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REVIEW

Natural Bioactive-Based Advanced Wound Dressings for Diabetic Wound Healing: A Systematic Review of Emerging Biomaterial Platforms

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Background: Diabetic ulcers are complex wounds that are difficult to treat due to persistent inflammation, excessive oxidative stress, impaired angiogenesis, and microbial infections that disrupt normal healing. Advanced wound dressings such as hydrogels, nanofibre matrices, hydrocolloids, and 3D bioprinted constructs are increasingly developed to incorporate natural bioactive compounds with multi-functional therapeutic properties. However, systematic understanding of their mechanisms and translational relevance remains limited.

Objective: This study aims to systematically review natural-based hydrogel, hydrocolloid, and hydrofiber formulations in diabetic wound healing.

Methods: A Systematic Literature Review following PRISMA guidelines was conducted using ScienceDirect, SpringerLink, PubMed, and Scopus (2020–2025). Risk of bias was assessed using SYRCLE's tool.

Results: From 5256 initial records, 4412 articles were screened, and 14 studies were included after applying eligibility criteria. These studies examined advanced dressings such as hydrogels, hydrocolloids, nanofibers, 3D bioprinted constructs, and hybrid nanocomposites incorporating natural bioactive compounds. The formulations demonstrated antimicrobial, anti-inflammatory, antioxidant, pro-angiogenic, and re-epithelialization effects. Common compounds included curcumin, berberine, propolis, bee venom, and plant extracts combined with polymers such as chitosan, alginate, hyaluronic acid, collagen, and GelMA. Advanced fabrication improved drug delivery, physicochemical properties, and healing outcomes. At the molecular level, these systems modulated pathways such as NF-κB, PI3K/Akt, MAPK, VEGF, and TGF-β/Smad, contributing to reduced inflammation, oxidative stress suppression, enhanced angiogenesis, and extracellular matrix remodeling. Risk of bias assessment indicated unclear risks in randomization and blinding, although internal validity was generally acceptable Translational readiness remained limited (TRL 2–6), with hydrogels and nanosystems showing the highest potential, while 3D bioprinting faces scalability and regulatory challenges.

Conclusion: Natural-based advanced dressings offer a promising strategy for diabetic wound management. Successful clinical translation requires alignment with scalability, stability, cost-effectiveness, and regulatory compliance. Future research should prioritize standardized preclinical models, controlled release systems, and scalable, regulation-compliant biomaterial designs to accelerate clinical application.

Keywords: natural product, niosome, hydrofiber, hydrocolloid, hydrogel, diabetic wound healing

Introduction

Diabetes mellitus may lead to complications such as diabetic wounds or ulcers, which are difficult to heal and often occur unpredictably. According to the IDF (2019), approximately 19–34% of patients with diabetes are expected to develop diabetic ulcers during their lifetime. These ulcers disrupt tissue regeneration, increase oxidative stress, and heighten susceptibility to microbial infections.[1] Prolonged inflammation caused by infection and excessive production of reactive oxygen species (ROS) further damages the skin's intrinsic healing mechanisms, ultimately resulting in chronic wounds.[2]

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The pathophysiology of diabetic ulcers is highly complex, involving hyperglycemia, neuropathy, microvascular disorders (eg., arterial disease), hypoxia, anemia, barrier dysfunction, infection, and impaired immune responses.[1]

Hyperglycemia contributes to oxidative damage by reducing the activity of key antioxidant enzymes such as glutathione peroxidase and superoxide dismutase, thereby impairing the wound healing process. Elevated and uncontrolled blood glucose levels also increase the skin's vulnerability to injury and infection.[3] Effective wound management in diabetic patients therefore requires not only antimicrobial agents but also therapies capable of accelerating tissue regeneration, suppressing inflammation, and restoring cellular homeostasis. Persistent hyperglycemia induces chronic inflammation and oxidative stress, both of which disrupt normal healing.[4] Consequently, impaired wound healing may exacerbate inflammation and lead to severe tissue damage.[5]

Standard management of diabetic wounds generally includes debridement, topical dressings, pressure offloading, vascular assessment, and glycemic control. The application of topical dressings is intended to improve healing rates, reduce hospitalization time, and lower treatment costs.[6] However, conventional dressings primarily act as passive protective barriers and often lack the ability to actively regulate the wound microenvironment. Their limited capacity to control infection, maintain optimal moisture, or deliver bioactive agents in a sustained and targeted manner reduces their effectiveness.[6–8] As a result, these dressings are often inadequate for addressing the multifactorial nature of diabetic wounds, which involves persistent inflammation, oxidative stress, impaired angiogenesis, and microbial colonization.[9] This limitation underscores the need for advanced therapeutic systems with multifunctional and responsive properties.

A comprehensive treatment strategy should also include systemic management of diabetes and its comorbidities. Current approaches encompass debridement, pressure reduction, glycemic control, and the use of various dressings ranging from conventional to bioactive types.[6–8] The TIME principle (Tissue, Infection, Moisture, Edge) serves as an important guideline in wound care.[9] Advanced therapies include hyperbaric oxygen therapy, negative pressure wound therapy, and photobiomodulation techniques.[10,11] In addition, nanotechnology-based approaches, such as nanoparticles and nanofibers, have shown potential in enhancing tissue regeneration.[8,12]

Silver-based topical agents, including silver nitrate and silver nanoparticles, have been widely used to accelerate healing and prevent infection. However, their effectiveness depends more on the formulation and structure of the dressing than on the silver content itself.[13,14] Some studies indicate that silver nanoparticles exhibit comparable efficacy to conventional treatments such as nano-chitosan and may be combined with growth factors.[15] Nevertheless, evidence also suggests potential toxicity, as observed in impaired regeneration of amputated zebrafish fins, indicating that AgNP-based dressings should be avoided during the early phase of wound healing.[16] Furthermore, advanced therapies such as negative pressure and oxygen therapy are costly, technically demanding, and may cause patient discomfort.[17,18] Long-term use of systemic antibiotics presents additional challenges due to adverse effects, including hepatotoxicity (eg., β-lactams), nausea, cytopenia, renal impairment, and skin reactions.[19] Given these limitations, single-modality therapies are often insufficient, highlighting the need for combination and personalized treatment approaches.[20]

These challenges emphasize the importance of developing topical therapies capable of delivering active and targeted therapeutic effects. In this context, advanced formulations such as hydrogels, hydrocolloids, and hydrofibers containing natural bioactive compounds have emerged as promising alternatives. Hydrogels, for instance, play a crucial role during the proliferative phase by promoting collagen regeneration and supporting newly formed tissue, thereby accelerating wound healing.[21] Hydrocolloids are also recommended due to their antimicrobial properties and ability to provide an occlusive barrier, which supports healing in chronic wounds and prevents irritation.[22]

Despite these advances, current therapies still face several limitations, including inadequate infection control and a focus on symptomatic relief rather than addressing underlying causes of impaired healing.[23,24] Many studies are also limited by short observation periods, which do not reflect the chronic nature of diabetic wounds.[25,26] Moreover, most therapeutic approaches target a single pathway, whereas diabetic wound pathology involves complex interactions between cells and cytokines, making single-target therapies less effective.[24] Additionally, discrepancies between animal models and human outcomes remain a concern.[27] Many existing dressings also lack essential characteristics such as antimicrobial activity, moisture retention, and sufficient mechanical strength.[28]

Although silver nitrate has been shown to accelerate healing and reduce wound size, its antimicrobial effectiveness is not directly correlated with the amount of silver released.[13] The therapeutic efficacy and toxicity of silver depend on its

formulation and delivery system. Furthermore, silver nitrate is recommended only for heavily infected, non-healing wounds and should be avoided in wounds already progressing toward healing due to potential cytotoxic effects on proliferating cells.[14] Similarly, systemic antibiotics, while useful, are associated with significant side effects when used long-term.[19] There remain several unmet clinical needs in diabetic wound management, including the development of multidimensional therapeutic strategies, improved translational relevance, advanced biomaterials, combination therapies, and personalized approaches. These factors are critical for improving angiogenesis, controlling inflammation and infection, enhancing tissue regeneration, and bridging the gap between laboratory findings and clinical application.[23,27–33]

Recent advances in formulation strategies include photocatalysis and photodynamic therapy, bioactive microbial hydrogels (BMH), and traditional Chinese medicine (TCM)-based hydrogels. These approaches aim to control infection, regulate the wound microenvironment, improve oxygenation, and modulate key cellular pathways involved in inflammation and oxidative stress.[34–36] Other emerging strategies involve nanotechnology and gene therapy, which enable targeted treatment and improved modulation of the wound environment.[34,37,38] In addition, stem cell therapy and 3D bioprinting technologies offer promising approaches by enhancing angiogenesis and tissue regeneration through localized delivery and structural customization.[39,40] Innovative dosage forms such as microneedle-based dressings and immunomodulatory hydrogels have also been developed to minimize invasiveness and regulate the immune microenvironment.[41–43] Combination therapies, integrating multiple modalities such as photodynamic therapy with antibiotics or growth factors, aim to simultaneously address various aspects of wound healing.[34,44]

However, despite these promising developments, available data remain limited, and several challenges persist, including variability in human responses and regulatory barriers.[27,45] Although personalized medicine approaches may improve therapeutic precision, their high cost and complexity, as well as challenges in ensuring data validity for regulatory approval, remain significant obstacles.

In recent years, natural bioactive compounds have gained increasing attention due to their broad therapeutic effects and relatively low toxicity. Curcumin, derived from *Curcuma longa*, exhibits antioxidant, antiviral, antibacterial, and antifungal properties that support wound healing. Propolis, a resinous product from bee hives, reduces inflammation by scavenging free radicals and interacts effectively with skin proteins due to its lipophilic and adhesive nature.[46] Mangosteen peel contains phenolic compounds such as benzoic acid, tyrosol, and protocatechuic acid, which exhibit antioxidant and anti-inflammatory activities.[47] Mangosteen-derived polyphenols have also demonstrated antimicrobial, anti-inflammatory, antioxidant, and anticancer properties in both in vitro and in vivo studies.[48]

Considering the complexity of diabetic wound healing and the need for safe, effective, and sustainable therapies, the development of topical formulations such as hydrogels, hydrocolloids, and hydrofibers incorporating natural bioactive compounds is highly warranted. These formulations, characterized by minimal side effects and multifunctional activities —including antibacterial, anti-inflammatory, and antioxidant effects—represent a strategic and promising approach for the future management of diabetic wounds.

Materials and Methods

Search Strategy

This study employed a Systematic Literature Review (SLR) methodology following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines, which consist of four sequential phases: identification, screening, eligibility, and inclusion. Relevant literature was retrieved through systematic searches of electronic databases, including ScienceDirect, SpringerLink, PubMed, and Scopus. The search strategy incorporated the following keyword combinations:

- (brazilin) AND (nanoparticle OR niosome) AND (diabetic wound OR diabetic ulcer) AND (hydrogel OR hydrocolloid OR hydrofiber)
- (mangosteen) AND (nanoparticle OR niosome) AND (diabetic wound OR diabetic ulcer) AND (hydrogel OR hydrocolloid OR hydrofiber)

- (curcumin) AND (nanoparticle OR niosome) AND (diabetic wound OR diabetic ulcer) AND (hydrogel OR hydrocolloid OR hydrofiber)
- (propolis) AND (nanoparticle OR niosome) AND (diabetic wound OR diabetic ulcer) AND (hydrogel OR hydrocolloid OR hydrofiber)
- (human epidermal growth factor) AND (nanoparticle OR niosome) AND (diabetic wound OR diabetic ulcer) AND (hydrogel OR hydrocolloid OR hydrofiber)

The search was limited to studies published from January 2020 onward.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria applied in this study are presented in Table 1, considering both feasibility and relevance as data sources for analysis.

