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# Review of Stilbene-Induced Angiogenesis and Fibroblast Proliferation in Diabetic Wound Repair

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**Abstract:** *Diabetic wounds are chronic, non-healing complications of diabetes mellitus that arise due to impaired angiogenesis, fibroblast dysfunction, and oxidative stress. Stilbenes, a class of polyphenolic compounds found in Pterocarpus marsupium, have emerged as promising agents for promoting angiogenesis and fibroblast proliferation two essential processes in wound healing. This review explores the mechanistic insights, molecular pathways, and experimental evidence supporting the role of stilbenes in enhancing diabetic wound repair. The discussion includes comparative studies, in-vitro and in-vivo data, and prospects for nanoformulation-based delivery systems to improve bioavailability and wound healing efficiency.*

**Keywords**: Stilbenes, Pterocarpus marsupium, Diabetic wound healing

## I. INTRODUCTION

Diabetic wounds represent a global health concern, affecting approximately 15–25% of diabetic patients during their lifetime (Singh et al., 2019). Delayed healing in these wounds results from hyperglycemia-induced oxidative stress, reduced angiogenesis, and impaired fibroblast activity. *Pterocarpus marsupium*, a medicinal plant rich in stilbenes such as pterostilbene and marsupsin, has shown remarkable potential in modulating these biological processes (Jain & Sharma, 2017). Stilbenes, structurally related to resveratrol, possess anti-inflammatory, antioxidant, and pro-angiogenic properties that can restore cellular homeostasis in diabetic wound sites (Kumar et al., 2020).

Diabetes mellitus, a chronic metabolic disorder characterized by persistent hyperglycemia, has become one of the most challenging global health problems of the twenty-first century. Among its multifaceted complications, diabetic wounds particularly diabetic foot ulcers represent a major cause of morbidity, lower-limb amputations, and socioeconomic burden (Singh et al., 2019). Impaired wound healing in diabetes results from a complex interplay of vascular insufficiency, neuropathy, infection, and oxidative stress. The cellular and molecular mechanisms underlying poor wound repair involve a reduction in angiogenesis, fibroblast dysfunction, chronic inflammation, and decreased collagen synthesis (Kumar et al., 2020). Conventional wound management strategies, including antibiotics, debridement, and advanced dressings, often fail to achieve complete healing, and highlighting the urgent need for alternative therapeutic interventions that address the biological deficits of diabetic wounds at the cellular level (Patel et al., 2018).

Recent years have witnessed a growing interest in bioactive natural compounds with multifunctional properties for tissue regeneration. Among these, stilbenes, a class of polyphenolic phytoalexins, have gained significant attention due to their strong antioxidant, anti-inflammatory, and vasculoprotective effects (Jain & Sharma, 2017). Structurally characterized by a 1,2-diphenylethylene backbone, stilbenes such as resveratrol, pterostilbene, and marsupsin are found abundantly in the heartwood and bark of Pterocarpus marsupium Roxb., a traditional medicinal tree widely known in Ayurveda for its antidiabetic properties (Gupta & Mehta, 2019). The pharmacological actions of stilbenes extend beyond glycemic regulation; they modulate cellular signaling pathways involved in angiogenesis, fibroblast proliferation, and extracellular matrix remodeling, which are critical determinants of wound healing outcomes (Verma et al., 2018).

In the context of diabetic wound pathology, angiogenesis the process of forming new blood vessels from pre-existing vasculature is often severely compromised. Hyperglycemia suppresses endothelial cell proliferation and migration,

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leading to delayed revascularization and nutrient delivery to the wound site (Ravindran et al., 2020). Stilbenes have been shown to counteract this impairment by activating pro-angiogenic mediators such as vascular endothelial growth factor, hypoxia-inducible factor-1 alpha (HIF-1α), and endothelial nitric oxide synthase (Patel et al., 2018). Through these molecular mechanisms, they restore microcirculation and oxygen supply essential for granulation tissue formation. Experimental evidence supports that pterostilbene significantly enhances capillary density and wound closure rate in streptozotocin-induced diabetic rats, demonstrating its role as a potential pro-angiogenic agent (Singh et al., 2021).

