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ORIGINAL ARTICLE

Comparative Effects of Topically Applied Tocotrienol (T3) Isomers in Promoting Cutaneous Wound Healing in Obese Type 2 Diabetes Mice

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ABSTRAK

Ulser kaki diabetes merupakan komplikasi signifikan terutama bagi pesakit diabetes jenis 2 dan obes. Ini disebabkan oleh persekitaran keradangan dan tekanan oksidatif yang melampau serta berterusan di dalam luka, justeru menghalang penyembuhan. Tokotrienol, sejenis fitokimia dengan sifat antioksidan dan anti-radangnya, berpotensi sebagai terapeutik yang berkesan. Oleh itu, kajian ini bertujuan menyelidik kesan penyembuhan isomer tokotrienol (α-, β-, δ- dan γ-T3) secara topikal terhadap luka kulit eksisi ketebalan penuh pada mencit jantan B6.V-Lepob/JRj. Keberkesanan rawatan dinilai melalui kadar penutupan luka, histopatologi, pemendapan kolagen, kandungan hidroksiprolin dan tahap superoksida dismutase, katalase, glutation peroksidase, glutation, malondialdehid dan mieloperoksidase dalam tisu granul luka. Tahap sitokin, kemokin dan faktor pertumbuhan diukur menggunakan asai Luminex. Kehadiran isomer dalam tisu granulasi luka ditentukan oleh kromatografi cecair berprestasi tinggi. Keputusan menunjukkan bahawa isomer T3 membantu penjanaan semula tisu dan mempercepatkan penutupan luka. Ia mengurangkan tekanan oksidatif dengan menurunkan tahap malondialdehid dan mieloperoksidase, sambil meningkatkan aktiviti dan pengeluaran antioksidan. Isomer ini berkesan mengurangkan sitokin dan kemokin pro-radang, sambil meningkatkan sitokin anti-radang dan memodulasi faktor pertumbuhan, dengan itu menggalakkan penyembuhan luka dalam mencit B6.V-Lepob/JRj. Penemuan ini menunjukkan bahawa isomer T3 mampu berfungsi sebagai agen bioaktif terapeutik yang mempercepatkan penyembuhan luka kulit bagi individu yang menghidap diabetes.

Kata kunci: *Anti-radang; antioksidan; mencit diabetik jenis 2; penyembuhan luka kulit; tokotrienol, rawatan topikal*

ABSTRACT

Diabetic foot ulcers are a significant complication, especially for type 2 diabetes and obese patients. This is mainly caused by an excessive and persistent inflammatory-oxidative stress environment in the wounds, which impedes healing. Tocotrienol, a phytochemical with antioxidant and anti-inflammatory properties, holds notable therapeutic potential. Therefore, this study aimed to investigate the healing effects of topically applied tocotrienol isomers (α-, β-, δ- and γ-T3) on full-thickness excisional cutaneous wounds in male *B6.V-Lepob/JRj* mice. Treatment effects were evaluated through wound closure rate, histopathology, collagen deposition, hydroxyproline content and the levels of superoxide dismutase, catalase, glutathione peroxidase, glutathione, malondialdehyde and myeloperoxidase in the wound granulation tissues. Cytokine, chemokine, and growth factor levels were quantified using the Luminex assay. The presence of isomers in wound granulation tissue was determined by high-performance liquid chromatography. Results showed that T3 isomers facilitated tissue regeneration and hastened wound closure. They significantly reduced oxidative stress by lowering malondialdehyde and myeloperoxidase levels and by enhancing antioxidant activity and production. These isomers effectively diminished pro-inflammatory cytokines and chemokines, while increasing anti-inflammatory cytokines and modulating growth factors, thereby promoting wound healing in *B6.V-Lepob/JRj* mice. These findings suggest that T3 isomers may serve as therapeutic agents that enhance cutaneous wound healing in individuals with diabetes.

Keywords: Anti-inflammatory; antioxidant; skin wound healing; tocotrienol; topical treatment; type 2 diabetic mice

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a highly prevalent chronic disease, accounting for ~90% of all diabetes cases (Rasouli et al. 2023). It is characterised by persistent hyperglycaemia, which impairs wound healing and increases the risk of diabetic foot ulcers (Kibibi 2024). Cutaneous wound healing involves four overlapping phases: haemostasis, inflammation, proliferation and remodelling, which are essential for restoring skin integrity (Ciucanu et al. 2024; Landén et al. 2016). In T2DM, healing is delayed due to chronic inflammation, oxidative stress, impaired angiogenesis and defective granulation tissue formation (Bitar 2019; Chen et al. 2022; Ramachandran et al. 2022; Saeed & Martins-Green 2024). Obesity, present in 80-90% of T2DM patients, exacerbates insulin resistance and further impairs tissue repair (Baldeon-Gutierrez et al. 2025; Gostoli et al. 2024).

Hyperglycaemia-induced reactive oxygen species (ROS) overwhelm antioxidant defences, including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione (GSH), causing oxidative stress that impairs cellular protection and wound healing (Abdul Jalil et al. 2024; Bhatti et al. 2022; Deng et al. 2021; González et al. 2023). Elevated malondialdehyde (MDA) and myeloperoxidase (MPO) contribute to tissue damage and sustained inflammation in diabetic ulcers (Memarpour et al. 2024; Thimmappa et al. 2023). Dysregulated cytokines, including chemokines, interferons, interleukins and growth factors, further disrupt healing by prolonging inflammation (Ahmad et al. 2025; Alexeev et al. 2025; Da Silva et al. 2025; Siebeler et al. 2023).

Tocotrienols, a natural bioactive form of vitamin E, are derived from various plant sources, including rice bran, palm oil and annatto (Ibrahim et al. 2015; Pierpaoli et al. 2017; Yeganehjoo et al. 2024; Younes et al. 2024). The distinctive structural properties of tocotrienols contribute to their diverse biological activities, rendering them a subject of growing research interest, encompassing neuroprotective, radioprotective, anticancer, anti-inflammatory and lipid-lowering effects (Medvedev & Medvedeva 2018; Morgan

et al. 2024; Yeganehjoo et al. 2024). Tocotrienol comprises four forms: α-, β-, γ- and δ-tocotrienols (Razali et al. 2025; Yeo et al. 2021), and exhibits antioxidant and anti-inflammatory properties, thereby rendering it suitable for counteracting inflammatory processes and oxidative stress (Razali et al. 2025). Tocotrienols have shown promise in enhancing wound healing due to their antioxidant, anti-inflammatory and cell-signalling properties. Recent research has focused on their application in various wound healing models, including diabetic wounds and burn injury, highlighting tocotrienols' ability to modulate oxidative stress and inflammation and promote tissue regeneration, making them a viable alternative to traditional wound healing agents (Guo et al. 2020; Guo et al. 2022; He et al. 2023; Nair et al. 2022; Shahrim et al. 2022; Xu et al. 2017).

Despite extensive evidence supporting the antioxidant and anti-inflammatory properties of tocotrienols, most previous investigations have utilised mixed tocotrienol-rich fractions (TRF), making it difficult to discern the distinct biological contributions of each isomer. Furthermore, while DFUs occur in both type I and type II diabetes, their prevalence is higher in type II diabetes (Wang et al. 2025). A genetic type 2 diabetic mouse model closely mimics the chronic hyperglycaemia, oxidative stress and impaired angiogenesis characteristic of real diabetic wound pathology. Therefore, this study was conducted to investigate the isomer-specific effects of tocotrienols on type 2 diabetic cutaneous wound healing in B6.V-Lepob/JRj mice, as an emerging bioactive agent that may generate mechanistic and translational insights that existing TRF-based wound studies lack.

