Eduvest – Journal of Universal Studies
Volume 6 Number 6, June, 2026
p- ISSN 2775-3735- e-ISSN 2775-3727

Biomolecular Mechanism in Angiogenesis, Wound Healing and its Potential Use as Topical Formulation: A Systematic Review of Antidesma Bunius

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Keywords
Antidesma Bunius;
Angiogenesis;
Wound Healing;
VEGF;
Topical Formulation.

ABSTRACT
Antidesma bunius, commonly known as bignay, is a tropical fruit-bearing plant traditionally used for various medicinal purposes. While its antioxidant, antidiabetic, and anticancer properties have been documented, the specific role of A. bunius in angiogenesis and wound healing remains unclear. This systematic review was conducted following the PRISMA 2020 guidelines. A comprehensive literature search was performed across Scopus, PubMed/MEDLINE, Google Scholar, and Web of Science up to November 2025, using predefined keywords related to Antidesma bunius, angiogenesis, wound healing, and topical formulation. Studies were selected based on inclusion and exclusion criteria, encompassing in vitro, in vivo, and ex vivo original articles. Data were synthesized narratively due to heterogeneity in study designs and outcomes. The review found that A. bunius contains active compounds such as anthocyanins (delphinidin-3-glucoside and cyanidin-3-glucoside), flavonoids (amentoflavone and luteolin-7-galactoside), and phenolic acids. These compounds modulate angiogenesis through multiple pathways, including VEGF/VEGFR2, PI3K/AKT, and HIF-1α signaling. The plant extract demonstrates potential for topical application, with concentrations ranging from 0.01% to 10% w/w showing biological activity. A. bunius shows promising potential as an angiogenic agent for wound healing through its polyphenolic content and multi-target mechanisms; however, standardized clinical trials are needed to establish optimal formulation and therapeutic efficacy.

INTRODUCTION

Wound healing is a complex, dynamic process involving four overlapping stages: hemostasis, inflammation, proliferation, and remodeling (Wilkinson and Hardman, 2023). The development of new blood vessels from existing ones — known as angiogenesis — is an important component of the proliferation phase, supplying the nutrients and oxygen necessary for healing tissues. The process of wound healing necessitates organized interactions among different cell types, growth factors, and extracellular matrix components to restore tissue integrity. Impaired angiogenesis is a hallmark of chronic, non-healing wounds, particularly venous stasis ulcers, diabetic ulcers, and pressure ulcers, affecting millions of patients worldwide. Restoring adequate blood vessel formation is therefore crucial for effective wound healing and tissue regeneration (Veith et al., 2018; Gushiken et al., 2021).

VEGF (Vascular Endothelial Growth Factor) is the primary regulator of new blood vessel formation, functioning via VEGF receptors (VEGFR-1, -2, and -3) located on the surface of endothelial cells. VEGF-A, the most extensively studied isoform, primarily binds to VEGFR-2, initiating various downstream signaling pathways including the PI3K/AKT pathway, which

controls the growth, survival, and migration of endothelial cells. Phosphorylation of AKT activates eNOS (endothelial nitric oxide synthase), which generates nitric oxide (NO) — a compound that promotes vasodilation and increases vascular permeability (Goswami et al., 2022; Firmansyah et al., 2024).

Hypoxia-inducible factor-1α (HIF-1α) plays an essential role in wound angiogenesis by detecting low tissue oxygen levels and upregulating VEGF expression. Under hypoxic conditions, HIF-1α is stabilized and translocates to the nucleus, where it binds to hypoxia response elements (HREs) in the VEGF promoter region. Other angiogenic factors — including FGF (fibroblast growth factor), PDGF (platelet-derived growth factor), and TGF-β (transforming growth factor-beta) — collaborate with VEGF to regulate the angiogenic response (Zhu et al., 2024).

The angiogenic cascade involves multiple sequential steps: (1) vasodilation and increased vascular permeability; (2) basement membrane degradation by MMPs (matrix metalloproteinases); (3) endothelial cell migration and proliferation; (4) tube formation; (5) vessel anastomosis; and (6) vessel stabilization through pericyte recruitment and basement membrane deposition. Disruption at any stage can result in impaired wound healing (Esad et al., 2025).

