

TiO₂/Chitosan-Moringa oleifera Nanocomposites for Wound Dressings: A Systematic Review

Nanokomposit TiO₂/Kitosan-Moringa oleifera untuk Penyembuh Luka: Tinjauan Sistematis

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Abstract

Chronic wounds present a major clinical challenge due to persistent infection, oxidative stress, and inflammation that delay healing. TiO₂/chitosan nanocomposites enriched with Moringa oleifera extract have shown potential to enhance wound healing through antibacterial, antioxidant, and anti-inflammatory activities. This systematic review aimed to synthesize current evidence on the development, properties, and biological mechanisms of these composites. A literature search was conducted in PubMed, Embase, and Web of Science up to September 2025 following PRISMA 2020 guidelines. Eligible studies included experimental, preclinical, and clinical research. Data extraction and quality assessment were performed independently. Thirteen studies met the inclusion criteria. The findings indicate that TiO₂ nanoparticles improve mechanical strength and antibacterial activity, while chitosan contributes biocompatibility and intrinsic antimicrobial effects. Moringa oleifera extract provides bioactive compounds that enhance antioxidant activity and modulate inflammation. These composites promote wound closure and tissue regeneration. However, most studies remain preclinical with methodological heterogeneity. Further standardized in vivo studies and clinical trials are required to confirm their long-term safety and therapeutic effectiveness.

Kata kunci:

Kitosan, Moringa oleifera, nanokomposit, pembalut luka, titanium dioksida

Abstrak

Luka kronis merupakan tantangan klinis akibat infeksi persisten, stres oksidatif, dan peradangan yang menghambat penyembuhan. Nanokomposit TiO₂/kitosan yang diperkaya ekstrak Moringa oleifera berpotensi meningkatkan penyembuhan luka melalui aktivitas antibakteri, antioksidan, dan anti-inflamasi. Tinjauan sistematis ini bertujuan mensintesis bukti terkait pengembangan, sifat, dan mekanisme biologis komposit tersebut. Pencarian literatur dilakukan pada PubMed, Embase, dan Web of Science hingga September 2025 sesuai pedoman PRISMA 2020. Studi yang memenuhi kriteria meliputi penelitian eksperimental, praklinis, dan klinis. Ekstraksi data dan penilaian kualitas dilakukan secara independen. Sebanyak 13 studi memenuhi kriteria inklusi. Hasil menunjukkan bahwa nanopartikel TiO₂ meningkatkan kekuatan mekanik dan aktivitas antibakteri, sementara kitosan memberikan biokompatibilitas dan efek antimikroba. Ekstrak Moringa oleifera berkontribusi melalui senyawa bioaktif yang meningkatkan aktivitas antioksidan dan modulasi inflamasi. Komposit ini terbukti mempercepat penutupan luka dan regenerasi jaringan. Namun, sebagian besar studi

masih bersifat praklinis dengan metodologi yang beragam. Diperlukan penelitian *in vivo* terstandar dan uji klinis untuk memastikan efektivitas dan keamanan jangka panjang.

INTRODUCTION

Wound healing is a complex and dynamic process involving hemostasis, inflammation, proliferation, and remodeling (Fernández-Guarino et al., 2023). Disruption of this sequence, often caused by microbial infection, oxidative stress, or persistent inflammation, can delay recovery and lead to chronic wounds such as diabetic ulcers, burns, and pressure sores (Dasari et al., 2021). These conditions impose significant health burdens, not only causing pain and functional impairment but also increasing the risk of systemic infection and long-term disability (Briggs et al., 2023; Nguyen et al., 2024). As the prevalence of chronic wounds rises globally, there is a pressing need for advanced therapeutic strategies that actively support tissue regeneration while also addressing infection and inflammation, limitations often observed with conventional wound dressings (Alberts et al., 2025; Deng et al., 2022).

Chitosan, a naturally derived polysaccharide from chitin, has emerged as one of the most promising biomaterials for wound management due to its biocompatibility, biodegradability, and ease of modification (Rajkumar et al., 2024). Beyond serving as a structural scaffold, chitosan exhibits hemostatic, antimicrobial, and tissue-regenerative properties, making it suitable for accelerating wound closure and re-epithelialization (Zhang et al., 2025). Its versatility allows formulation into films, hydrogels, sponges, and nanocomposites, enabling integration with other bioactive agents (Thang et al., 2023). Titanium dioxide (TiO₂) nanoparticles, for instance, possess strong antibacterial activity and have been shown to promote collagen deposition and angiogenesis, further enhancing healing (Sutanti et al., 2022). When combined, chitosan provides a stable and biocompatible matrix, while TiO₂ contributes antimicrobial and regenerative functions, creating a synergistic platform for advanced wound dressings (Ul-Islam et al., 2024).

