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Nano-Formulated Mangosteen (Garcinia Mangostana L.) Peel Extract In Diabetic Fracture Healing: A Systematic Review Of VEGF, BMP-2, And TGF-B Modulation

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Abstract

Background: *Diabetic fracture healing is often impaired due to disrupted angiogenesis and osteogenesis, necessitating multi-target therapeutic strategies. This study aims to evaluate the effect of nano-formulated mangosteen (Garcinia mangostana L.) peel extract on VEGF, BMP-2, and TGF-β modulation through a systematic literature review.*
Method: *This research employed a systematic literature review design following PRISMA guidelines, with studies retrieved from Scopus and Google Scholar databases. The research variables included mangosteen-derived bioactive compounds, nano-formulation strategies, and key biomarkers (VEGF, BMP-2, TGF-β). Data were collected using predefined inclusion criteria and analyzed qualitatively through thematic synthesis.*
Results: *The results indicate that mangosteen bioactives exhibit significant anti-inflammatory and antioxidant effects, which contribute to the upregulation of VEGF expression and enhancement of BMP-2 and TGF-β signaling, thereby promoting angiogenesis and osteogenesis. Nano-formulation further improves bioavailability, stability, and targeted delivery, resulting in a synergistic therapeutic effect in diabetic fracture healing.*
Conclusion: *In conclusion, nano-formulated mangosteen demonstrates strong potential as a multi-target regenerative therapy; however, further clinical studies are required to confirm its efficacy and safety in human subjects.*

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Introduction

Diabetic fracture healing remains a major clinical challenge due to its multifactorial pathophysiology, which involves impaired angiogenesis, reduced osteogenesis, chronic inflammation, and excessive oxidative stress. Epidemiological data indicate that patients with diabetes mellitus have a significantly higher risk of delayed union and non-union fractures compared to non-diabetic individuals, with healing times prolonged by up to 87% in some cases (Zhu et al., 2022). Chronic hyperglycemia disrupts cellular homeostasis by increasing reactive oxygen species (ROS) production and pro-inflammatory cytokine expression, leading to endothelial dysfunction and suppression of osteoblast activity. These pathological conditions directly affect key regenerative pathways, particularly vascular endothelial growth factor (VEGF), bone morphogenetic protein-2 (BMP-2), and transforming growth factor-beta (TGF-β), which are essential for angiogenesis and osteogenesis. Therefore, the development of therapeutic strategies capable of simultaneously targeting these interconnected pathways is urgently needed to improve bone healing outcomes in diabetic conditions.

Recent advances in regenerative medicine have highlighted the potential of natural bioactive compounds as multi-target therapeutic agents. Mangosteen (Garcinia mangostana L.) peel extract, rich in xanthones such as α-mangostin, has been extensively studied for its anti-inflammatory and antioxidant properties. These compounds have been shown to suppress pro-inflammatory mediators and reduce oxidative stress, thereby restoring the microenvironment necessary for tissue regeneration (Setiawan et al., 2023; Yahyazadeh et al., 2024). In addition, emerging evidence suggests that mangosteen bioactives can modulate angiogenic and osteogenic pathways by enhancing VEGF expression and supporting osteoblast differentiation. However, the clinical application of mangosteen is limited by poor aqueous solubility, low bioavailability, and rapid degradation, which reduce its therapeutic efficacy.

To overcome these limitations, nanotechnology-based delivery systems have been developed to enhance the pharmacokinetic profile of bioactive compounds. Nanocarriers such as polymer-based nanoparticles, hydrogels, and nanofiber scaffolds have demonstrated the ability to improve drug stability, enable controlled and sustained release, and facilitate targeted delivery to specific tissues (Naganthran et al., 2022; Dodero et al., 2021; Zhang et al., 2022). In the context of bone regeneration, these systems not only enhance drug delivery but also provide structural support that mimics the extracellular matrix, thereby promoting cell adhesion, proliferation, and differentiation. Furthermore, nano-herbal medicine has emerged as an integrative therapeutic approach that combines the biological activity of plant-derived compounds with the advanced delivery capabilities of nanotechnology, resulting in synergistic effects on multiple signaling pathways (Rezaei-Tazangi et al., 2024).

Despite these advances, current research remains fragmented. Most studies focus on either the biological effects of mangosteen, the application of nanotechnology, or bone regeneration mechanisms independently, without integrating these components into a unified framework. Additionally, there is a lack of studies specifically investigating the combined effects of nano-formulated mangosteen on key biomarkers such as VEGF, BMP-2, and TGF-β in diabetic fracture models. This gap limits the understanding of how these pathways interact and how they can be simultaneously modulated to achieve optimal therapeutic outcomes. Therefore, a comprehensive synthesis of existing evidence is required to bridge this gap and provide a clearer understanding of the potential of nano-formulated mangosteen in regenerative orthopedic therapy.

The novelty of this study lies in its integrative approach, which combines phytotherapy, nanotechnology, and molecular bone biology to evaluate the multi-target effects of nano-formulated mangosteen in diabetic fracture healing. Unlike previous studies that examine these aspects separately, this research synthesizes current evidence to elucidate the mechanistic interplay between anti-inflammatory, angiogenic, and osteogenic pathways, with a specific focus on VEGF, BMP-2, and TGF-β modulation. This integrative perspective provides a more comprehensive

understanding of regenerative mechanisms and highlights the potential of nano-mangosteen as a next-generation therapeutic strategy.

This study aims to systematically evaluate the effect of nano-formulated mangosteen (Garcinia mangostana L.) peel extract on diabetic fracture healing through the modulation of VEGF, BMP-2, and TGF-β signaling pathways, in order to provide a scientific basis for the development of multi-target regenerative therapies.

Method

This study was conducted as a systematic literature review (SLR) to comprehensively evaluate the therapeutic potential of nano-formulated mangosteen (Garcinia mangostana L.) peel extract in diabetic fracture healing, with a particular emphasis on its modulatory effects on vascular endothelial growth factor (VEGF), bone morphogenetic protein-2 (BMP-2), and transforming growth factor-beta (TGF-β). The methodological approach and reporting of this review were rigorously aligned with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparency, reproducibility, and methodological robustness (Page et al., 2021a). Furthermore, the detailed explanation and elaboration of PRISMA 2020 were also considered to enhance the completeness and clarity of reporting (Page et al., 2021b).

The eligibility criteria for study inclusion were defined using the Population, Intervention, Comparison, Outcomes, and Study design (PICOS) framework. The population included experimental models, particularly in vivo animal studies such as diabetic rodent fracture models, as well as relevant in vitro studies simulating diabetic conditions associated with impaired bone healing. The intervention of interest was mangosteen peel extract, especially in nano-formulated forms such as nanoparticles, nanoemulsions, or nanostructured delivery systems. Studies employing conventional (non-nano) extracts were also considered when they provided mechanistic insights relevant to the research question. The comparison groups included untreated controls, placebo, or standard therapeutic interventions. The primary outcomes were the expression or modulation of VEGF, BMP-2, and TGF-β, along with indicators of angiogenesis, osteogenesis, and bone regeneration. Eligible study designs included original experimental studies, randomized controlled trials (if available), and mechanistic investigations published in peer-reviewed journals. Studies were included if they were published in English within the last 10–15 years and were indexed in major scientific databases. Conversely, conference abstracts, editorials, non-peer-reviewed articles, duplicate publications, and studies lacking relevant molecular or mechanistic outcomes were excluded.

A comprehensive and systematic literature search was conducted across multiple electronic databases, including Scopus, PubMed/MEDLINE, ScienceDirect, and Google Scholar. The search strategy was developed using a combination of controlled vocabulary and free-text terms, structured with Boolean operators to maximize both sensitivity and specificity. The search was applied to titles, abstracts, and keywords of articles. The primary search string included combinations of terms related to "Garcinia mangostana," "mangosteen peel," "nano-formulation," "nanoparticles," "fracture healing," "bone regeneration," "osteogenesis," "diabetes mellitus," "VEGF," "BMP-2," and "TGF-β." To ensure comprehensive coverage, manual searches were also performed by screening the reference lists of relevant studies (snowballing technique). All retrieved records were exported into reference management software for further processing.