MATERIALS AND METHODS

Materials and Topical Formulation

Palm tocotrienol (T3) isomers, with respective purities of alpha-tocotrienol (α-T3, 97%), beta-tocotrienol (β-T3, 97%), delta-tocotrienol (δ-T3, 97%) and gamma-tocotrienol (γ-T3, 97%), were purchased from Davos Life Science Pvt. Ltd. (Singapore). The base formulation (vehicle) consisted of polyethene glycol (PEG)-400 and Tween 80, purchased from Sigma-Aldrich (St. Louis, MO, USA). The mixture was prepared as previously described (Ali et al. 2010; Alqahtani et al. 2013; Shahrim et al. 2022), composed of tocotrienol isomers (10%, w/w) and was loaded into the formulation base containing PEG-400 (85%, w/w) and Tween 80 (5%, w/w) (Suminar et al. 2017). The mixture was stored in a refrigerated temperature (4°C) and kept in an amber, airtight container.

Experimental Mice and Animal Husbandry

A male *B6.V-Lepob/JRj* (T2D/OB control) mouse, aged 10 weeks, was obtained from Janvier Laboratories (Le Genest-Saint-Isle, France) and exhibited numerous characteristics of human type 2 diabetes (Suriano et al. 2021). Additionally, their corresponding normoglycemic, non-obese wild-type (WT) mice, aged 10 weeks, were obtained from InVivos, Singapore and used solely to establish baseline wound-healing parameters in the absence of complications related to diabetes and obesity. The mice were acclimated for one week and housed in individually ventilated cages (IVCs) at 21 ± 1 °C and 50 ± 10% relative humidity, under a 12-hour light-dark cycle, with ad libitum access to food and water. Following a 12-hour fast, blood samples were collected from the tail vein to assess blood glucose and serum insulin levels using an Accu-Chek device (Roche GmbH, Mannheim, Germany) and an ELISA kit (Millipore, St. Charles, MO, USA), respectively. All procedures received approval from the Universiti Kebangsaan Malaysia Ethics Committee (UKMAEC; Procedure number: BIOK/PP2017/SUZANA/25-JAN./817-JAN.-2017-SEPT.-2018) and complied with Animal Research: Reporting of In Vivo Experiments guidelines.

Sample Size and Animal Grouping

An a *priori* power analysis was performed using G*Power, version 3.1.9.4 9 Heinrich-Heine-

Universität Düsseldorf, Düsseldorf, Germany) to estimate the necessary sample size. Considering a large effect size (f = 0.4) (Abdo et al. 2025, Cohen 2013; Lakens 2013; Salem et al. 2024), with $\alpha = 0.05$ and a target power of 90%, it was determined that 24 mice per group were needed, leading to a total sample size of n = 144.

The mice were grouped as follows: (i) Group 1: WT (receive vehicle alone); (ii) Group 2: T2D/OB control (receive vehicle alone); (iii) Group 3: T2D/OB+α-T3 (receive α-tocotrienol in vehicle); (iv) Group 4: T2D/OB+β-T3 (receive β-tocotrienol in vehicle); (v) Group 5: T2D/OB+δ-T3 (receive δ-tocotrienol in vehicle); (vi) Group 6: T2D/OB+γ-T3 (receive γ-tocotrienol in vehicle).

Wounding Procedures and Treatment

Body weights, glucose and insulin levels were recorded at baseline (day 0) and on days 1, 3, 7 and 14 after wounding. Following anaesthesia with sodium pentobarbital (60 mg/kg), the dorsal fur was depilated using hair removal cream (Veet, UK) (Medina et al. 2024). The skin was disinfected with 75% alcohol, and four wounds were created using a 5-mm punch biopsy (Kai Industries Co., Ltd., Seki, Japan). To prevent wound contraction (Miller et al. 2025), the wound perimeter was secured with a silicone splint (Grace Bio-Labs, Oregon, USA) and cyanoacrylate glue (Krazy Glue, Elmer's Inc., Columbus, Ohio, USA), then sutured with 3.0 nylon sutures (Ethicon, Somerville, NJ, USA). 10% (w/w in vehicle) of tocotrienol isomers was applied topically daily for 14 days. The wound was then covered with a transparent semi-permeable dressing (3M Tegaderm, St. Paul, MN, USA) and bandaged with gauze. Day 0 was defined as the day on which the wounds were created. To harvest the tissue, mice were euthanised by CO_2 inhalation and cervical dislocation at the specified days for histopathological and biochemical analyses.

Wound Closure Kinetics

Wound size was monitored daily and images were captured on days 0, 1, 3, 7 and 14 using a digital camera, subsequently quantified utilising Fiji software (NIH Image, USA) (Gomes et al. 2025) with the following formula: Wound closure (%) = 100 [Area of the wound (day 0) – Area of the wound (day n)] / Area of the wound (day 0), where n represented the day after wounding.

Histopathological and Histomorphometry Analyses

Skin samples were excised as described elsewhere (Shao et al. 2021), fixed in 10% neutral buffered formalin (Sigma-Aldrich, St. Louis, MO, USA), dehydrated, embedded in paraffin, sectioned at 4 μm, deparaffinised, dehydrated again and stained with haematoxylin and eosin (H&E) and Masson's trichrome (MT). A semi-quantitative wound assessment of histopathological findings, skin regeneration and scoring (Table 1) was performed by a pathologist in a single-blind manner. Sections were examined under a light microscope (Olympus DP73 camera; Olympus Corporation, Tokyo, Japan) mounted on an Olympus BX53 microscope. Masson's trichrome-stained collagen was analysed using Fiji/ImageJ (NIH, USA) (Verly et al. 2021).

TABLE 1: Histological features and scoring scheme

Histological features	Score				
	0	1	2	3	4
Inflammatory cells	Absence	Occasionally presence	Light scattering	Abundance	Confluence
Fibroblast proliferation	Absence	Occasionally presence	Light scattering	Abundance	Confluence
Angiogenesis	Absence	Occasionally presence	Light scattering	Abundance	Confluence

Preparation of Tissue Homogenate

For biochemical assays, wound granulation tissues were homogenised using a TissueLyser LT (Qiagen, Hilden, Germany) with 5 mm beads in TPER® buffer (Thermo Fisher Scientific, Rockford, IL, USA) at 50 Hz. The lysed tissue was centrifuged for 30 minutes at 5,000 rpm at 4°C and then stored at -80°C for further analysis.

Oxidative Markers and Hydroxyproline Content

Oxidative marker activities in wound granulation tissues, including SOD (Cat. No. 706002), CAT (Cat. No. 707002), GPx (Cat. No. 703102), GSH (Cat. No. 703002) and to measure the MDA, TBARS Assay (Cat. No. 10009055) Cayman assay kits (Cayman Chemical, Ann Arbour, MI, USA) were used. Meanwhile, MPO (Cat. No. K747-100), activity and hydroxyproline content (Cat. No. K555-100) were determined using the BioVision assay kit (Biovision, Milpitas, CA, USA). All procedures were performed according to the manufacturer's instructions.