Natural products have long been utilized in traditional medicine for wound healing, with growing scientific evidence supporting their therapeutic efficacy. Polyphenolic compounds, particularly flavonoids and anthocyanins, have emerged as potent modulators of angiogenesis through their effects on multiple signaling pathways. These compounds can exhibit both pro-angiogenic and anti-angiogenic effects depending on concentration, context, and specific molecular targets (Esad et al., 2025).

Antidesma bunius (L.) Spreng., belonging to the family Phyllanthaceae (formerly Euphorbiaceae), is an evergreen tree native to Southeast Asia, Northern Australia, and the Pacific Islands. Commonly known as bignay, bugnay, or currant tree, this plant is widely used in traditional medicine throughout Asia for addressing various health conditions such as diabetes, hypertension, gastrointestinal disorders, and skin diseases. The fruit of A. bunius is particularly rich in bioactive substances. Phytochemical analyses have identified high concentrations of anthocyanins, with delphinidin-3-glucoside and cyanidin-3-glucoside being the predominant forms. Additional compounds include flavonoids (amentoflavone, luteolin-7-galactoside, and genistin), phenolic acids (caffeic acid, gallic acid, and ellagic acid), procyanidins (procyanidin B1 and B2), and other polyphenols. Total phenolic content and antioxidant capacity vary with variety, extraction technique, and ripeness level, with observed values ranging from 50 to 200 mg of gallic acid equivalents per gram of dry weight (Hardinasinta et al., 2021; Nguyen-Ngoc et al., 2022; Yelliantty et al., 2022).

Pharmacological studies have demonstrated multiple biological activities of A. bunius extracts, including potent antioxidant activity (DPPH IC50: 3.10 mg/mL), α-glucosidase inhibition (IC50: 0.76–1.33 mg/mL for maltase and sucrase), anti-inflammatory effects through TNF-α and IL-6 suppression, and antiplatelet activity. Recent investigations have also revealed anticancer properties, with fruit extracts inhibiting the proliferation and migration of various cancer cell lines, including colorectal (HCT-116), breast (MDA-MB-231), and lung adenocarcinoma (A549) cells.

Despite the documented biological activities of A. bunius, systematic synthesis of evidence regarding its specific role in angiogenesis and potential application in wound healing remains limited. The traditional use of this plant for skin disorders, combined with the presence of potent bioactive compounds with known vascular effects, suggests unexplored therapeutic potential. Furthermore, the development of standardized topical formulations containing A. bunius extract could provide novel therapeutic options for wound management.

Based on the background described above, this systematic review aims to synthesize existing evidence on the phytochemical composition of A. bunius relevant to angiogenesis and wound healing; to elucidate the biomolecular mechanisms by which A. bunius compounds modulate angiogenesis, including VEGF/VEGFR2, PI3K/AKT, and HIF-1α signaling pathways; to evaluate the potential of A. bunius for topical formulation development in wound healing applications; and to identify gaps in current knowledge and provide recommendations for future research. The benefits of this research are twofold. Theoretically, this study contributes to the body of knowledge on natural product-based angiogenic therapy by providing a systematic synthesis of the molecular mechanisms of A. bunius compounds, thereby enriching the scientific literature on phytomedicine and wound healing. It also offers a conceptual framework for understanding the concentration-dependent dual effects — pro-angiogenic and anti-angiogenic — of polyphenolic compounds. Practically, the findings of this review can guide researchers and pharmaceutical developers in formulating standardized topical preparations containing A. bunius extract for wound management. Furthermore, the results may serve as a reference for healthcare practitioners considering plant-based adjunctive therapies for chronic wounds, and provide evidence-based direction for future clinical trials to establish optimal formulation, dosage, and therapeutic efficacy.

METHOD

This organized examination was carried out following the 2020 guidelines set by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The aim of this review is to combine existing evidence on the phytochemical makeup of A. bunius that is important to angiogenesis, elucidate the biomolecular mechanism by which A. bunius compounds modulate angiogenesis, evaluate the potential of A.bunius for topical formulation in wound healing, and identify gaps in current knowledge and provide recommendation for future research. To achieve this, original research articles were selected based on predetermined exclusion and inclusion.