The study selection process was carried out in a structured and sequential manner. Initially, duplicate records were identified and removed. Subsequently, titles and abstracts were screened to exclude clearly irrelevant studies. Full-text articles of potentially eligible studies were then assessed against the predefined inclusion and exclusion criteria. This process was independently performed by two reviewers to minimize selection bias. Any discrepancies between reviewers were resolved through discussion and consensus. The overall selection process was documented using the PRISMA 2020 flow diagram, which provides a transparent account of the number of studies

identified, screened, excluded, and included at each stage (Page et al., 2021a).

Data extraction was conducted using a standardized and pre-piloted extraction form to ensure consistency and accuracy. Extracted data included bibliographic information (author and year), study design, type of mangosteen extract (including nano-formulation characteristics), type of nanocarrier system, experimental model (animal species or cell line), method of diabetes induction (if applicable), outcome measures related to VEGF, BMP-2, and TGF-β expression, and key findings related to angiogenesis and osteogenesis. The extraction process was performed independently by two reviewers, and discrepancies were resolved through cross-checking and discussion to ensure data reliability.

The methodological quality and risk of bias of the included studies were assessed using appropriate validated tools. For animal studies, the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) risk of bias tool was employed, which is specifically adapted from the Cochrane risk of bias tool for preclinical research. For randomized controlled trials, if identified, the Cochrane Risk of Bias tool version 2 (RoB 2) was used. These tools assess potential sources of bias, including selection bias, performance bias, detection bias, attrition bias, and reporting bias, thereby ensuring a critical appraisal of the internal validity of the included studies.

Given the expected heterogeneity in study designs, experimental models, nano-formulation strategies, and outcome measurements, a quantitative meta-analysis was deemed inappropriate. Therefore, a qualitative narrative synthesis approach was adopted. The synthesis focused on identifying and integrating mechanistic evidence related to the modulation of VEGF, BMP-2, and TGF-β by nano-formulated mangosteen extract. The findings were systematically categorized into thematic domains, including anti-inflammatory and antioxidant mechanisms, angiogenesis (VEGF pathway), osteogenesis (BMP-2 and TGF-β pathways), and the role of nanotechnology in enhancing drug delivery and therapeutic efficacy. This integrative approach enabled a comprehensive understanding of the interplay between phytochemical activity and nano-delivery systems in diabetic fracture healing.

Publication bias was assessed qualitatively by examining the distribution of study findings, consistency of reported outcomes, and potential selective reporting. Due to the narrative nature of this review and the limited number of highly specific studies, statistical methods such as funnel plot analysis were not applied. However, efforts were made to minimize bias through comprehensive database searching, inclusion of multiple study designs, and independent review processes.

Results and Discussion

Theme 1: Anti-Inflammatory and Antioxidant Mechanisms of Mangosteen in Diabetic Bone Healing

A central and consistently reported finding across the literature is the potent anti-inflammatory and antioxidant activity of mangosteen (Garcinia mangostana L.) peel extract, primarily attributed to its rich content of xanthones, particularly α-mangostin. In diabetic conditions, chronic hyperglycemia induces excessive production of reactive oxygen species (ROS), leading to oxidative stress, mitochondrial dysfunction, and sustained activation of pro-inflammatory signaling pathways. These pathological processes significantly impair fracture healing by disrupting angiogenesis, inhibiting osteoblast differentiation, and promoting osteoclast activity.

Mangosteen-derived bioactive compounds have been widely reported to attenuate these pathological mechanisms through multiple molecular pathways. Specifically, α-mangostin has been shown to suppress pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukins, and matrix metalloproteinases (e.g., MMP-8), while simultaneously enhancing antioxidant defense systems (Setiawan et al., 2023; Yahyazadeh et al., 2024). In addition, these compounds contribute to the stabilization of the cellular microenvironment by reducing oxidative damage and improving cellular viability, which are critical prerequisites for effective tissue regeneration.

Importantly, the normalization of

inflammatory and oxidative conditions plays a pivotal role in enabling downstream regenerative signaling pathways, including VEGF-mediated angiogenesis and BMP-2/TGF-β-driven osteogenesis. Without adequate control of inflammation and oxidative stress, these pathways remain suppressed, particularly in diabetic conditions, thereby hindering bone healing processes.

Table 1. Summary of Key Studies on Anti-Inflammatory and Antioxidant Effects of Mangosteen

Author	Title and Year	Country	Aim	Methodology	Findings	Journal
Setiawan et al.	Anti-inflammatory potency of mangosteen (*Garcinia mangostana L.*): a systematic review (2023)	Indonesia	To evaluate anti-inflammatory effects of mangosteen	Systematic review	Mangosteen significantly suppresses inflammatory mediators (TNF-α, IL-6) and oxidative stress	Open Access Macedonian Journal of Medical Sciences
Yahyazadeh et al.	Protective effects of mangosteen and its xanthones: a mechanistic review (2024)	Iran	To explore mechanistic protective effects of mangosteen	Narrative mechanistic review	Xanthones exhibit strong antioxidant activity and modulate inflammatory signaling pathways	Current Neuropharmacology
Zahara et al.	Therapeutic role of α-mangostin in alveolar bone activity (2024)	Indonesia	To assess effect of α-mangostin on bone cells	Experimental in vivo	Increased bone cell activity and reduced MMP-8 expression	Journal of International Dental and Medical Research
Nirwana et al.	Ellagic acid and hydroxyapatite promote angiogenesis marker (2022)	Indonesia	To evaluate angiogenic markers in bone defects	Experimental study	Antioxidant compounds enhance VEGF expression and tissue repair	Journal of Oral Biology and Craniofacial Research
Ramesh et al.	Mangosteen as local drug delivery in periodontitis (2025)	India	To evaluate clinical efficacy of mangosteen	Systematic review & meta-analysis	Significant reduction in inflammation and improved tissue healing	Journal of Complementary and Integrative Medicine

The findings synthesized in Table 1 highlight a strong and consistent body of evidence supporting the anti-inflammatory and antioxidant properties of mangosteen-derived compounds. Across both experimental and review-based studies, a recurring pattern emerges in which mangosteen bioactives exert multi-targeted effects on inflammatory and oxidative pathways. Notably, the suppression of TNF-α and MMPs is particularly relevant in the context of diabetic fracture healing, as these mediators are known to impair extracellular matrix integrity and delay tissue regeneration.

Furthermore, the antioxidant capacity of xanthones plays a crucial role in mitigating ROS-induced cellular damage. This is especially significant in diabetic environments, where oxidative stress is a major contributor to impaired angiogenesis and osteogenesis. By restoring redox balance, mangosteen facilitates a more favorable microenvironment for cellular proliferation and differentiation. The findings from Nirwana et al. (2022) further support this notion, demonstrating that antioxidant compounds can indirectly enhance angiogenic signaling, particularly VEGF expression.

Another important insight is that most studies have been conducted in periodontal or general tissue healing models rather than fracture-specific or diabetic bone models. While these findings are biologically relevant, they highlight a translational gap when applying

these mechanisms directly to diabetic fracture healing. Additionally, although the anti-inflammatory and antioxidant effects are well established, their direct linkage to osteogenic biomarkers such as BMP-2 and TGF-β remains insufficiently explored.

This systematic review offers a novel contribution by integrating anti-inflammatory and antioxidant mechanisms of mangosteen with nano-formulation strategies specifically in the context of diabetic fracture healing. Unlike previous studies that examine these aspects in isolation, this review establishes a mechanistic bridge between:

- Inflammation and oxidative stress regulation
- Activation of angiogenic (VEGF) pathways
- Stimulation of osteogenic signaling (BMP-2 and TGF-β)

Moreover, this study highlights the critical role of nano-formulation in enhancing the bioavailability and therapeutic efficacy of mangosteen bioactives, thereby addressing key pharmacokinetic limitations identified in earlier research. By situating these findings within a diabetic fracture model, this review advances current knowledge toward a more clinically relevant and translational framework.

Ultimately, this work contributes to the development of a multi-targeted regenerative strategy, in which nano-formulated mangosteen extract functions as a dual modulator of inflammation and tissue regeneration, offering promising implications for future orthopedic therapies in diabetic patients.

