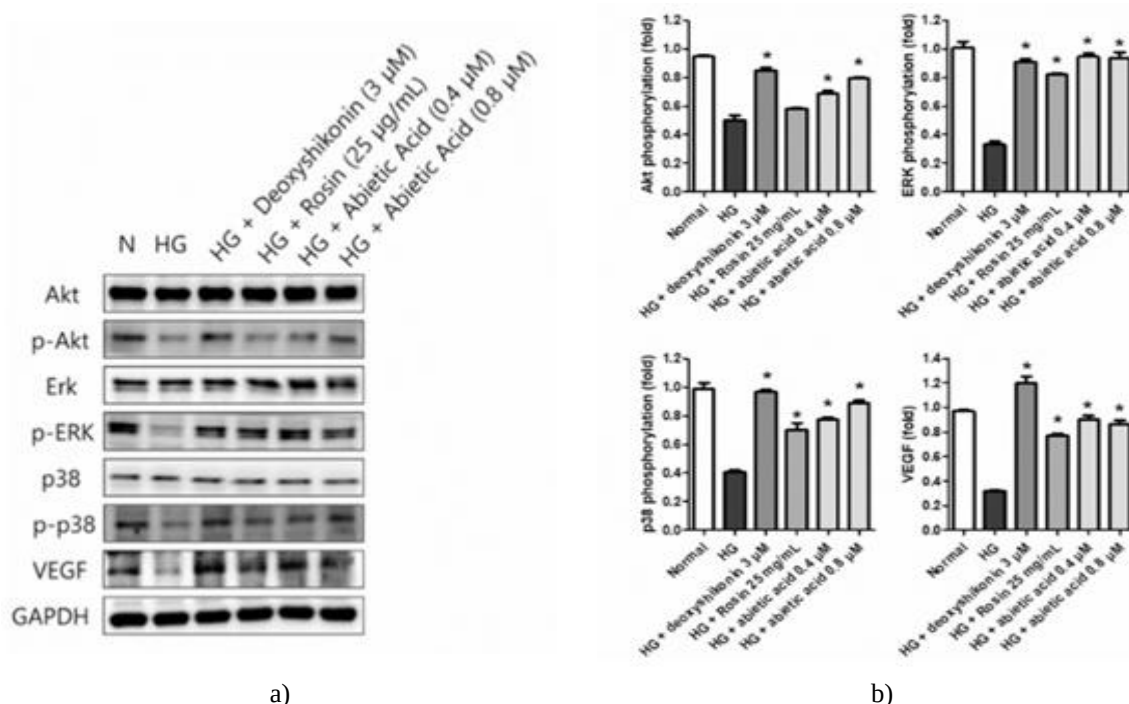


Figure 3. Influence of rosin, abietic acid, and deoxyshikonin on protein expression profiles in HUVECs. Western blotting was used to evaluate p-Akt, p-ERK, p-p38, and VEGF expression under normal glucose and high-glucose conditions. a) Representative Western blot images depicting bands for p-Akt, p-ERK, p-p38, and VEGF. b) Densitometric quantification of protein bands normalized to control. Results are expressed as fold change relative to the normal control group. * $p < 0.05$ versus the HG group. Treatment groups included: normal glucose, HG alone, HG + rosin (25 $\mu\text{g/mL}$), HG + abietic acid (0.4 μM), HG + abietic acid (0.8 μM), and HG + deoxyshikonin (3 μM).

Further confirmation through Western blot analysis demonstrated elevated expression of key angiogenic and survival proteins—including p-Akt, p-ERK, p-p38, and VEGF—following exposure to abietic acid [21, 22]. These molecules are vital regulators of tissue repair and new vessel growth. Phosphorylation of Akt supports cell survival and mitotic activity. The observed rise in p-Akt upon abietic acid treatment points to strengthened endothelial cell resilience and proliferative capacity, both essential for effective angiogenesis and wound closure [23, 24].

ERK activation is closely linked to cell cycle progression and differentiation. Heightened p-ERK following abietic acid exposure implies that the compound drives endothelial cell multiplication and maturation, thereby facilitating neovascularization [25, 26]. The p38 pathway participates in cellular adaptation to stress and inflammatory signals. Increased p-p38 levels suggest abietic acid helps balance inflammatory processes, creating a more favorable setting for tissue regeneration [27, 28]. Overall, abietic acid produced effects comparable to the positive control deoxyshikonin, robustly activating angiogenic signaling cascades that support the wound healing cascade [29, 30].

