The Role of Bioactive Compounds from Paraboea leuserensis on VEGF expression of Wound Healing

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Abstract. This study explores the role of bioactive compounds from Paraboea leuserensis in enhancing vascular endothelial growth factor expression, a critical factor in wound healing. Using liquid chromatography-tandem mass spectrometry, compounds such as quercetin, kaempferol, ellagic acid, myricetin, and betaine were identified and assessed for their biological activity. In vitro assays demonstrated that these compounds promote angiogenesis, regulate inflammation, and enhance extracellular matrix remodeling by influencing key molecular pathways. The findings highlight their ability to stimulate endothelial cell proliferation, migration, and capillary formation, all essential for effective tissue repair. This research underscores the potential of natural products as therapeutic agents for improving wound healing outcomes, particularly in chronic or difficult-to-heal wounds. By elucidating the mechanisms underlying the effects of these bioactive compounds, this study contributes valuable insights into their application in regenerative medicine and natural product-based therapeutic development.

Keywords: Bioactive compounds, VEGF, Wound healing, LC-MS/MS

1 Introduction

Wound healing is a multifaceted biological process involving inflammation, angiogenesis, re-epithelialization, and extracellular matrix remodeling [10]. One of the pivotal factors in this process is vascular endothelial growth factor (VEGF), a potent proangiogenic molecule, that stimulates endothelial cell migration, proliferation, and new blood vessel formation [11]. VEGF's role in revascularization is critical for supplying oxygen and nutrients to regenerating tissues, making it a key target for enhancing wound healing therapies [14].

Our previous study published in HAYATI Journal of Bioscience reported that Paraboea leuserensis, an endemic medicinal plant, exhibited promising bioactivity linked to wound healing [11]. The phytochemical analysis, conducted via liquid chromatography-tandem mass spectrometry (LC-MS/MS), revealed a

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spectrum of bioactive compounds with potential pharmacological activities [11]. Our preliminary findings indicate that several bioactive compounds, including quercetin, kaempferol, myricetin, ellagic acid, and betaine, show the potential to enhance VEGF expression and accelerate the wound healing process [11]. The purpose of this study is twofold. First, it aims to identify specific bioactive compounds from P leuserensis that contribute to VEGF-mediated wound healing using phytochemical insights obtained through advanced LC-MS/MS techniques. Second, it seeks to elucidate the molecular pathways through which these compounds regulate VEGF expression, providing a clearer understanding of their therapeutic potential. Addressing these objectives will fill a critical knowledge gap and potentially lay the groundwork for translating these findings into clinical applications.

This paper will explore the role of bioactive compounds identified in P leuserensis on VEGF expression within the context of wound healing. By advancing the understanding of the molecular mechanisms underlying these effects, the study aims to contribute valuable knowledge to both scientific and clinical domains, fostering the development of innovative, natural product-based therapeutic strategies.

2 Methods

2.1 Study design

The research was designed to systematically identify bioactive compounds using liquid chromatography-tandem mass spectrometry (LC-MS/MS) and evaluate their biological activity through in-vitro and in-silico approaches based on literature [33]. This methodological approach ensures the findings' reliability, validity, and reproducibility, aligning with best practices in natural product research [17].

2.2 Phytochemical screening with LC-MS/MS

Bioactive compounds were extracted from dried leaves of P leuserensis using a solvent extraction method optimized for flavonoids and polyphenols. Ethanol 96% was used for five days as the primary solvent due to its high efficiency in extracting a wide range of bioactive metabolites [25; 31]. The crude extract was then filtered and concentrated using a rotary evaporator. Then, LC-MS/MS was employed for phytochemical profiling, leveraging its high sensitivity and accuracy for compound identification [21].

2.3 Identification of key bioactive compounds

Compounds with known bioactivity related to wound healing were prioritized based on existing literature and databases such as PubChem and DrugBank. Specific focus was placed on compounds like quercetin, kaempferol, myricetin, ellagic acid, and betaine due to their established roles in angiogenesis and oxidative stress modulation [9; 14]. The bioinformatics analysis involved cheminformatics tools to predict biological activity and interaction with VEGF pathways.