Study Selection

Following the literature search, all potentially relevant articles were independently reviewed by the authors for further evaluation. The final set of eligible studies was subsequently subjected to data extraction. Two reviewers (AF and SS), with comparable expertise, independently screened titles and abstracts. When insufficient information was available from the title and abstract, the full text was retrieved for detailed assessment. Any disagreements were resolved through discussion and consensus with the third and fourth reviewers (AYC and LP).

The selection process adhered strictly to the predefined inclusion and exclusion criteria outlined in Table 1. Studies included in this systematic review were determined using the PICO framework as follows:

- Populations (P): diabetic animal models
- Interventions (I): treatment with bioactive or biomimetic agents administered topically or via biomaterials
- Control (C): vehicle-only or placebo groups
- Outcomes (O): primary outcome—wound closure rate; secondary outcomes—histological parameters including fibroblast, neutrophil, and macrophage counts, as well as VEGF, TNF-α, and SOD levels

These criteria served as the basis for study inclusion, as summarized in Table 1.

Table 1 Inclusion and Exclusion Criteria

Criteria	Inclusion	Exclusion
Publication Type	Research studies published in English	Reviews, conference abstracts, editorial letters
Animals/Population	Animals models established using different methods, regardless of species, age, weight, or gender.	Non-diabetic animal model and based solely on in vitro studies, study used human subject, study with ex vivo method
Intervention/Exposure medication/treatment	Experimental groups based on bioactive or biomimetic materials administered topically or through biomaterials	Experimental groups received used antibiotic synthetic or conventional without bioactive natural/ biomimetic
Study design	Observational studies with separate treatment groups both in vivo and in vitro	Cross sectional studies and uncountable numeric only descriptive data
Outcome measure	Outcome related to diabetic wound healing, such as ulcer size, ulcer depth, wound closure rate, and histopathological changes, parameter of inflammation or bacterial profile	Lack of outcome indicator

Data Extraction

Data were extracted using a standardized extraction table containing study title, authors and year, study design, type of natural material, dosage form, key findings, and conclusions. The extraction process was conducted independently by two authors (AF and SS), with discrepancies verified by the third and fourth investigators (AYC and LP). A structured spreadsheet was utilized to compile detailed study characteristics, including author names, publication year, animal species, sample size, method and duration of diabetes induction, type and dose of bioactive compounds, frequency and duration of treatment, control group characteristics, route of administration, analysis period, primary and secondary outcomes, and the delivery system used. For continuous outcomes, mean values, standard deviations (SD), and sample sizes were recorded. In studies with multiple intervention groups, only the groups receiving natural bioactive or biomimetic agents and the corresponding control groups were included. Final data synthesis was discussed among all investigators to achieve consensus.

Data Analysis

To evaluate methodological quality and potential bias in experimental animal studies, SYRCLE's Risk of Bias (RoB) tool was employed. This approach aims to ensure the validity and reliability of findings while enhancing transparency in methodological assessment.

Results

Overview of All Included Studies

The database search yielded 5,256 records, of which 844 were excluded based on publication year (2020–2025). After screening for accessibility and relevance, 23 articles were retained. Following duplicate removal and eligibility assessment, 14 studies met the inclusion criteria and were included in the final analysis (Figure 1).

Primary Outcome results

The primary objective of this systematic review was to identify hydrogel, hydrocolloid, and hydrofiber formulations for diabetic wound treatment using natural bioactive or biomimetic materials. A total of 5,256 articles were initially retrieved from ScienceDirect, SpringerLink, Scopus, and PubMed. Filtering based on publication date reduced this number to 4,412 articles. Subsequent screening for accessibility and article type further refined the dataset. Additional screening based on study completeness and inclusion criteria resulted in 23 eligible articles. The final selection step involved removing duplicates and ensuring inclusion of in vivo studies, excluding in vitro and ex vivo designs. Ultimately, 14 studies met all inclusion criteria, encompassing natural materials, diverse polymeric platforms, and emerging hybrid technologies applied in topical or biomaterial-based wound therapies. All 14 studies demonstrated the use of natural materials with potential efficacy in diabetic wound healing. Additionally, three studies reported that 3D-printed hydrogel formulations significantly enhanced wound healing rates.

The included studies were further evaluated using SYRCLE's Risk of Bias (RoB) tool (Table 2) to assess methodological quality and data reliability. The assessment indicated that most studies did not fulfill criteria related to assessor and caregiver blinding, although other domains generally demonstrated low risk of bias. Based on SYRCLE indicators, most studies were considered to have acceptable internal validity. However, many studies did not clearly report the handling of unused or outlier data. The 14 selected studies were subsequently synthesized to characterize research trends, particularly in the development of advanced dressings incorporating natural active compounds. Comparative analysis was also conducted at the molecular level and in relation to preclinical outcomes.

Risk of Bias Assessment Using SYRCLE's Tool

A comprehensive risk of bias assessment was conducted using SYRCLE's Risk of Bias tool, specifically designed for preclinical animal studies. The results indicated that the majority of studies exhibited an unclear risk of bias across several critical domains, particularly in random sequence generation, allocation concealment, and blinding of both study personnel and outcome assessors.

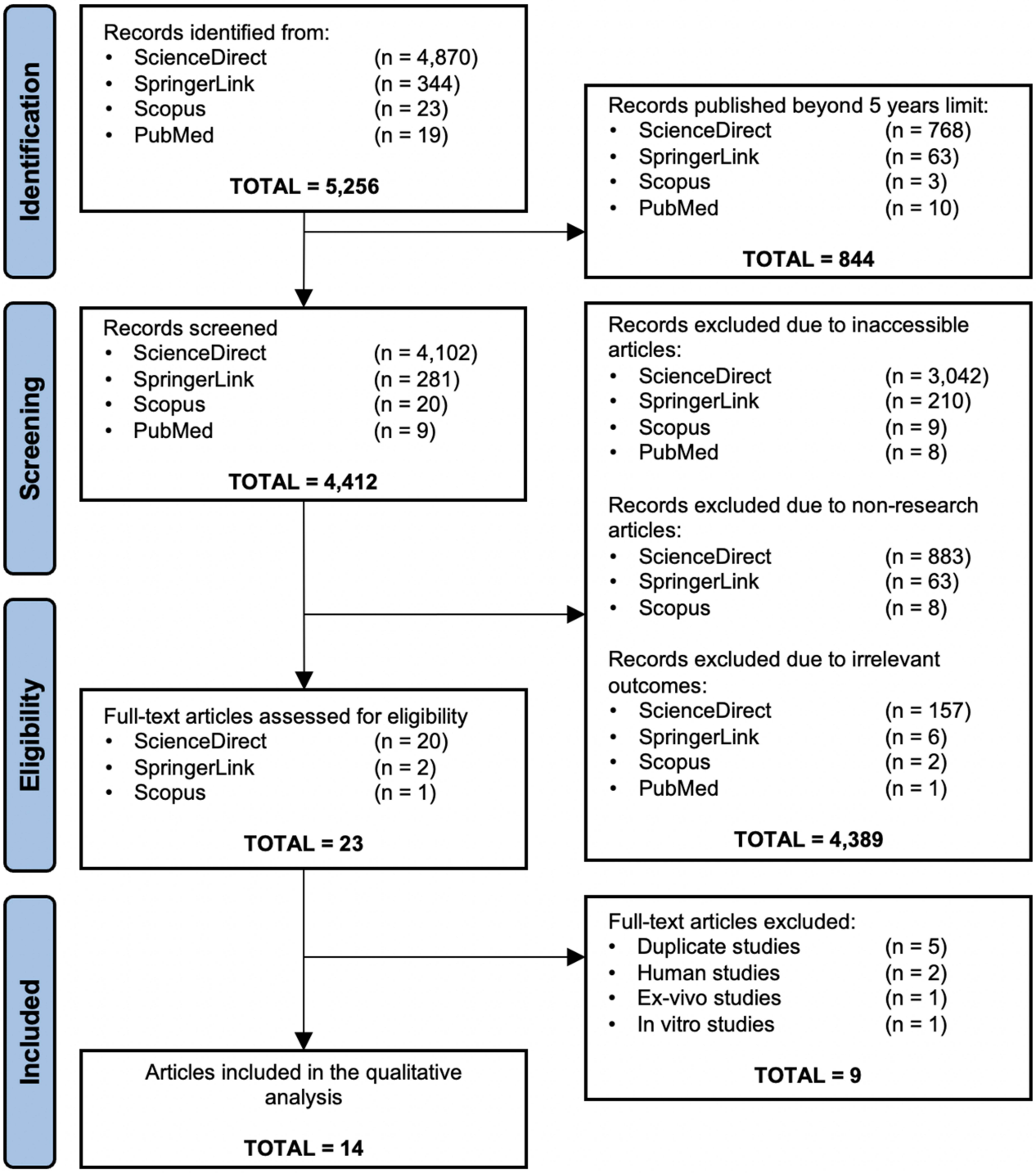

Figure 1 Flowchart of the literature search and selection process.

Baseline characteristics were generally well reported, indicating a low risk of bias in this domain. However, only a limited number of studies explicitly described randomization procedures and allocation concealment, thereby increasing the likelihood of selection bias. Furthermore, reporting of blinding for caregivers/investigators and outcome assessors was limited, suggesting potential risks of performance and detection bias.

Regarding attrition bias, most studies demonstrated a low risk, as outcome data were reported comprehensively. Nevertheless, potential reporting bias remained due to insufficient reporting of study protocols or inconsistencies between

Table 2 Internal Validity Assessment of Preclinical Studies Investigating Natural Bioactive-Based Wound Dressings

Study ID	Sequence Generation	Baseline Characteristics	Allocation Concealment	Random Housing	Blinding Caregiver	Random Outcome Assessment	Blinding Assessor	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias
[49]	Yes	Yes	Yes	Yes	No	No	No	Unclear	Yes	No
[50]	Yes	Yes	Yes	Yes	No	No	No	No	Yes	No
[51]	No	Yes	Unclear	Unclear	No	No	Unclear	Unclear	Yes	Yes
[5]	Yes	Yes	Yes	Yes	No	Unclear	No	No	Yes	No
[52]	Yes	Yes	Yes	Unclear	Unclear	Yes	No	No	Yes	No
[53]	Yes	Yes	Yes	Yes	No	Yes	No	Unclear	Unclear	No
[54]	Yes	Yes	Yes	Unclear	No	Yes	No	No	Yes	Yes
[55]	Yes	Yes	Yes	Yes	No	Yes	No	Unclear	Yes	No
[56]	Yes	Yes	Yes	Yes	No	Yes	No	Unclear	Yes	No
[57]	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No
[58]	Yes	Yes	No	Yes	No	Yes	No	Unclear	Yes	No
[4]	Yes	Yes	Yes	Unclear	No	No	Unclear	No	Unclear	No
[59]	No	No	No	No	Unclear	Yes	Unclear	Unclear	Yes	Unclear
[60]	Unclear	Unclear	Yes	Unclear	No	Unclear	No	Unclear	Unclear	Unclear

Notes: Explanation: "yes" indicates a low risk of bias; "no" indicates high risk of bias; "unclear" if insufficient details have been reported to assess the risk of bias properly.

described methods and reported findings. Overall, the predominance of the "unclear risk" category highlights that the primary limitation lies in inadequate transparency in methodological reporting rather than in the inherent quality of the experimental design itself.