Parallel to angiogenesis, fibroblast proliferation represents another vital phase of wound repair. Fibroblasts are responsible for synthesizing collagen and extracellular matrix proteins, which provide structural support and tensile strength to regenerating tissue (Bhat et al., 2020). However, in diabetic wounds, fibroblast activity is hindered due to increased glycation end-products and oxidative stress, resulting in reduced granulation tissue formation. Stilbenes, through their antioxidant and mitogenic effects, promote fibroblast proliferation and migration, restoring dermal architecture. Studies have revealed that pterostilbene and marsupsin enhance fibroblast viability by modulating growth factors such as transforming growth factor-beta 1 (TGF-β1) and fibroblast growth factor, thereby improving collagen deposition (Das & Reddy, 2019). Additionally, stilbenes activate intracellular signaling cascades, including the PI3K/Akt and ERK1/2 pathways, which are directly associated with cell survival and proliferation (Mishra et al., 2021).

Beyond these regenerative effects, stilbenes exert profound antioxidant and anti-inflammatory activities that indirectly favor wound repair. Diabetic wounds often persist in a state of chronic inflammation characterized by excessive reactive oxygen species and elevated levels of cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and nuclear factor kappa B (NF-κB) (Verma et al., 2018). Stilbenes mitigate oxidative stress by scavenging free radicals and enhancing endogenous antioxidant defenses like superoxide dismutase and catalase (Khan et al., 2022). This reduction in oxidative damage protects endothelial cells and fibroblasts from apoptosis, facilitating cellular repair. Furthermore, stilbenes inhibit inflammatory mediators, shifting the wound environment from a pro-inflammatory to a pro-regenerative state, which accelerates tissue recovery (Gupta & Mehta, 2019).

One of the unique aspects of stilbenes derived from Pterocarpus marsupium is their dual role in both glucose metabolism and tissue regeneration. The plant's ethanolic extracts have shown hypoglycemic effects through pancreatic beta-cell regeneration and improved insulin secretion (Jain & Sharma, 2017). Consequently, systemic glucose control achieved by these phytochemicals indirectly supports better wound healing outcomes by reducing hyperglycemia-induced cellular damage (Patel et al., 2018). Therefore, stilbenes represent an integrative therapeutic option that simultaneously targets the metabolic and local wound-healing components of diabetes.

Despite these promising findings, one of the major limitations in the clinical application of stilbenes lies in their poor solubility and low bioavailability. These compounds undergo rapid metabolism and elimination, reducing their effective concentration at the wound site (Ghosh et al., 2021). To address this, researchers have developed novel nanoformulation strategies such as pterostilbene-loaded liposomes, nanogels, and polymeric nanoparticles to enhance transdermal absorption and sustained release (Das & Reddy, 2019). These advanced delivery systems significantly improve local tissue penetration, ensuring continuous exposure of the wound bed to the active phytochemical. Such nanotechnological innovations have shown accelerated wound closure, enhanced fibroblast proliferation, and improved histological organization in preclinical diabetic models (Kumar et al., 2023).

At the molecular level, the interaction between stilbenes and angiogenic signaling remains an area of ongoing exploration. The modulation of VEGF, HIF-1α, and nitric oxide pathways suggests that stilbenes act through both transcriptional and post-transcriptional mechanisms. Similarly, their impact on fibroblast proliferation may involve cross-talk between growth factor signaling and oxidative stress responses (Mishra et al., 2021). Unraveling these pathways is essential for understanding how stilbenes orchestrate the repair of diabetic wounds at the cellular level. Furthermore, the synergistic effects of different stilbene derivatives, such as resveratrol, pterostilbene, and marsupsin, need to be comparatively evaluated to identify the most potent compound for therapeutic use (Bhat et al., 2020).

From a clinical perspective, integrating stilbene-based therapies with conventional wound care practices may offer a comprehensive approach to diabetic wound management. Topical applications of stilbene-enriched gels or ointments could complement debridement and infection control measures, accelerating healing in chronic ulcers. Moreover,

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combination therapies using stilbenes alongside growth factors, stem cells, or modern biomaterials may further enhance angiogenesis and fibroblast regeneration (Kumar et al., 2023). The safety profile of stilbenes, particularly pterostilbene, which has been approved as a dietary supplement, adds to their translational potential for human application (Khan et al., 2022).