In addition to synthetic and biopolymer-based components, natural plant-derived extracts such as *Moringa oleifera* have attracted increasing interest in regenerative medicine (Mamgain et al., 2024). Rich in flavonoids, phenolics, and alkaloids, *Moringa* extracts display antimicrobial, antioxidant, and anti-inflammatory properties, all of which are crucial for preventing wound chronicity and promoting tissue repair (Villegas-Vazquez et al., 2025). Experimental evidence suggests that *Moringa* formulations accelerate wound closure, enhance collagen maturation, and strengthen regenerated tissue (Mohammad Shafie et al., 2022). Incorporating *Moringa* into chitosan/TiO₂-based nanocomposites offers an innovative strategy to amplify their bioactivity, combining structural support with phytochemical-mediated modulation of the wound microenvironment (Ganesh et al., 2025).

Despite a growing body of literature, available studies remain heterogeneous, often limited to *in vitro* or small-scale *in vivo* models with variable formulations and outcome measures. This fragmentation makes it difficult to establish standardized protocols or fully understand the synergistic effects of chitosan, TiO₂, and *Moringa*-based systems in wound healing. Therefore, this systematic review aims to consolidate current evidence on these

multifunctional wound dressings, focusing on their antibacterial, antioxidant, and anti-inflammatory activities, as well as their capacity to enhance wound repair.

MATERIALS AND METHODS

Study design

This systematic review was conducted according to the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Pagano et al., 2020). The protocol was designed to ensure transparency, reproducibility, and methodological rigor in synthesizing evidence on multifunctional wound dressings based on TiO₂/chitosan nanocomposites incorporating *Moringa oleifera* extract.

Literature search strategy

A comprehensive search was performed in PubMed, Embase, and Web of Science from database inception to September 2025. Both controlled vocabulary (MeSH and Emtree) and free-text terms were used, focusing on *Moringa oleifera*, chitosan, titanium dioxide (TiO₂), and wound dressing or wound healing applications. Boolean operators (AND, OR) and truncation were applied where appropriate, and the complete search strategies for each database are presented in Table 1. No restrictions were applied to publication year or language, and reference lists of included articles and relevant reviews were manually screened to identify additional records.

Table 1. Search strategies used for online databases

Database	Search Strategies	Records
PubMed	(<i>Moringa oleifera</i> OR moringa OR kelor) AND (chitosan OR kitosan OR chitin derivative* OR titanium dioxide OR TiO ₂ OR titania) AND (wound healing OR wound dressing* OR wound heal* OR biomedical application*)	62
Web of Science	(<i>Moringa oleifera</i> OR moringa OR kelor) AND (chitosan OR kitosan OR chitin derivative* OR titanium dioxide OR TiO ₂ OR titania) AND (wound dressing* OR wound heal* OR biomedical application*)	36
Medline & EMBASE	(<i>Moringa oleifera</i> OR moringa OR kelor) AND (chitosan OR kitosan OR chitin derivative* OR titanium dioxide OR TiO ₂ OR titania) AND (wound healing OR wound dressing* OR wound heal* OR biomedical application*)	72

Eligibility criteria

Studies were eligible if they reported the preparation, characterization, or evaluation of TiO₂/chitosan nanocomposites combined with *Moringa oleifera* extract in the context of wound dressings or wound healing. Eligible study types included *in vitro*, *in vivo* (animal), and clinical research. Exclusion criteria were studies unrelated to wound healing, those not involving *Moringa oleifera*, chitosan, or titanium dioxide, narrative reviews, conference abstracts without full text, editorials, and opinion pieces.