Engineering and Physicochemical Determinants of Advanced Bioactive Delivery Systems in Diabetic Wound Healing

The manufacturing of pharmaceutical formulations for diabetic wound therapy encompasses both conventional and advanced techniques. These include electrospinning, nanotechnological encapsulation, thin-film hydration, freeze–thaw cycling, and freeze-drying hydrogelation. In addition, more advanced strategies such as 3D printing, photo-crosslinking, ionotropic gelation, and thermo-responsive polymerization have been extensively developed.

This study also evaluates the application of various natural compounds, including berberine, curcumin, epidermal growth factor (EGF), mangosteen extract, bee venom, propolis extract, *Camellia sinensis* extract, *Teucrium polium* methanolic extract, and *Kunzea ericoides* leaf extract (KELE), alongside modifications of biopolymers and biointeractive, pro-regenerative platforms such as EGF-NP + PHMB + perfluorocarbon. Additional systems include the QK peptide (a 15-mer VEGF-mimetic peptide; Ac-KLTWQELYQLKYKGI-NH_2), ε-poly-L-lysine (PLL), amorphous Ca-polyP nanoparticles combined with bovine collagen, and crosslinking systems based on sodium alginate (SA), oxidized sodium alginate (OSA), gelatin (Gel), and $CaCO_3$. Other explored combinations involve curcumin with stem cells, exosomes derived from mesenchymal stem cells combined with *Momordica charantia*, wormwood essential oil (WEO) with black phosphorus, and AlgHA-anthocyanin-rich mulberry fruit extract (MFE) with miR-210-3p engineering (Tri-Act).

A wide range of polymeric matrices—such as chitosan, alginate, hyaluronan, polyvinyl alcohol (PVA), collagen, GelMA, and PEG—has been utilized, highlighting the modular and adaptable nature of natural-based wound biomaterials. In vivo preclinical models included C57BL/6J mice, male rats (Sprague-Dawley, Wistar, and SD strains), and young female New Zealand white rabbits. Diabetes induction was commonly achieved using a high-fat diet (HFD) combined

with streptozotocin administration, with doses ranging from 25 mg/kg for four consecutive days up to 60 mg/kg, adjusted according to body weight.

The development of wound-healing biomaterials has advanced considerably, particularly through innovative strategies targeting chronic and diabetic wounds. For instance, alginate- and pectin-based hydrogel films containing mangosteen extract encapsulated within niosomes have demonstrated high biocompatibility and low toxicity, which are critical considerations for clinical application.[51] Natural compounds such as propolis and bee venom have also shown antimicrobial activity, especially against multidrug-resistant *Staphylococcus aureus* (MRSA), while promoting wound healing without adverse effects.[51]

Another promising approach involves nanohydrogel systems, which have demonstrated significant pharmacological activity and enhanced re-epithelialization in both in vitro and in vivo diabetic models. An example is a cholesterol–hyaluronan nanohydrogel incorporating curcumin, assembled supramolecularly with liposomes or glycerosomes.[57] Additionally, a 3D-printed scaffold system (StemCurCol), combining curcumin–chitosan nanoparticles, collagen, and mesenchymal stem cells, has shown synergistic effects in promoting tissue regeneration and modulating diabetic wound healing.[5]

Hydrogels containing bioactive components such as hyaluronic acid, chitosan, curcumin, and epidermal growth factor (EGF) exhibit synergistic therapeutic effects, emphasizing the importance of integrating biomimetic materials with growth factors.[50,58] Similarly, the incorporation of PVA into sericin-based scaffolds enhances mechanical strength and stability, while *Moringa oleifera* leaf extract contributes additional therapeutic benefits in diabetic wound healing.[61]

Exosome-based systems have emerged as novel therapeutic platforms. Multifunctional MEMC-Gel hydrogels containing mesenchymal exosomes derived from *Momordica charantia* represent an innovative strategy that leverages intercellular communication to accelerate wound healing.[4] Furthermore, nanogel formulations based on chitosan and *Teucrium polium* extract exhibit antioxidant, anti-inflammatory, and pro-angiogenic properties that support tissue regeneration in chronic diabetic wounds.[55] Other promising approaches include thermo-responsive hydrogels and systems integrating essential oils into hydrogel matrices, which have demonstrated improved antimicrobial and antioxidant activity alongside good biocompatibility. Hydrogel-based formulations also exhibit multifunctional therapeutic effects.[59,62,63]

Hybrid systems combining natural and synthetic materials, such as GelMA-based hydrogels containing *Kunzea ericoides* extract (KELE@Gel), have been shown to improve the diabetic wound microenvironment and provide multifunctional therapeutic benefits.[56] Similarly, the HyDrO-DiAb multifunctional dressing has been reported to be both safe and effective for chronic wound management.[64] In contrast, cellulose acetate/gelatin nanofiber dressings loaded with berberine demonstrate strong antimicrobial properties and excellent regenerative capacity, making them promising candidates for diabetic foot ulcer therapy.[49]

Based on the reviewed studies, dosage forms can be broadly classified into five categories: hydrogel, hydrocolloid, hydrofiber/nanofiber, 3D bioprinted or composite systems, and nanocomposite/hybrid-based systems (Table 3). Each category exhibits distinct physicochemical characteristics and biological activities, yet all demonstrate significant potential for diabetic wound healing depending on the incorporated active compounds. Hydrogel-based systems, in particular, exhibit homogeneous distribution of active ingredients and stable morphology under photothermal conditions. These systems are capable of sustaining drug release for up to six days and display temperature-dependent viscosity. Such physicochemical properties correlate with favorable biological outcomes, including reduced inflammation and oxidative stress, enhanced collagen deposition, stimulation of angiogenesis, improved granulation tissue formation, increased vascularization, and accelerated re-epithelialization. Meanwhile, hydrocolloid formulations—especially those in nanoparticle form—offer controlled drug release while effectively absorbing excess exudate, thereby maintaining wound homeostasis. In vivo studies further demonstrate their capacity to enhance fluid absorption, accelerate wound closure, and promote collagen deposition.

Key Mechanistic Pathways

Common pathways identified across studies (Table 3) include antibacterial activity against pathogens such as MRSA, particularly in propolis-, bee venom-, and berberine-based systems; anti-inflammatory effects through cytokine reduction,

Table 3 Experimental Characteristics of Included Studies on Natural Bioactive-Based Advanced Dressings for Diabetic Wounds

Study	Animal Model	Dressing Platform	Natural Bioactive	Sample Size	Duration	Key Outcomes	Mechanistic Evaluation	Major Findings	Notable Limitations
[49]	STZ-induced male adult Wistar rats (200–230 g)	Electrospun cellulose acetate (CA)/gel nanofiber	Berberine	n=24	16 days	Collagen density and angiogenesis score	MMP-9, IL-6, AP-1, ERK	Exhibited antibacterial activity and enhanced collagen density, angiogenesis, and epithelialization	Allocation concealment and caregiver blinding were not reported, introducing potential performance bias
[50]	STZ-induced male C57BL/6 mice (50 mg/kg)	HA–chitosan hydrogel (OHA-CMC/CNP/EGF)	Curcumin & EGF	n=75	15 days	Granulation tissue formation and re-epithelialization	IL-6, MMP-9	Improved neovascularization, reduced inflammatory cell infiltration, and enhanced re-epithelialization and granulation tissue formation	Limited clinical applicability due to testing under controlled laboratory conditions
[51]	Young female New Zealand White rabbits (2,000–3,000 g)	Niosome-loaded patch system	Mangosteen extract	n=3	74 hours	Erythema, eschar formation, and edema	Adenosine diphosphate	No erythema or edema observed	Short observation period limited evaluation of long-term tissue remodeling
[5]	Male Wistar rats (8 weeks old, 180–200 g)	Hydrogel	Bee venom and 1.5% ethanolic extract of propolis	n=15	17 days	Antibacterial activity	IL-2, TGF-β/Smad	Promoted collagen fiber formation and inhibited bacterial biofilm	Small sample size may increase risk of type II error
[52]	STZ-induced diabetic Sprague–Dawley rats (8–10 weeks, 250–300 g; IV 65 mg/kg)	Heterocomposite hydrogel	EGF-NP + PHMB + perfluorocarbon	n=30	15 days	Collagen deposition, re-epithelialization, and inflammatory response	IL-1β, IL-8	Reduced inflammation, accelerated collagen deposition, and improved tissue integrity	Did not evaluate angiogenesis-related mechanisms
[53]	STZ-induced diabetic Sprague–Dawley rats (8 weeks, 65 mg/kg, i.p).	Bilayer hydrogel (Gel-PLL/MeTro)	QK peptide and ε-poly-L-lysine (PLL)	Not described	Not described	Angiogenesis, granulation, collagen formation, and inflammation	TIMP-1, MMP-9, CD34	Accelerated re-epithelialization and increased angiogenesis	Lack of mechanistic detail and incomplete reporting
[54]	STZ-induced male Sprague–Dawley rats (8 weeks, 250–300 g; IP 50 mg/kg)	3D-printed porous hydrogel scaffold	SA/OSA/Gel + $CaCO_3$	n=12	14 days	Angiogenesis and collagen deposition	CD31	Enhanced angiogenesis and collagen deposition	No molecular pathway analysis performed

(*Continued*)

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Table 3 (Continued).