2.4 In vitro VEGF expression assay

In our previous study, immunohistochemical staining with HE was performed to evaluate VEGF expression with IRS scores [23]. The Immunoreactive Score (IRS) is a scoring system commonly used to assess the expression and distribution of specific proteins or markers in tissue sections using immunohistochemistry [29;20].

2.5 Pathway analysis

Pathway analysis was performed in literature studies using https://scite.ai/assistant to understand the molecular mechanisms underlying VEGF regulation. These analyses elucidated the signaling pathways modulated by the bioactive compounds, such as the PI3K/Akt and MAPK/ERK pathways, which are critical for angiogenesis [5].

2.6 Ethical considerations

Ethical clearance was issued by Komite Etik Penelitian Kesehatan (KEPK) Universitas Prima Indonesia No. 013/KEPK/UNPRI/VII/2022. All experimental procedures were designed to minimize variability and bias, supporting reproducibility and reliability.

3 Results

3.1 Phytochemical analysis with LC-MS/MS

Based on LC-MS/MS data, we have obtained 67 metabolite compounds (Suppl. Table 1. (Heryani et al., 2024). Here, we only present five compounds with the most potential for wound healing effects correlating with VEGF expression

Table 1. LC-MS/MS data of five bioactive compounds from P. leuserensis

No.	Compounds	Formula	Molecular Weight	RT [min]	Area[Max.]	mz
1	Quercetin	C15H10O7	302.04256	8.125	218,365,277.43	99.7
2	Kaempferol	C15H10O6	286.04784	8.843	6,231,657.95	99.6
3	Myricetin	C15H1O8	318.03789	7.277	12,758,981.98	99.5
4	Ellagic acid	C14H6O8	302.00627	7.248	79,509,340.55	96.5
5	Betaine	C5H11NO2	117.07921	26.359	4,768,404.23	93.7

3.2 Molecular structure of bioactive compounds

The molecular structure of bioactive compounds from P. leuserensis ethanolic extract is presented in Figure 1. Quercetin, Kaempferol, and Myricetin were classified as flavonoids, Ellagic acid as polyphenol, and betaine as amino acid derivatives.

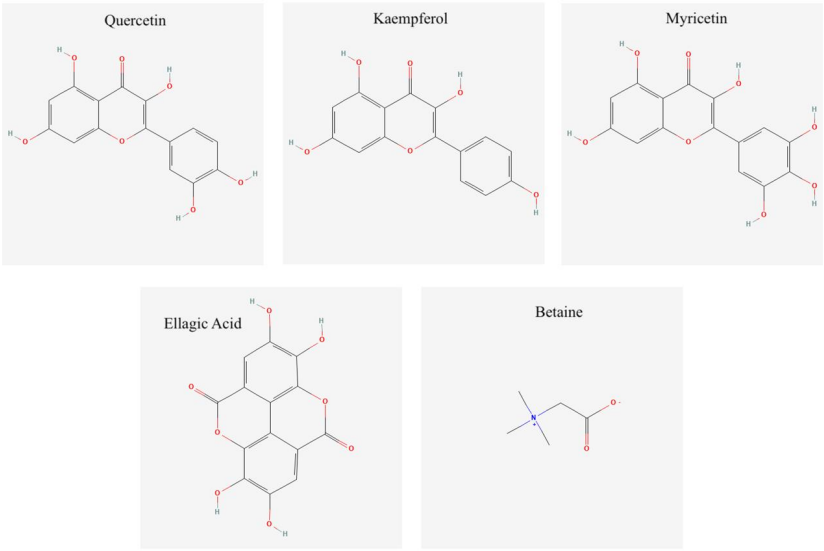

Fig. 1. 2D Chemical structure of five bioactive compounds from P. leuserensis (images adapted from https://pubchem.ncbi.nlm.nih.gov/)