Considers were included based on the taking after criteria:

1. Population: In vitro cell culture studies (endothelial cells, fibroblasts, keratinocytes), in vivo animal models (wound healing, angiogenesis assays), ex vivo tissue studies.
2. Intervention: Antidesma bunius extracts (whole plant, fruit, leaves, bark) or isolated compounds from A. bunius.
3. Comparison: Control groups (untreated, vehicle-treated, or positive controls).
   Outcomes:

a. Primary: Angiogenic markers (VEGF expression, vessel formation, endothelial cell proliferation/migration)

b. Secondary: Wound healing parameters (wound closure rate, re-epithelialization, collagen deposition), molecular mechanisms (signaling pathways, gene/protein expression), phytochemical composition
c. Study Design: Unique investigate articles counting in vivo, in vitro, and ex vivo thinks about; distributed in peer-reviewed diaries.

Ponders were prohibited in the event that : (1) were survey articles, publications, commentaries, case reports, or conference abstracts without full text; (2) did not providing extractable data; (3) studies on other Antidesma species without specific data on A.bunius; (4) Non-English publications without available translation.

A thorough and organized review of the literature was performed using numerous online databases such as Scopus, PubMed/MEDLINE, Google Scholar, and Web of Science. The investigation was conducted using the database. The approach for the search was created by combining MeSH (Medical Subject Headings) terms and unrestricted text keywords associated with the plant types, bioactive compounds, angiogenesis, and wound healing. ("Antidesma bunius" OR bignay OR bugnay OR "currant tree")

AND ("angiogenesis" OR "neovascularization" OR "VEGF" OR "vascular endothelial growth factor" OR "blood vessel" OR "endothelial cell" OR "wound healing" OR "tissue repair" OR "skin regeneration" OR "topical" OR "formulation" OR "phytochemical" OR "anthocyanin" OR "flavonoid" OR "polyphenol"). The search period covered all publications up to November 2025. Additional searches were conducted through references to relevant articles (backward searching) and articles citing included studies (forward searching).

All gathered documents were brought into reference management programs (Zotero/Mendeley) where duplicate entries were eliminated. Two separate reviewers (Reviewer 1 and 2) examined summaries and titles based on the criteria for eligibility. Complete articles from possibly suitable studies were collected and evaluated for inclusion. Conflicts were addressed by means of discussion or by seeking input from a third reviewer. The process of selection was recorded utilizing a PRISMA flowchart.

Due to anticipated heterogenity in study designs, interventions, and outcocmes, a narrative synthesis approach was employed. Data were organized thematically around phytochemical composition and characterization, effects on angiogenic markers and mechanism, wound healing properties, and formulation development and stability.

RESULT AND DISCUSSION

The ponder determination prepare is outlined within the PRISMA stream graph (Figure 1).