Study	Animal Model	Dressing Platform	Natural Bioactive	Sample Size	Duration	Key Outcomes	Mechanistic Evaluation	Major Findings	Notable Limitations
[55]	STZ-induced diabetic male Wistar rats (180–200 g; 45 mg/kg)	Chitosan nanogel (TP-NP)	Teucrium polium methanolic extract	n=50	10 days	Antioxidant, anti-inflammatory, pro-angiogenic activity, and collagen synthesis	Col1A1, TGF-β1, VEGFA, PDGFRα	Improved inflammatory biomarkers, epithelial regeneration, and granulation tissue formation	Potential cytotoxicity not fully evaluated
[56]	Female db/db mice (6–8 weeks)	Hybrid GelMA hydrogel	Kunzea ericoides leaf extract (KELE)	n=36	21 days	Antioxidant, anti-inflammatory, and immunoregulatory activity	IL-1β, MPO, iNOS, CD206, CD31, α-SMA	Enhanced hair regeneration, re-epithelialization, and reduced pro-inflammatory cytokines	Limited clinical applicability due to controlled experimental conditions
[57]	STZ-induced diabetic male Sprague–Dawley rats (140–184 g; IP 30 mg/kg)	Nanohyaluronan glycerosomes	Curcumin	n=63	14 days	Skin regeneration and repair	TIMP-1, MMP-9, CD34	Enhanced granulation tissue formation and collagen deposition	Did not assess key inflammatory or angiogenic biomarkers
[58]	STZ/HFD-induced diabetic male C57BL/6 mice (6 weeks; IP 30 mg/kg)	3D-printed scaffold (StemCurCol)	Curcumin & stem cells	n=30	14 days	Tissue formation and wound closure	CD90, CD105, CD31, CD34	Accelerated wound closure and enhanced re-epithelialization	No caregiver blinding; short observation period for remodeling phase
[4]	STZ/HFD-induced male C57BL/6J mice (IP 25 mg/kg)	Exosome-loaded hydrogel (MEMC-Gel)	MSC-derived exosomes and Momordica charantia	n=40	7 days	Anti-inflammatory, antioxidant, angiogenic, and epithelialization effects	TNF-α, IL-1β, IL-6, SOD, MDA, GSH	Reduced oxidative stress, promoted fibroblast migration, enhanced angiogenesis, and regulated macrophage polarization	Short observation period limited long-term evaluation
[59]	STZ-induced male Sprague–Dawley rats (200–250 g; 60 mg/kg)	NIR-responsive hydrogel	Wormwood essential oil + black phosphorus	Not described	14 days	Inflammation, angiogenesis, macrophage differentiation	MPO, VEGF, IL-6, CD31, CD206, CD86	Accelerated hemostasis, collagen deposition, and vascularization	Sample size not clearly reported
[65]	STZ-induced diabetic male Sprague–Dawley rats (55 mg/kg)	Bilayer "Tri-Act" hydrogel	AlgHA–anthocyanin-rich mulberry extract + miR-210-3p	Not described	14 days	Macrophage M2 polarization and angiogenesis	SOD-1, HO-1, iNOS, CD206	Enhanced collagen deposition	Limited to proliferation phase; no evaluation of inflammatory and remodeling phases

prominently observed in curcumin and *Teucrium polium*; and antioxidant activity via reactive oxygen species (ROS) scavenging, as reported in chitosan/HA-based systems and natural extracts. Angiogenesis, mediated by VEGF and growth factors, is frequently observed in exosome-based systems (MSC-exo/MC-exo) and curcumin-loaded formulations, while re-epithelialization and collagen deposition are enhanced in nanofiber and scaffold-based designs.[66–71]

Biomaterial-based drug delivery systems incorporating various bioactive compounds have demonstrated the capacity to modulate key molecular pathways involved in diabetic wound healing. These pathways include the regulation of inflammation, stimulation of angiogenesis, reduction of oxidative stress, and modulation of extracellular matrix (ECM) remodeling. The interplay among these mechanisms contributes to accelerated tissue regeneration and restoration of physiological function in wound tissues.

Several natural compounds and biomaterials exhibit distinct molecular activities. For example, a combination of anthocyanin-rich mulberry extract with miR-210-3p modulates key signaling pathways, including NF-κB, TNF, and AMPK. Activation of these pathways promotes macrophage polarization from the pro-inflammatory M1 phenotype ($CD86^+$) to the reparative M2 phenotype, which is essential for inflammation resolution and initiation of tissue repair.[59,72,73]

Vascular endothelial growth factor (VEGF) signaling and M2 macrophage polarization (CD206 expression) play critical roles in physiological wound healing. Their modulation enhances endothelial cell proliferation, migration, neovascularization, and collagen deposition, thereby accelerating granulation tissue formation.[74,75] The incorporation of Wormwood essential oil (WEO) combined with black phosphorus in hydrogel systems reduces MPO and IL-6 expression, increases CD31 expression, and decreases CD86 expression, collectively promoting a shift from M1 (pro-inflammatory) to M2 (anti-inflammatory) macrophages. Additionally, anthocyanin-rich mulberry extract combined with miR-210-3p upregulates GRP78 expression, activating the PERK pathway in endoplasmic reticulum stress responses. This activation subsequently triggers the PI3K/Akt/VEGF pathway, enhancing angiogenesis and endothelial proliferation.[63,76] Furthermore, this system increases antioxidant enzyme activity, including superoxide dismutase (SOD-1) and heme oxygenase-1 (HO-1), thereby reducing oxidative stress and supporting M2 macrophage polarization.[77,78]

Bee venom (BV) exhibits anti-inflammatory, antimicrobial, and antioxidant properties, making it effective in addressing chronic inflammation and infection in diabetic wounds.[56,79,80] It also promotes keratinocyte and fibroblast migration, enhances collagen synthesis, and regulates growth factors such as TGF-β1 and VEGF, thereby accelerating wound healing.[80] When incorporated into hydrogels, BV demonstrates improved therapeutic efficacy.[79,80] Propolis, particularly in its ethanolic extract form, is rich in antioxidant and antimicrobial compounds that reduce oxidative stress and bacterial load. Its anti-inflammatory effects contribute to tissue regeneration by modulating inflammatory responses.[56] Propolis also regulates TGF-β signaling, reduces fibrosis, promotes collagen deposition, and stimulates VEGF production. Additionally, it suppresses ATF-3 and iNOS activity while modulating NF-κB signaling, leading to decreased oxidative stress and cytokine production.[81] It further enhances IL-2 signaling by restoring IL-2 levels and receptor function. The combined use of BV and propolis has demonstrated synergistic effects in suppressing inflammation, reducing oxidative stress, and inhibiting microbial infections.[56,79,80,82]

The QK peptide biomaterial promotes angiogenesis, endothelial proliferation, and vascular tube formation. It has been shown to accelerate wound closure, enhance collagen deposition, and reduce inflammation in diabetic models.[83–85] When incorporated into hydrogels or fibrous membranes, QK peptide enables sustained release and improved bioactivity, thereby enhancing re-epithelialization and granulation tissue formation.[83,84] ε-Poly-L-lysine (PLL) is a cationic polymer with antimicrobial properties that effectively reduces bacterial infections in wound environments. It has been applied in hydrogels and multilayer films to improve biocompatibility and antimicrobial efficacy.[86–88] PLL-based systems also serve as controlled drug delivery platforms and tissue scaffolds, contributing to improved healing outcomes.[87,89] Downregulation of phosphorylated ERK1/2 (pERK1/2) and modulation of PARP-1 reduce NF-κB activation, thereby attenuating pro-inflammatory gene expression. Regulation of matrix metalloproteinases (MMPs), particularly MMP-9, alongside increased expression of tissue inhibitor of metalloproteinases-1 (TIMP-1), restores MMP/TIMP balance and reduces inflammatory mediators such as NF-κB, TNF-α, IL-1β, and IL-6.[53,90,97]

At the molecular level, berberine activates the VEGF–PLCγ–ERK signaling pathway, promoting angiogenesis and endothelial proliferation. It also modulates PI3K/Akt/NF-κB and MAPK pathways, which are involved in inflammation regulation and cell migration, with ERK activation mediated through the VEGF–PLCγ–ERK1/2 axis in an EGFR-

dependent manner. In addition, berberine downregulates TGF-β/Smad signaling and promotes M2 macrophage polarization via AMP-activated protein kinase (AMPK). It suppresses PI3K/Akt/NF-κB and MAPK activity, thereby reducing inflammation. At the cellular level, berberine modulates keratinocyte signaling and STAT3 activation and regulates MMP expression, particularly MMP-2 and MMP-9.[49,72,73,98–107] It also suppresses MMP-9 expression while increasing collagen-related genes (types I and III), contributing to extracellular matrix stabilization. These effects enhance fibroblast migration, mesenchymal stem cell (MSC) proliferation, and granulation tissue formation.[104,106]

MSCs exhibit immunomodulatory properties and secrete growth factors such as VEGF, TGF-β, and PDGF, which support angiogenesis and tissue regeneration.[58,108] Expression of endoglin (CD105) on MSCs modulates Smad signaling and counteracts TGF-β1-mediated inhibition of cell proliferation, thereby promoting epidermal and dermal regeneration and accelerating granulation tissue formation.[67,109] Curcumin has been extensively studied for diabetic wound therapy. It upregulates caveolin-1 expression and suppresses the AGE/AGER/NF-κB axis, reducing ROS production and apoptosis. In MSC-based systems, curcumin modulates macrophage polarization by inhibiting NF-κB activation and regulates PI3K/Akt and ERK1/2 pathways through SPRY2 expression. It also inhibits Smad3 phosphorylation and nuclear translocation, enhances JNK1 phosphorylation and c-Jun activation, and modulates gene expression in dermal stem cells ($CD90^{+}$).[110,111]

Exosome-based systems derived from MSCs, combined with bioactive compounds such as *Momordica charantia*, curcumin, and *Teucrium polium*, as well as combinations involving EGF-NP, PHMB, and perfluorocarbon, demonstrate strong anti-inflammatory and antioxidant effects. These systems promote angiogenesis, ECM remodeling, collagen deposition, re-epithelialization, and granulation tissue formation while reducing fibrosis. At the molecular level, they decrease lactate dehydrogenase (LDH) and malondialdehyde (MDA) levels, increase antioxidant enzymes such as superoxide dismutase (SOD) and glutathione (GSH), and reduce pro-inflammatory cytokines (TNF-α, IL-1β, IL-6).[4,112] They also regulate p38 MAPK and PI3K/Akt pathways, enhancing fibroblast migration and keratinocyte proliferation, while suppressing pro-fibrotic mediators such as IL-6 and TGF-β1.

Reactive oxygen species (ROS) activate NF-κB signaling and upregulate pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), which in turn increase MMP-9 expression. However, increased TIMP-1 expression restores MMP/TIMP balance and supports ECM stability. These systems also reduce oxidative stress markers (LDH, MDA), decrease pro-inflammatory cytokines, and increase anti-inflammatory cytokines such as IL-10, thereby improving tissue repair. Regulation of keratinocyte signaling and STAT3 activity further enhances re-epithelialization, while maintenance of redox balance prevents excessive ROS-induced damage. Modulation of TNF-α signaling reduces NF-κB activation and apoptosis while promoting angiogenesis and cell survival. These effects are associated with increased hydroxyproline content, upregulation of collagen-related genes (eg., Col1A1), and enhanced expression of growth factors such as TGF-β1, VEGFA, and PDGFR-α. Additionally, incorporation of perfluorocarbon (PFC) systems and modulation of IL-1β signaling influence macrophage polarization and MMP/TIMP balance. However, excessive activation of pathways such as EGFR–ERK may lead to dysregulated matrix remodeling if not properly controlled.

