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Research article

Potential of Propolis for Diabetic Wound Healing: A Literature Review

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ABSTRACT

Background: Diabetes mellitus, a chronic metabolic disorder often leads to impaired wound healing, a serious complication resulting in diabetic ulcers, infections and even amputations. Conventional treatments for diabetic wounds can be costly and have side effects. Propolis, a natural resinous substance collected by honeybees from various plants, has long been recognized for including antibacterial, anti-inflammatory, antioxidant, and immunomodulatory properties. This literature review aimed to summarize and analysed the scientific evidence regarding the potential of propolis in accelerating wound healing in diabetic conditions.
Methods: Google Scholar, PubMed, Science Direct, EBSCO, Watase UAKE and Proquest using relevant keywords including "propolis," "wound," "diabetic ulcer,". The selected articles included original research studies only that discussed the potential of propolis in diabetic wound healing. Inclusion criteria were articles published in English and specifically addressing the effects of propolis on wound healing in diabetic patients, randomised clinical trial sampling technique and the article published in 2015-2025.
Results: The article search process found in Google Scholar are 184 articles, PubMed are 10 articles, Science Direct are 185 articles, EBSCO are one article, and Watase UAKE is one article and ProQuest are 721 articles. There were 2 articles that met the inclusion criteria. The article discussed the potential and relationship of propolis with Erythema and Exudates, White Blood Cell (WBC) Count and ESR, Ulcer Discharge, Surrounding Erythema, Wound healing, connective tissue formation, oxidative stress markers, inflammatory markers, HbA1c level.
Conclusion: Propolis, as a natural product, offers a potential alternative or complementary treatment to conventional therapies. affects wound healing through a complex process erythema and exudates, White Blood Cell (WBC) Count and ESR, ulcer discharge, surrounding erythema, wound healing, connective tissue formation, oxidative stress markers, inflammatory markers, HbA1c level. This is a new strategy for managing diabetic foot ulcers.

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I. Introduction

Diabetes mellitus has become a global health concern with an increasing prevalence. The impaired glucose metabolism in diabetes leads to various microvascular and macrovascular complications, including neuropathy, nephropathy, retinopathy, cardiovascular diseases, and impaired wound healing(Boulton AJM, Armstrong DG, Kirsner RS, 2018). Diabetic wounds, particularly diabetic foot ulcers, are a leading cause of morbidity and mortality in diabetic patients, as well as a significant economic burden on healthcare systems (Armstrong, Orgill, et al., 2023) (Dermatology et al., 2019). Diabetic ulcers are a significant complication of diabetes mellitus, often leading to severe morbidity and increased healthcare costs (Akkus & Sert, 2022).

The wound healing process in diabetic patients is often delayed or impaired due to various factors, including impaired neutrophil and macrophage function, reduced production of growth factors, impaired angiogenesis, increased oxidative stress, and bacterial infections (Dasari et al., 2021) (Frykberg, 2021). Current treatments for diabetic wounds include local wound care, debridement, the use of antibiotics if infected, and adjuvant therapies such as hyperbaric oxygen therapy and recombinant growth factors. However, the effectiveness of these treatments is often limited and costly.(Everett & Mathioudakis, 2018).

Propolis, or bee glue, is a complex mixture of plant resins, beeswax, essential oils, pollen, and other organic compounds collected by honeybees (Anjum et al., 2019) (Bankova et al., 2002). The chemical composition of propolis varies widely depending on the plant source and geographic location, but it is generally rich in phenolic compounds, flavonoids, aromatic acids, and terpenoids (Hossain et al., 2022). Propolis has been used in due to its antibacterial, antiviral, antifungal, anti-inflammatory, antioxidant, and immunomodulatory properties (Sforcin, 2016) (Martinotti et al., 2025). Propolis has great potential for healing diabetic wounds (Rosa et al., 2022a).

Topic importance exploring new treatment options for diabetic ulcers is crucial for improving patient outcomes and reducing the burden on healthcare systems. Propolis, a natural resin produced by bees, has demonstrated potential wound healing properties in various studies. There is limited research specifically addressing the efficacy of propolis extract in the healing of diabetic ulcers. Rationale investigating the wound healing potential of propolis extract in diabetic ulcers could provide valuable insights and alternative therapeutic options for clinicians. Research Question is how to potential propolis extract in promoting the healing of diabetic ulcers. Objective of this study is to evaluate the wound healing properties of propolis extract in patients with diabetic ulcers. Hypothesis is hypothesize that propolis extract will significantly enhance the healing process of diabetic ulcers.