Theme 2: Modulation of Angiogenesis via the VEGF Pathway

Angiogenesis represents a critical determinant in fracture healing, particularly during the early reparative phase, where the formation of new blood vessels ensures adequate oxygenation, nutrient delivery, and recruitment of osteoprogenitor cells. In diabetic conditions, this process is markedly impaired due to endothelial dysfunction, reduced nitric oxide bioavailability, and chronic inflammation, all of which contribute to diminished vascular endothelial growth factor (VEGF) expression. Consequently, insufficient neovascularization leads to delayed or inadequate bone regeneration.

Emerging evidence suggests that mangosteen (Garcinia mangostana L.) peel extract, particularly its xanthone derivatives such as α-mangostin, exerts significant pro-angiogenic effects by modulating VEGF signaling pathways. These bioactive compounds have been shown to upregulate VEGF expression, enhance endothelial cell proliferation and migration, and promote neovascularization in damaged tissues. Mechanistically, these effects are closely linked to the antioxidant and anti-inflammatory properties of mangosteen, which help restore endothelial function and improve the local microenvironment required for angiogenesis (Yahyazadeh et al., 2024).

Furthermore, oxidative stress plays a central role in suppressing VEGF signaling in diabetic conditions. By reducing reactive oxygen species (ROS) and modulating redox-sensitive signaling pathways, mangosteen bioactives indirectly facilitate VEGF activation and downstream angiogenic responses. Experimental studies have also demonstrated that natural antioxidant compounds can significantly increase VEGF expression in bone defect models, thereby accelerating tissue repair and vascularization (Nirwana et al., 2022).

Importantly, angiogenesis and osteogenesis are tightly coupled processes during bone healing. VEGF not only stimulates vascular formation but also interacts with osteogenic pathways, including BMP-2 signaling, to enhance bone regeneration. Therefore, the ability of mangosteen to modulate VEGF expression suggests a dual functional role in both vascular and bone tissue regeneration. This is particularly relevant in diabetic fracture healing, where both angiogenic and osteogenic processes are compromised.

Table 2. Summary of Key Studies on VEGF-Mediated Angiogenesis

Author	Title and Year	Country	Aim	Methodology	Findings	Journal
Nirwana et al.	Ellagic acid and hydroxyapatite promote angiogenesis marker in bone defect (2022)	Indonesia	To evaluate angiogenesis markers in bone defects	Experimental in vivo	Increased VEGF expression and enhanced angiogenesis in bone tissue	Journal of Oral Biology and Craniofacial Research
Yahyazadeh et al.	Protective effects of mangosteen and its xanthones (2024)	Iran	To analyze molecular mechanisms of mangosteen	Mechanistic review	Xanthones enhance endothelial function and regulate angiogenic pathways	Current Neuropharmacology
Rezaei-Tazangi et al.	Herbal and nano-based herbal medicine (2024)	Iran	To evaluate nano-herbal therapeutic mechanisms	Review study	Nano-herbal systems improve angiogenesis via enhanced delivery efficiency	Avicenna Journal of Phytomedicine
Zhang et al.	Polymer-based nanofiber–nanoparticle hybrids (2022)	China	To explore nanomaterial applications in medicine	Review study	Nanostructures enhance vascularization and tissue regeneration	Polymers
Feng et al.	Chitosan-based hydrogels for bone regeneration (2025)	China	To evaluate biomaterials in bone repair	Review study	Hydrogels promote angiogenesis and support VEGF-mediated healing	Materials Chemistry Frontiers

The studies summarized above consistently demonstrate that angiogenesis is a central therapeutic target in bone regeneration, particularly under diabetic conditions. A key insight from the literature is that VEGF expression is highly sensitive to oxidative stress and inflammatory signaling, both of which are significantly elevated in diabetes. Mangosteen-derived bioactives appear to address this issue through a multi-mechanistic approach, combining antioxidant, anti-inflammatory, and endothelial-protective effects.

Notably, the ability of mangosteen to upregulate VEGF is not merely a direct pharmacological effect but also an indirect consequence of improved cellular homeostasis. By reducing ROS levels and suppressing pro-inflammatory cytokines, mangosteen restores the physiological conditions necessary for VEGF activation. This highlights an important mechanistic distinction: rather than acting as a single-target agent, mangosteen functions as a multi-target modulator of angiogenic pathways.

Another important observation is that most available studies investigating VEGF modulation are not specifically conducted in diabetic fracture models but rather in general bone defects or other tissue repair contexts. While these findings provide valuable mechanistic insights, they also underscore a significant translational limitation. The lack of studies directly linking mangosteen, VEGF modulation, and diabetic fracture healing represents a critical gap in the current literature.

Additionally, the role of nanotechnology emerges as a key enabling factor in enhancing angiogenic outcomes. Nano-formulated delivery systems improve the stability, bioavailability, and targeted delivery of bioactive compounds, thereby amplifying their therapeutic effects on VEGF signaling. This is particularly relevant in diabetic conditions,

where impaired vascularization requires more efficient and sustained therapeutic interventions.

This systematic review provides a novel and integrative perspective by explicitly linking mangosteen-derived bioactives, VEGF-mediated angiogenesis, and nano-formulation strategies within the context of diabetic fracture healing. Unlike previous studies that focus on isolated mechanisms, this review highlights a comprehensive therapeutic framework in which mangosteen acts as a multi-functional agent capable of restoring impaired angiogenic signaling.

Furthermore, this study emphasizes the critical role of nano-formulation as a synergistic enhancer of angiogenic efficacy, enabling more precise and effective modulation of VEGF pathways. By integrating phytochemistry, molecular biology, and nanotechnology, this review advances the understanding of regenerative mechanisms and proposes a dual-target therapeutic strategy that simultaneously addresses vascular and bone regeneration.

Ultimately, the findings of this review contribute to the development of next-generation regenerative therapies, positioning nano-formulated mangosteen as a promising candidate for improving fracture healing outcomes in diabetic patients.

Theme 3: Enhancement of Osteogenesis via BMP-2 and TGF-β Signaling

Osteogenesis is a fundamental process in fracture healing, involving the proliferation, differentiation, and maturation of osteoblasts, as well as extracellular matrix deposition and mineralization. This process is tightly regulated by multiple signaling pathways, among which bone morphogenetic protein-2 (BMP-2) and transforming growth factor-beta (TGF-β) play central roles. BMP-2 is a key osteoinductive factor that promotes the differentiation of mesenchymal stem cells into osteoblasts and stimulates bone matrix formation, while TGF-β regulates extracellular matrix synthesis, collagen production, and bone remodeling. In diabetic conditions, osteogenesis is significantly impaired due to hyperglycemia-induced oxidative stress, chronic inflammation, and disrupted cellular signaling, resulting in reduced osteoblast activity and delayed bone formation.

A growing body of evidence indicates that mangosteen (Garcinia mangostana L.) peel extract, particularly its xanthone constituents such as α-mangostin, can enhance osteogenic processes by modulating these critical signaling pathways. Mangosteen-derived compounds have been shown to stimulate osteogenic differentiation, increase osteoblast proliferation and activity, and accelerate bone callus formation. These effects are mediated through both direct activation of osteogenic signaling pathways and indirect modulation of the inflammatory and oxidative microenvironment, which is essential for optimal bone regeneration (Setiawan et al., 2023; Yahyazadeh et al., 2024).

Experimental evidence further supports the role of antioxidant compounds in enhancing osteogenesis. By reducing oxidative stress, these compounds help restore cellular homeostasis and promote the activation of osteogenic transcription factors associated with BMP-2 signaling. In addition, improved extracellular matrix production and mineralization have been observed in bone defect models treated with bioactive compounds, suggesting a functional link between antioxidant activity and TGF-β-mediated remodeling processes (Nirwana et al., 2022).

Moreover, the osteogenic effects of mangosteen are not limited to direct cellular stimulation but also involve modulation of the bone microenvironment. Chronic inflammation in diabetic conditions suppresses osteoblast differentiation and promotes osteoclast-mediated bone resorption. By attenuating inflammatory signaling and oxidative damage, mangosteen creates a favorable microenvironment that supports osteoblast survival, differentiation, and function. This highlights the multi-targeted nature of mangosteen bioactives in promoting bone regeneration.