Immunomarker Profiling

The Luminex assay using Invitrogen ProcartaPlex™ Multiplex Immunoassays (ThermoFisher, Waltham, MA, USA) was performed according to the manufacturer's instructions to measure tumour necrosis factor alpha (TNF-α), interleukin (IL)-1α, -6, -1β, -12p40, -17A, -4, -9, -10, leucine inhibitory factor (LIF), receptor activator of nuclear factor kappa-B ligand (RANKL), interferon (IFN)-γ, C-X-C motif chemokine ligand (CXCL) (CXCL1, CXCL2, CXCL5, CXCL10), and chemokine (C-C motif) ligand (CCL) (CCL2, CCL5, CCL7), vascular endothelial growth factor (VEGF)-A, betacellulin (BTC), and granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF) in wound granulation tissues. The luminescent signal was detected using the Luminex® 200TM system with xPONENT 3.1 software, version 3.1 (Luminex Corporation, Austin, Texas, USA).

High-Performance Liquid Chromatography Analysis

The presence of tocotrienol isomers in wound granulation tissue after topical application was determined by High-Performance Liquid Chromatography (HPLC). Briefly, the tissues were weighed, homogenised using 0.1 M Tris-HCl (pH 7.5) at 4°C, and then centrifuged at 10,000 × g for 10 minutes. The top layer was collected (100 µL), mixed with 10 mg/mL butylated hydroxytoluene in 95% ethanol, and then with 500 µL of 100% ethanol. The mixture was centrifuged at 3,000 × g for 15 minutes at 18°C. The supernatant obtained was mixed with 1.5 mL of hexane (Merck, Germany) and centrifuged at 3,000 × g for 15 minutes at 18°C. The top layer (2.5 ml) was transferred to a fresh tube, vacuum-dried (Heto Lab Equipment, Allerød, Denmark) and stored at -20°C for subsequent analysis. The samples were prepared using HPLC-grade hexane (1:100). HPLC analysis was performed using an LC-10AT system (SCL-10A system controller and SIL-10A auto-injector) and a cooler (Shimadzu, Kyoto, Japan). The isomer concentrations were presented in µg/mL as described elsewhere (Taridi et al. 2014).

Statistical Analysis

Statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS), version 22.0 (IBM Corp., Armonk, NY, USA), with six biological replicates per group. All graphs were created with Prism 9 (GraphPad Software Inc., USA). Statistical significance was set at $p < 0.05$, and data are presented as mean ± SEM. Groups were compared using two-way ANOVA followed by *Tukey's* post hoc test.

RESULTS

Body Weight, Glucose and Insulin Levels

The representative photograph of WT and T2D/OB mice used was shown in Figure 1A. All T2D/

OB mice had higher body weights than WT (Figure 1B). Higher mean fasting blood glucose was also observed in T2D/OB compared to the WT group (Figure 1C), as well as higher insulin levels compared to the WT group on day 14 after wounding (Figure 1D).

T3 Isomers Improve Wound Healing in T2D/OB Mice

Representative images of the excisional wound and sutured created (Figure 2A). Gross appearance of wounds at 0, 1, 3, 7 and 14 days after surgery (Figure 2B). At the macroscopic level, the WT group showed the highest wound closure percentage (99.4%) and visible hair growth by day 14 post-wounding. The T2D/OB control group, however, had the lowest rate, with a closure rate of 39%. Nevertheless, treatment with T3 isomers demonstrated significant improvement, with higher closure rates: α-T3 (77%) > γ-T3 (63%) > δ-T3 (60%) > β-T3 (59%) compared to the T2D/OB control (Figure 2C).

Microscopic Examination of the T3 Isomer-Treated T2D/OB Wound

Representative H&E photomicrographs at days 7 and 14 were shown in Figure 3, with corresponding histological scores summarised in Table 2. T3 isomer treatment significantly attenuated inflammatory cell infiltration while promoting fibroblast proliferation and angiogenesis relative to the T2D/OB control. Quantitative analysis revealed greater epidermal thickness in wounds treated with α-T3 > γ-T3 > δ-T3 > β-T3 at both days 7 and 14 (Figure 4A). Similarly, dermal thickness increased in the order α-T3 > δ-T3 > γ-T3 > β-T3 on day 7 and α-T3 > γ-T3 > δ-T3 > β-T3 on day 14, compared to T2D/OB control (Figure 4B), indicating enhanced tissue remodelling under T3 isomer treatment.

T3 Isomers Enhanced Collagen Deposition and Hydroxyproline Levels in the T2D/OB

Representative Masson's Trichrome-stained photomicrographs (Figure 5A) demonstrate collagen deposition within wound tissues. The WT group exhibited substantial collagen accumulation by day 14 post-injury, whereas the T2D/OB control showed minimal deposition at day 7 with only a modest increase by day 14. However, treatment with the T3 isomers markedly enhanced collagen synthesis, as evidenced by intensified Trichrome staining from day 7 to day 14 compared with the T2D/OB control. Quantitative assessment (Figure 5B) indicated that collagen deposition followed the order α-T3 > γ-T3 > δ-T3 > β-T3 at both time points. Consistently, hydroxyproline quantification (Figure 5C) revealed elevated levels in the order α-T3 > γ-T3 > β-T3 > δ-T3 on day 7 and α-T3 > γ-T3 > δ-T3 > β-T3 on day 14, compared with the T2D/OB control.

T3 Isomers Improved Antioxidant Status and Reduced Oxidative Stress in the T2D/OB Wound

The T2D/OB control group exhibited significantly lower activities of SOD (Figure 6A), CAT (Figure 6B), GPx (Figure 6C) and GSH (Figure 6D) on days 3, 7 and 14 compared with the WT group. In contrast, MDA concentrations (Figure 6E) and MPO activity (Figure 6F) were elevated in the diabetic control group. However, treatment with α-T3 resulted in the highest SOD activity on days 7 and 14 and CAT activity on days 3, 7 and 14, compared with the T2D/OB control, respectively. Moreover, GPx activity was highest in the α-T3 group on days 3 and 14, and in the β-T3 group on day 7, whereas GSH levels peaked in δ-T3 on day 3 and in α-T3 on days 7 and 14, compared to T2D/OB control, respectively. Conversely, MDA levels were most reduced in group α-T3 on days 3 and 14 and in group δ-T3 on day 7. The greatest MPO suppression was observed in group δ-T3 on day 3 and in group γ-T3 on days 7 and 14 compared to the T2D/OB control.

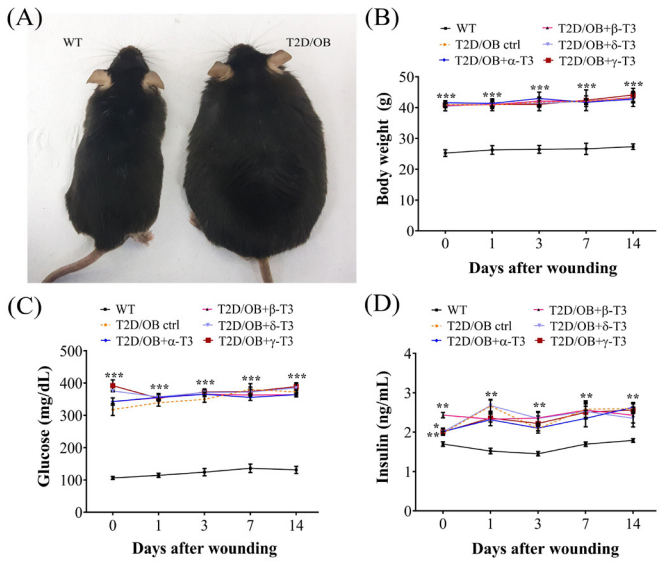

FIGURE 1: Physiological and metabolic parameters. (A) Representative images of WT and T2D/OB mice; (B) body weight; (C) glucose; and (D) insulin. Data were presented as mean ± SEM (n = 12); $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$ *vs* WT group.