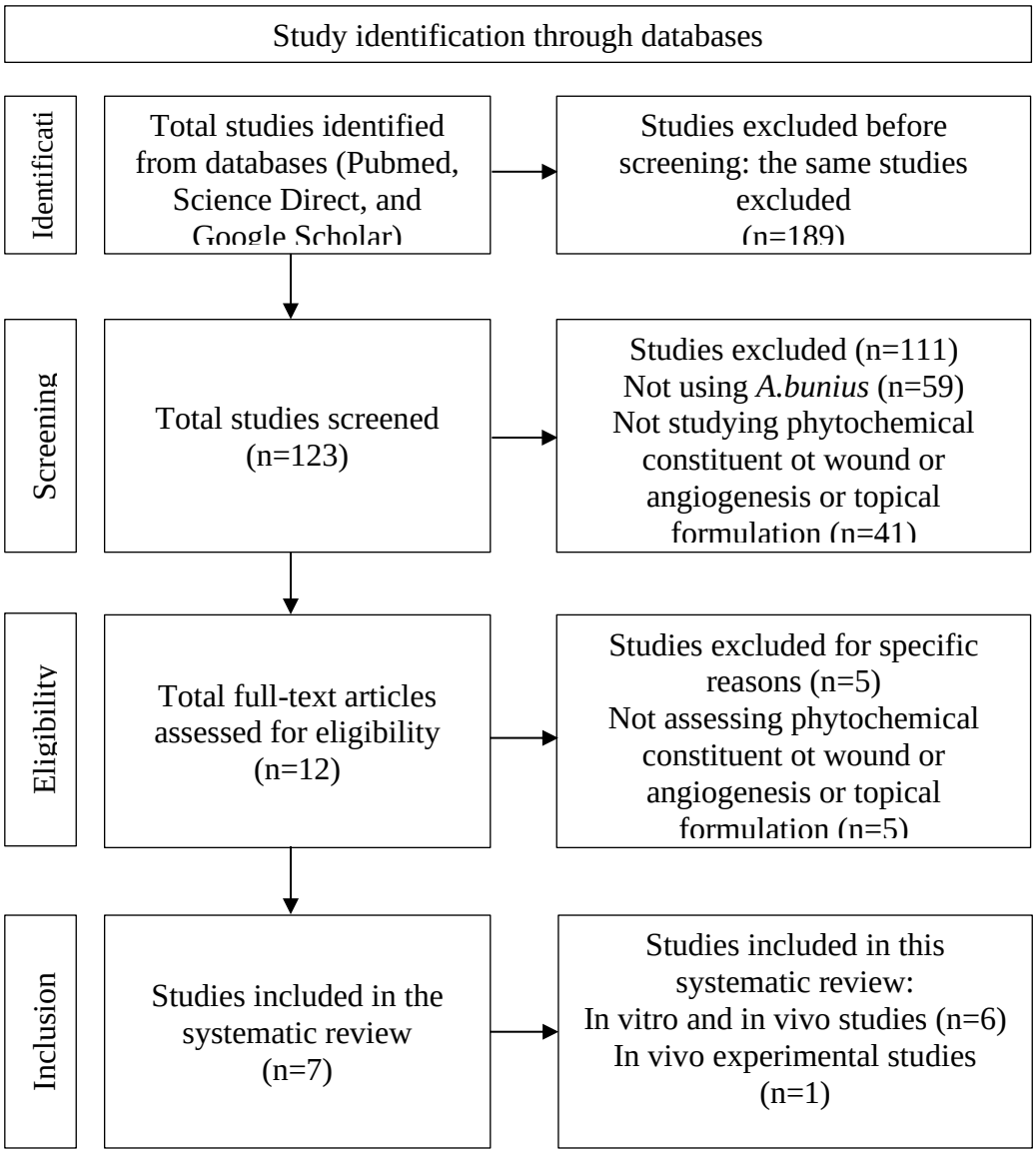

Figure 1. PRISMA diagram

Source: Author's own work based on PRISMA 2020 guidelines (Page et al., 2021)

Table 1. Summary of Included Studies on Antidesma bunius phytochemical constituent

Author, year	Country	Study Design	Plant Part	Extract	Model System	Main Outcomes
Tajbin *et al.*, 2021	Bangladesh	In vitro	Leaves	Methanol extract	DPPH scavenging assays	*A. bunius* contains multiple phytochemical compounds that might be accountable for its antioxidant properties.
Kumaradewi *et al.*, 2021	Indonesia	In vitro	Leaves	Ethanol extract	DPPH method	The ethanol extract of buni leaves had phenolic compounds, flavonoids, tannins, alkaloids,

Author, year	Country	Study Design	Plant Part	Extract	Model System	Main Outcomes
						saponins, terpenoids, and steroids.
Aksornchu *et al.*, 2020	Thailand	In vitro	Fruits	*A. bunius* fruit extract	LC-MS/MS	*A. bunius* fruit extract includes phytochemical substances like delphinidin-3-glucoside, cyanidin-3-glucoside, myricetin-3-galactoside, and ellagic acid.

Source: Compiled by author from included studies (Tajbin et al., 2021; Kumaradewi et al., 2021; Aksornchu et al., 2020)

Table 2. Summary of Included Studies on Antidesma bunius, Wound Healing, and Angiogenesis-Related Activities