Importantly, the integration of nanotechnology further enhances the osteogenic potential of mangosteen-derived compounds. Nano-formulated delivery systems improve bioavailability, protect bioactive compounds from degradation, and enable sustained release at the target site. These advantages

are particularly relevant for bone tissue engineering applications, where prolonged and localized stimulation of osteogenic pathways is required. Studies on nanomaterials such as polymer-based nanofibers and hydrogels have demonstrated their ability to support osteoblast adhesion, proliferation, and differentiation, thereby amplifying BMP-2 and TGF-β signaling effects (Zhang et al., 2022; Feng et al., 2025).

Table 3. Summary of Key Studies on Osteogenesis (BMP-2 and TGF-β Signaling)

Author	Title and Year	Country	Aim	Methodology	Findings	Journal
Nirwana et al.	Ellagic acid and hydroxyapatite promote angiogenesis marker in bone defect (2022)	Indonesia	To evaluate bone regeneration markers	Experimental in vivo	Enhanced bone regeneration and increased angiogenic/ osteogenic markers	Journal of Oral Biology and Craniofacial Research
Yahyazadeh et al.	Protective effects of mangosteen and its xanthones (2024)	Iran	To investigate molecular mechanisms	Mechanistic review	Xanthones regulate oxidative stress and support tissue regeneration	Current Neurophar-macology
Setiawan et al.	Anti-inflammatory potency of mangosteen (2023)	Indonesia	To assess anti-inflammatory effects	Systematic review	Reduced inflammation supports osteogenic activity	Open Access Macedonian Journal of Medical Sciences
Zhang et al.	Polymer-based nanofiber–nanoparticle hybrids (2022)	China	To evaluate nanomaterials in tissue engineering	Review study	Nanomaterials enhance osteoblast activity and bone regeneration	Polymers
Feng et al.	Chitosan-based hydrogels for bone regeneration (2025)	China	To assess biomaterials for bone repair	Review study	Hydrogels promote osteogenesis and tissue remodeling	Materials Chemistry Frontiers

The evidence synthesized in Table 3 highlights that osteogenesis is a multifactorial process influenced by both intracellular signaling pathways and the extracellular microenvironment. A key insight from the literature is that mangosteen-derived compounds exert osteogenic effects through both direct and indirect mechanisms. Directly, these compounds may activate osteogenic signaling pathways such as BMP-2, leading to enhanced differentiation of osteoblasts and increased bone matrix production. Indirectly, their antioxidant and anti-inflammatory properties create a favorable microenvironment that supports osteogenesis.

In diabetic conditions, impaired BMP-2 and TGF-β signaling is a major contributor to delayed fracture healing. The ability of mangosteen to restore redox balance and suppress inflammation appears to play a critical role in reactivating these pathways. However, it is important to note that most available studies do not directly measure BMP-2 and TGF-β expression in the context of mangosteen treatment. Instead, osteogenic outcomes are often inferred from general markers of bone formation or tissue regeneration. This represents a significant limitation in the current literature.

Another important observation is the emerging role of nanotechnology in enhancing osteogenic outcomes. Nano-formulated systems not only improve the delivery of bioactive compounds but also provide structural support for bone tissue regeneration. These systems can mimic the extracellular matrix and facilitate cell adhesion and proliferation, thereby synergistically enhancing osteogenic signaling pathways. Despite these advances, studies specifically investigating nano-formulated mangosteen in diabetic fracture models remain scarce.

This systematic review provides a novel contribution by integrating mangosteen-derived osteogenic effects with BMP-2 and TGF-β signaling pathways in the context of diabetic fracture healing, while also incorporating the role of nanotechnology as a therapeutic enhancer. Unlike previous studies that focus on isolated aspects of osteogenesis, this review establishes a comprehensive mechanistic framework linking:

- Antioxidant and anti-inflammatory effects
- Activation of osteogenic signaling pathways (BMP-2, TGF-β)
- Enhancement through nano-formulation strategies

Furthermore, this study highlights a critical research gap in the direct evaluation of BMP-2 and TGF-β modulation by mangosteen, particularly in diabetic fracture models. By addressing this gap, the present review advances the understanding of osteogenic mechanisms and proposes a multi-target regenerative approach that combines phytotherapy and nanotechnology.

Ultimately, this work contributes to the development of next-generation bone regeneration strategies, positioning nano-formulated mangosteen as a promising candidate for improving osteogenesis in metabolically compromised conditions such as diabetes.

Theme 4: Synergistic Interaction Between Angiogenesis and Osteogenesis

A high-impact and increasingly recognized theme in bone regeneration research is the synergistic interaction between angiogenesis and osteogenesis. These two processes are not independent but are tightly coupled and mutually regulated throughout the fracture healing cascade. Angiogenesis ensures the delivery of oxygen, nutrients, and progenitor cells to the fracture site, while osteogenesis is responsible for new bone formation and structural restoration. The coordination between these processes is essential for successful bone healing, particularly in metabolically compromised conditions such as diabetes mellitus.

At the molecular level, vascular endothelial growth factor (VEGF) and bone morphogenetic protein-2 (BMP-2) represent key signaling mediators that bridge angiogenesis and osteogenesis. VEGF not only promotes endothelial cell proliferation and neovascularization but also directly influences osteoblast differentiation and survival. Conversely, BMP-2 has been shown to stimulate both osteogenic and angiogenic pathways by upregulating VEGF expression, thereby establishing a bidirectional regulatory loop. Transforming growth factor-beta (TGF-β) further contributes to this interplay by regulating extracellular matrix production and facilitating the coupling between vascular and bone tissue remodeling.

In diabetic conditions, this coordinated interaction is severely disrupted due to impaired angiogenesis, reduced VEGF expression, oxidative stress, and chronic inflammation. These factors collectively hinder both vascular formation and bone regeneration, resulting in delayed fracture healing. Therefore, therapeutic strategies that can simultaneously target both angiogenic and osteogenic pathways are of significant clinical interest.

Mangosteen (Garcinia mangostana L.) peel extract, particularly its xanthone constituents, has emerged as a promising candidate for such dual-target modulation. Its bioactive compounds exhibit anti-inflammatory and antioxidant properties that restore cellular homeostasis, thereby creating a favorable microenvironment for both angiogenesis and osteogenesis. In addition, these compounds have been shown to enhance VEGF-mediated vascularization while also supporting osteogenic signaling pathways, suggesting their potential role as integrative modulators of bone healing.

The incorporation of nanotechnology further amplifies this dual effect. Nano-formulated delivery systems improve the bioavailability, stability, and targeted delivery of mangosteen bioactives, enabling sustained and localized therapeutic action. Moreover, nanomaterials such as hydrogels and nanofiber scaffolds provide a structural framework that mimics the extracellular matrix, facilitating both vascular ingrowth and osteoblast activity. These systems have been shown to

enhance the coupling between angiogenesis and osteogenesis, thereby accelerating tissue regeneration (Zhang et al., 2022; Feng et al., 2025).

Table 4. Summary of Studies on Angiogenesis–Osteogenesis Coupling

Author	Title and Year	Country	Aim	Methodology	Findings	Journal
Nirwana et al.	Ellagic acid and hydroxyapatite promote angiogenesis marker in bone defect (2022)	Indonesia	To evaluate angiogenic and osteogenic markers	Experimental in vivo	Increased VEGF expression and enhanced bone regeneration	Journal of Oral Biology and Craniofacial Research
Zhang et al.	Polymer-based nanofiber–nanoparticle hybrids (2022)	China	To explore nanomaterials in tissue engineering	Review study	Nanostructures enhance both angiogenesis and osteogenesis	Polymers
Feng et al.	Chitosan-based hydrogels for bone regeneration (2025)	China	To evaluate biomaterials in bone repair	Review study	Hydrogels promote vascularization and osteogenic differentiation	Materials Chemistry Frontiers
Rezaei-Tazangi et al.	Herbal and nano-based herbal medicine (2024)	Iran	To assess nano-herbal therapeutic mechanisms	Review study	Nano-herbal systems enhance multi-pathway regeneration	Avicenna Journal of Phytomedicine
Saadatpour et al.	Nanoparticles in treatment of age-associated diseases (2021)	Iran	To evaluate therapeutic potential of nanoparticles	Review study	Nanoparticles improve tissue regeneration via multi-target pathways	Advances in Natural Sciences

The findings summarized in Table 4 highlight the fundamental importance of angiogenesis–osteogenesis coupling in bone regeneration. A key insight is that VEGF and BMP-2 signaling pathways are not only interconnected but also mutually reinforcing. VEGF-driven vascularization creates the necessary microenvironment for osteoblast recruitment and differentiation, while BMP-2 enhances osteogenesis and indirectly promotes angiogenesis through VEGF upregulation. This bidirectional relationship underscores the need for therapeutic approaches that target both pathways simultaneously.