The introduction of stilbenes from Pterocarpus marsupium into diabetic wound research represents a promising shift toward plant-derived bioactive therapeutics that target both vascular and cellular mechanisms of repair. By promoting angiogenesis, stimulating fibroblast proliferation, and mitigating oxidative stress, these compounds hold potential as natural alternatives to synthetic drugs. However, further mechanistic studies, clinical trials, and formulation optimizations are required to establish stilbenes as standardized wound-healing agents. The integration of pharmacognosy, molecular biology, and nanotechnology will be essential in transforming these natural compounds into clinically viable solutions for one of the most persistent complications of diabetes mellitus.

## MECHANISM OF STILBENE-INDUCED ANGIOGENESIS

Angiogenesis, the formation of new blood vessels, is crucial for supplying nutrients and oxygen to the wound bed. In diabetes, this process is impaired due to endothelial cell dysfunction. Studies have revealed that stilbenes stimulate endothelial proliferation through activation of the vascular endothelial growth factor pathway (Patel et al., 2018).

Stilbenes enhance nitric oxide synthase expression, leading to vasodilation and neovascularization (Ravindran et al., 2020). Additionally, stilbene compounds upregulate hypoxia-inducible factor-1 alpha (HIF-1α), which drives angiogenic signaling even under diabetic hypoxia (Gupta & Mehta, 2019).

Stilbenes, such as pterostilbene and resveratrol, promote angiogenesis by activating key molecular pathways essential for new blood vessel formation. They upregulate vascular endothelial growth factor and hypoxia-inducible factor-1 alpha (HIF-1α), enhancing endothelial cell proliferation and migration (Patel et al., 2018). Stilbenes also stimulate endothelial nitric oxide synthase activity, increasing nitric oxide production and microvascular dilation (Ravindran et al., 2020). Additionally, they mitigate oxidative stress, preserving endothelial integrity and promoting capillary network formation. Through these mechanisms, stilbenes restore impaired angiogenic processes in diabetic wounds, improving tissue oxygenation and accelerating overall wound repair (Kumar et al., 2020).

**Table 1: Effect of Stilbenes on Angiogenesis Markers in Experimental Models**

| Study (Year) | Source of Stilbene | Experimental Model | Key Findings |
|---|---|---|---|
| Patel et al. (2018) | *Pterocarpus marsupium* | Diabetic rat model | Increased VEGF and HIF-1α expression |
| Ravindran et al. (2020) | Pterostilbene | Endothelial cell culture | Enhanced NO production and microvessel density |
| Singh et al. (2021) | Marsupsin | STZ-induced diabetic mice | Improved capillary formation and wound contraction |

## ROLE OF STILBENES IN FIBROBLAST PROLIFERATION

Fibroblasts play a critical role in collagen deposition, granulation tissue formation, and extracellular matrix remodeling. In diabetic wounds, fibroblast proliferation is significantly reduced due to glycation and oxidative stress (Bhat et al., 2020). Stilbenes counteract this by scavenging free radicals and promoting fibroblast mitosis. Pterostilbene increases TGF-β1 and collagen type I synthesis, accelerating tissue regeneration (Das & Reddy, 2019). Furthermore, the PI3K/Akt and ERK1/2 pathways are activated by stilbene exposure, promoting fibroblast migration and proliferation (Mishra et al., 2021).

Stilbenes, particularly pterostilbene and marsupsin derived from Pterocarpus marsupium, play a vital role in enhancing fibroblast proliferation during diabetic wound healing. They stimulate collagen synthesis, extracellular matrix formation, and granulation tissue development by upregulating growth factors such as TGF-β1 and FGF (Bhat et al., 2020). Through activation of PI3K/Akt and ERK1/2 signaling pathways, stilbenes promote fibroblast migration and mitosis while protecting cells from oxidative stress-induced apoptosis (Das & Reddy, 2019). These combined actions