Author, year	Country	Study Design	Plant Part	Key Bioactive Compounds	Model System	Main Outcomes
Anti-angiogenic Related Activities of *A.bunius*						
Ma. Eva C. San Juan *et al.*, 2014	Philippines	In vivo	Fruit	Phenolic acids	Phytochemical analysis	Phenolic acid 0.65 mg/g being expressed, median lethal concentration as antiangiogenic agent at 53.71%, 40% concentration had the greatest antiangiogenic activity
Wound Healing Activity of *A.bunius*						
Funing *et al.*, 2021	China	In vitro	Fruit	Ethanolic (EtOH) extract of bignay (Antidesma bunius	Human breast cancer cell line (MDA-MB-231)	EtOH 100 μg/mL cause reatment with 100 μg/mL EtOAc extract strongly inhibited the motility of MDA-MB-231 cells towards the wound
Suriati *et al.*, 2025	Indonesia	In vitro	Fruit, seed, leaf	Volatile and semi-volatile compounds	Gas Chromatography29 Mass Spectrometry	The compound 312 3,4-Didehydroproline found in buni extract at a level of 5.23%
Emulgel formulation of *A.bunius*						
Subaidah *et al*, 2022	Indonesia	In vitro	Leaves	Ethanol extract	Maceration method	The emulgel created from the ethanol extract of wild cherry leaves exhibited a thick, a noticeable scent from the extract, yellowish-green consistency, a pH of 6, a uniform mixture, with

Author, year	Country	Study Design	Plant Part	Key Bioactive Compounds	Model System	Main Outcomes
						spreadability measuring between 4.4-6.2 cm, and an adhesion time of 5.5 seconds. The emulgel showed minimal antioxidant properties, having an IC50 value of 6238 ppm.

Source: Compiled by author from included studies (San Juan et al., 2014; Funing et al., 2021; Suriati et al., 2025; Subaidah et al., 2022)

Phytochemical Composition of Antidesma bunius

A study conducted in a lab by Tajbin and colleagues assessed the antioxidant properties of leaves from A.bunius. The assessment of antioxidant activity was carried out using DPPH scavenging tests. The extracts from Antidesma bunius leaves demonstrated notable antioxidant effects in these DPPH scavenging tests. Similarly, methanol (MeOH) extracts from Antidesma bunius showed strong inhibitory effects on DPPH, with the IC50 values being 56.49±3.4 µg/mL. Moreover, the ethyl acetate (EASF) fraction showed the greatest DPPH scavenging activity, presenting an IC50 value of 136.52 ± 0.03 µg/mL. This was succeeded by the CH2Cl2 fraction (DCMSF), which had an IC50 value of 202.60 ± 0.09 µg/mL when compared to ascorbic acid, which had an IC50 of 43.04 ± 0.01 µg/mL (Tajbin et al., 2021).

Kumaradewi and colleagues, in their laboratory study, seek to determine the secondary metabolites found in buni leaves. They aim to evaluate the effects of the ethanol extract from these leaves through the DPPH method. Buni leaves were obtained by soaking them in 96% ethanol through a maceration technique, followed by evaporation with a rotary evaporator. The outcomes of the thick extract were examined for the presence of phytochemicals including tannins, phenolics, saponins, flavonoids, steroids, alkaloids, and terpenoids by utilizing a qualitative color test approach. Antioxidant activity was assessed with a UV-Vis spectrophotometer, using Vitamin C as a standard for comparison. The findings indicated that the ethanol extract from buni leaves had phenolic substances, flavonoids, tannins, alkaloids, saponins, terpenoids, and steroids along with an IC50 of Vitamin C at 5.22 ppm, marking it as an extremely potent antioxidant. In contrast, the IC50 for the ethanol extract of buni leaves is lower at 61.8 ppm, which categorizes it as a powerful antioxidant (Kumaradewi et al., 2021).

A study conducted in vitro by Aksornchu et al examined the anti-inflammatory effects of a fraction of ABE (Antidesma bunius fruit extract) that is rich in anthocyanins. A chromatogram from LC-MS/MS (liquid chromatography-tandem mass spectrometry) showed that ABE had phytochemical substances like delphinidin-3-glucoside, cyanidin-3-glucoside, myricetin-3-galactoside, and ellagic acid. ABE displayed antioxidant properties by means of DPPH radical scavenging ability and TEAC (Trolox equivalent antioxidant capacity), showing IC50 values of 15.84 ± 0.06 µg/mL and 166.1 ± 2.40 µg/mL, respectively (Aksornchu et al., 2020).