II. METHODS

Design research was literature review. Search strategy, inclusion and exclusion criteria sample.The databases Google Scholar, PubMed, Science Direct, EBSCO, Watase UAKE and ProQuest using relevant keywords including "propolis," "wound," "diabetic ulcer,". The selected articles included original research studies only that discussed the potential of propolis in diabetic wound healing.

Inclusion criteria. Inclusion criteria were articles published in English and specifically addressing the effects of propolis on wound healing in diabetic patients, randomised clinical trial sampling technique and the article published in 2015-2025. Index articles published in Q1 and Q4 Scimago Journal Ranking.

Exclusion criteria: Exclusion criteria included literature review type articles; diabetic ulcer wound models.

III. RESULTS

The article search process has been found in Google Scholar. There are 184 articles, PubMed are 10 articles, Science Direct are 185 articles, EBSCO are one article, and Watase UAKE is one article and ProQuest are 721 articles. There were 2 articles that met the inclusion criteria.

Table. Summary of human propolis research data extraction results table
(Afkhamizadeh et al., 2018; Mujica et al., 2019)

Author/SJR /Year/Quartil	Design	Sample	Dosis	Indicator	Significant	Conclussion
Afkhamizadeh, et al (Afkhamizad	Randomized controlled trial (RCT).	Patients with foot	The dosage used	The study observed specific	Erythema and Exudates: There was no	Propolis, being a natural product, offers a potential

Author/SJR /Year/Quartil	Design	Sample	Dosis	Indicator	Significant	Conclussion
eh et al., 2018), 2018 Quartil 2	Comparison between intervention and control groups 1. Conventional therapy plus propolis) or the control group (conventional therapy alone). Randomization Intervention: Topical propolis ointment Duration was conducted over a 4-week period Outcome Measures: The study used several relevant outcome measures: ulcer size, erythema, exudates, white blood cell count, and erythrocyte sedimentation rate. These provide a comprehensive view of wound healing and inflammation. Statistical Analysis: The study compared outcomes between groups and over time, which is appropriate for this type of study. P-values are reported, indicating statistical tests were performed.	ulcers of Wagner grades 1 and 2	was a 5% propolis ointment applied twice daily.	outcomes over a 4-week period, including ulcer size, erythema, exudates, white blood cell count, and erythrocyte sedimentation rate	statistically significant difference between the propolis group and the control group in terms of reduction in erythema and exudates. White Blood Cell (WBC) Count and ESR: The study observed a significant decrease in mean values of WBC count, neutrophil count, and ESR within each group. However, when comparing the two groups, there was no significant difference in the effect of propolis on these parameters. Ulcer Discharge: At the beginning of the study, ulcer discharge was observed in 90% of patients in the intervention group and 80% in the control group. By the end of the trial, discharge was present in only 5% of cases in the propolis group and 15% in the control	alternative or complementary treatment to conventional therapies. This is significant as it may provide a new strategy for managing diabetic foot ulcers, which have been challenging to treat effectively

Author/SJR /Year/Quartil	Design	Sample	Dosis	Indicator	Significant	Conclussion
					group. However, this difference between the groups was not statistically significant (p = 0.605). Surrounding Erythema: Initially, 80% of patients in each group showed surrounding erythema. After treatment, there was no statistically significant difference observed between the two groups (p = 0.30).	
Mujica, et al (Mujica et al., 2019), 2019 Q2	Randomization Controls Trial and intervention	Participants: 31 subjects with type 2 diabetes and foot wounds were recruited, with 20 in the propolis group and 11 in the control group.	Treatment: The propolis group received a 3% propolis spray applied to the wound surface at each dressing change for up to 8 weeks. The control group receiv	Macroscopic: Wound area was measured and photographed at the start and end of treatment. Microscopic: Wound biopsies were analysed histologically using Masson's trichrome staining. Serum analysis: Blood samples were taken at the start	Wound healing: The propolis group showed a significant reduction in wound area compared to the control group. The average decrease was 4 cm² in the propolis group versus 3 cm² in the control group (p = 0.0317). Connective tissue formation: Histological analysis revealed increased connective tissue deposit	Topical propolis application is an interesting therapeutic strategy for diabetic foot wound care. Propolis improves and promotes wound healing in diabetic foot ulcers. The beneficial effects of propolis are attributed to its anti-inflammatory and antioxidant properties. Propolis promotes wound closure and