Interconnection and Synergies

Compounds such as curcumin exhibit multifunctional activity across anti-inflammatory, antioxidant, and angiogenic pathways, and demonstrate synergistic effects when combined with chitosan or hyaluronic acid (HA), particularly in supporting sustained release and tissue remodeling. Natural extracts, including mangosteen, *Moringa*, and *Kunzea ericoides* leaf extract (KELE), complement synthetic scaffolds such as PVA/sericin and GelMA by enhancing biocompatibility and promoting wound contraction. In addition, multifunctional hydrogel systems, such as MEMC-Gel and Tri-Act, integrate multiple therapeutic pathways, enabling a more comprehensive approach to diabetic wound management. Collectively, these interconnected mechanisms highlight the critical role of biomaterials in overcoming key limitations of diabetic wound healing, including persistent inflammation and impaired vascularization.[29,70,113–115]

Mechanistically, Table 4 illustrates the convergence of diverse bioactive compounds onto a relatively limited but highly interconnected network of signaling pathways. The most consistently modulated pathways include anti-inflammatory signaling (NF-κB, TNF-α, IL-6), antioxidant responses (Nrf2/HO-1), pro-angiogenic pathways (VEGF, PI3K/Akt, HIF-1α), and extracellular matrix remodeling (TGF-β1/Smad and collagen type I synthesis). Notably, many

Table 4 Comparative Functional of Advances Dressing and Mechanistic Pathways of Natural Bioactives for Chronic Diabetic Wound Therapy

Formulation Type	Technology Type	Structural Characteristics	Bioactive Compound	Key Molecular Mediator	Main Target/Signaling Pathway	Cellular Effect	Tissue/Physiological Outcome	Reference
Hydrogel-based	Physical extrusion (400 nm polycarbonate membrane)	Uniform vesicle formation; high stability; adaptable for various bioactives	Wormwood essential oil (WEO) + Black phosphorus	CD31, CD86, VEGF, IL-6, MPO, CD206	Modulation of macrophage polarization (M1→M2); NF-κB, TNF, IL-17, AMPK pathways	↓ IL-6, ↓ MPO; ↑ M2 macrophages (CD206); ↓ M1 (CD86)	Enhanced angiogenesis, collagen deposition, epithelialization, and immune modulation	[59, 72–76, 101, 116–125]
	Layer-by-layer (Schiff base crosslinking)	Controlled, stage-dependent release	MFE + miR-210-3p	iNOS, SOD-1, HO-1, CD206	PERK/ER stress pathway → PI3K/Akt/VEGF; ↑ IL-10, ↓ TNF-α and IL-1β	↑ antioxidant enzymes; ↑ M2 polarization	Promotes angiogenesis, ECM formation, and inflammation resolution	[65, 74, 76–78, 84, 119, 121, 126–132]
	Physical gelation	Suitable for chronic wound environment	Bee venom + propolis extract	IL-2, TGF-β, VEGF, NF-κB, ATF-3, iNOS	Modulation of NF-κB and TGF-β/Smad pathways	↓ pro-inflammatory cytokines; ↑ collagen synthesis	Enhanced re-epithelialization and collagen remodeling	[5, 80, 133–135]
	Nano-encapsulation	Protects bioactives from degradation	Curcumin + EGF	MMP-9, CD31, VWF	EGFR signaling activation	↓ MMP-9; ↑ endothelial and keratinocyte proliferation	Improved angiogenesis, granulation tissue, and wound closure	[41, 50, 96, 108, 136, 137]
	LbL casting + photopolymerization	Time-controlled release	QK peptide + PLL	MMP-9, TIMP-1, ERK1/2, NF-κB	ERK activation; restoration of MMP/TIMP balance	↑ endothelial survival and proliferation; ↓ cytokines	Enhanced angiogenesis, collagen deposition, and tissue repair	[53, 90–92, 94–97, 138, 139]
Hydrofiber/ Nanofiber-based	Electrospinning	Enhances fibroblast adhesion, migration, and proliferation; enables controlled drug release	Berberine	IL-6, AP-1, ERK, TGF-β/Smad, PI3K/Akt/NF-κB, MAPK, STAT3	VEGF–PLCγ–ERK1/2 pathway (EGFR-dependent); modulation of PI3K/Akt/NF-κB and MAPK pathways; regulation of AP-1 via microRNA-139-5p inhibition	↑ proliferation of stem cells (eg., hPDLSCs); ↓ IL-6, MMP-9, and MMP-3; ↓ α-SMA, collagen I/III, and fibronectin expression	Anti-inflammatory effects; enhanced collagen deposition; improved migration and proliferation of fibroblasts, keratinocytes, and MSCs; promotion of tissue regeneration	[49, 72, 73, 98–102, 105–107]
3D Bioprinted or Composite-based	Photocrosslinking	Tunable mechanical properties and adhesion tailored to the wound site	*Kunzea ericoides* leaf extract (KELE)	CD206, IL-1β, IL-6, TNF-α, iNOS, NF-κB, CD31, α-SMA	Downregulation of NF-κB and pro-inflammatory cytokines; suppression of iNOS/NO; activation of p38 MAPK; modulation of MMP/TIMP balance; TGF-β–mediated α-SMA regulation	↓ IL-1β, IL-6, TNF-α; ↑ M2 macrophage polarization (CD206); ↑ collagen I & III; ↑ macrophage proliferation	Reduced inflammation; enhanced collagen deposition and tissue remodeling; improved angiogenesis and endothelial function; promoted neovascularization	[41, 56, 74, 76, 84, 96, 119, 121, 127, 129, 130, 137, 140–143]
	3D bioprinting (extrusion)	Scalable, patient-specific scaffold with precise architecture	Curcumin + stem cells	CD105, CD90, caveolin-1, NF-κB, PI3K/Akt, ERK1/2, JNK1, CD34	Activation of PI3K/Akt and ERK1/2 pathways; inhibition of NF-κB; CD105-mediated modulation of TGF-β/Smad; JNK1–c-Jun axis suppressing Smad3	↑ keratinocyte differentiation and proliferation; ↓ inflammatory signaling; ↑ stem cell survival and activity	Increased granulation tissue and angiogenesis; improved vascularization and dermal–epidermal remodeling; accelerated wound closure with reduced scarring; enhanced collagen synthesis	[58, 67, 96, 97, 108, 109, 136, 139, 140, 143–150]

(*Continued*)

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Table 4 (Continued).

Formulation Type	Technology Type	Structural Characteristics	Bioactive Compound	Key Molecular Mediator	Main Target/Signaling Pathway	Cellular Effect	Tissue/Physiological Outcome	Reference
Nanocomposite/ Hybrid-based	Thin-film hydration process	Biocompatible system with high entrapment efficiency and controlled drug release	Mangosteen extract	Adenosine diphosphate (ADP); NLRP3 inflammasome; TGF-β1; VEGF	Activation of NLRP3 inflammasome → upregulation of TGF-β1 and VEGF; ADP signaling via purinergic receptors ($P2Y_{12}$ and $P2Y_1$)	Enhanced migration and proliferation of L929 fibroblast cells; modulation of IL-6 and IL-8 secretion	Promotes angiogenesis and granulation tissue formation; reduces inflammation; enhances collagen deposition	[51, 151–153]
	Ultrasonication & lecithin–glycerol hydration (vesicles)	High skin penetration and retention of bioactive compounds	Curcumin	MMP-9; IL-6; TGF-β1; TIMP-1; CD34	Downregulation of IL-6 and TGF-β1; ROS-mediated NF-κB activation regulates MMP-9; TIMP-1 restores MMP/TIMP balance	Reduced keratinocyte and fibroblast apoptosis; decreased TNF-α expression	Enhances angiogenesis, extracellular matrix remodeling, collagen deposition, epithelialization, and hair follicle regeneration; reduces fibrosis	[57, 91–93, 96, 97, 154]
	GelMA photopolymerization and dopamine crosslinking	High bioadhesion, antibacterial properties, and oxygen permeability	Exosomes (MSC-derived) + *Momordica charantia* extract	IL-6; GSH; LDH; MDA; IL-10; TNF-α; IL-1β; SOD; p38 MAPK; PI3K/Akt; STAT3	Downregulation of LDH and MDA; suppression of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6); activation of antioxidant pathways (↑ SOD, GSH); modulation of p38 MAPK and PI3K/Akt signaling	Reduced inflammatory cell infiltration; enhanced antioxidant activity; improved fibroblast and keratinocyte function	Accelerates collagen remodeling; reduces inflammation; enhances angiogenesis and tissue regeneration; promotes stem cell proliferation and migration	[4, 72, 100, 101, 112, 124, 141, 142, 155–161]
	Ionotropic gelation + ultrasonic homogenization	Suitable for ionic materials with stable nanoparticle formation	*Teucrium polium* methanolic extract	VEGFA; PDGFRα; Col1A1; TGF-β1	Upregulation of VEGFA, PDGFRα, and TGF-β1; increased hydroxyproline content and collagen gene expression	Enhanced expression of GLUT-1, IGF-1, FGF-2, and VEGF	Promotes collagen synthesis, fibroblast proliferation, epithelialization, and neovascularization; improves granulation tissue formation and inflammation regulation	[55, 125, 155, 162, 163]
	Modified freeze–thaw cycling method	Porous structure enabling oxygen transport and prevention of hypoxia	EGF-NP + PHMB + Perfluorocarbon	IL-1β; IL-8; EGFR–ERK pathway; MMPs/TIMPs	Activation of EGFR–ERK signaling; modulation of MMP/TIMP balance; IL-1β-mediated macrophage response; oxygen delivery via perfluorocarbon	Enhanced keratinocyte proliferation and oxygen availability	Accelerates re-epithelialization; reduces inflammation; promotes collagen deposition and tissue maturation; exhibits antimicrobial and pro-angiogenic effects	[52, 142, 164–167]

Notes: ↑ indicates increased or upregulated expression/activity; ↓ indicates decreased or downregulated expression/activity; → indicates signaling direction or pathway interaction.

active compounds exhibit multi-target mechanisms, resulting in synergistic therapeutic effects. As shown in Table 4, most bioactive agents act on multiple pathways simultaneously, thereby enhancing overall therapeutic efficacy in diabetic wound healing. The integration of these mechanisms is further supported by the diversity of dosage forms, which enables improved delivery, stability, and sustained activity of the active compounds. Consequently, the interplay between active ingredients, auxiliary components, manufacturing techniques, and pathway modulation plays a central role in the rational design of next-generation wound therapies. Overall, combination-based approaches appear to provide superior outcomes compared to single-agent therapies, despite the heterogeneity of their mechanisms of action.

Translational perspectives summarized in Table 5 reveal notable differences in Technology Readiness Levels (TRL) across various formulation platforms. Overall, translational readiness remains relatively low. Hydrogels and vesicular nanosystems demonstrate the highest maturity (TRL 5–6), supported by small-animal in vivo validation and preliminary scalability in manufacturing. In contrast, nanofiber-based systems, although biologically effective, remain at TRL 3–4

Table 5 Translational Readiness and Future Research Gaps

Translational Stage	Scientific Objective	Evidence Reported in Literature	Representative Technologies/Approaches	Current Limitations	Key Requirements for Next Stage
Basic Discovery	Identification of natural bioactive compounds and their biological activity in wound healing	In vitro antioxidant, anti-inflammatory, and antimicrobial assays, viability; skin sensitization; collagenase	Plant-derived polyphenols, flavonoids, polysaccharides, honey-derived compounds	Lack of standardization and limited mechanistic validation	Detailed molecular pathway analysis and compound characterization
Biomaterial Engineering	Integration of bioactive compounds into functional dressing platforms	Hydrogel-based systems; Hydrocolloid-based systems; Hydrofiber/Nanofiber-based systems; 3D Bioprinted/ Composite-based systems; Nanocomposite/Hybrid-based systems	Curcumin-loaded nanofibers; chitosan–herbal composites; mangostin-loaded electrospun scaffolds; Gelatin/alginate + plant extract blends; bioactive polymer composites; Metal nanoparticles combined with plant extracts; polymer–herbal hybrid matrices	Limited optimization of mechanical stability and release kinetics	Material optimization, controlled-release profiling, and structural characterization
Preclinical Validation	Evaluation of therapeutic efficacy in diabetic wound models	Rodent diabetic wound models, the collagen density, the angiogenesis score, granulation tissue formation and re-epithelialization, erythema, eschar formation and edema formation. Inflammation and oxidative stress, macrophage immune, angiogenesis, and epithelialization.	STZ-induced male adult Wistar rats, Streptozotocin (STZ)- The male C57BL/6 mice); Young female New Zealand white rabbits.; STZ - induced diabetic Sprague–Dawley rats; STZ/HFD - Induced diabetic male C57BL/6 mice	Animal models incompletely replicate human diabetic ulcer pathophysiology	Validation in large-animal models and extended observation periods
Safety and Biocompatibility Assessment	Evaluation of cytotoxicity, biodegradation, and systemic safety	Cell viability assays and short-term in vivo toxicity studies, morphology of cell; hemocompatibility	Biocompatibility testing of polymer matrices and nanomaterials	Limited long-term toxicity and biodegradation data	Comprehensive safety profiling and regulatory toxicology studies

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Table 5 (Continued).