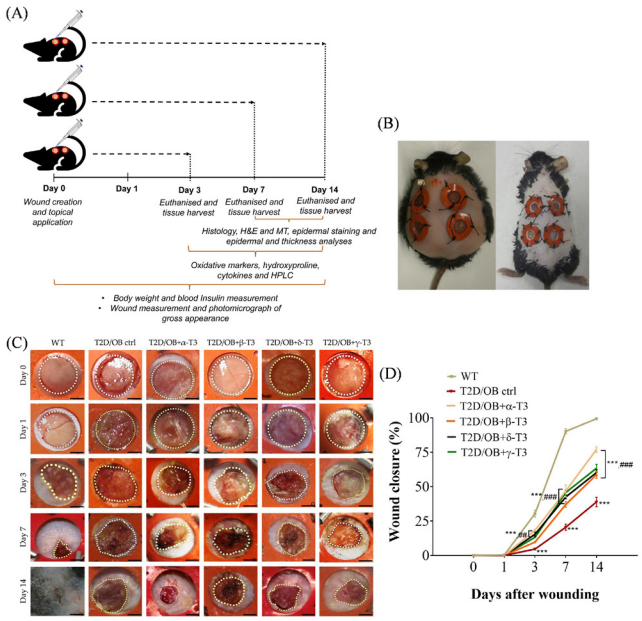

FIGURE 2: T3 isomers enhanced wound closure in T2D/OB wounds. (A) Treatment workflow. Representative images of the excisional wound made on mice (B), images of gross appearance after wounding (C) and percentage of wound closure rate (n = 12). Data were expressed as mean ± SEM (n = 6); $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$ *vs* WT group; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$ *vs* T2D/OB control (ctrl) group.

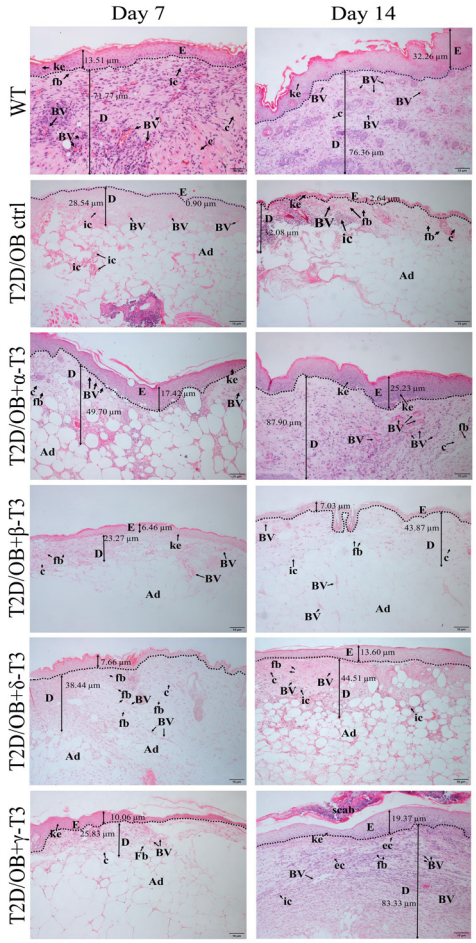

FIGURE 3: T3 isomers enhanced wound closure in T2D/OB wounds. (A) Treatment workflow. Representative images of the excisional wound made on mice; (B) images of gross appearance after wounding; (C) and percentage of wound closure rate (n = 12). A 7 mm silicon stent was used as an internal reference for pixel-to-millimeter calibration. Scale bar = 2 mm. Data were expressed as mean ± SEM (n = 6); *p < 0.05, **p < 0.01 and ***p < 0.001 vs WT group; #p < 0.05, ##p < 0.01, ###p < 0.001 vs T2D/OB control (ctrl) group

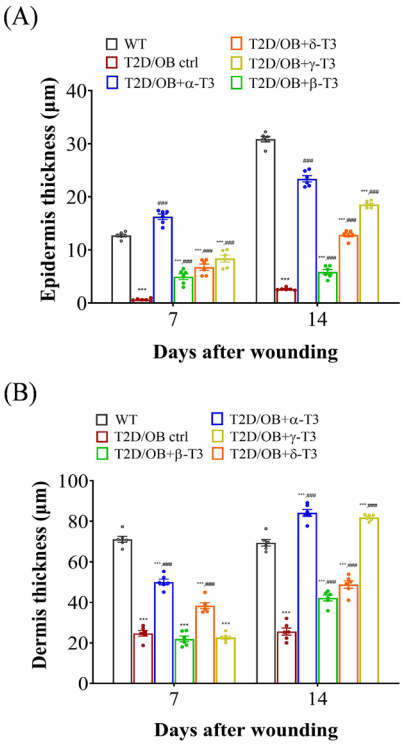

FIGURE 4: Skin thickness. Measurements of epidermal (A) and dermal (B) thickness. Data were expressed as mean ± SEM (n = 6); ***p < 0.001 *vs* WT group; ###p < 0.001 *vs* T2D/OB control (ctrl) group.

TABLE 2: Histological scores

Day	Group/Criteria	Inflammatory cells	Angiogenesis	Fibroblast proliferation
Day 7	WT	1.33 ± 0.17	2.67 ± 0.17	3.00 ± 0.13
	T2D/OB ctrl	3.50 ± 0.26^{c}	0.67 ± 0.17^{c}	0.83 ± 0.31^{c}
	T2D/OB+α-T3	2.17 ± 0.21$^{\$}$	2.67 ± 0.25$^{\$}$	2.67 ± 0.25$^{\$}$
	T2D/OB+β-T3	2.17 ± 0.28$^{\$}$	1.67 ± 0.25$^{b,\&}$	1.92 ± 0.27
	T2D/OB+δ-T3	1.83 ± 0.31$^{\$}$	1.33 ± 0.17^{c}	1.83 ± 0.31^{a}
	T2D/OB+γ-T3	1.50 ± 0.18$^{\$}$	1.25 ± 0.25^{c}	1.67 ± 0.33^{a}
Day 14	WT	1.00 ± 0.13	2.17 ± 0.21	2.83 ± 0.31
	T2D/OB ctrl	2.83 ± 0.31^{c}	1.00 ± 0.13^{b}	1.67 ± 0.33^{a}
	T2D/OB+α-T3	1.25 ± 0.25$^{\$}$	3.25 ± 0.25$^{b,\$}$	3.17 ± 0.31$^{\&}$
	T2D/OB+β-T3	1.83 ± 0.21$^{\#}$	2.25 ± 0.25$^{\$}$	2.67 ± 0.33
	T2D/OB+δ-T3	1.33 ± 0.17$^{\$}$	2.42 ± 0.27$^{\$}$	2.83 ± 0.31$^{\#}$
	T2D/OB+γ-T3	1.17 ± 0.21$^{\$}$	2.17 ± 0.21$^{\&}$	3.00 ± 0.37$^{\#}$

Data were expressed as mean ± SEM (n = 6); ^{a}p<0.05, ^{b}p<0.01 and ^{c}p<0.001 vs WT group; $^{\#}$p<0.05, $^{\&}$p<0.01, $^{\$}$p<0.001 vs T2D/OB control (ctrl) group.