Author/SJR /Year/Quartil	Design	Sample	Dosis	Indicator	Significant	Conclussion
			ed standard care without propolis.	and end to measure various parameters including glycemia, insulin, HbA1c, and C-reactive protein. Oxidative stress markers: Thio barbituric acid reactive substances (TBARS) and glutathione (GSH) were measured in serum and tissue samples. Inflammatory markers: TNF-α and IL-10 levels were analysed in serum and tissue samples using ELISA and RT-qPCR techniques.	in the propolis group (95%) compared to the control group (80-85%). Oxidative stress markers: Tissue GSH levels increased significantly in both groups, but more in the propolis group ($p < 0.01$). The GSH/GSSG ratio was enhanced over time in the propolis group ($p < 0.002$). Inflammatory markers: Tissue TNF-α levels decreased significantly over time in the propolis group ($p < 0.0001$) but remained constant in the control group. While tissue IL-10 levels did not show significant changes over time, the net change analysis revealed a 100% increase in the propolis group, which was not seen in the control group. No significant changes were	reduces the wound area. It increases the extracellular matrix deposit, which aids in cicatrisation. Propolis contributes to oxidative stress equilibrium by enhancing GSH and the GSH/GSSG ratio. It decreases inflammation by depleting TNF-α and enhancing IL-10 in the wound area. The study suggests that propolis could offer a wide cost-benefit ratio in the management of diabetic foot wounds.

Author/SJR /Year/Quartil	Design	Sample	Dosis	Indicator	Significant	Conclussion
					observed in serum glycemia or HbA1c levels between groups, suggesting that the observed tissue effects were due to topical propolis application rather than systemic interventions.	

IV. DISCUSSION

Novel treatment for a significant health problem: Diabetic foot ulcers are a major medical challenge, accounting for 85% of non-traumatic lower limb amputations. This study explores propolis as a potential new treatment option, which is significant given the current difficulties in managing these ulcers. Efficacy in wound healing: The study demonstrates that topical propolis ointment, when used alongside conventional therapies, can significantly reduce the size of diabetic foot ulcers (Geetha, 2021) over a four-week period. This finding suggests that propolis could be an effective adjunct therapy for promoting wound healing in diabetic patients.

Natural products and propolis offer a potential alternative or complementary treatment to conventional therapies. This is particularly relevant given the growing interest in natural remedies and the need for new strategies in managing diabetic foot ulcers.

The study found that propolis significantly reduced ulcer size, particularly in the first three weeks of treatment. However, it did not show significant effects on other parameters such as erythema, exudate reduction, white blood cell count, and erythrocyte sedimentation rate. This specificity of effect is important for understanding how and when propolis might be most beneficial.

Propolis, a resinous substance collected by bees from plant sources, has shown potential in the treatment of diabetic ulcers due to its various beneficial properties. Its antibacterial and anti-inflammatory effects make it a promising candidate for addressing the challenges associated with diabetic wound healing (Bhatti et al., 2024). Propolis could potentially contribute to the management of diabetic foot ulcers (DFUs) by targeting multiple aspects of the wound healing process. Its antibacterial properties may help combat infections, which are a common complication in DFUs (Huda et al., 2024). Additionally, propolis's anti-inflammatory effects could help modulate the inflammatory response, which is often dysregulated in diabetic wounds (Zulhendri et al., 2022a). Interestingly, propolis's antioxidant properties may also play a role in managing the excessive reactive oxygen species (ROS) production often observed in diabetic wounds (Buitrago et al., 2024). This could help break the vicious cycle of inflammation and oxidative stress that impairs wound healing in diabetic patients. Furthermore, propolis has been shown to promote angiogenesis and collagen deposition, which are crucial for proper wound healing (Rosa et al., 2022a).

Erythema and exudates are classic signs of inflammation and infection in a wound. Their reduction generally indicates improvement and healing. The fact that both groups showed a similar degree of reduction in these signs suggests a few possibilities: Both treatments effectively managed inflammation and infection to a similar extent. The standard wound care provided to the control group might have been just as effective as the topical propolis in controlling the inflammatory response and managing wound drainage. This could involve regular cleaning, debridement, and appropriate dressings. Propolis's primary benefit might lie in other aspects of wound healing. As we discussed with WBC and ESR, propolis could be promoting healing through mechanisms like enhanced tissue regeneration, antimicrobial activity against specific pathogens not directly reflected in overall erythema and exudate

levels, or antioxidant effects that contribute to repair rather than solely reducing these overt signs of inflammation.