Translational Stage	Scientific Objective	Evidence Reported in Literature	Representative Technologies/Approaches	Current Limitations	Key Requirements for Next Stage
Clinical Feasibility	Assessment of therapeutic efficacy in human subjects	Pilot clinical studies and early feasibility trials	Prototype wound dressing systems incorporating natural bioactives	Small sample size and lack of multicenter validation	Large-scale randomized clinical trials
Clinical Implementation	Integration into routine wound management practice	Regulatory approval and clinical adoption	Commercial advanced wound dressings	Limited translational continuity from preclinical research	Regulatory approval pathways and cost-effectiveness evaluation

due to challenges in sterilization and industrial reproducibility. Hybrid nanocomposites and smart-responsive hydrogels exhibit strong mechanistic performance but are still in early preclinical stages (TRL 2–4), primarily due to regulatory uncertainties surrounding multifunctional nanosystems. Similarly, 3D-printed constructs, particularly those incorporating living cells, show promising in vivo results but face significant regulatory and Good Manufacturing Practice (GMP) barriers, which limit their translational progress. Moreover, the advanced technological requirements of these systems may reduce cost-effectiveness and scalability for widespread clinical implementation. Variability in experimental outcomes and production processes further necessitates rigorous validation of these emerging platforms.

Finally, Table 5 outlines the future research landscape, emphasizing the development of integrative technologies such as exosome-loaded biomaterials, near-infrared (NIR)-triggered smart release systems, AI-assisted formulation optimization, bioprinting-based personalized scaffolds, and modular multimodal bioinks. These approaches converge toward a central translational objective: the development of wound dressings capable of temporally controlled therapeutic sequencing (anti-inflammatory → angiogenic → remodeling) while maintaining manufacturability and regulatory feasibility. Such advancements not only focus on technological innovation in formulation design but also emphasize the optimized integration of natural bioactive compounds as key therapeutic components. The transition from conventional monolithic systems to adaptive and programmable biomaterials is further illustrated in Figure 2.

Discussion

Implications of Methodological Bias on the Reliability and Translational Potential of Preclinical Findings

Based on the SYRCLE risk of bias evaluation (Table 2), most preclinical studies involving natural compounds or biomaterials exhibit notable limitations in methodological reporting, particularly in terms of randomization and blinding procedures. The predominance of the "unclear risk" classification suggests insufficient reporting detail to fully assess internal validity, which may result in an overestimation of the reported therapeutic benefits. Furthermore, although the included studies demonstrate relatively comprehensive experimental approaches, no clear efforts have been identified to directly compare these findings with clinical data.

Insufficient reporting of random sequence generation and allocation concealment increases the likelihood of selection bias, potentially affecting the distribution of experimental subjects and their responses to treatment. This issue is particularly critical in diabetic wound models, where biological variability among animals can substantially influence outcomes such as microbial load, inflammatory responses, re-epithelialization, granulation tissue formation, and angiogenesis.

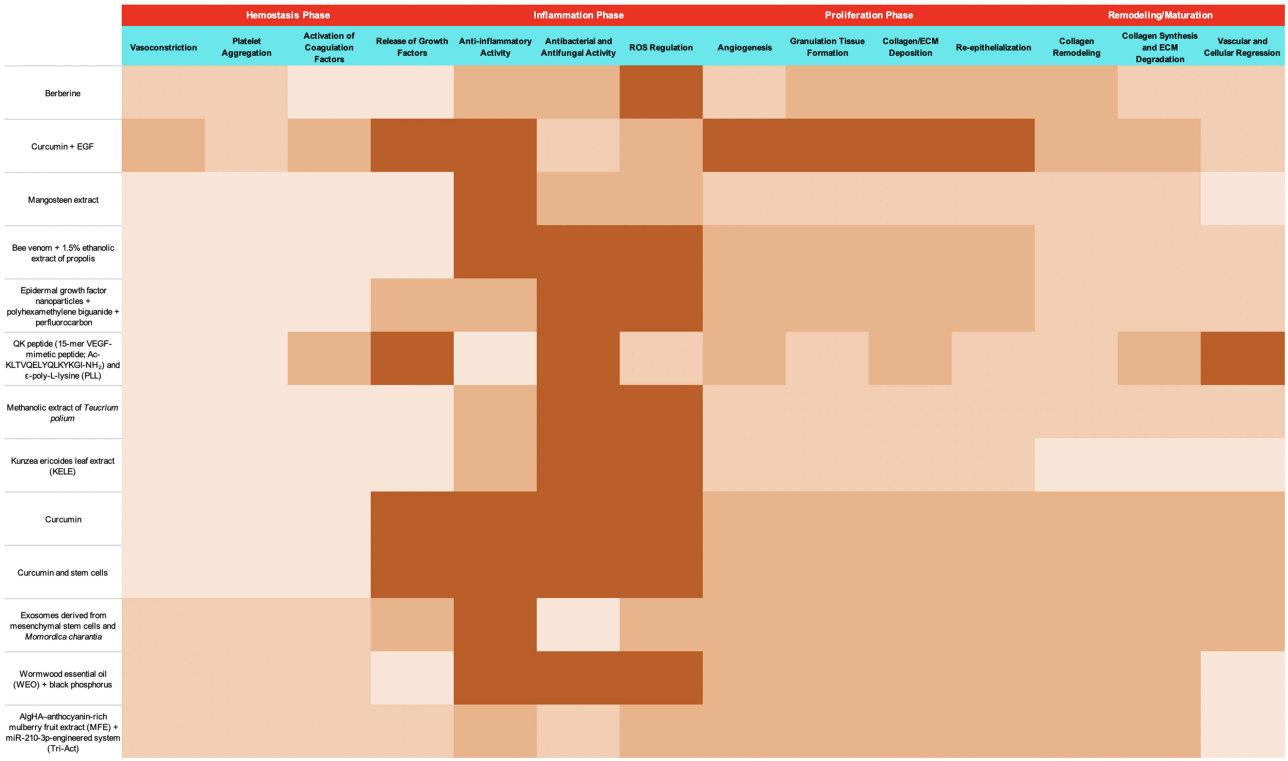

Figure 2 Heatmap of Bioactive Compounds vs Mechanistic Pathways in Diabetic Wound Healing Biomaterials (Created by the authors based on synthesized data from the reviewed studies). The heatmap illustrates the relative level of evidence supporting the effects of each bioactive compound across key biological processes involved in diabetic wound healing, including the hemostasis, inflammation, proliferation, and remodeling phases. Color intensity represents the strength of available evidence: light beige indicates insufficient or limited data; light Orange indicates moderate evidence with limited therapeutic validation; orange indicates adequate evidence with promising therapeutic potential; and dark orange indicates strong evidence with high therapeutic relevance. Each row represents a specific bioactive compound or formulation, while each column corresponds to a targeted mechanistic pathway or biological response.

Additionally, the absence of blinding procedures for investigators and outcome assessors elevates the risk of both performance and detection bias. In wound healing studies, which frequently rely on semi-quantitative assessments—such as histological evaluation, angiogenic marker expression (eg., VEGF and CD31), and collagen deposition—the lack of blinding may introduce considerable observational bias.

Selective reporting bias may further affect interpretation, especially if studies preferentially report favorable outcomes. This can lead to an inflated perception of therapeutic effectiveness. Therefore, validation through both rigorous preclinical and clinical investigations is essential to establish reliable conclusions and provide a robust framework for future research. These methodological shortcomings also have important implications for translating preclinical findings into clinical practice. Although many studies demonstrate that bioactive delivery systems can regulate key molecular pathways such as NF-κB, PI3K/Akt, and VEGF signaling, these findings should be interpreted cautiously due to the potential influence of bias. Limitations in study design—particularly regarding randomization and blinding—may compromise the accuracy of molecular biomarker measurements used to explain therapeutic mechanisms.

Consequently, improving methodological rigor in preclinical studies is essential. This includes implementing proper randomization, allocation concealment, and blinding procedures, as recommended by the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines. Enhancing reporting quality is crucial to ensure that observed therapeutic effects genuinely reflect outcomes that are translatable into clinical settings.

Considering these limitations, the association between molecular pathway modulation and therapeutic outcomes reported in preclinical studies requires further confirmation through more robust experimental designs. This is necessary to ensure that observed effects—such as antimicrobial and antifungal activity, anti-inflammatory responses, as well as improvements in re-epithelialization, granulation tissue formation, and angiogenesis—accurately represent clinical wound healing processes. Overall, although biomaterial- and bioactive-based strategies demonstrate strong potential

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for targeting molecular dysfunctions in diabetic wounds, improving preclinical methodological quality remains essential to bridge the gap between experimental research and clinical application.

This systematic review aimed to evaluate the effectiveness of hydrogel, hydrocolloid, and hydrofiber dressings in promoting diabetic wound healing. A total of 14 studies were included in the analysis. The primary objective was to identify the role of these dressing types in diabetic wound management. Overall, the included studies consistently indicate that hydrogel-based dressings show significant potential in enhancing wound healing outcomes.

Diabetic wounds represent a chronic complication arising from complex disruptions in the physiological wound healing process. These include metabolic disturbances, vascular impairment, microbial infection, and immune dysfunction. This condition is further exacerbated by persistent hyperglycemia, which leads to the accumulation of advanced glycation end products (AGEs), increased oxidative stress, and activation of inflammatory pathways such as nuclear factor kappa B (NF-κB). This activation promotes the production of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6).[73,76,101] Consequently, the wound microenvironment becomes imbalanced, prolonging the inflammatory phase and delaying progression to the proliferative stage.

Moreover, impaired angiogenesis is a hallmark of diabetic wounds, primarily due to reduced expression of vascular endothelial growth factor (VEGF) and endothelial dysfunction, which limits neovascularization within the wound tissue.[74,140] Dysregulation of extracellular matrix turnover is also observed, where increased activity of matrix metalloproteinases (MMPs) and decreased levels of tissue inhibitors of metalloproteinases (TIMPs) result in excessive matrix degradation. This imbalance ultimately hinders granulation tissue formation and collagen deposition.[119,168]

Conventional therapeutic approaches are often inadequate in addressing these multifactorial mechanisms simultaneously. Therefore, the development of advanced biomaterial-based drug delivery systems offers a promising strategy to enhance therapeutic efficacy through targeted modulation of the wound microenvironment.