Study selection and data extraction

All retrieved records were imported into a reference management tool, and duplicates were removed. Two reviewers independently screened titles and abstracts,

followed by full-text assessment according to eligibility criteria, with disagreements resolved by consensus or a third reviewer. Data were extracted into a standardized form capturing study characteristics, material composition, synthesis methods, physicochemical and biological outcomes (wound healing, cytotoxicity, and biocompatibility), as well as additional findings such as antibacterial, antioxidant, or anti-inflammatory activity when available. The methodological quality of the included studies was assessed using the Joanna Briggs Institute (JBI) critical appraisal checklists appropriate to each study type, with results summarized in Table 2.

Table 2. Quality assessment and risk of bias of included studies for meta-analysis

ID	Study (Publication year)	Were the criteria for inclusion in the sample clearly defined?	Were the study subjects and the setting described in detail?	Was the exposure measured in a valid and reliable way?	Were objective, standard criteria used for measurement of the condition?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the outcomes measured in a valid and reliable way?	Was appropriate statistical analysis used?	Total
1	Ahmed et al (2016)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
2	Al-Fathonah et al (2025)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
3	Alsulimani et al (2025)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
4	Bessalah et al (2024)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
5	Dai et al (2011)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
6	Gupta et al (2019)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
7	Harti et al (2024)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
8	Hassan et al (2021)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
9	Inayatullah et al (2022)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
10	Pagano et al (2020)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
11	Sivaranjani et al (2024)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
12	Soylu et al (2025)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
13	Yaqoob et al (2024)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7

Data synthesis

Given the heterogeneity in study designs, experimental models, material formulations, and reported outcomes, quantitative meta-analysis was not feasible. Instead, a qualitative synthesis was performed, highlighting the consistency and strength of evidence regarding the potential of TiO₂/chitosan/Moringa oleifera nanocomposites as multifunctional wound dressings and the biological mechanisms underpinning their activity.

RESULT AND DISCUSSION

RESULT

Study selection

The database search identified 170 records (PubMed, n = 62; Embase, n = 72; Web of Science, n = 36). After removing 17 duplicates, 153 articles remained for title and abstract screening. Of these, 127 were excluded as irrelevant, leaving 26 articles for full-text review. Thirteen reports were excluded for reasons such as exposure or intervention not reported (n = 6), outcomes not reported (n = 5), conference abstract or review (n = 1), and non-English publication (n = 1). Ultimately, 13 studies published between 2011 and 2025 were included in this review (Figure 1).

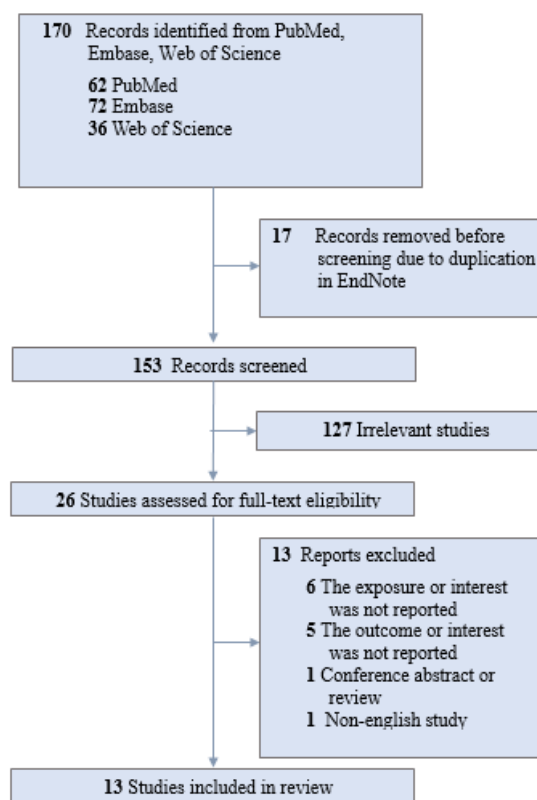


Figure 1. PRISMA 2020 flow diagram illustrating the study selection process, including identification, screening, eligibility, and inclusion stages.

DISCUSSION

Study characteristics

The included studies originated from Asia, Africa, Europe, and the Middle East, reflecting the global interest in biopolymer-based wound dressings. Most studies were experimental, including *in vitro* evaluations, *in vivo* animal models, or physicochemical characterization of nanocomposites, with only one clinical study involving human participants (Gupta et al., 2019). Chitosan was the most common base material (Ahmed & Ikram, 2016; Gupta et al., 2019; Hassan et al., 2021), often combined with gelatin, polyvinyl alcohol (PVA), or other polysaccharides to enhance structural stability and biofunctionality (Bessalah et al., 2024; Inayatullah et al., 2022; Yaqoob et al., 2024). *Moringa oleifera* extracts, derived from leaves, flowers, or seeds, were incorporated for their

phytochemical constituents such as flavonoids, tannins, alkaloids, and polyphenols, while TiO₂ nanoparticles were employed to contribute additional antibacterial and regenerative effects (Soylu et al., 2025).