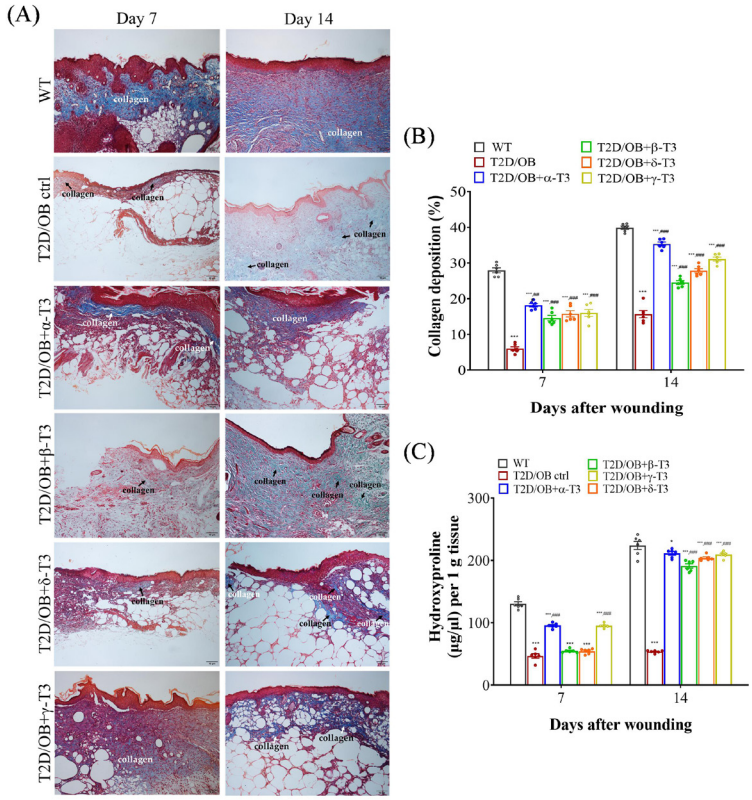

FIGURE 5: T3 isomers improve collagen deposition. (A) Representative images of Masson's trichrome staining on days 7 and 14 after wounding; (B) Collagen deposition (%)l and (C) Hydroxyproline. All slides were viewed at 10 magnification (bar length = 10 μm). Data were expressed as mean ± SEM (n = 6); ^{a}p < 0.05, ^{b}p < 0.001 vs WT group; $^{\#}$p < 0.05, $^{\&}$p < 0.01, $^{\$}$p < 0.001 vs T2D/OB control (ctrl) group

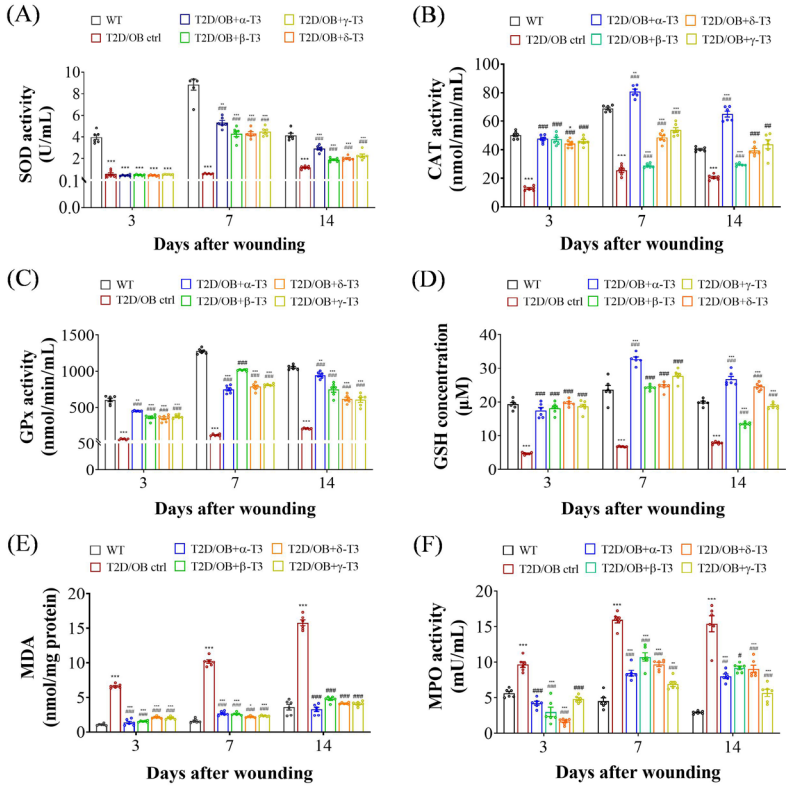

FIGURE 6: Oxidative markers in wound tissues. (A) SOD, (B) CAT, (C) GPx, (D) GSH, (E) MDA and (F) MPO. Data were expressed as mean ± SEM (n = 6); $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$ *vs* WT group; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$ *vs* T2D/OB control (ctrl) group

Effects of T3 Isomers on Cytokine Production in T2D/OB Wound

The T2D/OB control group exhibited a marked increase in proinflammatory cytokines, including TNF-α, IL-1α, IL-6, IL-1β, LIF, RANKL, IFN-γ, IL-12p40 and IL-17A, peaking on day 7 post-wounding compared to WT (Figure 7A-I). Treatment with T3 isomers, however, attenuated these cytokines, with γ-T3 being most effective in reducing TNF-α, IL-1α, IL-6 and IFN-γ. α-T3 strongly suppressed IL-12p40; β-T3 lowered LIF and IL-17A; and δ-T3 decreased IL-1β and RANKL. Conversely, anti-inflammatory cytokine production peaked on day 7, with IL-4 highest in the β-T3 group, IL-9 in α-T3, and IL-10 in γ-T3, compared to the T2D/OB control (Figure 7J-L).