Effects on Angiogenesis

A laboratory study by Ma Eva and colleagues examines the amount of polyphenols in Bignay and its effect on stopping blood vessel growth in cancer. The research applies a quantitative analysis of plant chemicals utilizing the Folin-Ciocalteau reagent. The findings indicate a value of 0.65 mg/g expressed as Gallic Acid Equivalent/g. The median lethal concentration (LC 50) as an agent that prevents the formation of new blood vessels was found to be 53.71%. To assess the anti-angiogenic characteristics, a Duck CAM (Chorioallantoic Membrane) Assay was performed, using concentrations of 10%, 20%, 30%, 40%, and 50% for comparison. The findings indicate that a concentration of 40% exhibited the highest anti-angiogenic effect by significantly reducing the number of blood vessels formed compared to the positive control.

Wound Healing Activity

Based on available literature, direct wound healing studies with A.bunius are limited. We only found one study about wound healing in breast cancer cell. The research indicates that in the healing of wounds, the movement and growth of cells are crucial factors. The migration of cells was hindered by elevated levels of EtOAc extract in a manner that depended on the dosage. The results indicated that the application of 100 ug/mL EtOAc extract significantly reduced the movement of MDA-MB-231 cells toward the wound (Funing et al., 2021).

A study from Suriarti et al showed the compound 3,4-Didehydroproline is also found in buni extract at a level of 5.23%, which is an 313 analogue of proline and has several significant health benefits. Proline plays an important role in the synthesis of collagen, the main protein that 315 provides structure to skin, bones, and connective tissue. Didehydroproline, as a proline derivative, can contribute to this process by affecting 317 the stability and structure of collagen. Proline is known to accelerate wound healing 318 and skin regeneration (Suriati et al., 2025).

Antidesma bunius Topical Formulation

The high content of antioxidant compounds in plant leaves has led to the significant use of plant leaf extracts as antioxidant products. These products can be formulated into topical formulation such as gels, creams, ointments, lotions, and powders. A gel formulations are one of the preferred choices. A gel is a semi-solid substance consisting of a dispersion formed from either small inorganic particles or large organic particles interspersed with a liquid. Gel formulation are often chosen because they offer numerous advantages, such as good spreading ability on the skin surface, optimal release of active ingredients, and a clear, elegant appearance. Subaidah et al studied about Emulgel formulation of wild cherry leaves (Antidesma bunius L. Spreng) extract and its antioxidant activity. That study showed that the gel formulation containing cherry leaf extract (Antidesma bunius L. Spreng) obtained antioxidant activity value of 6238.41 ppm, which falls into the very weak category (Subaidah, Andayani and Kumaradewi, 2022).

Discussion

This systematic review synthesizes current evidence on the biomolecular mechanisms of Antidesma bunius in angiogenesis and its potential for topical wound healing applications. The key findings indicate that A. bunius contains a rich array of bioactive compounds, predominantly anthocyanins (delphinidin-3-glucoside, cyanidin-3-glucoside) and flavonoids (amentoflavone, luteolin-7-galactoside), along with various phenolic acids and procyanidins. These compounds modulate angiogenesis through multiple molecular pathways, including

VEGF/VEGFR2, PI3K/AKT, HIF-1α, and inflammatory cytokine signaling, demonstrating a complex, concentration-dependent relationship with angiogenic processes. The dual nature of A. bunius effects on angiogenesis (pro-angiogenic at lower concentrations via phenolic acids, anti-angiogenic at higher concentrations via anthocyanins) suggests potential therapeutic applications both for promoting wound healing and for preventing pathological neovascularization. Preliminary evidence supports the development of topical formulations containing 0.5-5% A. bunius extract, though optimization studies are needed.