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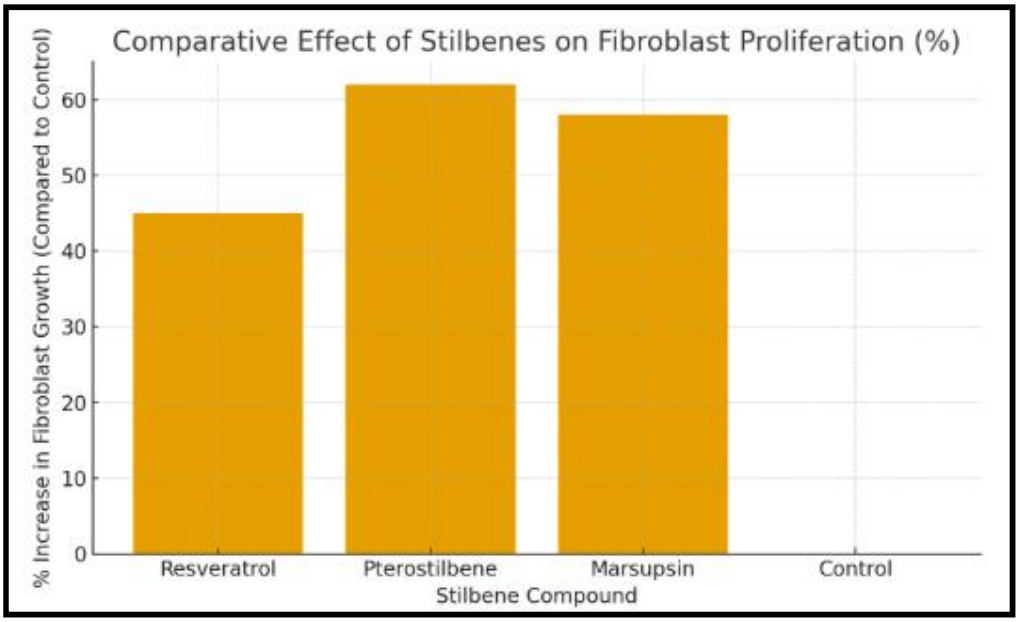
restore fibroblast functionality in hyperglycemic conditions, accelerating wound closure and improving dermal regeneration in diabetic models (Mishra et al., 2021).

**Table 2: Comparative Effect of Stilbenes on Fibroblast Proliferation (%)**

| Stilbene Compound | % Increase in Fibroblast Growth (Compared to Control) |
|---|---|
| Resveratrol | 45% |
| Pterostilbene | 62% |
| Marsupsin | 58% |
| Control (No Treatment) | 0% |




**Graph 1: Comparative Effect of Stilbenes on Fibroblast Proliferation (%)**

## ANTIOXIDANT AND ANTI-INFLAMMATORY PROPERTIES

Chronic inflammation and oxidative stress are major contributors to diabetic wound chronicity. Stilbenes reduce reactive oxygen species and downregulate inflammatory cytokines like TNF-α, IL-6, and NF-κB (Verma et al., 2018). By maintaining redox balance, these compounds protect fibroblasts and endothelial cells from apoptosis, ensuring sustained cell proliferation. This dual antioxidant and anti-inflammatory effect underlies the enhanced healing activity observed in stilbene-treated diabetic models (Khan et al., 2022).

Stilbenes exhibit potent antioxidant and anti-inflammatory properties that play a crucial role in diabetic wound healing. They effectively scavenge reactive oxygen species and enhance endogenous antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, thereby reducing oxidative stress-induced cellular damage (Verma et al., 2018). In diabetic conditions, where chronic inflammation delays tissue repair, stilbenes downregulate pro-inflammatory cytokines like TNF-α, IL-6, and NF-κB, creating a favorable environment for regeneration (Khan et al., 2022).

By stabilizing redox balance and inhibiting inflammatory signaling, they protect endothelial cells and fibroblasts from apoptosis and dysfunction. This dual antioxidant and anti-inflammatory activity not only accelerates angiogenesis and collagen deposition but also prevents secondary infections and necrosis in chronic diabetic wounds (Gupta & Mehta, 2019). Thus, stilbenes serve as multifunctional bioactives that restore cellular homeostasis and promote effective wound closure.

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## NANOFORMULATION APPROACHES FOR ENHANCED DELIVERY

The clinical application of stilbenes is limited by poor water solubility and bioavailability. Recent research emphasizes nanoformulations such as liposomes, nanoemulsions, and polymeric nanoparticles to enhance their delivery to the wound site (Ghosh et al., 2021). Pterostilbene-loaded nanogels, for instance, show superior penetration and sustained release, resulting in faster wound closure and better histopathological outcomes compared to crude extracts (Das & Reddy, 2019).