VEGF stood out as a central factor in this investigation due to its pivotal function in vessel development and tissue repair. The pronounced increase in VEGF expression after abietic acid administration highlights its contribution to improved vascularization, ensuring better perfusion and nutrient supply to injured areas [31, 32].

The efficacy of abietic acid for treating diabetic wounds was tested in an STZ-induced diabetic mouse model (**Figure 4**). Animals received daily topical application of abietic acid (1.6 μ M) directly to the wound for a period of 10 days. Wound progression was documented photographically at regular daily intervals (**Figure 4a**). In the diabetic control group, healing progressed slowly through the initial five days. In contrast, the abietic acid-treated cohort displayed markedly faster wound contraction. By day 10, wound closure was substantially advanced in the treatment group compared with STZ controls. Visible improvements in the abietic acid group became apparent starting around day 4.

Quantitative measurements of wound area (**Figure 4b**) supported these visual findings. On day 2, wound size decreased by 12.6% in the abietic acid group versus only 3.6% in the STZ-only group. By day 4, reductions reached 40.3% and 18.7%, respectively. On day 6, the abietic acid group achieved a 57.6% reduction compared with 28.5% in controls. Day 8 showed an 82.3% decrease in the treated group against 39.2% in untreated diabetic mice. By day 10, wound area had diminished by 93.3% in animals receiving abietic acid, while the STZ-only group exhibited just 46.5% closure.

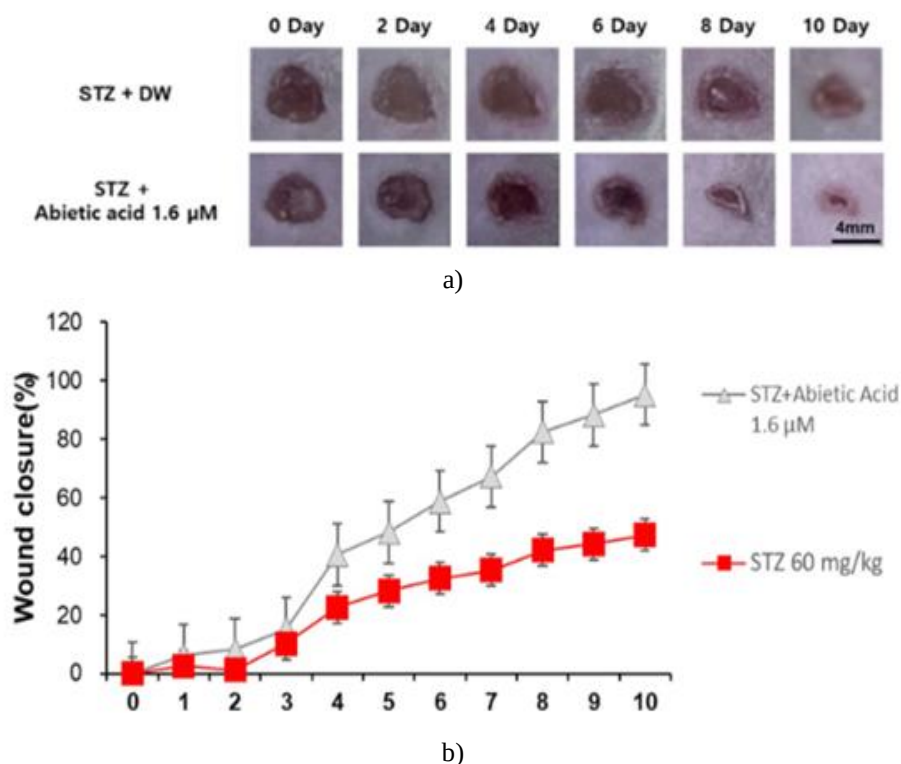


Figure 4. Impact of abietic acid on cutaneous wound repair in a diabetic mouse model. a) Side-by-side comparison of wound closure progression between the treatment group (1.6 μ M abietic acid) and the untreated control group. Representative photographs taken on days 0, 2, 4, 6, 8, and 10 post-treatment. b) Graph showing quantitative changes in wound area for the abietic acid-treated mice versus controls. * $p < 0.05$ compared with the control group.

Experiments conducted in STZ-induced diabetic mice confirmed that topical application of abietic acid markedly sped up wound closure relative to untreated diabetic animals. Wounds receiving abietic acid displayed improved tissue repair and accelerated recovery overall.

To explore the underlying molecular interactions responsible for these benefits, computational docking studies were carried out to assess potential direct binding between abietic acid and VEGF, a major driver of new blood vessel formation. The simulations indicated a high binding affinity of -10.11 kcal/mol, with abietic acid docking into the critical N-terminal region of VEGF that interacts with its receptor. The binding site was largely hydrophobic, involving residues such as PHE17, MET18, VAL20, TYR21, CYS60, and CYS61, which created a stable pocket enclosing the ligand. Two-dimensional interaction mapping showed approximately 120 hydrophobic interactions with very limited hydrogen bonds, suggesting a primarily entropy-driven and robust association (**Figure 5**).

