



Review article

FOOD-WASTE-DERIVED BIOACTIVE, GREEN EXTRACTION TECHNOLOGIES AND GEL-BASED WOUND HEALING FORMULATIONS: A PRISMA-GUIDED SYSTEMATIC REVIEW

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ABSTRACT

The valorisation of food-waste-derived bioactive materials offers a potential route for developing wound-care products while supporting more sustainable resource utilisation. This PRISMA-guided systematic review synthesised 33 Q1/Q2 original research articles published between 2019 and 2024 that investigated natural waste- and related plant-derived bioactive sources relevant to extraction technologies, formulation strategies, and wound-healing applications. Maceration was reported in nine studies, followed by ultrasound-assisted extraction in eight, Soxhlet extraction in five, microwave-assisted extraction in four, pressurised or accelerated solvent extraction in two, and supercritical fluid extraction in one. These categories were not mutually exclusive because some studies employed multiple extraction techniques. Nineteen studies were classified as *in vitro*, seven as *in vivo*, and seven had insufficiently reported experimental designs and were therefore classified as unclear. Wound-healing or regenerative outcomes were reported in 23 studies, anti-inflammatory activity in 21, and antimicrobial and antioxidant activities in 20 studies each. Extracts and natural bioactive materials were incorporated into gels, hydrogels, films, nanofibrous dressings, and related delivery systems. However, direct comparisons were limited by substantial heterogeneity in feedstock characteristics, extraction conditions, analytical procedures, formulation composition, bioactive concentration, experimental models, and outcome measures. Evidence concerning stability, safety, scale-up, environmental performance, and clinical effectiveness was also limited. Overall, the findings demonstrate preclinical therapeutic potential but do not establish the superiority or clinical effectiveness of the reviewed extraction technologies and formulations. Standardised extraction and chemical-characterisation procedures, complete formulation testing, stability and safety evaluation, and well-designed clinical investigations are required before reliable translation into wound-care applications.

1.Introduction

Wound healing is a complex and tightly regulated process involving four overlapping phases: haemostasis, inflammation, proliferation, and remodelling, as illustrated in Figure 1.1. Although acute wounds generally progress through these phases without major complications, wounds associated with diabetes, vascular disease, infection, surgery, or trauma may remain unresolved for weeks or months,

resulting in persistent inflammation, impaired tissue regeneration, fibrotic scarring, and loss of function (Fernández-Guarino et al., 2023). Chronic wounds impose substantial healthcare expenditure, reduce patients' quality of life, and increase the demand for wound-care strategies that are effective, safe, affordable, and environmentally sustainable.

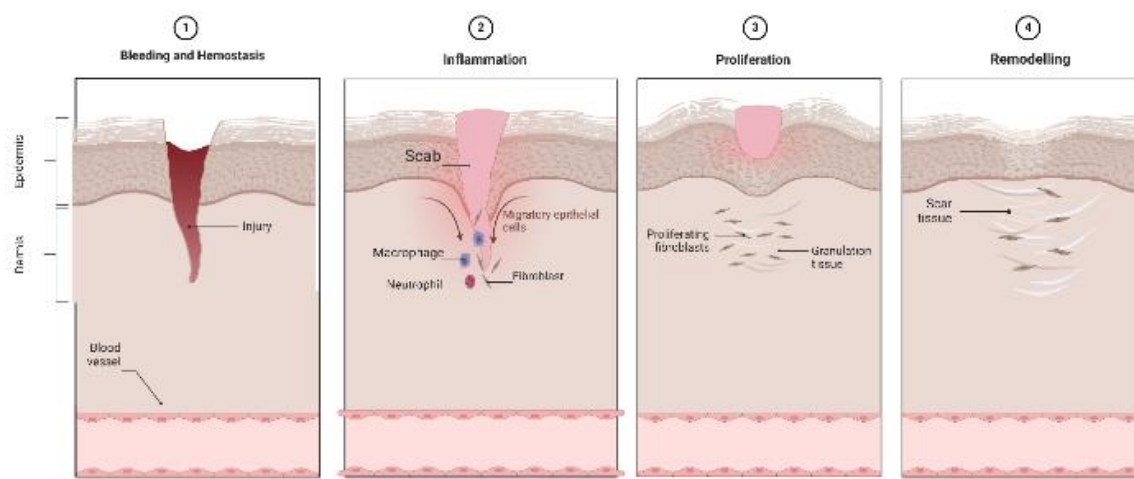


Figure 1.1. The four overlapping phases of wound healing: haemostasis, inflammation, proliferation, and remodelling. (<https://www.biorender.com/>). Accessed on December 12, 2024