3.3 In vitro VEGF expression

In the previous study, we employed the Immunoreactive Score (IRS) to evaluate the VEGF expression of an excision wound treated by Paraboea Gel Ethanolic Extract (PGEE). The average of IRS scores after 12 days of observation was presented in a previous report [11]. The results of the VEGF data, as expressed by the IRS score, were aligned with established theories of wound healing. Bioplacenton, PGEE 5%, and PGEE 10% exhibited moderate VEGF expression in endothelial cells, while Base gel and PGEE 2.5% demonstrated high expression in vascular endothelial, fibroblast, and epithelial cells. Research by [20] indicated that hypoxic conditions significantly elevated VEGF levels in wound healing contexts, which correlates with our findings of reduced collagen density, suggesting the completion of the remodeling phase. Additionally, nitric oxide (NO), a VEGF mediator, enhances collagen deposition in diabetic wounds by activating fibroblasts [27]. While PDGF and TGF-β are known to aid skin wound healing,

VEGF uniquely stimulates various wound healing components independently of these factors, emphasizing its critical role in the healing process [2],[24].

4 Discussion

Wound healing is a complex biological process involving inflammation, angiogenesis, re-epithelialization, and tissue remodeling. VEGF, a key proangiogenic factor, is pivotal in vascularization and granulation tissue formation, accelerating wound repair. Bioactive compounds such as quercetin, kaempferol, myricetin, ellagic acid, and betaine enhance these processes by modulating VEGF expression and associated signaling pathways. The role of five bioactive compounds against the VEGF expression is described below:

4.1 Quercetin

Quercetin is a bioactive flavonoid recognized for its antioxidant, anti-inflammatory, and angiogenic properties, making it a potent agent in wound healing. Quercetin supports tissue regeneration and accelerates wound closure by promoting collagen synthesis and reducing pro-inflammatory cytokines like TNF-α [15]. It enhances VEGF expression, a critical factor in angiogenesis that drives endothelial cell migration, proliferation, and capillary formation, essential for restoring blood flow to injured tissues [14]. Quercetin's effects on VEGF are mediated through multiple biological mechanisms. It stabilizes hypoxia-inducible factor-1 (HIF-1), enhancing VEGF transcription under hypoxic conditions, a key step in angiogenesis [13]. Additionally, it regulates integrins, facilitating fibroblast migration and extracellular matrix remodeling [6]. A meta-analysis confirmed quercetin derivatives' effectiveness in VEGF-driven angiogenesis, reducing inflammation, and promoting tissue repair in animal models [34]. By modulating VEGF through HIF-1 activation, anti-inflammatory effects, and integrin pathways, quercetin represents a promising natural compound for enhancing wound healing outcomes.

4.2 Kaempferol

Kaempferol is a naturally occurring flavonoid that plays a complex role in wound healing by modulating VEGF expression and associated angiogenic pathways. While it is primarily known for its anti-inflammatory and antioxidative properties, kaempferol exerts both anti-angiogenic and pro-healing effects, depending on the context. It significantly reduces VEGF and placenta growth factor (PGF) expression by inhibiting the PI3K-Akt-Erk1/2 signaling pathway, which is implicated in pathological angiogenesis [35]. This regulatory action prevents excessive vascular growth and is beneficial in diseases such as diabetic retinopathy. However, kaempferol mitigates oxidative stress and inflammatory cytokines in wound healing, creating a conducive environment for VEGF-mediated angiogenesis and

re-epithelialization. These effects indirectly support endothelial cell migration, fibroblast proliferation, and extracellular matrix remodeling, which are crucial for tissue repair [34]. Despite having fewer hydroxyl groups than quercetin, resulting in slightly reduced antioxidant capacity, kaempferol remains highly effective in modulating inflammation and angiogenesis [35]. Kaempferol's dual role as an anti-inflammatory agent and an angiogenic modulator makes it a promising candidate for chronic wound management, highlighting its potential for therapeutic applications [18].