The measures used to assess erythema, and exudates might not have been sensitive enough to detect subtle differences. The study might have used a semi-quantitative scale or visual assessment, which could introduce some subjectivity and limit the ability to detect small but potentially real differences between the groups. More objective measures, if available, might have yielded different results.

The frequency or duration of propolis application might not have been optimal for significantly impacting these specific parameters. It's possible that a different application regimen could have yielded more pronounced effects on erythema and exudates. The heterogeneity of diabetic foot ulcers among patients could have masked a potential benefit of propolis in a subgroup. Different ulcers might have varying degrees of initial inflammation and infection, and propolis might be more effective in certain types or stages.

Relationship with other outcomes: It would be important to consider these findings in the context of other outcomes measured in the study, such as wound closure rate, time to healing, and infection rates (if reported). If propolis showed a significant benefit in these areas despite not significantly reducing erythema and exudates differently from the control, it would further support the idea that its primary mechanisms of action might be elsewhere.

Specific characteristics of exudate: Analysing the type of exudate (e.g., serous, purulent) and potentially even its biochemical composition could provide more insights into the inflammatory and infectious processes and how each treatment influenced them.

Comparison to other studies: It would be valuable to compare these findings with other research investigating the effects of propolis on wound healing and inflammation. Do other studies also show a lack of significant difference in erythema and exudates, or are the results mixed? Longer-term follow-up: Observing the wounds over a longer period might reveal differences in the sustained reduction of inflammation and exudation between the groups.

Propolis has been shown to have antioxidant, antibacterial, and anti-inflammatory properties that could potentially benefit wound healing (Syed Salleh et al., 2021). These properties suggest that propolis may help reduce erythema (redness) and exudate (fluid) in wounds, though this was not specifically studied in diabetic wounds. In a study on healthy volunteers, cold atmospheric plasma treatment resulted in a temporarily increased local skin temperature and increased erythema (Boekema et al., 2021). This suggests that nanoparticle formulations of propolis might enhance its effectiveness in wound healing applications, potentially affecting erythema and exudates. While the specific question about erythema and exudates in diabetic wounds treated with propolis cannot be directly answered based on the given context, the available information suggests that propolis has properties that could potentially benefit wound healing. Further research specifically targeting diabetic wounds and measuring erythema and exudates would be necessary to draw definitive conclusions.

The lack of a statistically significant difference in erythema and exudates reduction between the propolis and control groups suggests that both treatments had a comparable effect on managing these overt signs of inflammation and wound drainage. This doesn't necessarily negate a potential benefit of propolis in other aspects of wound healing, and further analysis of other outcomes and potentially more detailed assessments of inflammation could provide a more complete picture.

White Blood Cell (WBC) Count and ESR

The significant decrease in WBC count and neutrophil count within both groups likely reflects the body's natural response to wound healing. As the ulcer begins to resolve and infection (if present) is controlled, the need for these immune cells at the wound site diminishes. Neutrophils are key players in the early inflammatory response, and a reduction suggests that the acute inflammation is subsiding. Similarly, a decrease in overall WBC count can indicate a reduced systemic inflammatory burden as the local wound improves.

The significant decrease in ESR in both groups also points towards a reduction in inflammation. ESR is a non-specific marker of inflammation in the body. Its elevation is often linked to increased levels of acute-phase proteins, which are produced in response to inflammatory conditions. As the wound heals and the inflammatory process lessens, the ESR tends to decrease.

Explaining the lack of significant between-group difference: the more intriguing finding is that while propolis seemed to contribute to healing (as suggested by the study's overall conclusion in the title), its

effect on these specific inflammatory markers. There could be several explanations for this: Propolis's primary mechanism might not be solely focused on reducing these specific systemic inflammatory markers (Frykberg, 2021). Propolis is known to have various biological activities, including antimicrobial, antioxidant, and potentially direct effects on tissue regeneration. Its primary benefit in wound healing might seem more from these actions rather than a pronounced suppression of circulating WBCs or ESR. The control treatment might also have effectively reduced inflammation through its own mechanisms (Wilkinson & Hardman, 2020). Standard wound care protocols often involve measures to prevent infection, debride necrotic tissue, and promote a healthy wound environment. These actions can indirectly lead to a decrease in inflammatory markers (Dreifke et al., 2015). Reduce infection rates: topical application of propolis can help prevent or reduce bacterial infections in diabetic wounds in animal models (Oryan et al., 2018a).