Conventional wound management includes synthetic or semi-synthetic dressings, such as polyurethane films, foams, and hydrocolloids, as well as antiseptics, antibiotics, and anti-inflammatory agents (Rezvani Ghomi et al., 2019; Yousefian et al., 2023). These products perform important functions, including exudate management, physical protection, moisture regulation, and infection control. However, inappropriate or prolonged exposure to certain antimicrobial or antiseptic agents may cause cytotoxicity, delay tissue repair, or contribute to antimicrobial resistance (Yousefian et al., 2023). These limitations have increased interest in plant-derived bioactive compounds with antioxidant, antimicrobial, and anti-inflammatory activities that may support the wound-healing environment (Rezvani Ghomi et al., 2019; Abdelsattar et al., 2022).

Agro-industrial residues and food-processing by-products represent potentially

valuable sources of bioactive compounds. Fruit peels, seeds, pomace, and cereal brans are frequently discarded or directed towards low-value applications despite containing phytochemicals with potential biomedical value. Banana peel has been reported to contain phenolic acids, flavonoids, and tannins associated with antioxidant and wound-healing-related activities (Kumar et al., 2023). Citrus peel contains flavanones such as hesperidin and naringin, together with other phenolic and limonoid constituents associated with antioxidant, antimicrobial, and anti-inflammatory activities (Kaur et al., 2023). Pomegranate peel contains ellagitannins, ellagic acid, and related polyphenols that have been investigated for inflammation-modulating and tissue-regenerative applications (Costa et al., 2020). Recovering these compounds for potential wound-care applications may create value from underutilised residues while

supporting waste-reduction and circular-bioeconomy objectives.

The potential performance of food-waste-derived ingredients is strongly influenced by the extraction method used to recover and preserve their bioactive constituents. Conventional techniques such as maceration and Soxhlet extraction may require extended processing periods, substantial solvent volumes, and considerable energy input, depending on the operating conditions employed (Rafińska et al., 2019; Araujo et al., 2021). Intensified technologies, including ultrasound-assisted extraction, microwave-assisted extraction, pressurised or accelerated solvent extraction, and supercritical fluid extraction, have therefore been investigated as alternatives or complementary approaches (Hassim et al., 2019; Araujo et al., 2021). Under appropriately selected conditions, these technologies may enhance mass transfer, shorten extraction time, or reduce solvent consumption. Nevertheless, extraction performance depends on the feedstock, targeted compound class, solvent system, equipment configuration, and operating parameters. No single extraction technology can therefore be regarded as universally optimal.

Following extraction, bioactive fractions must be incorporated into delivery systems that protect their activity and enable application at the wound site. Hydrogels and related gel-based formulations are attractive because they can maintain a moist wound environment, conform to irregular wound surfaces, and incorporate bioactive compounds within biocompatible polymer networks (Witkowska et al., 2023; Yadav et al., 2024). Other delivery systems, including films and nanofibrous dressings, have also been investigated to provide physical protection and controlled or sustained release of bioactive constituents. Plant- and food-waste-derived extracts have been incorporated into matrices containing chitosan, poly(vinyl alcohol), and other natural or synthetic polymers, with reported antioxidant, antimicrobial, anti-inflammatory, and wound-regenerative activities (Rezvani Ghomi et al., 2019; Ferreira et al., 2022; Witkowska et al., 2023). However, variability in extract

composition, degradation of sensitive bioactive compounds, interactions between complex extracts and polymer matrices, and limited long-term stability, safety, and efficacy evidence continue to restrict reproducibility and clinical translation (Gościński et al., 2025; Sharifi & Bahrami, 2024).