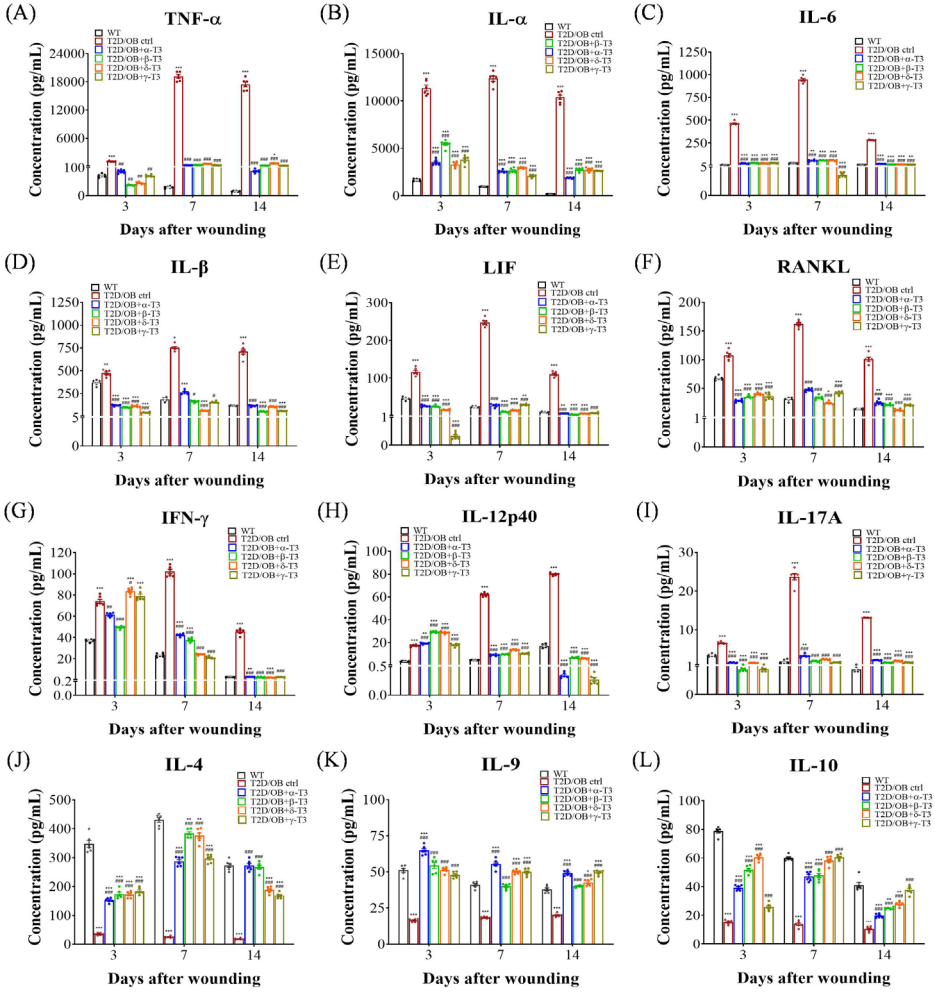

FIGURE 7: Effects of T3 isomers on pro-inflammatory and anti-inflammatory cytokines. Pro-inflammatory cytokines: (A) TNF-α, (B) IL-1α, (C) IL-6, (D) IL-1β, (E) LIF, (F) RANKL, (G) IFN-γ, (H) IL-12p40, (I) IL-17A, and anti-inflammatory cytokines (J) IL-4, (K) IL-9 and (L) IL-10. Data were expressed as mean ± SEM (n = 6); $^{*}p<0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$ *vs* WT group; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$ *vs* T2D/OB control (ctrl) group.

T3 Isomers Modulate Chemokine Levels in the T2D/OB Wound

The T2D/OB control exhibited a significant elevation in the expression of chemokines CXCL1, CXCL2, CXCL5, CXCL10, CCL2, CCL5 and CCL7 compared with WT (Figure 8A-G). Treatment with α-T3 markedly attenuated CXCL2 (days 3 and 7), CCL5 (day 7) and CCL7 (days 3, 7 and 14). Meanwhile, β-T3 selectively reduced CXCL1 and CXCL2 (day 14), CXCL10 (day 7), and CCL2 (day 14). Treatment with δ-T3 suppressed CXCL1 (day 7), CXCL5 (days 3, 7, 14) and CCL5 (day 14). γ-T3 exhibited the most pronounced inhibition of CXCL1 (days 3 and 7), CXCL10 (days 3 and 14), CCL2 (days 3 and 7), and CCL5 (days 3 and 14) following wounding compared to T2D/OB respectively.

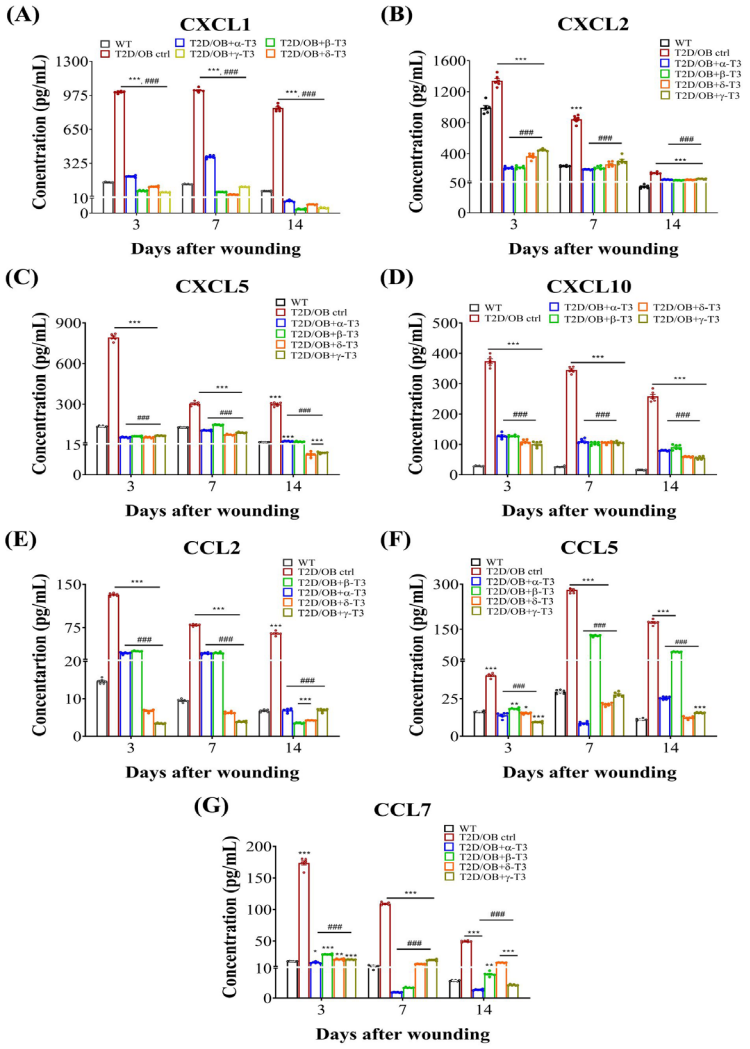

FIGURE 8: Effects of T3 isomers on chemokine production. (A) CXCL1, (B) CXCL2, (C) CXCL5, (D) CXCL10, (E) CCL2, (F) CCL5 and (G) CCL7. Data were expressed as mean ± SEM (n = 6); $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$ *vs* WT group; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$ *vs* T2D/OB control (ctrl) group.

T3 Isomers Enhance Growth Factors in the T2D/OB Wound

The T2D/OB control group exhibited significantly lower levels of VEGF-A (Figure 9A), BTC (Figure 9B) and G-CSF (Figure 9C), but higher GM-CSF (Figure 9D) than WT. Treatment with α-T3 markedly increased VEGF-A on days 3, 7 and 14 and BTC on day 14 compared with diabetic control. Treatment β-T3 enhanced BTC on day 7 and G-CSF on day 14, while treatment δ-T3 increased G-CSF on day 7. Treatment with γ-T3 induced the highest BTC on day 7, whereas G-CSF induced the highest BTC on day 3. Notably, GM-CSF levels were reduced, with the greatest decreases observed in D (days 3 and 7) and B (day 14), compared with the T2D/OB control.

The Concentration of T3 Isomers in the Wound Granulation Tissues

Accumulation of α-T3 (172 μg/mL), β-T3 (168.07 μg/mL), δ-T3 (170.85 μg/mL) and γ-T3 (173.50 μg/mL) was observed in the wound granulation tissues on days 3, 7 and 14 as shown in Figure 10.