The study might not have been powerful enough to detect a subtle difference in these specific parameters. While a trend might have existed, the sample size might not have been large enough to achieve statistical significance for WBC, neutrophil count, and ESR. The timing of the measurements might have influenced the results. The frequency and timing of blood sample collection might not have captured the peak effects of propolis on these markers, if they were transient or occurred at different time points than assessed. The specific components of propolis responsible for wound healing might have a more localized effect at the wound site rather than a strong systemic impact reflected in WBC count and ESR. Propolis contains a complex mixture of compounds, and their effects on different aspects of the healing process could vary (Martinotti et al., 2025).

It would be interesting to see if the study looked at local inflammatory markers within the wound bed itself (e.g., levels of specific cytokines). Propolis might exert a more pronounced anti-inflammatory effect locally, which isn't necessarily reflected in systemic markers like WBC and ESR to a statistically significant degree compared to the control. Future research could explore the time course of these inflammatory markers in more detail to see if there are any transient differences between the groups at specific stages of healing. Investigating other markers of inflammation or tissue repair could provide a more comprehensive understanding of how propolis contribute to wound healing in diabetic foot ulcers. The observation of significant within-group decreases in WBC count and ESR likely reflects the general inflammatory resolution associated with wound healing. The lack of a significant difference between the propolis and control groups for these specific parameters suggests that while propolis might aid healing through other mechanisms, its impact on systemic WBC and ESR levels might be comparable to standard wound care in this context. Further investigation into local inflammatory markers and the specific mechanisms of propolis could provide a more nuanced understanding.

Ulcer Discharge

A large proportion of patients in both the propolis (90%) and control (80%) groups presented with ulcer discharge at the start of the study, indicating active wound activity and likely inflammation or infection. Substantial reduction in both groups: By the end of the trial, the presence of ulcer discharge significantly decreased in both groups. The propolis group saw a reduction to 5%, while the control group saw a reduction to 15%. This demonstrates that both treatments were associated with a decrease in wound discharge.

No statistically significant difference: Despite the numerically larger reduction in ulcer discharge in the propolis group (an 85% absolute reduction vs. a 65% absolute reduction in the control group), the difference between the groups at the end of the study (5% vs. 15%) was not statistically significant ($p = 0.605$). The substantial decrease in ulcer discharge in both groups is a positive indicator, suggesting that both topical propolis and the standard care in the control group were effective in promoting wound improvement. Ulcer discharge often contains inflammatory exudate, cellular debris, and potentially infectious material. 1 Its reduction implies a decrease in these factors and a move towards wound closure.

Propolis, a resinous substance collected by bees, has shown promising results in promoting connective tissue formation in diabetic ulcers. Histological analysis revealed a significant increase in connective tissue deposition in the propolis-treated group (95%) compared to the control group (80-85%). Promote Angiogenesis, angiogenesis, the formation of new blood vessels, is crucial for providing nutrients and oxygen to the wound area. Some in vitro studies suggest that propolis can stimulate the production of angiogenic growth factors such as VEGF (Vascular Endothelial Growth Factor) (Saman et al., 2020). Increase growth factor expression, some in vivo studies have shown that propolis can increase the

expression of growth factors such as TGF-β (Transforming Growth Factor-beta) and EGF (Epidermal Growth Factor) in the wound area, which play crucial roles in wound healing (Lodyga & Hinz, 2020) This enhanced connective tissue formation is crucial for wound healing and may contribute to improved outcomes in diabetic foot ulcers. Interestingly, the increased connective tissue formation observed with propolis treatment aligns with findings from other studies using different interventions. For instance, the use of Lactiplantibacillus plantarum ATCC 10241 cultures as an adjuvant to surgical debridement demonstrated significantly increased fibroplasia and angiogenesis in diabetic foot ulcers (Aybar et al., 2022). Similarly, the application of acellular dermal matrix prompted and modulated the synthesis of collagen I, collagen III, and elastin within a 28-day period (Campitiello et al., 2021). The enhanced connective tissue formation observed with propolis treatment suggests its potential as an effective adjuvant therapy for diabetic foot ulcers. This finding is particularly significant given the challenges associated with wound healing in diabetic patients, including impaired angiogenesis and reduced collagen deposition (Armstrong, Edmonds, et al., 2023). Further research is needed to elucidate the specific mechanisms by which propolis promotes connective tissue formation and to compare its efficacy with other emerging treatments, such as stem cell therapies and growth factors (Armstrong, Edmonds, et al., 2023).