Physicochemical Design and Formulation Strategies of Advanced Bioactive Delivery Systems for Diabetic Wound

Modern drug delivery systems enable simultaneous targeting of multiple molecular pathways involved in diabetic wound healing. In general, these therapeutic mechanisms can be categorized into four main aspects. First, suppression of chronic inflammation through modulation of the NF-κB pathway, resulting in reduced expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. Second, stimulation of angiogenesis via activation of the VEGF signaling pathway, which promotes endothelial cell proliferation and neovascularization. Third, reduction of oxidative stress through enhancement of antioxidant enzyme activity, including superoxide dismutase (SOD) and glutathione, thereby protecting cells from ROS-induced damage. Fourth, regulation of extracellular matrix remodeling through balancing MMP and TIMP activity, facilitating collagen deposition and proper tissue maturation.

Biomaterial-based therapeutic systems that integrate natural bioactive compounds, growth factors, and nanotechnology-based approaches demonstrate considerable potential in improving diabetic wound treatment outcomes. These integrated strategies not only accelerate wound closure but also enhance the quality of tissue regeneration by reducing scar formation. Several formulation strategies have been explored in diabetic wound therapy, including:

Hydrogel-Based

Hydrogels represent one of the most extensively developed biomaterial systems for chronic wound management due to their capacity to retain moisture, facilitate oxygen exchange, and enable controlled release of bioactive agents. In addition, hydrogels exhibit excellent biocompatibility and can be tailored through chemical or physical modifications to meet specific therapeutic needs.[50,136] Various fabrication techniques have been designed to produce hydrogel systems with optimal physicochemical characteristics alongside significant pharmacological activity in chronic wound healing. The following examples highlight preparation strategies aimed at improving the efficacy of incorporated active compounds.

One approach involves the fabrication of vesicular hydrogels through physical extrusion using a 400 nm porous polycarbonate membrane, allowing the formation of uniformly sized and stable vesicles. This system is capable of encapsulating natural bioactive agents such as wormwood essential oil (WEO) and black phosphorus, both known for their anti-inflammatory and pro-angiogenic properties.

At the molecular level, such formulations modulate wound-healing mediators, including the upregulation of platelet endothelial cell adhesion molecule-1 (PECAM-1/CD31), which is closely associated with angiogenesis. Simultaneously, they suppress the expression of inflammatory markers such as myeloperoxidase (MPO) and interleukin-6 (IL-6), which are indicative of acute inflammation in chronic wounds.

Physical gelation represents another widely applied method in hydrogel fabrication. This technique influences the gel's capacity to absorb exudate, maintain a moist wound environment, and ensure structural integrity.[169,170] Additionally, hydrogels produced via physical gelation often demonstrate high mechanical strength and excellent biocompatibility, both critical for chronic wound repair. For example, freeze-dried hydrogels exhibit high fluid absorption capacity and effectively rehydrate the wound environment.[170] The development of such systems also enables the formation of porous structures, which enhance fluid uptake and support tissue regeneration.[171] These advancements have led to the emergence of thermosensitive hydrogels, which exist as liquids at lower temperatures and transition into gels at body temperature, ensuring atraumatic application and removal.[172] Overall, hydrogels produced through physical gelation have demonstrated improved healing outcomes, including reduced inflammation, enhanced angiogenesis, and accelerated epithelialization, largely due to their ability to maintain optimal moisture and deliver therapeutic agents efficiently.[170,173]

Another strategy involves layer-by-layer hydrogel systems with Schiff base crosslinking, enabling phase-dependent and sustained release of bioactive compounds. One example includes the incorporation of anthocyanin-rich mulberry extract with miR-210-3p, a key regulator of hypoxia response and angiogenesis. Similarly, hydrogels co-loaded with curcumin and epidermal growth factor (EGF) demonstrate synergistic effects in accelerating wound healing. Curcumin exerts anti-inflammatory activity by inhibiting the NF-κB pathway and reducing MMP-9 expression, while EGF activates the EGFR signaling pathway, promoting keratinocyte and endothelial cell proliferation.[50,136] Activation of these pathways enhances the expression of angiogenic markers such as von Willebrand factor (vWF) and CD31. Moreover, increased keratinocyte proliferation contributes to faster re-epithelialization, a critical phase in wound repair.[108]

The integration of layer-by-layer (LbL) casting with photopolymerization is another advanced fabrication technique that enables precise structural customization. LbL casting allows the construction of multilayer systems with controlled thickness, porosity, and composition, facilitating the incorporation of therapeutic agents. This approach supports angiogenesis, tissue regeneration, and faster wound closure. Additionally, it enables sustained release of drugs such as antibiotics and growth factors, reducing dosing frequency and improving patient compliance.[174,175] Enhanced cellular uptake further promotes re-epithelialization and neovascularization in chronic wound models.[176]

Photopolymerization techniques, including digital light processing (DLP), allow the fabrication of high-resolution, patient-specific scaffolds with properties that mimic soft tissue while providing mechanical support and controlled drug delivery. This approach has been applied to develop bilayer hydrogels with combined anti-inflammatory and neurovascular regenerative functions. For instance, hydrogels composed of chitosan methacrylate and decellularized amniotic membrane promote scar-free healing in diabetic wound models. Incorporation of nanoparticles into such systems further improves mechanical strength, antibacterial properties, and photothermal responsiveness.

Polymerization within these biomaterials may involve $Sn(oct)_2$-catalyzed lactone ring-opening initiated by PEG, enabling controlled polymer chain growth for hydrogel formation.[177] MADIX polymerization preserves the characteristic MEA fragment signal at 3.6 ppm in NMR spectra, confirming functional xanthate groups for reversible chain transfer processes.[178]

Dopamine methacrylamide (DMA), inspired by mussel adhesive proteins, forms hydrogen bonds with moist skin surfaces, ensuring strong adhesion. Methoxyethyl acrylate (MEA) contributes to hydrophobic stabilization, while NIPAM imparts thermo-responsive behavior through LCST transitions, enabling temperature-dependent adhesion and detachment.[63]

Branched copolymer surfactants (BCS) form nano-oblate structures at oil interfaces under low temperatures, while temperature increases induce DEGMA-driven polymer association, enhancing viscoelasticity without gel formation.[179] These properties support the development of dynamic wound dressings with tunable mechanical behavior and high biocompatibility.

pH-responsive behavior also plays an important role in hydrogel systems. Acidification due to PEG-based ionic permeability enables controlled degradation and pH-dependent drug release. At physiological pH (7.4), drug release

remains controlled, whereas at lower pH (5.5), accelerated release occurs during degradation. Slow degradation of PCEC ensures prolonged retention and sustained therapeutic effects.[177] Biocompatibility evaluations, such as HaCaT keratinocyte assays, confirm the safety of systems like WAME (wet-adhesive multi-electrode) interfaces, particularly in p(DMA-co-MEA-co-NIPAM) polymer layers.[63]

Functionally, hydrogels absorb exudate and retain moisture, reducing cellular damage and enabling gas exchange (O_2, CO_2, water vapor). They also promote autolytic debridement and keratinocyte migration. Hydrophilic functional groups (-OH, -COOH) enhance water binding, allowing up to 96% exudate absorption while maintaining slightly acidic conditions that inhibit bacterial growth and attract fibroblasts and keratinocytes. Their porous architecture facilitates nutrient and growth factor diffusion (eg., VEGF, FGF), enhances cytokine secretion (IL-1α, TGF-α, IL-8), and promotes MMP-9-mediated remodeling. These effects accelerate keratinocyte migration via integrin interactions while preserving cell viability. In fibroblasts, materials such as silk fibroin activate TLN1 signaling, upregulating adhesion proteins (vinculin, paxillin, p-FAK) and promoting proliferation and collagen deposition.[86,180]

Despite these advantages, hydrogel systems face challenges related to degradation control and mechanical stability. Ideally, hydrogels should maintain structural integrity for at least 14 days without disrupting the wound microenvironment. Stability can be improved through chemical (covalent) or physical (ionic/hydrogen bond) crosslinking. Hybrid polymer systems (eg., chitosan/PVA) further enhance mechanical strength and reduce syneresis while enabling controlled degradation through enzymatic or hydrolytic processes aligned with wound healing phases. Excessive degradation may cause rapid erosion and loss of structural integrity, whereas insufficient degradation may hinder tissue remodeling. Key challenges remain in scalability and adaptability to varying wound conditions.[181,182]

Hydrocolloid-Based

Hydrocolloid dressings function by absorbing excess exudate and forming a gel-like matrix that maintains moisture balance while creating an occlusive barrier. This environment supports hemostasis and re-epithelialization. The incorporation of antimicrobial or antioxidant agents further reduces the risk of infection, particularly under anaerobic conditions.

The mechanism begins with the formation of a flexible film combined with a hydrophilic polymer matrix that absorbs exudate, expands, and covers the wound surface. This reduces fluid loss and protects the wound from external contamination. At the molecular level, hydrophilic functional groups regulate fluid balance and form cohesive gel networks that enable controlled release of active compounds. The effectiveness of hydrocolloid systems depends on polymer composition, barrier properties, and their influence on the wound microenvironment.[183,184]

Hydrocolloid dressings form an occlusive gel in situ upon contact with wound exudate. Ionic interactions between Ca^{2+} or Na^{+} ions and the polymer matrix trigger crosslinking, forming a semi-permeable barrier that reduces water evaporation by up to 90% and limits microbial infiltration. This barrier also reduces friction on the wound surface and supports autolytic debridement. Structurally, ionic crosslinking (eg., alginate-Ca^{2+} egg-box model) generates a porous matrix that maintains moisture without causing maceration. Ionic binding enhances adhesion, prevents detachment, and maintains an optimal pH range (5–6) during the early inflammatory phase, leading to polymer expansion and stabilization.[185–187]

However, the occlusive nature of hydrocolloids may create low-oxygen conditions that favor anaerobic bacterial growth. Therefore, incorporation of antimicrobial agents (eg., AgNPs, chitosan) or antioxidants (eg., curcumin) is necessary to control biofilm formation below 10^5 CFU/cm^2, particularly in highly contaminated or necrotic wounds. Continuous monitoring is essential to prevent secondary infections, and the use of semi-permeable materials is recommended to allow adequate gas exchange.[185–188]

Hydrofiber/Nanofiber-Based

Electrospinning technology enables the fabrication of nanofibers with structures that closely resemble the natural extracellular matrix (ECM-mimicking architecture). This structural similarity provides a favorable microenvironment that supports cell adhesion, fibroblast migration, and keratinocyte proliferation, all of which are essential for skin regeneration.[49,98]

Hydrofiber and nanofiber-based dressings consist of fine fibers (50–500 nm in diameter) with nanoscale topography that can enhance fibroblast and keratinocyte adhesion and migration by up to 2–3 times compared to conventional scaffolds. Their high surface area-to-volume ratio (>100 m^2/g) allows efficient loading of bioactive compounds, making them suitable for controlled-release applications. Furthermore, fiber dimensions enable tunable degradation profiles aligned with wound healing phases (approximately 5–21 days). Mechanotransduction is also influenced by fiber stiffness (1–10 kPa), which activates the YAP/TAZ pathway to promote cell proliferation, while angiogenesis is stimulated through spatially controlled VEGF release that enhances endothelial sprouting. Despite these advantages, excessive stimulation of granulation tissue formation may increase the risk of hypertrophic scarring, potentially affecting the remodeling phase.[2,189–192]

Nanofiber systems also provide spatial control over drug release through core–shell or aligned fiber designs. This allows an initial burst release for antibacterial action, followed by sustained release during subsequent healing phases, while also regulating fibroblast migration and collagen organization. High porosity (80–90%) further improves nutrient diffusion without facilitating bacterial penetration, making these systems highly suitable for chronic wounds. However, their relatively low mechanical strength (<5 MPa) makes them prone to tearing under shear stress, which may result in scaffold collapse and compromise therapeutic outcomes.[2,189,190]

3D Bioprinted or Composite-Based

3D bioprinting technology allows the fabrication of scaffolds with architectures that closely mimic native skin tissue. These scaffolds can be designed with controlled porosity to enhance oxygen and nutrient diffusion while supporting the migration of regenerative cells. Scaffolds incorporating curcumin and mesenchymal stem cells (MSCs) have demonstrated strong regenerative potential in diabetic wound healing. MSCs exhibit immunomodulatory properties and secrete growth factors such as VEGF, TGF-β, and PDGF, which contribute to angiogenesis and tissue regeneration.[58,108] At the molecular level, such systems activate key signaling pathways, including PI3K/Akt and ERK1/2, which regulate cell proliferation, keratinocyte differentiation, and neovascularization.