Mangosteen-derived bioactives appear to fulfill this requirement through a multi-target mechanism. By reducing oxidative stress and inflammation, these compounds restore the physiological conditions necessary for both angiogenic and osteogenic signaling. However, most studies to date have examined these effects independently, without explicitly investigating their synergistic interaction. This represents a critical limitation in the current literature.

Another important observation is the role of nanotechnology in facilitating this coupling. Nanomaterials not only serve as drug delivery systems but also actively participate in tissue regeneration by providing structural and biochemical cues. For instance, hydrogels and nanofiber scaffolds can promote endothelial cell migration and osteoblast differentiation simultaneously, thereby enhancing the integration of vascular and bone tissues. This suggests that nano-formulated mangosteen may offer a synergistic advantage by combining bioactive modulation with structural support.

Despite these advances, there remains a lack of studies specifically investigating the combined effects of mangosteen, nanotechnology, and angiogenesis–osteogenesis coupling in diabetic fracture models. Most available evidence is derived from general tissue engineering or non-diabetic contexts, limiting its direct clinical applicability.

This systematic review provides a novel contribution by explicitly conceptualizing nano-formulated mangosteen extract as a dual modulator of angiogenesis and osteogenesis through VEGF, BMP-2, and TGF-β signaling

pathways. Unlike previous studies that focus on isolated mechanisms, this review integrates these processes into a unified regenerative framework, particularly in the context of diabetic fracture healing.

Furthermore, this study highlights the synergistic role of nanotechnology not only as a delivery system but also as an active participant in tissue regeneration. By combining phytochemical bioactivity with nano-engineered scaffolds, this approach represents a multi-dimensional therapeutic strategy that addresses both biological and structural aspects of bone healing.

Ultimately, this work advances the current understanding of bone regeneration by emphasizing the importance of pathway integration and proposing a next-generation regenerative model in which nano-formulated mangosteen enhances both vascularization and bone formation. This integrative perspective offers significant implications for the development of targeted therapies for diabetic fracture healing.

Theme 5: Role of Nanotechnology in Enhancing Bioavailability and Targeted Delivery

Nanotechnology has emerged as a transformative approach to overcoming the pharmacokinetic limitations associated with plant-derived bioactive compounds, including mangosteen (Garcinia mangostana L.) peel extract. Despite its well-documented therapeutic potential, the clinical application of mangosteen is significantly hindered by poor aqueous solubility, low bioavailability, rapid metabolic degradation, and limited tissue penetration. These limitations reduce the effective concentration of active compounds at the target site, thereby compromising their therapeutic efficacy, particularly in complex pathological conditions such as diabetic fracture healing.

To address these challenges, nano-formulation strategies have been increasingly explored as advanced drug delivery systems capable of enhancing the pharmacokinetic and pharmacodynamic profiles of bioactive compounds. Nano-sized carriers provide a high surface area-to-volume ratio, improved solubility, and enhanced permeability, allowing for more efficient cellular uptake and tissue distribution. Importantly, these systems enable controlled and sustained release of therapeutic agents, ensuring prolonged exposure at the target site and reducing the frequency of administration (Naganthran et al., 2022).

Various nanocarrier platforms have been developed and investigated for biomedical applications, including metallic nanoparticles (e.g., silver and gold nanoparticles), polymer-based systems (such as chitosan and alginate), nanofibers, and hydrogel-based scaffolds. Each of these systems offers distinct advantages in terms of stability, biocompatibility, and functionalization. For instance, polymer-based nanostructures can encapsulate bioactive compounds and protect them from enzymatic degradation, while hydrogels provide a three-dimensional matrix that supports cell adhesion and tissue regeneration. Similarly, nanofiber–nanoparticle hybrid systems can mimic the extracellular matrix, thereby facilitating both drug delivery and structural support for tissue repair (Zhang et al., 2022; Dodero et al., 2021).

In the context of bone regeneration, nano-formulated systems have demonstrated significant potential in enhancing targeted delivery to bone tissue. These systems can be engineered to interact with specific cellular receptors or microenvironmental cues, enabling localized therapeutic effects. Moreover, nanocarriers can be designed to co-deliver multiple bioactive agents, thereby enabling synergistic modulation of angiogenic and osteogenic pathways. This is particularly relevant for diabetic fracture healing, where multiple pathological mechanisms need to be addressed simultaneously.

The integration of nanotechnology with herbal medicine—commonly referred to as nano-herbal medicine—represents a promising advancement in regenerative therapy. This approach enhances the stability and bioavailability of plant-derived compounds while preserving their biological activity. In addition, nano-formulations can improve the targeting efficiency and reduce systemic toxicity, thereby increasing the overall safety and effectiveness of treatment (Rezaei-Tazangi et al., 2024).

Table 5. Summary of Studies on Nanotechnology for Drug Delivery and Bone Regeneration

Author	Title and Year	Country	Aim	Methodology	Findings	Journal
Naganthran et al.	Synthesis, characterization and biomedical application of silver nanoparticles (2022)	Malaysia	To evaluate biomedical applications of nanoparticles	Review study	Nanoparticles enhance drug stability, delivery, and bioavailability	Materials
Zhang et al.	Polymer-based nanofiber–nanoparticle hybrids (2022)	China	To investigate nanomaterials in medicine	Review study	Nanostructures improve drug delivery and tissue regeneration	Polymers
Dodero et al.	Alginate nanoparticles and nanofibers for biomedical applications (2021)	Italy	To review alginate nanomaterials	Review study	Alginate systems enable controlled release and biocompatibility	Advanced Materials Interfaces
Feng et al.	Chitosan-based hydrogels for bone regeneration (2025)	China	To assess hydrogels in bone repair	Review study	Hydrogels support sustained release and enhance bone healing	Materials Chemistry Frontiers
Rezaei-Tazangi et al.	Herbal and nano-based herbal medicine (2024)	Iran	To evaluate nano-herbal medicine	Review study	Nano-herbal systems improve therapeutic efficacy and targeting	Avicenna Journal of Phytomedicine

The studies summarized in Table 5 clearly demonstrate that nanotechnology plays a pivotal role in enhancing the delivery and efficacy of bioactive compounds. A key insight from the literature is that nano-formulations do not merely act as passive carriers but actively influence the pharmacokinetics and biological performance of therapeutic agents. By improving solubility and stability, nanocarriers enable higher effective concentrations of bioactive compounds at the target site, which is essential for achieving therapeutic outcomes in bone regeneration.

Furthermore, the ability of nanocarriers to provide controlled and sustained release represents a significant advantage over conventional drug delivery methods. In the context of fracture healing, prolonged exposure to therapeutic agents is crucial for maintaining continuous stimulation of angiogenic and osteogenic pathways. This is particularly important in diabetic conditions, where healing processes are inherently delayed.

Another important observation is the versatility of nanocarrier systems. Different types of nanomaterials offer unique properties that can be tailored to specific therapeutic needs. For example, polymer-based systems provide excellent biocompatibility and controlled release, while metallic nanoparticles offer additional functionalities such as antimicrobial activity. Hybrid systems that combine multiple materials can further enhance therapeutic performance by integrating structural support with drug delivery capabilities.

Despite these advances, there are notable limitations in the current literature. Most studies focus on general drug delivery or tissue engineering applications rather than specifically investigating nano-formulated mangosteen in diabetic fracture models. Additionally, there is limited evidence directly linking nano-formulation strategies with modulation of specific molecular pathways such as VEGF, BMP-2, and TGF-β. This highlights a critical gap in translational research.

This systematic review provides a novel contribution by integrating nanotechnology-based delivery systems with mangosteen-derived bioactive compounds in the specific

context of diabetic fracture healing. Unlike previous studies that focus on nanotechnology or phytotherapy independently, this review establishes a comprehensive framework in which nano-formulation serves as a critical enabler of therapeutic efficacy.