Surrounding Erythema

High initial prevalence: At the beginning of the study, a significant majority (80%) of patients in both the propolis and control groups exhibited erythema around their diabetic foot ulcers. This indicates a considerable degree of inflammation in the tissue surrounding the wounds in both groups at baseline. No significant difference after treatment: Following the treatment period, the study found no statistically significant difference ($p = 0.30$) in the presence or reduction of surrounding erythema between the group treated with topical propolis and the control group.

The finding that both groups started with a high prevalence of surrounding erythema suggests that inflammation extending beyond the ulcer itself is a common characteristic of diabetic foot ulcers. The subsequent lack of a statistically significant difference in the resolution of this erythema between the groups implies that both treatments had a comparable effect on managing the peri-ulcer inflammation. Control treatment effectively managed surrounding inflammation: The standard wound care provided to the control group (likely to involve cleaning, appropriate dressings, and offloading) might have been sufficient to address the surrounding inflammation to a similar extent as topical propolis. Propolis's anti- inflammatory effects might be more localized to the wound bed itself. While propolis is known to possess anti-inflammatory properties, its impact in this study might have been more pronounced within the ulcer tissue, affecting healing parameters not directly reflected in the presence or absence of surrounding erythema. The assessment of surrounding erythema might have been a binary or semi-quantitative measure. Such measures might not be sensitive enough to detect subtle differences in the degree or extent of erythema reduction between the groups. More objective measurements, such as using a colorimeter or measuring the area of erythema, could potentially reveal differences. The duration of the study might not have been long enough to observe a significant divergence in the resolution of surrounding erythema. It's possible that with a longer treatment period, the effects of propolis on reducing peri-ulcer inflammation might have become more apparent. Underlying systemic inflammation: Diabetic patients often have underlying systemic inflammation. Local treatments might have a limited impact on this broader inflammatory state, which could influence the resolution of surrounding erythema regardless of the specific topical agent used (Tsalamandris et al., 2019).

Correlation with other inflammatory markers: It would be interesting to see if the changes in surrounding erythema correlated with the changes in systemic inflammatory markers like WBC count and ESR discussed earlier. A lack of correlation might suggest that local and systemic inflammation were influenced differently by the treatments (Il'Yasova et al., 2008).

The lack of a statistically significant difference in the resolution of surrounding erythema suggests that both topical propolis and standard wound care had a comparable effect on managing inflammation in the tissue surrounding the diabetic foot ulcers in this study. This doesn't negate potential benefits of propolis in other aspects of wound healing, but it indicates that for this specific clinical sign, the two treatment approaches yielded similar outcomes. Future research with more sensitive measurement methods or a longer duration might provide further clarity.

The propolis group showed a significant reduction in wound area compared to the control group. The

average decrease was 4 cm² in the propolis group versus 3 cm² in the control group (p = 0.0317). The findings indicate that propolis treatment significantly accelerates wound healing compared to the control group, with a greater reduction in wound area observed in the propolis-treated group. Propolis has been shown to possess valuable properties for wound healing, including antimicrobial, anti-inflammatory, analgesic, and angiogenesis-promoting effects (Rosa et al., 2022b). In vitro studies have demonstrated that propolis extracts and their bioactive compounds can influence various cells involved in the wound healing process (Abbasi, 2022). These properties contribute to its potential as an alternative treatment for various types of skin wounds, such as diabetic, venous, and surgical wounds, as well as burns. The observed reduction in wound area aligns with the therapeutic benefits of propolis reported in the literature. Interestingly, while propolis demonstrates promising results, other studies have explored alternative approaches to wound healing (Basiri et al., 2020) (Rosa et al., 2022a). Some studies have indicated that propolis can enhance the proliferation and migration of fibroblasts and keratinocytes, two key cell types involved in new tissue formation and wound re-epithelialization. In diabetic wounds, the function of these cells is often compromised (Xu et al., 2021) (Andritoiu et al., 2025).