Despite increasing research interest, the available evidence remains fragmented across several related fields. Previous reviews have generally examined natural products for wound healing, green extraction technologies, or the valorisation of food-processing by-products for functional ingredients and biomaterials as separate topics. Comparatively limited attention has been given to integrating natural-waste feedstocks, extraction technologies, bioactive composition, formulation strategies, and wound-healing-related biological activities within a single systematic synthesis. This review therefore focuses on studies published between 2019 and 2024 that investigated the extraction of bioactive compounds from natural waste- and related plant-derived materials and their application in hydrogels, gels, films, nanofibrous dressings, and other wound-care delivery systems.

Guided by the PRISMA framework for study identification, screening, eligibility assessment, and reporting (Sarkis-Onofre et al., 2021), this review aimed to: (i) map the natural-waste and related plant-derived bioactive sources, extraction technologies, and wound-care formulations investigated in the included studies; (ii) quantitatively summarise the reported extraction methods, experimental study designs, and wound-healing-related biological activities; (iii) examine the reported efficacy, stability, and safety of the investigated formulations, including any available comparisons with conventional wound-care products; (iv) evaluate the completeness of methodological reporting across the included studies; and (v) identify technological, reporting, sustainability, scale-up, and translational gaps requiring further investigation.

2..Materials & Methods

2.1. Review Design

This systematic review was conducted and reported with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 framework (Sarkis-Onofre et al., 2021). The review process comprised the formulation of research questions, development of the database-search

strategy, removal of duplicate records, title and abstract screening, full-text eligibility assessment, data extraction, and qualitative synthesis, as summarised in Figure 2.1. Owing to substantial heterogeneity in the included extraction methods, formulations, biological models, and reported outcomes, a meta-analysis was not considered appropriate.



Figure 2.1. Overview of the systematic-review process employed in this study

2.2. Research Questions

The review was guided by five research questions addressing the technological, biological, methodological, and translational dimensions of natural waste-derived wound-healing products:

RQ1: Which extraction technologies have been used to recover bioactive compounds from natural waste- and related plant-derived materials for potential wound-healing applications?

RQ2: What formulation strategies have been employed to incorporate the recovered bioactive compounds into wound-care products, and what advantages and challenges have been reported?

RQ3: What evidence is available regarding the efficacy, stability, and safety of natural waste-derived wound-healing formulations, including any reported comparisons with synthetic or conventional wound-care products?

RQ4: What technological advances have been reported in the development of natural waste-derived wound-healing products, and

what evidence supports their potential environmental sustainability?

RQ5: What methodological limitations, evidence gaps, and future research priorities have been identified for the clinical and industrial translation of these products?

These questions were formulated to integrate extraction technologies, formulation strategies, reported biological activities, methodological reporting, sustainability considerations, and translational limitations within a single systematic synthesis.