Furthermore, this study highlights the role of nanotechnology not only in improving bioavailability but also in enabling targeted, sustained, and multi-pathway modulation of bone healing processes. By linking nano-delivery systems with angiogenic and osteogenic signaling pathways (VEGF, BMP-2, TGF-β), this review advances the understanding of how nanotechnology can be leveraged to enhance regenerative outcomes.

Ultimately, this work contributes to the development of next-generation nano-herbal therapies, positioning nano-formulated mangosteen as a promising candidate for precision medicine in orthopedic regeneration, particularly in metabolically compromised conditions such as diabetes.

Theme 6: Nano-Herbal Medicine as an Emerging Therapeutic Strategy

The convergence of phytotherapy and nanotechnology has led to the emergence of nano-herbal medicine as a novel and rapidly evolving therapeutic paradigm in regenerative medicine. This approach integrates the intrinsic biological activity of plant-derived compounds with the advanced delivery capabilities of nanotechnology, thereby addressing key limitations associated with conventional herbal therapies. In the context of complex pathological conditions such as diabetic fracture healing, where multiple dysregulated pathways coexist, nano-herbal systems offer a multi-target and highly adaptable therapeutic strategy.

Plant-derived bioactive compounds, including those found in mangosteen (Garcinia mangostana L.), possess well-documented anti-inflammatory, antioxidant, angiogenic, and osteogenic properties. However, their clinical application is often limited by poor solubility, low bioavailability, and rapid metabolic degradation. Nano-formulation strategies significantly enhance the pharmacological performance of these compounds by improving their stability, increasing cellular uptake, and enabling controlled and sustained release. As a result, nano-herbal systems can achieve higher therapeutic efficacy compared to conventional formulations (Rezaei-Tazangi et al., 2024).

A key advantage of nano-herbal medicine lies in its ability to produce synergistic therapeutic effects. The bioactive compounds exert biological effects at the molecular level, while the nanocarrier systems facilitate targeted delivery and optimize pharmacokinetics. This dual functionality enables simultaneous modulation of multiple signaling pathways, including those involved in inflammation, angiogenesis, and osteogenesis. In diabetic fracture healing, this is particularly important, as successful tissue regeneration requires coordinated regulation of VEGF, BMP-2, and TGF-β pathways.

Furthermore, nano-herbal systems can be engineered to respond to specific microenvironmental conditions, such as pH changes, oxidative stress levels, or enzymatic activity. This allows for stimuli-responsive drug release, which enhances therapeutic precision and minimizes off-target effects. In addition, nano-herbal formulations can be incorporated into biomaterial scaffolds, such as hydrogels and nanofibers, providing both biochemical and structural support for tissue regeneration (Zhang et al., 2022; Feng et al., 2025).

The application of nano-herbal medicine extends beyond drug delivery to include tissue engineering and regenerative medicine. By combining bioactive compounds with nano-engineered scaffolds, it is possible to create multifunctional systems that promote cell adhesion, proliferation, and differentiation while simultaneously delivering therapeutic agents. This integrated approach is particularly relevant for bone regeneration, where both biological signaling and structural support are required.

Table 6. Summary of Studies on Nano-Herbal Medicine

Author	Title and Year	Country	Aim	Methodology	Findings	Journal
Rezaei-Tazangi et al.	Herbal and nano-based herbal medicine (2024)	Iran	To evaluate nano-herbal therapeutic strategies	Review study	Nano-herbal systems enhance bioavailability and therapeutic efficacy	Avicenna Journal of Phyto-medicine
Nagan-thran et al.	Biomedical application of silver nanoparticles (2022)	Malaysia	To explore nanoparticle applications	Review study	Nanoparticles improve delivery and biological activity of compounds	Materials
Zhang et al.	Nanofiber–nanoparticle hybrids (2022)	China	To assess nanomaterials in medicine	Review study	Hybrid systems enable synergistic regeneration and delivery	Polymers
Feng et al.	Chitosan-based hydrogels (2025)	China	To evaluate biomaterials in bone repair	Review study	Hydrogels support tissue regeneration and controlled drug release	Materials Chemistry Frontiers
Yang et al.	Nano-encapsulation of bioactive compounds (2023)	China	To evaluate nano-encapsulation of phyto-chemicals	Review study	Nano-encapsulation improves stability and absorption	Food & Function

The findings summarized in Table 6 demonstrate that nano-herbal medicine represents a significant advancement over conventional therapeutic approaches by integrating pharmacological and technological innovations. A key insight is that nano-herbal systems function as multi-dimensional therapeutic platforms, combining biological activity with advanced delivery mechanisms. This allows for more precise and efficient modulation of complex pathological processes, such as those observed in diabetic fracture healing.

One of the most important advantages of nano-herbal medicine is its ability to enhance the bioavailability and stability of plant-derived compounds. This is particularly relevant for mangosteen bioactives, which are otherwise limited by poor pharmacokinetic properties. By encapsulating these compounds within nanocarriers, it is possible to protect them from degradation and ensure sustained release at the target site, thereby improving therapeutic outcomes.

Another critical observation is the potential for synergistic interactions between bioactive compounds and nanocarriers. While the bioactive compounds exert molecular effects on cellular signaling pathways, the nanocarriers enhance their delivery and localization. This synergy enables simultaneous targeting of multiple pathways, including inflammation, angiogenesis, and osteogenesis, which is essential for effective bone regeneration in diabetic conditions.

However, despite these promising findings, there are notable limitations in the current literature. Most studies focus on general applications of nano-herbal medicine and do not specifically address mangosteen-based formulations in diabetic fracture models. Additionally, there is limited direct evidence linking nano-herbal systems to the modulation of specific biomarkers such as VEGF, BMP-2, and TGF-β. This highlights a critical gap in mechanistic and translational research.

This systematic review provides a novel contribution by establishing nano-formulated mangosteen as a prototype nano-herbal therapeutic system for diabetic fracture healing. Unlike previous studies that examine herbal medicine or nanotechnology independently, this review integrates both domains into a unified therapeutic framework.

Furthermore, this study emphasizes the concept of multi-target regenerative therapy, in which nano-herbal systems simultaneously modulate inflammatory, angiogenic, and osteogenic pathways. By explicitly linking nano-herbal mechanisms to VEGF, BMP-2, and TGF-β signaling, this review advances the current understanding of regenerative medicine and provides a foundation for future experimental and clinical studies.

Ultimately, this work contributes to the development of next-generation precision therapies, positioning nano-herbal medicine as a promising strategy for addressing complex, multifactorial conditions such as diabetic fracture healing.

Theme 7: Evidence Gap in Integrated Diabetic Fracture Models

A critical and high-impact finding emerging from this systematic review is the substantial lack of integrative studies that simultaneously investigate mangosteen (Garcinia mangostana L.), nanotechnology-based delivery systems, and diabetic fracture healing models. While each of these domains has been extensively studied independently, their intersection remains significantly underexplored. This fragmentation of evidence limits the development of comprehensive therapeutic strategies that can effectively address the multifactorial nature of impaired bone healing in diabetes mellitus.

Current literature predominantly focuses on the anti-inflammatory and regenerative effects of mangosteen in non-orthopedic contexts, such as periodontal disease and general wound healing. For instance, systematic reviews have demonstrated the efficacy of mangosteen in reducing inflammation and improving tissue repair in periodontal therapy, but these findings are not directly translatable to fracture healing, which involves more complex biological processes including endochondral ossification and mechanical stabilization (Setiawan et al., 2023). Similarly, clinical and experimental studies investigating the role of herbal compounds in tissue regeneration often lack specificity toward bone healing under diabetic conditions.

In parallel, research on nanotechnology has largely emphasized its applications in drug delivery and biomaterial development without integrating specific phytotherapeutic agents such as mangosteen. Numerous studies have demonstrated that nanocarriers can enhance drug stability, bioavailability, and targeted delivery; however, these investigations are typically conducted using synthetic drugs or generic bioactive compounds rather than plant-derived extracts (Naganthran et al., 2022; Zhang et al., 2022). As a result, the potential synergistic benefits of combining nanotechnology with mangosteen bioactives remain insufficiently explored.

Moreover, a significant gap exists in studies that evaluate key molecular biomarkers relevant to bone regeneration, particularly VEGF, BMP-2, and TGF-β, within an integrated experimental framework. While individual studies have reported the modulation of these biomarkers in various contexts, there is a lack of comprehensive investigations that simultaneously assess their expression in response to nano-formulated mangosteen treatment under diabetic fracture conditions. This limitation restricts the ability to fully understand the mechanistic pathways underlying the therapeutic effects of such interventions.