4.3 Myricetin

Myricetin is a flavonoid with notable bioactive properties vital in enhancing VEGF expression, making it a promising compound for wound healing. It upregulates VEGF, which is crucial for angiogenesis, a key process in wound repair. VEGF facilitates endothelial cell migration and tube formation, restoring blood supply to damaged tissues. This mechanism is particularly beneficial for accelerating wound closure and tissue regeneration [34] Myricetin promotes keratinocyte migration, an essential step in epithelialization, and enhances fibroblast proliferation and extracellular matrix deposition, contributing to effective tissue repair [7]. Its anti-inflammatory properties improve wound healing by reducing scar formation and inflammation, leading to better cosmetic outcomes and functional tissue recovery [3]. These combined effects make myricetin particularly suitable for acute and diabetic wounds, where angiogenesis and epithelialization are often impaired [8]. By modulating VEGF expression and promoting key cellular processes in wound healing, myricetin holds significant potential for therapeutic applications in managing chronic and complex wounds [28]. This multifaceted approach underscores its value as a natural compound for enhancing wound healing outcomes.

4.4 Ellagic acid

Ellagic acid is a polyphenolic compound that plays a significant role in wound healing by enhancing vascular endothelial growth factor (VEGF) expression and promoting collagen synthesis, both crucial for extracellular matrix remodeling. Research indicates that ellagic acid stabilizes collagen through cross-linking, which fosters endothelial cell proliferation and capillary formation, essential for effective wound healing [36]. By reducing oxidative damage and inflammatory markers, ellagic acid enhances VEGF expression, facilitating angiogenesis and improving blood supply to the injured tissue [16]. The antioxidant properties of ellagic acid are particularly beneficial under stress conditions, as they help mitigate reactive oxygen species (ROS) levels, which can otherwise impair VEGF activity and wound healing [26]. A study demonstrated that ellagic acid derived from pomegranate extract significantly accelerated the healing process in incised wounds by improving collagen deposition and promoting angiogenesis [1]. Furthermore, ellagic acid's modulation of inflammatory cytokines contributes to a favorable wound-healing environment, enhancing tissue repair and regeneration

[10]. Overall, ellagic acid's multifaceted mechanisms, including its antioxidant effects and promotion of VEGF expression, underscore its therapeutic potential in wound healing applications.

4.5 Betaine

Betaine is an organic osmolyte crucial in wound healing by enhancing vascular endothelial growth factor (VEGF) signaling and supporting fibroblast function[4]. By stabilizing the cellular environment, betaine improves fibroblast hydration and resilience, essential for creating an optimal wound microenvironment conducive to granulation and re-epithelialization [19]. This stabilization is particularly beneficial in wounds subjected to osmotic stress, such as burns, where maintaining cellular hydration is critical for effective healing. Betaine might indirectly enhance VEGF expression by improving granulation tissue quality and promoting angiogenesis. Its ability to reduce oxidative stress and inflammatory markers further supports VEGF activity, facilitating endothelial cell proliferation and capillary formation [4]. In summary, betaine's multifaceted mechanisms, including its role as an osmolyte that enhances cellular resilience and promotes VEGF signaling, underscore its therapeutic potential in managing wounds and improving healing outcomes.

Based on the pieces of literature, we summarize that the bioactive compounds from ethanolic extract of P. leuserensis may activate VEGF pathways via transcriptional regulation or indirect oxidative stress mitigation. VEGF-mediated endothelial proliferation and migration are enhanced by these compounds, promoting angiogenesis. Reduced pro-inflammatory cytokines ensure a conducive environment for VEGF activity.

5 Conclusion

This study highlights the significant role of bioactive compounds from P leuserensis—including quercetin, kaempferol, myricetin, ellagic acid, and betaine—in modulating VEGF expression and promoting wound healing. These compounds, characterized by their flavonoid, polyphenol, or osmolyte properties, enhance angiogenesis, reduce inflammation, and stabilize the extracellular matrix, thereby supporting tissue regeneration. The findings underscore the potential of natural products as therapeutic agents for managing wounds, especially in chronic conditions. Future research should focus on clinical applications and deeper exploration of molecular mechanisms to translate these insights into effective treatments.

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