Photocrosslinking is commonly used to stabilize hydrogels such as GelMA, enhancing both mechanical strength and biocompatibility while enabling sustained release of bioactive compounds such as KELE, thereby prolonging antioxidant and anti-inflammatory effects.[56,193] Furthermore, 3D bioprinting enables precise deposition of bioactive materials (eg., KELE-loaded hydrogels), closely replicating native tissue structures and facilitating targeted delivery to diabetic wounds, ultimately improving angiogenesis and tissue repair.[193]

Compared to conventional composites, 3D bioprinted systems provide highly controlled pore structures (200–500 μm interconnected networks) and high shape fidelity (>95% retention after printing). These properties allow spatial positioning of cells and biomolecules (eg., VEGF-loaded layers), unlike traditional composite systems that rely primarily on diffusion-based release. Additionally, multi-nozzle printing enables layer-specific functionalization (eg., inner VEGF/FGF layers and outer collagen matrices), whereas composite systems are typically homogenously mixed. Gradient mechanical properties (soft epidermal layers 1–5 kPa to stiffer dermal layers 10–50 kPa) can also be achieved, ensuring biomechanical compatibility with native tissue—an advantage not available in conventional composites.[194–198]

3D bioprinting further enables personalized wound dressings based on imaging data (MRI/CT), achieving high anatomical conformity (~95%). These systems support staged therapeutic delivery (initial antimicrobial burst followed by sustained growth factor release) and hierarchical porosity for in situ vascularization. As a result, they can achieve 2–3 times faster wound closure in full-thickness wounds compared to traditional scaffolds.[194,195,199]

Nanocomposite/Hybrid-Based

Nanocomposite systems provide a multifunctional therapeutic platform by integrating multiple bioactive components into a single formulation. These systems act not only as drug carriers but also as multi-target therapeutic platforms capable of addressing the complex pathophysiology of diabetic wounds. Various preparation techniques are employed, including ultrasonication with lecithin–glycerol hydration (vesicle formation), GelMA photopolymerization with dopamine cross-linking, ionotropic gelation combined with ultrasonic homogenization, and modified freeze–thaw cycles. Each method offers specific advantages; overall, nanocomposite systems demonstrate high skin penetration and retention, strong

bioadhesion, antimicrobial activity, and good oxygen permeability. Their porous structure further supports oxygen transport and prevents hypoxic conditions, making them highly suitable for wound therapy.

For instance, nanocomposite systems combining mesenchymal stem cell-derived exosomes with natural extracts such as *Momordica charantia*, curcumin, and *Teucrium polium*, along with EGF-loaded chitosan nanoparticles (EGF-NP), polyhexamethylene biguanide (PHMB), and perfluorocarbon, exhibit strong anti-inflammatory and antioxidant activities. These systems promote angiogenesis, extracellular matrix remodeling, collagen deposition, epithelialization, and hair follicle regeneration, while reducing fibrosis and enhancing granulation tissue formation.

Nanocomposite dressings typically incorporate multiple active agents, such as AgNPs (antibacterial) and ZnO (anti-inflammatory), along with small extracellular vesicles (sEVs) for cellular signaling. These are embedded within vesicular carriers (liposomes, niosomes, glycerosomes) capable of encapsulating both hydrophilic and hydrophobic compounds, and subsequently integrated into polymer matrices (eg., chitosan/PVA). The resulting system forms a synergistic network through electrostatic interactions and hydrogen bonding, improving stability and enabling controlled release triggered by external stimuli such as near-infrared (NIR) irradiation or magnetic fields.

Antibacterial activity is primarily achieved through reactive oxygen species (ROS) generation, where ZnO and AgNPs disrupt biofilm structures, leading to up to 99% reduction in pathogens such as *S. aureus* and *P. aeruginosa*. Additional mechanisms include membrane disruption and quorum sensing inhibition. sEV-based components further enhance angiogenesis and immunomodulation, particularly when combined with controlled or stimulus-responsive release systems. Vesicular systems such as niosomes and glycerosomes also regulate drug release kinetics, improving overall therapeutic performance.[151,200–202]

Nanohybrid systems allow simultaneous therapeutic actions, including antibacterial effects (AgNP burst release), antioxidant activity (ZnO-mediated ROS scavenging), angiogenesis (sEVs or VEGF-loaded liposomes), and immunomodulation (eg., IL-10-loaded systems), aligned with wound healing phases (inflammation to proliferation). These systems can sustain drug release for up to 14 days, potentially accelerating wound healing.[200–202] However, safety considerations remain critical. Risks such as long-term toxicity (eg., Ag^+ accumulation above 100 μg/kg), nanoparticle aggregation, cytotoxicity at high concentrations (>50 μg/mL), and environmental release must be addressed. Strategies to mitigate these risks include core–shell coating (eg., PEG/chitosan) and dose optimization through long-term in vivo studies demonstrating minimal toxicity over extended periods.[151,201–203]

Hydrogel-based systems also demonstrate enhanced permeability, facilitating deeper penetration of active compounds into wound tissue. Their pH-responsive behavior further supports controlled release at the wound site. For instance, hydrogels containing mangosteen extract exhibit antibacterial activity against *S. epidermidis* in vitro.[51] At low to moderate concentrations, these formulations are non-cytotoxic and do not inhibit fibroblast growth. In vivo studies also confirm their biocompatibility and safety for skin tissue.

Propolis is another natural compound with proven antibacterial and antioxidant properties due to its free radical scavenging ability. Curcumin-loaded hydrogels promote significant wound closure through enhanced re-epithelialization and improved vascularization in diabetic animal models. Hydrogels containing *Momordica charantia* demonstrate strong mechanical properties, adhesion, and controlled degradation. In vivo studies show reduced inflammation through suppression of neutrophil infiltration and oxidative stress, accompanied by increased epidermal thickness and accelerated wound healing. Importantly, these formulations show no hemolytic effects.[4] Similarly, nanogels containing *Teucrium polium* demonstrate progressive wound contraction, minimal inflammatory response, and improved re-epithelialization, supporting faster healing through antioxidant, anti-inflammatory, and pro-angiogenic mechanisms.[55]

Lee and Lin further reported that hydrogel systems effectively absorb exudate, maintain moisture, and improve oxygen availability, thereby reducing hypoxia in diabetic wounds. These systems also promote keratinocyte proliferation and reduce inflammation, ultimately leading to faster wound closure, improved collagen deposition, and enhanced tissue regeneration.[52]

Future Perspective

This review demonstrates that topical technologies based on natural bioactive compounds for diabetic wound therapy have advanced considerably over the past decade. Nevertheless, several critical gaps remain before these approaches can be translated into widespread clinical use. Key challenges include optimizing formulations in accordance with the

physiological characteristics of diabetic wounds, ensuring standardization and quality control as part of methodological validation, integrating tissue engineering technologies, and designing preclinical-to-clinical studies that comply with regulatory frameworks. Current research largely emphasizes general material efficacy, with limited consideration of wound-specific physiological conditions. Future formulations should therefore be tailored to the dynamic wound microenvironment, including the different phases of wound healing and their underlying causes.

The concept of *adaptive spatiotemporal delivery* represents a promising direction and warrants further exploration, particularly through the development of stimuli-responsive hydrogels capable of releasing bioactive agents in response to wound-specific triggers such as pH, enzymes, or reactive oxygen species (ROS), as well as through stem cell–based approaches. In addition, molecular-level strategies are expected to play a greater role, including the use of multi-marker panels (eg., NF-κB, Nrf2, PI3K/Akt, VEGF, HIF-1α, TGF-β1) and advanced techniques such as single-cell RNA sequencing to validate cellular targets. Incorporating time-course analyses will also be essential to better understand the chronic progression of diabetic wounds and to support the development of more individualized therapeutic strategies.

Another emerging direction involves integrating bioactive compounds and biomaterials within tissue engineering platforms. Although current technologies remain relevant, they are often insufficient for long-term or chronic wound management. Based on current evidence and technological trends, single-agent, monolithic systems are unlikely to meet clinical demands. Instead, modular and hybrid platforms—such as combinations of hydrogels, nanofibers, and 3D-bioprinted constructs—are anticipated to represent the next generation of translational therapies.

Despite these advances, the overall Technology Readiness Level (TRL) for diabetic wound therapies remains relatively low. This highlights the need for progressive steps to facilitate clinical translation. Future studies should therefore prioritize long-term toxicity and skin irritation testing in humans, utilize diabetic animal models with relevant comorbidities (eg., obesity and neuropathy) to improve clinical relevance, define Critical Quality Attributes (CQA) of biomaterials, and evaluate manufacturing readiness, including scalability, sterilization, and shelf-life stability. The implementation of a "standardized research-to-registry pipeline" is proposed as a strategic approach to accelerate the transition from laboratory findings to clinical investigation.

Conclusion

Based on a systematic review of 14 studies, hydrogel, hydrocolloid, and hydrofiber formulations containing natural bioactive compounds play a significant role in promoting diabetic wound healing. Their mechanisms of action include antibacterial, anti-inflammatory, antioxidant, re-epithelialization, and tissue regeneration effects. Several formulations also demonstrate additional advantages, such as high biocompatibility, favorable mechanical properties, and controlled drug release tailored to different stages of wound healing. Moreover, the incorporation of advanced technologies, such as 3D printing, further enhances therapeutic efficacy. Overall, these findings support the continued development of natural-based topical therapies as innovative and environmentally friendly approaches for diabetic wound management. Importantly, effective therapy depends not only on the selection of potent bioactive compounds but also on the strategic integration of material design, mechanistic targeting, and translational feasibility. Notably, technologies that are closest to clinical application are not necessarily the most biologically complex; rather, they are those that achieve a balance between therapeutic efficacy, scalability, stability, cost-efficiency, and regulatory compliance. Therefore, successful clinical translation will depend on several key factors: (i) standardization of preclinical evaluation methods, (ii) optimization of bioactive release profiles, (iii) prioritization of scalable manufacturing processes, and (iv) alignment of biomaterial design with medical device regulatory pathways rather than more complex drug-based regulatory requirements.

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