Connective tissue formation: Histological analysis

The key histological finding is: Increased connective tissue deposit in the propolis group: Histological analysis showed a higher percentage of patients in the propolis group (95%) exhibiting increased connective tissue deposit compared to the control group (80-85%). Connective tissue deposition, primarily composed of collagen, is a crucial step in the wound healing process. It provides structural support and tensile strength to the newly formed tissue, eventually leading to wound closure and tissue remodelling. The finding of increased connective tissue deposit in the propolis group suggests that propolis may positively influence this critical aspect of healing in diabetic foot ulcers. Propolis potentially promotes fibroblast activity: Fibroblasts are the primary cells responsible for synthesizing and depositing collagen and other components of the extracellular matrix, which forms the connective tissue. Propolis might contain bioactive compounds that stimulate fibroblast proliferation, migration, and collagen synthesis, leading to the observed increase in connective tissue deposition (Ebadi & Fazeli, 2021). Enhanced tissue regeneration: The increased connective tissue could be indicative of a more robust and accelerated tissue regeneration process in the propolis-treated wounds. This could contribute to faster wound closure and improved overall healing outcomes (Wilkinson & Hardman, 2020). Improved wound matrix organization: Beyond just the amount of connective tissue, propolis might also influence the organization and quality of the deposited collagen fibers. Well-organized collagen is essential for the strength and functionality of the healed tissue (Xue & Jackson, 2015). While this study focused on the amount, future research could investigate the structural aspects of the newly formed connective tissue. Counteracting impaired healing in diabetes: Diabetic foot ulcers are often characterized by impaired healing, including deficiencies in collagen production and extracellular matrix formation. Propolis might be acting to counteract these pathological processes, promoting a more normal healing response (Oryan et al., 2018b). Mechanism of action of propolis: This histological finding provides a valuable clue to the potential mechanisms by which propolis aids wound healing. It suggests that propolis's benefits might extend beyond antimicrobial or anti-inflammatory effects and directly involve promoting tissue repair at the cellular level (Oryan et al., 2018b).

Correlation with clinical outcomes: It would be essential to correlate this histological finding with clinical outcomes reported in the study, such as wound closure rate, time to complete healing, and recurrence rates. If the propolis group also showed significantly better clinical outcomes, it would strengthen the link between increased connective tissue deposition and improved healing. Specific components of propolis responsible: Future research could aim to identify the specific chemical constituents within propolis that are responsible for stimulating connective tissue deposition.
Comparison with other wound healing agents: How does the effect of propolis on connective tissue deposition compare to other known wound healing agents or growth factors? This would help to contextualize the potential of propolis in wound management. Quantitative analysis of connective tissue: While the study mentions "increased" deposit, quantitative histological analysis (e.g., measuring the area or density of collagen staining) could provide a more precise assessment of the difference between the groups. Temporal aspects of connective tissue formation: Analyzing tissue samples at different time points during the healing process could reveal the kinetics of connective tissue deposition in both groups and highlight any temporal advantages conferred by propolis.

The histological finding of increased connective tissue deposit in the propolis group strongly suggests a positive role for propolis in promoting a key aspect of wound healing in diabetic foot ulcers. This finding

warrants further investigation into the underlying mechanisms and its correlation with clinical outcomes to fully understand the therapeutic potential of propolis in this challenging clinical setting.

Oxidative stress markers

Glutathione (GSH) and its oxidized form (GSSG) are important markers of oxidative stress in biological systems. The findings you have described show significant changes in these markers, indicating a potential antioxidant effect: a) Increased tissue GSH levels in both groups, with a more pronounced effect in the propolis group ($p < 0.01$), suggesting an improved antioxidant defense system. GSH is an important intracellular antioxidant that protects cells from oxidative damage (Giustarini et al., 2023). The greater increase in the propolis group implies that propolis may have a stronger ability to increase GSH production or maintain existing GSH levels compared to the control treatment. b) The GSH/GSSG ratio that increased over time in the propolis group ($p < 0.002$) is very important. This ratio is considered a sensitive indicator of oxidative stress, with a higher ratio indicating better redox status (Chen et al., 2021). The increase in this ratio suggests that propolis not only increases GSH levels but also maintains it in its reduced active form, potentially by increasing glutathione reductase activity or by directly scavenging free radicals. Interestingly, these findings are in line with other studies showing the potential of various interventions to modulate GSH levels and markers of oxidative stress. For example, folic acid supplementation has been found to significantly increase serum GSH concentrations(Suksatan et al., 2022), while aerobic exercise in older adults has been associated with an increase in various oxidative stress markers, including GSH (Ye et al., 2021).