DISCUSSION

The treatment of diabetic foot ulcers (DFUs) remains a major clinical challenge. Numerous studies have identified oxidative stress and persistent inflammation as central contributors to DFU pathogenesis (Chen et al. 2025; Dawi et al. 2025; Wang et al. 2025). Diabetic wounds exhibit both macroscopic and microscopic alterations that impair wound closure, fibroblast proliferation, angiogenesis and skin regeneration (Ali et al. 2024; Hegazi et al. 2024; Safoine et al. 2024; Stachura et al. 2022). In the present study, T2D/OB mice displayed increased body weight, glucose and insulin levels, indicative of hyperglycaemia and insulin resistance, thereby confirming key factors associated with delayed wound healing (Stachura et al. 2022).

The wound closure rate, a key determinant of healing efficacy, increased with isomers

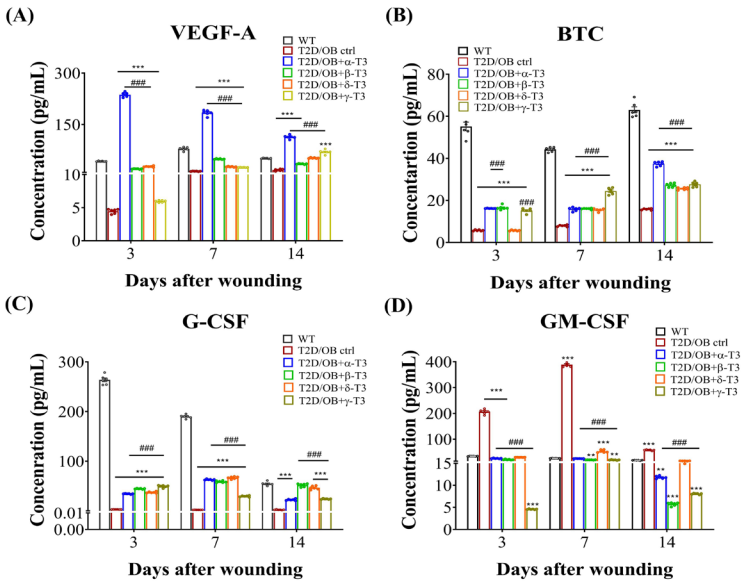

FIGURE 9: T3 increased growth factor production in the T2D/OB wounds. (A) VEGF-A, (B) BTC, (C) G-CSF and (D) GM-CSF. Data were expressed as mean ± SEM (n = 6); $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$ *vs* WT group; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$ *vs* T2D/OB control (ctrl) group

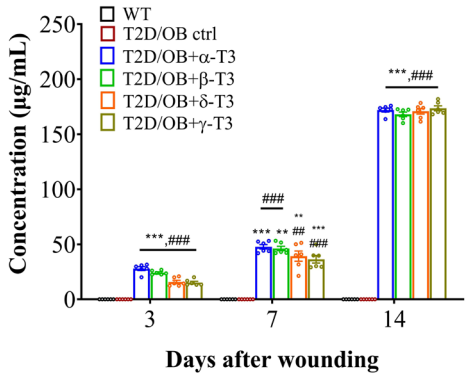

FIGURE 10: T3 isomer concentration in wound granulation tissues. Data were expressed as mean ± SEM (n = 6); $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$ *vs* WT group; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$ *vs* T2D/OB control (ctrl) group

in the sequence α-T3 > γ-T3 > δ-T3 > β-T3. These treatments attenuated inflammatory cell infiltration, likely by modulating signalling pathways and cytokine production, thereby promoting the transition from inflammation to tissue repair (Ji et al. 2021; Qureshi 2022) and preventing chronic inflammation (Hassanshahi et al. 2022).

Tocotrienol is known to regulate gene expression and activate signalling cascades that potentiate fibroblast proliferation (He et al. 2023; Nair et al. 2022; Xu et al. 2017) and angiogenesis through activation of the PI3K/AKT pathway, upregulation of VEGF-A and PDGF-B, and suppression of ferroptosis (Chong et al. 2022; He et al. 2023; Liao et al. 2019; Xu et al. 2017). Therefore, enhanced fibroblast proliferation observed in T3 isomer-treated groups in this study may facilitate differentiation into myofibroblasts, supporting collagen synthesis, wound contraction and neovascularisation (Boraldi et al. 2024; Farooq et al. 2021; Wong et al. 2019).

Wound thickness plays a pivotal role in determining both the rate and quality of tissue regeneration (Shpichka et al. 2019). Fourteen days after injury, epidermal thickness was markedly greater in T3-treated groups (α-T3 > γ-T3 > δ-T3 > β-T3) than in T2D/OB control, indicating enhanced re-epithelialisation and improved barrier restoration (Muse et al. 2023). A similar trend was observed in the dermis, where increased thickness in T3 isomer–treated wounds (α-T3 > γ-T3 > δ-T3 > β-T3) likely provided superior mechanical support and elasticity, facilitating wound contraction, collagen deposition, and extracellular matrix (ECM) remodelling processes, essential for tissue repair (Ahmad et al. 2025; Choi et al. 2025; Shpichka et al. 2019; Zhao et al. 2023). These histological findings were corroborated by Masson's trichrome staining and quantitative analyses of collagen deposition. Tocotrienols have been shown to stimulate collagen biosynthesis by upregulating the expression of *COL1* and *COL3* genes in fibroblasts (Han et al. 2025; Makpol et al. 2011) and by increasing the levels of transforming growth factor-β1 (TGF-β1), a key modulator of collagen production (Ain et al. 2018; Shahrim et al. 2022). Consistent with these mechanisms, T3-treated tissues exhibited increased hydroxyproline content, reflecting greater collagen stability and structural integrity. This enhancement likely promotes angiogenesis and improves nutrient delivery by expanding the vascular network (Alfaris et al. 2022; Elsy et al. 2017; Huang et al. 2023).

Tocotrienols regulate key antioxidant defences, supporting tissue repair (Nair et al. 2012; Shahrim et al. 2022; Xu et al. 2017). In diabetes, reduced antioxidant defences (including diminished SOD, CAT, GPx and GSH) compromise healing

by failing to detoxify reactive oxygen species (Deng et al. 2021). Superoxide dismutase (SOD), often reduced in diabetes, detoxifies superoxide radicals, thereby protecting cells from oxidative damage (Subramanya 2021). Increased CAT activity facilitates the decomposition of hydrogen peroxide, thereby limiting ROS accumulation that drives chronic inflammation and delays healing (Ahmad et al. 2025; Cai et al. 2024). Along with CAT and GPx, GSH scavenges ROS, promotes collagen contraction and protects keratinocytes from apoptosis (Gao et al. 2025; Khandaker et al. 2022).

The present study demonstrates that although all T3 isomers exert measurable antioxidant and anti-inflammatory effects, their wound-healing efficacy follows a distinct order of potency (α-T3 > γ-T3 > δ-T3 > β-T3). All T3 isomers reduced lipid peroxidation, as reflected by decreased MDA levels; however, α-T3 consistently induced a stronger and more sustained activation of endogenous antioxidant enzymes, including SOD, CAT, GPX and GSH, particularly during the proliferative and remodelling phases (days 7 and 14). This coordinated antioxidant response may preserve redox homeostasis, which is essential for fibroblast proliferation, keratinocyte migration, and extracellular matrix deposition. In contrast, β-T3 showed weaker or inconsistent induction of antioxidant enzymes despite reducing MDA, suggesting that reducing oxidative damage alone is insufficient to maximise tissue repair. Tocotrienols are known to reduce MDA, thereby alleviating oxidative stress in diabetic models (Mahjabeen et al. 2021; Shahrim et al. 2022; Ting et al. 2021). The suppression of MPO is particularly relevant, as this neutrophil-derived enzyme generates ROS that sustain the oxidative stress-inflammation cycle, resulting in the tissue damage observed in diabetic ulcers (Ibrahim et al. 2024).