These *in silico* observations align well with the experimental data, where abietic acid increased phosphorylation of Akt, ERK, and p38 while elevating VEGF levels in high-glucose conditions, ultimately promoting stronger angiogenic responses and better endothelial performance.

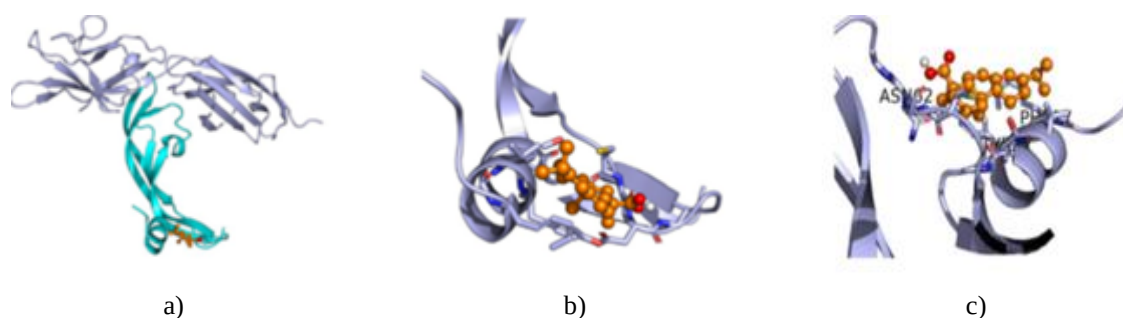


Figure 5. Computational docking of abietic acid with VEGF. a) Global view of abietic acid (shown in yellow) docked onto the VEGF dimer structure (blue). b) Enlarged image of the binding site highlighting surrounding key amino acid residues (PHE17, MET18, VAL20, TYR21, CYS60–61) interacting with the ligand. c) Two-dimensional diagram depicting the hydrophobic contacts and any hydrogen-bond interactions between abietic acid and VEGF. Docking analysis demonstrated a favorable binding energy of -10.1 kcal/mol, with abietic acid positioned in the region of VEGF critical for VEGFR interaction.

The accelerated wound repair observed is primarily attributed to strengthened angiogenesis and stimulation of beneficial signaling cascades identified in the cell-based experiments. Although oxidative stress and inflammation markers were not examined in the current work, upcoming investigations should explore abietic acid's potential effects on these aspects in diabetic wound contexts [33, 34]. While lower doses were selected for *in vitro* experiments to prevent cell toxicity, a higher concentration ($1.6 \mu\text{M}$) was applied topically in the animal studies. This elevated dose proved safe with no apparent adverse effects, possibly because of rapid metabolism, binding to plasma proteins, and tissue distribution that collectively reduce the free concentration of abietic acid at the wound site.

By enhancing new blood vessel formation, abietic acid represents a promising option for treating diabetic ulcers. The present results are consistent with earlier reports on its tissue repair capabilities, reinforcing its therapeutic promise [10, 35].

Additional studies are required to determine optimal dosing regimens and suitable delivery systems for potential human use. Extended trials will be important to confirm long-term safety and effectiveness across varied diabetic patient groups. Investigating possible combined therapies with other agents may also yield more effective strategies for comprehensive diabetic wound management.

Several limitations of this study should be noted. The experiments utilized an STZ-induced type 1 diabetes model in mice, whereas the majority of human diabetic wounds arise in type 2 diabetes. Physiological distinctions between these conditions need careful consideration when interpreting the outcomes. Furthermore, the full-thickness wounds were created on the back skin of mice, which differs significantly from typical human diabetic foot ulcers in location, exposure to pressure, and healing characteristics. These factors may restrict immediate applicability to clinical settings. Future work should therefore incorporate type 2 diabetes models and wound systems that better replicate human pathology to improve translational relevance of abietic acid.

Conclusion

In summary, abietic acid derived from pine rosin shows considerable promise as a therapeutic compound for supporting diabetic wound healing. Its capacity to improve endothelial cell survival, stimulate angiogenesis, and trigger important intracellular pathways such as Akt, ERK, VEGF, and p38 highlights its value for managing diabetic ulcers. The data presented here establish a solid basis for continued exploration and potential clinical development of abietic acid-based treatments.

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Conflict of Interest: None

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Ethics Statement: None

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