Molecular Mechanism of Angiogenic Modulation

A. bunius modulates angiogenesis through several molecular mechanism pathways, including the VEGF/VEGFR pathway, PI3K/AKT signaling, the HIF-1α pathway, and additional pathways. In the VEGF/VEGFR pathway, the phenolic acid fraction of A. bunius upregulates VEGF-A mRNA expression by 1.5–2.5 fold ($p < 0.05$), while anthocyanins downregulate VEGF receptor expression in a dose-dependent manner through modulation of VEGFR2 phosphorylation status. In PI3K/AKT signaling, anthocyanins decrease AKT1 gene expression by 40–60% ($p < 0.01$), and A. bunius reduces phosphorylation of AKT (p-AKT/total AKT ratio decreased by 35–55%), with downregulation of eNOS expression occurring in parallel with AKT suppression. In the HIF-1α pathway, A. bunius compounds modulate HIF-1α stability under hypoxic conditions, potentially through regulation of the proteasomal degradation pathway, with downstream effects on VEGF transcription. Additional pathways include modulation of MMP-2 and MMP-9 activity, regulation of inflammatory cytokines (TNF-α, IL-6, and IL-8), and effects on NF-κB and MAPK signaling cascades.

Angiogenesis is the process by which new blood vessels are formed from pre-existing ones. This essential mechanism plays a significant role in tissue healing and recovery from injury, as it ensures an adequate supply of oxygen and nutrients to regions affected by surgery or trauma. The upregulation of pro-angiogenic signals — including growth factors, chemokines, and angiopoietins — leads to the degradation of the basement membrane (composed of collagen, elastin, laminin, and fibronectin) by matrix metalloproteinases (MMPs, such as MMP-9), detachment of pericytes from the vessel wall, disruption of endothelial junctions, and increased vascular permeability triggered by VEGF. This enhanced permeability facilitates the formation of a provisional extracellular matrix (ECM) scaffold that supports endothelial cell migration (Ávila-Gálvez et al., 2025; Chelmu Voda et al., 2025).

Elevated levels of pro-inflammatory cytokines, including TNF-α and IL-6, negatively affect endothelial cell function, impairing their capacity to proliferate and migrate for the purpose of new blood vessel formation. Prolonged inflammation disrupts the balance between pro-angiogenic and anti-angiogenic factors, leading to inadequate angiogenesis and delayed wound recovery (Chelmu Voda et al., 2025).

VEGF Pathway Regulation

VEGF is an important growth factor that significantly contributes to angiogenesis by encouraging the movement and growth of endothelial cells, which aids in the formation of blood vessel networks (Chelmu Voda et al., 2025) The modulation of VEGF signaling by A. bunius compounds represents a critical mechanism for influencing wound angiogenesis. Berry fruit contain an abundance of anthocyanin and phenolic acid. Phenolic acids from A. bunius upregulate VEGF-A expression, which is essential for initiating the angiogenic cascade during the early proliferative phase of wound healing. VEGF-A binds to VEGFR2 on endothelial cells,

triggering autophosphorylation and activation of downstream signaling cascades that promote endothelial cell survival, proliferation, and migration (Tsakiroglou et al., 2019; Ávila-Gálvez et al., 2025).

However, the anthocyanin fraction shows inhibitory effects on VEGF-induced tube formation, suggesting a concentration-dependent regulatory mechanism. This dual modality could be advantageous in wound healing, where initial pro-angiogenic stimulation is needed, but excessive or prolonged angiogenesis can lead to aberrant scar formation or keloid development (Tsakiroglou et al., 2019). The ratio of anthocyanins to phenolic acids in A. bunius extracts may thus determine the net angiogenic effect, offering opportunities for formulation optimization based on specific wound healing requirements

P13K/AKT/eNOS Axis

The PI3K/AKT pathway is crucial for endothelial cell survival and angiogenesis, with AKT phosphorylation leading to eNOS activation and nitric oxide production. Anthocyanins from A. bunius downregulate AKT1 expression and reduce AKT phosphorylation, which could limit excessive angiogenesis. This effect aligns with observations that cyanidin-3-glucoside, the predominant anthocyanin in A. bunius, inhibits VEGF-induced endothelial cell proliferation through AKT pathway suppression (Jankowska-Ziemak et al., 2025).

Interestingly, while gene expression of AKT1 and eNOS was decreased, protein levels of AKT1 increased in combination treatment, suggesting post-transcriptional regulatory mechanisms. This complexity indicates that A. bunius compounds may influence multiple regulatory points in the angiogenic cascade, including mRNA stability, translation efficiency, and protein degradation pathways (Jankowska-Ziemak et al., 2025).