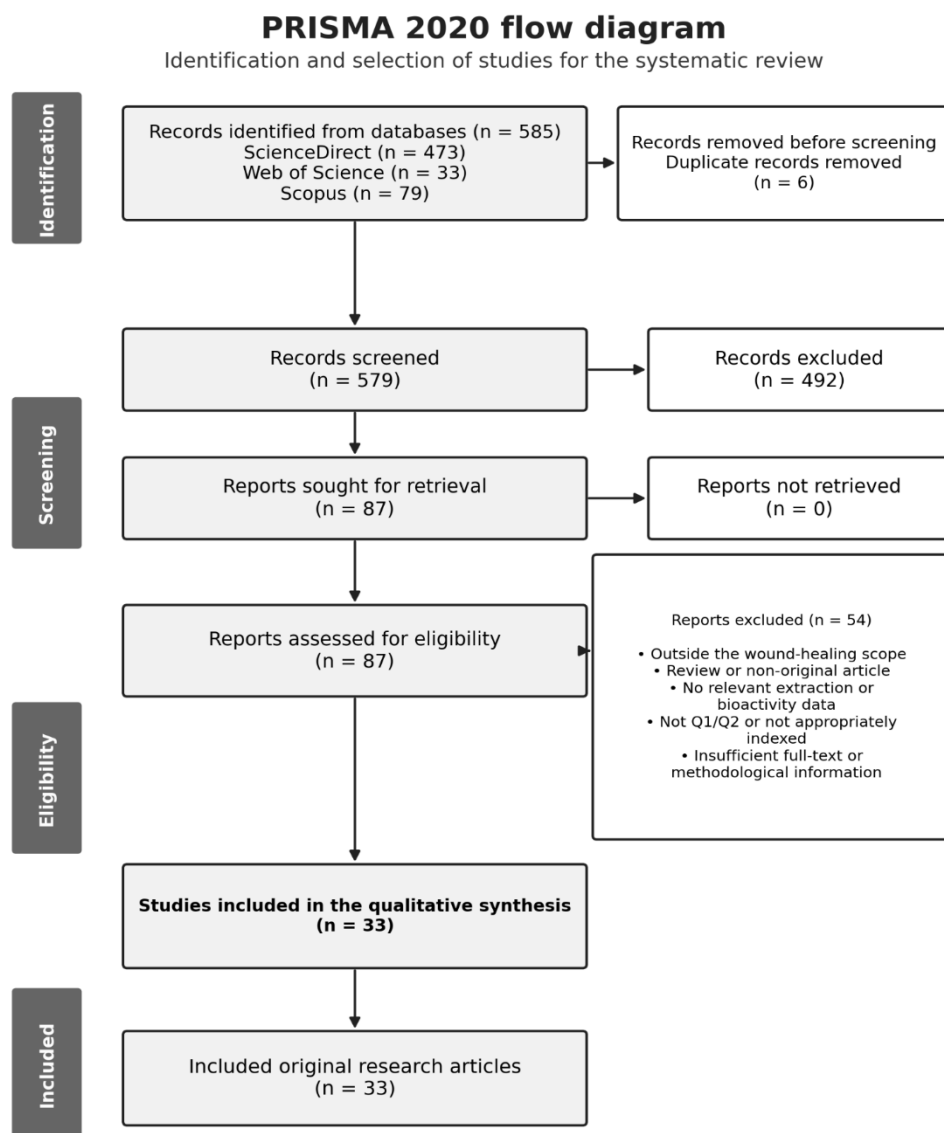
2.3. Search strategy

The literature search followed the PRISMA identification, screening, eligibility, and inclusion pathway summarised in Figure 2.2. Scopus, Web of Science Core Collection, and ScienceDirect were searched for publications dated from January 2019 to October 2024. The initial search retrieved multiple publication types, but only peer-reviewed original research articles were eligible for inclusion following screening and full-text assessment. Conference

papers, reviews, book chapters, and other non-original publications were subsequently excluded according to the eligibility criteria.

The search strategy addressed three principal concepts: (i) wound healing and related wound-care applications; (ii) conventional, green, or intensified extraction technologies and formulation strategies; and (iii) bioactive compounds obtained from natural

waste- or plant-derived sources. Boolean operators, phrase searching, and truncation were applied where supported by the respective database. Database-specific field restrictions and syntax were used because the three platforms differed in their search interfaces and indexing structures. The complete search strings applied to ScienceDirect, Web of Science, and Scopus are presented in Table 2.1.



Adapted from the PRISMA 2020 flow-diagram structure.

Figure 2.2. PRISMA 2020 flow diagram for the identification, screening, eligibility assessment, and inclusion of studies.

Table 2.1. Database-specific search fields and search strings used for literature identification

Database	Search field	Search string
ScienceDirect	Title, abstract, or keywords	(“wound healing” OR “wound care”) AND (“extraction technologies” OR “extraction methods” OR “formulation strategies”) AND (“bioactive compounds” OR “plant extracts”)
Web of Science Core Collection	Topic (TS)	TS = (“wound healing” AND (“extraction technologies” OR “extraction methods”) AND “bioactive compounds” AND “plant extracts”)
Scopus	Title, abstract, and keywords	TITLE-ABS-KEY (“wound healing” AND “plant extract” AND “extraction method” AND “bioactive compound” AND “natural”)

Note: Search syntax and field tags were adapted to the requirements of each database. Consequently, the exact combinations of terms differed across platforms while retaining the principal concepts of wound healing, extraction or formulation, and natural or plant-derived bioactive compounds.

2.4. Screening

The database searches identified 585 records: 473 from ScienceDirect, 33 from Web of Science, and 79 from Scopus. After six duplicate records were removed, 579 unique records remained for title and abstract screening. Of these, 492 records were excluded because they were unrelated to the wound-healing scope, represented reviews or other non-original publication types, or did not satisfy the language criterion. The remaining 87 reports were sought for full-text retrieval, and all were successfully obtained (reports not retrieved, $n = 0$). The identification and screening process is presented in Figure 2.2.