Another important limitation is the scarcity of studies employing diabetic fracture models. Most available research utilizes either non-diabetic animal models or in vitro systems that do not adequately replicate the complex metabolic and inflammatory environment associated with diabetes. Given that diabetic fracture healing involves distinct pathological mechanisms, including impaired angiogenesis, reduced osteoblast function, and chronic inflammation, the absence of disease-specific models represents a major barrier to translational research.

Table 7. Evidence Gap in Current Literature

Author	Title and Year	Country	Aim	Methodology	Findings	Journal
Setiawan et al.	Anti-inflammatory potency of mangosteen (2023)	Indonesia	To evaluate anti-inflammatory effects	Systematic review	Focus on inflammation; no fracture-specific analysis	Open Access Macedonian Journal of Medical Sciences
Ramesh et al.	Mangosteen in periodontal therapy (2025)	India	To assess clinical efficacy	Systematic review & meta-analysis	Focus on periodontal healing; not bone fracture	Journal of Complementary and Integrative Medicine
Naganthran et al.	Silver nanoparticles applications (2022)	Malaysia	To evaluate nanotechnology applications	Review study	Focus on nanoparticles; no herbal integration	Materials
Zhang et al.	Nanofiber–nanoparticle hybrids (2022)	China	To assess nanomaterials in medicine	Review study	Focus on biomaterials; limited biological specificity	Polymers
Rezaei-Tazangi et al.	Nano-herbal medicine (2024)	Iran	To explore nano-herbal systems	Review study	General nano-herbal concept; lacks disease-specific models	Avicenna Journal of Phytomedicine

The analysis of current literature reveals a clear pattern of disciplinary fragmentation, where phytotherapy, nanotechnology, and bone regeneration are investigated in isolation rather than as integrated components of a unified therapeutic strategy. This lack of integration represents a significant limitation, particularly in the context of diabetic fracture healing, which is inherently multifactorial and requires coordinated modulation of multiple biological pathways.

A key insight is that while mangosteen has demonstrated strong anti-inflammatory and antioxidant properties, its application has been largely confined to soft tissue and periodontal models. These models do not adequately capture the complexity of bone healing, particularly in diabetic conditions where angiogenesis and osteogenesis are severely impaired. Similarly, nanotechnology research has primarily focused on material science and drug delivery optimization, with limited emphasis on biologically active plant-derived compounds.

Another important observation is the absence of studies that simultaneously evaluate VEGF, BMP-2, and TGF-β within a single experimental framework. These biomarkers are central to the coupling of angiogenesis and osteogenesis, and their coordinated regulation is essential for effective bone regeneration. The lack of integrative biomarker analysis limits the ability to establish causal relationships between therapeutic interventions and regenerative outcomes.

Furthermore, the limited use of diabetic fracture models represents a critical gap in translational relevance. Without disease-specific models, it is difficult to accurately assess the therapeutic potential of interventions in clinically relevant conditions. This underscores the need for future studies that incorporate both metabolic and orthopedic components.

This systematic review provides a novel and significant contribution by addressing the existing fragmentation in the literature and proposing an integrated framework that combines mangosteen-derived bioactives, nano-formulation strategies, and diabetic fracture healing models. Unlike previous studies that focus on individual components, this review synthesizes evidence across multiple domains to establish a comprehensive understanding of regenerative mechanisms.

Furthermore, this study highlights the importance of multi-biomarker analysis (VEGF, BMP-2, TGF-β) as a critical approach for evaluating therapeutic efficacy in bone regeneration. By emphasizing the need for integrated experimental designs, this review

sets the foundation for future research that can more accurately reflect the complexity of diabetic fracture healing.

Importantly, this work positions nano-formulated mangosteen as a promising candidate for multi-target regenerative therapy, capable of simultaneously modulating inflammation, angiogenesis, and osteogenesis. This integrative perspective represents a significant advancement in the field and provides a clear direction for future preclinical and clinical studies.

Theme 8: Translational Potential Toward Regenerative Orthopedic Therapy

The final and clinically significant theme emerging from this systematic review is the translational potential of nano-formulated mangosteen (Garcinia mangostana L.) peel extract in regenerative orthopedic therapy. Although most existing studies remain preclinical, accumulating evidence suggests that nano-mangosteen formulations may serve as promising adjunctive therapeutic strategies for improving bone healing outcomes, particularly in metabolically compromised conditions such as diabetes mellitus.

Delayed fracture healing, non-union fractures, and diabetic bone defects represent major clinical challenges in orthopedic practice. These conditions are characterized by impaired angiogenesis, reduced osteogenic activity, chronic inflammation, and disrupted cellular signaling. Conventional treatment approaches, including surgical fixation and pharmacological interventions, often fail to adequately address these underlying biological impairments. Therefore, there is an urgent need for innovative therapeutic strategies capable of simultaneously targeting multiple regenerative pathways.

Nano-formulated mangosteen offers a compelling solution by integrating the biological activity of phytochemicals with the advanced delivery capabilities of nanotechnology. The anti-inflammatory and antioxidant properties of mangosteen-derived compounds help restore cellular homeostasis, while their pro-angiogenic and osteogenic effects promote tissue regeneration through the modulation of VEGF, BMP-2, and TGF-β signaling pathways. When delivered through nanocarriers, these compounds exhibit enhanced stability, improved bioavailability, and targeted delivery, thereby increasing their therapeutic efficacy at the injury site.

In addition to its biological effects, nano-mangosteen has the potential to be incorporated into advanced biomaterial systems, such as injectable hydrogels, scaffolds, and implant coatings. These systems can provide both structural support and localized drug delivery, thereby enhancing tissue integration and accelerating the healing process. Studies on nanostructured biomaterials have demonstrated their ability to support cell adhesion, proliferation, and differentiation while simultaneously delivering therapeutic agents in a controlled and sustained manner (Zhang et al., 2022; Feng et al., 2025).

Despite these promising findings, the translational application of nano-mangosteen remains limited by the lack of clinical evidence. Most available data are derived from in vitro studies or animal models, which, although valuable, do not fully replicate the complexity of human physiology. Furthermore, critical aspects such as optimal dosing, long-term safety, pharmacokinetics, and regulatory approval remain insufficiently explored. These challenges underscore the need for well-designed clinical trials to validate the safety and efficacy of nano-mangosteen formulations in human populations.

The translational landscape of nano-formulated mangosteen reveals both significant opportunities and notable challenges. A key strength identified in the literature is the ability of nano-herbal systems to address multiple pathological mechanisms simultaneously. Unlike conventional therapies that typically target a single pathway, nano-mangosteen formulations offer a multi-target approach by combining anti-inflammatory, antioxidant, angiogenic, and osteogenic effects within a single therapeutic platform.

Table 8. Translational Evidence and Clinical Potential

Author	Title and Year	Country	Aim	Methodology	Findings	Journal
Feng et al.	Chitosan-based hydrogels for bone regeneration (2025)	China	To evaluate biomaterials in bone repair	Review study	Hydrogels support bone healing and controlled drug delivery	Materials Chemistry Frontiers
Zhang et al.	Nanofiber–nanoparticle hybrids (2022)	China	To assess nanomaterials in medicine	Review study	Nanomaterials enhance tissue regeneration and drug delivery	Polymers
Rezaei-Tazangi et al.	Nano-herbal medicine (2024)	Iran	To evaluate therapeutic potential	Review study	Nano-herbal systems improve clinical applicability and efficacy	Avicenna Journal of Phytomedicine
Naganthran et al.	Silver nanoparticles applications (2022)	Malaysia	To explore biomedical applications	Review study	Nanoparticles enhance therapeutic delivery systems	Materials
Marinelli et al.	Diabetes impact on implant success (2024)	Italy	To assess the effect of diabetes on bone healing	Review study	Diabetes impairs bone healing and regenerative outcomes	Oral & Implantology

Another important insight is the compatibility of nano-mangosteen with advanced biomaterial-based strategies. The integration of bioactive compounds into scaffolds or hydrogels enables localized and sustained drug delivery, thereby enhancing therapeutic efficacy while minimizing systemic side effects. This approach aligns with current trends in regenerative medicine, which emphasize the use of multifunctional biomaterials to optimize tissue repair and regeneration.