Antibacterial activity

Antibacterial effects were the most consistently observed outcomes across the included studies. Chitosan-based membranes demonstrated notable inhibition of *Staphylococcus aureus* and *Escherichia coli*, particularly when blended with polyvinyl alcohol and subjected to crosslinking processes, which enhanced their antimicrobial activity compared with native polymers (Hassan et al., 2021). The incorporation of Moringa extracts into composite membranes or microparticles also provided antibacterial benefits, particularly against Gram-positive bacteria such as *S. aureus*, with additional effects on bacterial motility and biofilm formation (Bessalah et al., 2024; Inayatullah et al., 2022).

Similarly, green-synthesized nanoparticles, including TiO₂ and SnO₂ prepared using Moringa extracts, demonstrated dose-dependent bactericidal effects that in some cases were comparable to standard antibiotics (Alsulimani et al., 2025). Formulations such as Moringa seed oil-based oleogels with chitosan further extended antibacterial activity, especially against Gram-negative species such as *E. coli* (Yaqoob et al., 2024). Together, these findings confirm the strong antimicrobial potential of TiO₂/chitosan/Moringa-based composites through a combination of cell membrane disruption, reactive oxygen species generation, and phytochemical-mediated bacterial inhibition.

Antioxidant activity

Antioxidant mechanisms were also prominent in several studies, supporting the role of these composites in reducing oxidative stress at wound sites. Gelatin-chitosan-Moringa biopolymers effectively prevented oxidative DNA damage, highlighting their ability to act as radical scavengers (Bessalah et al., 2024). Microparticles loaded with *Moringa oleifera* extract released quercetin derivatives with both antioxidant and cell-proliferative effects, promoting keratinocyte growth and thereby contributing to wound closure (Pagano et al., 2020). Similarly, Moringa-based oleogels formulated with chitosan exhibited strong antioxidant activity, with measurable free radical scavenging capacity that protected tissues from oxidative injury (Yaqoob et al., 2024). In addition, TiO₂ nanoparticles synthesized with Moringa leaf extract were shown to mitigate oxidative burden during wound healing, indirectly contributing to antioxidant defense (Santhosh et al., 2025). These findings suggest that antioxidant activity is a critical complementary mechanism in wound healing, preventing secondary tissue damage and supporting the regenerative process.

Anti-inflammatory activity

Anti-inflammatory effects were reported in multiple formulations, reflecting both the intrinsic properties of chitosan and the bioactive compounds of Moringa. Chitosan scaffolds were described as modulators of inflammatory responses, with the ability to reduce pro-inflammatory signaling while promoting tissue repair (Ahmed & Ikram, 2016; Dai et al., 2011). Extracts of Moringa leaves and flowers also provided notable anti-inflammatory activity, although results varied; for instance, Al-Fathonah (2025) found no significant differences in collagen formation *in vivo*, suggesting model-specific or dose-dependent limitations. By contrast, Bessalah et al., (2024) demonstrated that a gelatin–chitosan–Moringa composite strongly suppressed inflammatory markers while maintaining biocompatibility.

Additional support comes from experimental formulations such as galenic anti-inflammatory creams based on chitosan and natural extracts, which effectively reduced inflammation across various wound models including burns and diabetic ulcers (Harti et al., 2024). Reviews of multifunctional polymeric wound dressings further emphasized the integration of anti-inflammatory properties as a crucial step toward optimizing wound healing outcomes (Soylu et al., 2025).

DISCUSSION

This systematic review synthesized evidence from thirteen studies published between 2011 and 2025, examining the potential of TiO₂/chitosan/*Moringa oleifera*-based composites as multifunctional wound dressings. The included studies comprised *in vitro* experiments, *in vivo* animal models, material characterization studies, and one clinical trial, highlighting the growing global interest in biopolymer–nanoparticle–plant extract hybrids for regenerative medicine. Across all studies, these nanocomposites demonstrated promising antibacterial, antioxidant, and anti-inflammatory properties, underscoring their potential to accelerate wound healing through multimodal mechanisms.