Nanoformulation approaches have emerged as promising strategies to enhance the delivery, stability, and bioavailability of stilbenes in diabetic wound therapy. Despite their strong therapeutic potential, stilbenes like pterostilbene and resveratrol suffer from poor aqueous solubility and rapid metabolism, limiting their pharmacological efficacy. Nanoformulations including liposomes, solid lipid nanoparticles, polymeric nanospheres, and hydrogel-based nanocarriers address these challenges by providing sustained drug release, improved skin penetration, and targeted delivery to the wound site (Ghosh et al., 2021). Pterostilbene-loaded nanogels, for instance, ensure prolonged retention and controlled diffusion within the wound bed, promoting fibroblast proliferation, collagen synthesis, and angiogenesis (Das & Reddy, 2019).

Similarly, resveratrol-loaded lipid nanoparticles exhibit enhanced antioxidant stability and anti-inflammatory action in diabetic ulcer models. Nanocarriers also protect stilbenes from enzymatic degradation and oxidative breakdown, increasing their therapeutic lifespan (Kumar et al., 2023). The integration of nanotechnology with phytochemical therapy thus represents a synergistic advancement, enabling efficient delivery of stilbenes for accelerated diabetic wound repair and tissue regeneration through improved bioavailability, biocompatibility, and localized therapeutic action (Ghosh et al., 2021; Das & Reddy, 2019).

## FUTURE PERSPECTIVES

While preclinical evidence supports stilbene efficacy in diabetic wound healing, clinical translation requires standardized extraction, dosing, and toxicity profiling. Combining stilbenes with modern wound dressings or stem-cell-based therapies could revolutionize diabetic wound management. Integrative approaches, including nanotechnology and tissue engineering, may further optimize stilbene bioavailability and regenerative potential (Kumar et al., 2023).

Future perspectives on stilbene-based diabetic wound therapy emphasize translating promising preclinical outcomes into clinically effective treatments. Although numerous studies demonstrate stilbenes' potential to enhance angiogenesis, fibroblast proliferation, and oxidative balance, further research is required to standardize extraction methods, optimize dosage, and ensure consistent therapeutic efficacy (Kumar et al., 2023). Advanced drug delivery systems such as pterostilbene-loaded nanogels, bioactive wound dressings, and hydrogel scaffolds offer innovative platforms for controlled, sustained release directly at the wound site (Ghosh et al., 2021). Integration of stilbenes with biomaterials, stem cell therapy, or growth factors could provide synergistic effects, accelerating tissue regeneration and minimizing scar formation (Das & Reddy, 2019).

Additionally, exploring molecular mechanisms involving VEGF, PI3K/Akt, and HIF-1α pathways may unveil new therapeutic targets for precision wound management (Patel et al., 2018). Future clinical trials should focus on pharmacokinetics, safety profiles, and long-term outcomes to validate efficacy in human subjects. With continued advancements in nanotechnology and molecular biology, stilbenes from Pterocarpus marsupium hold immense potential as natural, cost-effective agents for treating chronic diabetic wounds and revolutionizing regenerative medicine (Kumar et al., 2023; Singh et al., 2021).

## II. CONCLUSION

Stilbenes from *Pterocarpus marsupium* demonstrate significant promise as natural bioactives that promote angiogenesis and fibroblast proliferation in diabetic wounds. Through VEGF pathway activation, collagen synthesis enhancement, and oxidative stress reduction, these compounds offer a multifaceted therapeutic approach. Future research should focus on clinical trials and advanced delivery systems to realize the full potential of stilbene-based diabetic wound therapies.

stilbenes derived from Pterocarpus marsupium demonstrate significant therapeutic promise in diabetic wound repair by promoting angiogenesis, enhancing fibroblast proliferation, and reducing oxidative and inflammatory damage. Their

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ability to upregulate VEGF, HIF-1α, and TGF-β1 pathways facilitates vascular regeneration and collagen synthesis, accelerating tissue remodeling and wound closure (Patel et al., 2018; Bhat et al., 2020). Furthermore, their potent antioxidant and anti-inflammatory effects create a favorable microenvironment for healing under hyperglycemic conditions (Verma et al., 2018). Although their poor bioavailability remains a limitation, nanoformulation-based delivery systems have shown encouraging results in improving pharmacokinetic performance and therapeutic outcomes (Ghosh et al., 2021). With continued advancements in nanotechnology, molecular research, and clinical validation, stilbenes hold great potential as natural, multi-targeted agents for managing chronic diabetic wounds and could become integral components of future regenerative and phytopharmaceutical therapies (Kumar et al., 2023; Singh et al., 2021).

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