Upregulation of pro-inflammatory cytokines drives prolonged inflammation and delayed wound healing in both diabetic patients and mouse models (Strang et al. 2020). In this study, γ-tocotrienol (γ-T3) markedly inhibited key pro-inflammatory cytokines in T2D/OB wounds. Elevated IL-1α, IL-6, IL-17A, IL-12p40, IFN-γ, TNF-α, LIF and RANKL impede healing by activating immune cells, disrupting angiogenesis, fibroblast function, ECM integrity and tissue remodelling (Chen et al. 2022; Lacina et al. 2024; Worsley et al. 2023; Hegazi et al. 2024; Kitanaka et al. 2019; Dasari et al. 2021; Wang et al. 2025). T3 isomers suppressed these cytokines, potentially creating a pro-healing environment by modulating the NF-κB pathway (Shahrim et al. 2022; Yang & Jiang 2019). Furthermore, the suppression of pro-inflammatory chemokines (CXCL1, CXCL2, CXCL5, CXCL10, CCL2, CCL5 and CCL7) by T3 isomers mitigated persistent inflammation, improved endothelial function and enhanced neovascularisation (Chen et al. 2023; Chang et al. 2024; Pan et al. 2021).

In terms of inflammation, α-T3 promoted a physiologically appropriate inflammatory profile, characterised by an early elevation of inflammatory mediators followed by effective downregulation at later stages. This pattern supports immune cell recruitment and growth factor release in the early phase while allowing a timely transition to tissue regeneration. Conversely, δ-T3 was associated with prolonged elevation of pro-inflammatory cytokines such as TNF-α and IL-1β, which may delay wound resolution, while β-T3 appeared to either insufficiently activate early inflammation or fail to resolve it efficiently. Excessive suppression or persistence of inflammation can both impair angiogenesis and fibroblast activity, thereby limiting wound closure. Furthermore, α-T3 exhibited better regulation of MPO activity, indicating effective neutrophil clearance during later stages of healing. It also favourably modulated key cytokines involved in tissue remodelling, including IL-6, IFN-γ, RANKL and LIF, supporting re-epithelialisation and matrix remodelling. γ-T3 showed moderate efficacy across these parameters, while δ- and β-T3 were less consistent. Collectively, these findings suggest that the superior wound-healing potency of α-T3 arises from its ability to integrate antioxidant defence, controlled inflammatory resolution and regenerative signalling, rather than from isolated reductions in oxidative stress

or inflammatory markers.

Treatment with α-, β- and γ-T3 enhanced anti-inflammatory cytokines, including IL-4, IL-9 and IL-10, promoting macrophage polarisation toward the M2 phenotype, resolving chronic inflammation, and supporting angiogenesis and tissue repair (Callejas et al. 2025; Short et al. 2022; Shrum et al. 2023; Zhao et al. 2023). T3 treatment also increased growth factor production. α-T3 strongly induced VEGF-A, facilitating angiogenesis (Xu et al. 2017), meanwhile, α-, β- and γ-T3 elevated betacellulin (BTC), supporting peripheral nerve repair and diabetic wound healing (Oh et al. 2015; Wang et al. 2021; Xie et al. 2022). G-CSF was upregulated by γ- and β-T3, reducing infection and inhibiting the production of pro-inflammatory cytokines, whereas GM-CSF was suppressed, limiting neutrophil extracellular trap formation and chronic inflammation (Kulkarni et al. 2013; Lin et al. 2021; Manoj et al. 2024). Collectively, T3 isomers modulate the wound microenvironment by suppressing pro-inflammatory mediators, enhancing anti-inflammatory cytokines and promoting growth factor-mediated tissue repair, thereby offering a promising strategy for improving wound healing in T2D/OB (Figure 11).

Despite the promising findings, several limitations should be considered. This study was conducted exclusively in a T2D/OB mouse model, which may not fully replicate the complexity of diabetic foot ulcers in humans, including comorbidities and variability in ulcer aetiology. The study primarily focused on short-term outcomes, with assessments limited to 14 days post-injury; the long-term effects of tocotrienol (T3) isomer treatment on scar formation, functional recovery and wound recurrence were not evaluated. Mechanistic pathways were inferred rather than directly validated and clinical translation may be affected by differences in dosing, delivery and bioavailability of T3 isomers in humans. Although the effects of all four individual tocotrienol isomers were evaluated and compared, the lack of a well-established wound-healing agent as a positive control may limit direct benchmarking of tocotrienol efficacy against a recognised standard. Future studies should include an appropriate positive control to enable a more robust comparative assessment and further validate the therapeutic potential of individual tocotrienol isomers. Finally, multiple wounds generated on the same mouse were analysed as independent samples, which may not fully account for potential intra-animal correlations and could influence the interpretation of the results.

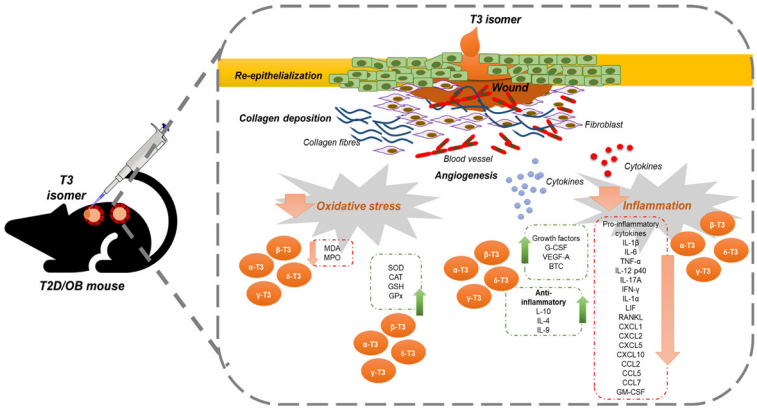

FIGURE 11: Schematic representation of the proposed mechanism of T3 isomers in promoting T2D/OB mice cutaneous wound healing. *Schematic diagrams were constructed using Microsoft PowerPoint, version 2021 (Microsoft Corp., Redmond, USA).*

CONCLUSION

T3 isomers provide a multifaceted therapeutic strategy for diabetic wounds by modulating the microenvironment, suppressing pro-inflammatory mediators and upregulating critical growth factors. Notably, α-T3 emerged as the most potent isomer, surpassing γ-, δ- and β-T3 in overall healing efficacy. The superior performance of α-T3 suggests that successful tissue regeneration is driven by the sustained activation of antioxidant defences and coordinated inflammatory resolution. These results underscore the potential of α-T3 as a targeted therapy for clinical translation, warranting further investigation into dosing strategies and human efficacy.

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Conflict of interest: The authors declare no conflict of interest. The funders had no role in the design of the study, in the collection, analysis, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

Ethics statement: All animal procedures were performed in accordance with the Universiti Kebangsaan Malaysia Ethics Committee (UKMAEC) (Approval No. BIOK/PP2017/SUZANA/25-JAN./817-JAN.-2017-SEPT.-2018)

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