The findings confirm that chitosan remains a critical base material due to its biocompatibility, biodegradability, and inherent antimicrobial activity, which can be further enhanced through chemical modifications or blending with other polymers (Ahmed & Ikram, 2016; Dai et al., 2011). Incorporation of TiO₂ nanoparticles provided additional antimicrobial and regenerative, tannins benefits, largely through the generation of reactive oxygen species that disrupt bacterial membranes and stimulate tissue remodeling (Soylu et al., 2025). *Moringa oleifera* extracts, rich in flavonoids, and phenolic compounds, contributed to both antibacterial and antioxidant effects, and in some formulations demonstrated anti-inflammatory activity by modulating cytokine expression and collagen deposition (Bessalah et al., 2024; Inayatullah et al., 2022; Pagano et al., 2020). The synergy between these components arises from complementary mechanisms, where TiO₂ generates reactive oxygen species for antibacterial action, chitosan provides membrane disruption and biocompatible scaffolding, and *Moringa oleifera* extracts contribute antioxidant and anti-inflammatory effects, collectively enhancing wound healing outcomes beyond single-component systems.

Antibacterial activity was consistently reported, with multiple studies showing inhibition of *Staphylococcus aureus* and *Escherichia coli* through membrane disruption, biofilm inhibition, and oxidative stress pathways (Bessalah et al., 2024; Hassan et al., 2021). These results align with previous literature on chitosan-based biomaterials, where cationic interactions with bacterial cell walls were identified as a key mechanism (Petroni et al., 2023). The addition of *Moringa* extracts appears to broaden the antibacterial spectrum, while TiO₂ nanoparticles contribute durable, photocatalytic antibacterial effects (Pranoto et al., 2025). Taken together, these findings suggest that multifunctional composites can provide sustained protection against infection, a crucial factor in wound management.

The antioxidant properties observed in several studies further support their role in protecting tissues from secondary damage caused by free radicals during the wound healing process (Pagano et al., 2020; Yaqoob et al., 2024). Oxidative stress is a well-documented barrier to tissue regeneration, particularly in chronic wounds, and the presence of *Moringa*-derived phytochemicals may represent a natural solution to this challenge (Divya et al., 2024). Similarly, anti-inflammatory outcomes highlight the therapeutic value of these composites (Olson et al., 2024). By suppressing pro-inflammatory responses and promoting granulation tissue formation, chitosan/*Moringa*-based dressings appear capable of modulating the wound microenvironment to favor tissue repair (Ahmed & Ikram, 2016; Harti et al., 2024). However, results were not entirely consistent, as one study (Dewi, 2024) did not observe significant improvements in collagen formation, suggesting that dose, formulation, or experimental model may influence efficacy.

Despite these promising findings, several limitations must be acknowledged. First, some of the included studies were preclinical, with only one small-scale clinical investigation, limiting the generalizability of results to human populations. Second, there was heterogeneity in study design, including differences in extraction methods, nanoparticle synthesis, polymer modifications, and wound models, which restricts direct comparison and precludes meta-analysis. Third, outcome measures were highly variable, with some studies focusing on antibacterial activity alone, while others evaluated broader endpoints such as collagen deposition, oxidative stress markers, or

functional wound closure. Fourth, the absence of standardized long-term follow-up data means that the durability, safety, and potential cytotoxicity of these nanocomposites remain incompletely understood. Finally, the possibility of publication bias cannot be excluded, as positive findings are more likely to be reported than neutral or negative results

CONCLUSION

This systematic review suggests that TiO₂/chitosan/*Moringa oleifera*-based composites represent a promising class of multifunctional wound dressings with demonstrated antibacterial, antioxidant, and anti-inflammatory properties. By combining the biocompatibility and antimicrobial activity of chitosan, the photocatalytic and regenerative effects of TiO₂ nanoparticles, and the bioactive phytochemicals of *Moringa oleifera*, these hybrid materials address several key barriers in wound healing, including infection, oxidative stress, and chronic inflammation. However, current evidence is largely derived from preclinical studies with heterogeneous methodologies, limited clinical validation, and short-term outcomes. Future research should focus on standardized protocols, *in vivo* translational models, and well-designed clinical trials to confirm safety, efficacy, and long-term performance.

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