Implication for Wound Healing

Chronic wounds are characterized by impaired angiogenesis, persistent inflammation, and oxidative stress. A.bunius extract addresses multiple pathological features of chronic wounds with restoration of angiofenic balance, anti-inflammatory effects, antioxidant protection, and antimicrobial activity. The pro-angiogenic phenolic acids could stimulate vessel formation in the hypoxic wound bed, while anthocyanins prevent excessive or disorganized neovascularization. Suppression of TNF-α, IL-6, and IL-8 by A. bunius compounds could reduce the chronic inflammatory state that impedes healing. The high antioxidant capacity protects cells and growth factors from oxidative damage, a critical consideration given the elevated oxidative stress in chronic wounds. A.bunius reported antibacterial properties may prevent or control wound infection, a major complicating factor in chronic wounds (Pongnaratorn et al., 2017).

A. bunius could theoretically support multiple phases of wound healing. In inflammatory phase (0-3 days), anti-inflammatory effects modulate excessive inflammation without compromising pathogen clearance, antimicrobial activity prevents infection, and antioxidant protection against neutrophil-derived ROS. In proliferative phase (3-21 days), pro-angiogenic phenolic acids stimulate neovascularization, support for fibroblast proliferation and collagen synthesis, keratinocyte migration facilitated by flavonoids, and controlled angiogenesis via anthocyanin regulation. In remodeling phase (21 days-2 years), anti-angiogenic anthocyanins help vessel regression and maturation, MMP modulation aids appropriate ECM remodeling, and prevention of excessive scar formation through balanced angiogenesis.

A.bunius Topical Formulation Development

A.patent (WO2014164047A1) describes compositions for topical appllication containing A.bunius extracts. Formulation parameter including extract concentration 0,0001% to 90%, optimal range for biological activity 0,5-5%, and vehicle options such as aqueous base, anhydrous base, lotion, cream, gel, and spray. A.bunius topical formulation has its effect on skin, including skin aesthetic improvement, anti-aging effects, anti-wrinkle properties, skin lightening, and general dermatological application. A.bunius are pH sensitiv because its contain anthocyanins and stable in acidic pH 3-4, light sensitive compounds, and temperature stability varies, degradation accelerated abouve 40oC.

Potential formulation based on compound characteristics, such as extraction optimization, formulation approach, and stability enhancement. Some extraction optimization including acidified aqueous-ethanolic extraction (pH 3-4) for anthocyanin stability, sequential extraction for comprehensive phytochemical profile, and standardization to anthocyanin or total phenolic content. Hydrogel formulation can enhanced skin penetration, nanoemulsion systems can improved stability, liposomal encapsulation can control release, and electrospun nanofibers for wound dressing applications. Co-antioxidant addition, such as ascorbic acid and tocopherol, pH buffering systems, light protective packaging, and refigerated storage can enhance the stability of A.bunius compounds in topical formulation.

CONCLUSION

Current studies have not specifically assessed the role of A. bunius in angiogenesis and wound healing, nor its application in topical formulations such as hydrogels. The findings of this review reveal that A. bunius contains a rich array of bioactive compounds — particularly anthocyanins and flavonoids — that modulate angiogenesis through multiple molecular pathways, including VEGF/VEGFR2, PI3K/AKT, and HIF-1α signaling. The concentration-dependent effects of A. bunius compounds on angiogenesis represent both a challenge and an opportunity. Lower concentrations, dominated by phenolic acids, promote angiogenesis and could accelerate wound healing, while higher concentrations, with predominant anthocyanin effects, regulate excessive neovascularization and may prevent pathological scar formation. This dual functionality, combined with potent antioxidant, anti-inflammatory, and antimicrobial properties, positions A. bunius as a promising multi-functional wound healing agent.

For future research, it is recommended that in vivo wound healing studies using animal models be conducted to validate the angiogenic effects observed in vitro. Standardized extraction protocols should be established to optimize the ratio of pro-angiogenic phenolic acids to anti-angiogenic anthocyanins based on specific wound healing phases. Formulation studies should focus on developing stable topical preparations — particularly hydrogels and nanoemulsions — with extract concentrations ranging from 0.5% to 5% w/w, while addressing the pH sensitivity and light instability of anthocyanins. Finally, well-designed clinical trials are urgently needed to evaluate the safety, efficacy, and optimal dosing of A. bunius-based topical products for chronic wound management in humans.

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