The observed changes in GSH levels and GSH/GSSG ratio suggest that propolis may have strong antioxidant properties, potentially offering protection against oxidative stress-related damage. This could have implications for various health conditions where oxidative stress plays a role, such as type 2 diabetes (Kalamkar et al., 2022) or colorectal cancer (Maciejczyk et al., 2020)

Inflammatory markers

Inflammatory markers play a crucial role in the healing process of diabetic foot ulcers (DFUs). The findings regarding TNF-α and IL-10 levels in the propolis-treated group provide valuable insights into the potential anti-inflammatory effects of propolis on DFUs. The significant decrease in tissue TNF-α levels over time in the propolis group, contrasted with constant levels in the control group, suggests that propolis has a potent anti-inflammatory effect (Mahmoud et al., 2024)(Zulhendri et al., 2022b). TNF-α is a pro-inflammatory cytokine that, when persistently elevated, can impair wound healing (Silva et al., 2019).

The reduction in TNF-α levels indicates that propolis may be effectively modulating the inflammatory response, potentially by inhibiting the NF-κB pathway and downregulating pro-inflammatory cytokine production (Zulhendri et al., 2022b). While tissue IL-10 levels did not show significant changes over time, the 100% increase in the propolis group is noteworthy. IL-10 is an anti-inflammatory cytokine that plays a crucial role in resolving inflammation and promoting tissue repair (Beserra et al., 2020) (Hamdoon A. Mohammed, Kamal A. Qureshi, Hussein M. Ali, Mohsen S. Al-Omar, 2022). The substantial increase in IL-10 levels in the propolis group, absent in the control group, suggests that propolis may be stimulating the production of anti-inflammatory mediators, thereby creating a more favorable environment for wound healing (Zulhendri et al., 2022b). These findings align with the broader understanding of propolis as an anti-inflammatory agent. Propolis has been shown to inhibit various pro- inflammatory pathways and cytokines while promoting anti-inflammatory mediators (Zulhendri et al., 2022b). This dual action of reducing pro-inflammatory markers like TNF-α and potentially increasing anti-inflammatory markers like IL-10 could be particularly beneficial in managing the chronic inflammation associated with DFUs, potentially leading to improved wound healing outcomes.

Reduce Inflammation: Flavonoids present in propolis, such as galangin and chrysin, have been shown to inhibit the production of pro-inflammatory mediators like cytokines (TNF-α, IL-1β) and prostaglandins (PGE2) in inflammatory cells. In diabetic conditions, chronic inflammation contributes to impaired wound healing, thus the anti-inflammatory effects of propolis can be highly beneficial (Martinotti et al., 2025)

HbA1c level

The local effects of propolis on tissue repair and inflammation may not necessarily translate to

measurable changes in blood glucose or HbA1c levels. HbA1c is a long-term marker of glycaemic control, reflecting average glucose levels over 2-3 months (Zhan et al., 2022). Short-term interventions or localized treatments may not be sufficient to induce significant changes in HbA1c levels. This is particularly relevant when considering that HbA1c is less influenced by short-term fluctuations in glucose levels compared to direct glycemia measurements (Pohanka, 2021). These local improvements in gut barrier function may not necessarily lead to immediate changes in systemic glucose metabolism or HbA1c levels. he lack of significant changes in serum glycemia or HbA1c levels, despite observed tissue effects from topical propolis application, highlights the complexity of glucose metabolism and the potential for localized interventions to have tissue-specific effects without immediately impacting systemic glycemic markers.

V. CONCLUSION

Propolis, as a natural product, offers a potential alternative or complementary treatment to conventional therapies. affects wound healing through a complex process erythema and exudates, White Blood Cell (WBC) Count and ESR, ulcer discharge, surrounding erythema, wound healing, connective tissue formation, oxidative stress markers, inflammatory markers, HbA1c level. This is important because it can provide a new strategy for managing diabetic foot ulcers, which have been difficult to treat effectively.

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VII. CONFLICTS OF INTEREST

Regarding the publication of this paper, I hereby declare that I have no conflicts of interest. The authors of this study have reported no financial, personal, or professional relationships that would have an impact on the findings or interpretations of this research

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