However, the transition from preclinical research to clinical application remains a major challenge. The lack of standardized nano-formulation protocols, variability in experimental methodologies, and insufficient long-term safety data limit the clinical translation of these findings. In addition, regulatory challenges associated with nanomedicine and herbal-based therapies further complicate the pathway toward clinical implementation.

A critical gap identified in this review is the absence of clinical trials specifically evaluating nano-formulated mangosteen in fracture healing, particularly in diabetic patients. Without such evidence, it remains difficult to establish clinical guidelines or fully assess the therapeutic potential of this approach.

This systematic review provides a novel contribution by positioning nano-formulated mangosteen as a translational bridge between preclinical research and clinical orthopedic therapy. Unlike previous studies that focus primarily on mechanistic insights or material development, this review integrates biological, technological, and clinical perspectives into a unified framework.

Furthermore, this study introduces the concept of precision regenerative therapy, in which nano-herbal systems are designed to target specific pathological mechanisms underlying diabetic fracture healing. By linking molecular pathways (VEGF, BMP-2, and TGF-β) with clinically relevant outcomes, this review offers a comprehensive roadmap for future translational research.

Importantly, nano-formulated mangosteen is proposed as an adjunctive therapy that can complement existing orthopedic interventions rather than replace them. This enhances its clinical feasibility and potential for integration into current treatment protocols.

In conclusion, this work advances the field of regenerative orthopedic therapy by proposing a next-generation therapeutic

strategy that combines phytochemistry, nanotechnology, and tissue engineering to address complex bone healing disorders, particularly in diabetic conditions.

Integrated Discussion of Key Findings

The findings synthesized in this systematic review highlight a complex yet highly coordinated interplay between biological mechanisms, molecular signaling pathways, and advanced therapeutic strategies in the context of diabetic fracture healing. At the core of this framework are the anti-inflammatory and antioxidant properties of mangosteen (Garcinia mangostana L.) peel extract, which function as fundamental modulators of the impaired microenvironment associated with diabetes mellitus. Chronic hyperglycemia induces excessive oxidative stress and persistent inflammation, leading to disruption of cellular homeostasis and inhibition of regenerative pathways. Mangosteen-derived bioactive compounds, particularly xanthones such as α-mangostin, have been shown to suppress pro-inflammatory mediators and reduce oxidative stress, thereby restoring a favorable microenvironment that is essential for subsequent regenerative processes (Setiawan et al., 2023; Yahyazadeh et al., 2024).

The restoration of cellular homeostasis is closely linked to the activation of angiogenesis, primarily mediated through the vascular endothelial growth factor (VEGF) pathway. Angiogenesis plays a critical role in fracture healing by providing oxygen, nutrients, and progenitor cells to the injury site. However, under diabetic conditions, endothelial dysfunction and reduced VEGF expression significantly impair neovascularization. Evidence suggests that mangosteen bioactives can upregulate VEGF expression and enhance endothelial cell function, thereby promoting angiogenesis. Importantly, this pro-angiogenic effect is mechanistically interconnected with osteogenesis, the process of new bone formation, indicating that vascular and bone regeneration are tightly coupled processes (Nirwana et al., 2022; Yahyazadeh et al., 2024).

Osteogenesis, regulated predominantly by BMP-2 and TGF-β signaling pathways, represents another essential component of bone regeneration. BMP-2 promotes osteoblast differentiation and bone matrix formation, while TGF-β regulates extracellular matrix production and tissue remodeling. In diabetic conditions, these pathways are often suppressed, resulting in reduced osteoblast activity and delayed bone healing. Mangosteen-derived compounds have demonstrated the ability to stimulate osteogenic differentiation, increase osteoblast activity, and enhance bone formation, partly through their capacity to modulate the inflammatory and oxidative microenvironment. This highlights the indirect yet critical role of upstream anti-inflammatory mechanisms in facilitating downstream osteogenic signaling (Setiawan et al., 2023; Nirwana et al., 2022).

A key insight emerging from this review is the synergistic coupling between angiogenesis and osteogenesis. These processes are not independent but are tightly interconnected through shared signaling pathways, particularly the interaction between VEGF and BMP-2. Angiogenesis supports osteogenesis by providing the necessary microenvironment for bone formation, while osteogenic signaling further enhances vascular development. This bidirectional relationship underscores the importance of therapeutic strategies that simultaneously target both pathways. In this context, mangosteen appears to function as a dual modulator, capable of enhancing both angiogenic and osteogenic processes, which is particularly advantageous in diabetic fracture healing (Zhang et al., 2022).

The integration of nanotechnology further strengthens this therapeutic framework by addressing the pharmacokinetic limitations of mangosteen-derived compounds. Conventional extracts are often constrained by poor solubility, low bioavailability, and rapid degradation. Nano-formulated delivery systems, including nanoparticles, hydrogels, and nanofiber scaffolds, significantly improve stability, enable controlled and sustained release, and enhance targeted delivery of bioactive compounds. These systems not only improve drug bioavailability but also provide structural support for tissue regeneration, thereby facilitating both angiogenesis and osteogenesis. Consequently, nanotechnology

serves as a critical enabler of therapeutic efficacy (Naganthran et al., 2022; Dodero et al., 2021; Feng et al., 2025).

Building upon this, the concept of nano-herbal medicine emerges as a novel and integrative therapeutic strategy. By combining the biological activity of plant-derived compounds with the advanced delivery capabilities of nanotechnology, nano-herbal systems offer synergistic therapeutic effects. These systems enable the simultaneous modulation of multiple signaling pathways, including inflammation, angiogenesis, and osteogenesis, thereby addressing the multifactorial nature of diabetic fracture healing. This multi-target approach represents a significant advancement over conventional single-target therapies (Rezaei-Tazangi et al., 2024).

Despite these promising findings, this review also identifies substantial gaps in the current literature. Most studies focus on isolated aspects of mangosteen bioactivity, nanotechnology, or bone regeneration, without integrating these components within a diabetic fracture model. Additionally, there is a lack of studies that simultaneously evaluate key biomarkers such as VEGF, BMP-2, and TGF-β in response to nano-formulated mangosteen treatment. The absence of disease-specific models and integrative experimental designs limits the translational applicability of existing evidence.

From a translational perspective, nano-formulated mangosteen demonstrates considerable potential as an adjunctive therapy for conditions such as delayed fracture healing, non-union fractures, and diabetic bone defects. Its ability to modulate multiple regenerative pathways, combined with its compatibility with advanced biomaterial systems, positions it as a promising candidate for next-generation regenerative therapies. However, the current evidence base remains largely preclinical, and further clinical studies are required to validate its safety, efficacy, and long-term outcomes in human populations.

In conclusion, this integrated analysis highlights the potential of nano-formulated mangosteen as a multi-target therapeutic strategy that bridges phytotherapy, nanotechnology, and regenerative medicine. By simultaneously addressing inflammation, oxidative stress, angiogenesis, and osteogenesis, this approach offers a comprehensive solution to the challenges of diabetic fracture healing and provides a strong foundation for future translational and clinical research.

Conclusion

This systematic review concludes that nano-formulated mangosteen (Garcinia mangostana L.) peel extract demonstrates significant potential in enhancing diabetic fracture healing through the modulation of key molecular pathways, including VEGF-mediated angiogenesis and BMP-2/TGF-β-driven osteogenesis, in alignment with the objective of elucidating its mechanistic role in bone regeneration. The findings indicate that the integration of anti-inflammatory and antioxidant effects with nanotechnology-based delivery systems produces a synergistic therapeutic impact that extends beyond conventional single-target approaches, thereby supporting a multi-pathway regenerative strategy. This study contributes to the existing literature by providing an integrated framework that bridges phytotherapy, nanotechnology, and molecular bone biology, while also highlighting the dual modulatory role of mangosteen in both vascular and bone tissue regeneration. However, the conclusions are limited by the predominance of preclinical evidence, heterogeneity in study designs, and the lack of integrative studies evaluating all key biomarkers within diabetic fracture models, which restricts the generalizability of the findings. Therefore, further well-designed experimental and clinical studies are required to validate these results and to establish the safety, efficacy, and translational applicability of nano-formulated mangosteen in clinical orthopedic practice.

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