2.5. Eligibility

The full texts of 87 reports were assessed against the predefined eligibility criteria presented in Table 2.2. Studies were eligible if they were peer-reviewed original research articles published in English between January 2019 and October 2024 in Q1 or Q2 journals indexed in Scopus or Web of Science. The studies were also required to investigate natural waste- or related plant-derived bioactive materials, report an identifiable extraction or preparation approach, and examine at least one wound-healing-related biological or formulation outcome. Relevant outcomes included antioxidant, antimicrobial, anti-inflammatory, cytocompatibility, cell-migration, collagen-

deposition, tissue-regeneration, or in vivo wound-closure measures. Journal quartile was applied solely as an eligibility criterion and was not interpreted as an indicator of the methodological quality of an individual study. Following full-text assessment, 54 reports were excluded, and 33 original research articles were included in the qualitative synthesis (Figure 2.2).

2.6. Preliminary Methodological Reporting Assessment

Owing to the heterogeneity of the included evidence, which comprised extraction investigations, formulation-characterisation studies, in vitro bioactivity assays, and in vivo wound-healing experiments, a preliminary descriptive assessment of methodological reporting was conducted. The assessment examined whether each of the 33 included articles provided sufficient information to identify: (i) the bioactive source; (ii) the extraction or preparation method; (iii) the investigated biological activity or wound-healing-related outcome; and (iv) the experimental study design. The availability of information within these domains was recorded during data extraction to support consistent study classification and evidence synthesis. No aggregate methodological-quality score was calculated. Journal quartile was used only as an eligibility criterion and was not considered a

substitute for methodological quality or risk-of-bias assessment. Owing to the diversity of study designs and the limited reporting of design-

specific information, a formal risk-of-bias score was not assigned.

Table 2.2. Eligibility criteria applied during full-text assessment.

Criterion	Inclusion	Exclusion
Publication type	Peer-reviewed original research article	Review, systematic review, book chapter, conference paper, editorial, commentary, or other non-original publication
Publication period	Published from January 2019 to October 2024	Published outside the specified period
Language	Full text available in English	Full text not available in English
Journal eligibility	Published in a Q1 or Q2 journal indexed in Scopus or Web of Science	Journal did not meet the predefined indexing or quartile requirement
Bioactive source	Natural waste- or related plant-derived material relevant to the review scope	Synthetic-only material or source unrelated to the review scope
Extraction or preparation	An identifiable extraction, recovery, or preparation approach was reported	No relevant extraction or preparation information could be identified
Biological or formulation relevance	At least one wound-healing-related biological, formulation, or regenerative outcome was investigated	No outcome relevant to wound healing, bioactivity, or wound-care formulation was reported
Full-text information	Sufficient full-text information was available to establish eligibility and extract the principal study characteristics	Insufficient information to determine relevance or extract the minimum required study characteristics

2.7. Descriptive Analysis

The 33 eligible articles were examined and synthesised according to the predefined research questions. Extracted information included the bioactive source, extraction or preparation method, reported biological activity, experimental study design, formulation characteristics, operating conditions, and principal findings. The study-design categories, extraction methods, and biological activities were summarised using frequencies and percentages where appropriate. Extraction-method and biological-activity categories were not mutually exclusive because individual studies could employ more than one extraction technique or investigate multiple biological activities. Owing to substantial heterogeneity in study design, experimental conditions, formulations, and outcome measures, the findings were synthesised qualitatively and no

meta-analysis or pooled effect estimate was calculated.

3. Results and Discussions

3.1. Study Classification and Design Overview

The final dataset comprised 33 original research articles published between 2019 and 2024. Of these, 19 studies (57.6%) were classified as *in vitro* and seven studies (21.2%) as *in vivo*. The experimental design of the remaining seven studies (21.2%) could not be determined confidently from the reported information and was therefore classified as unclear. Collectively, the evidence base was dominated by preclinical investigations, with no full clinical trials identified, indicating that this field remains at an early stage of clinical translation.

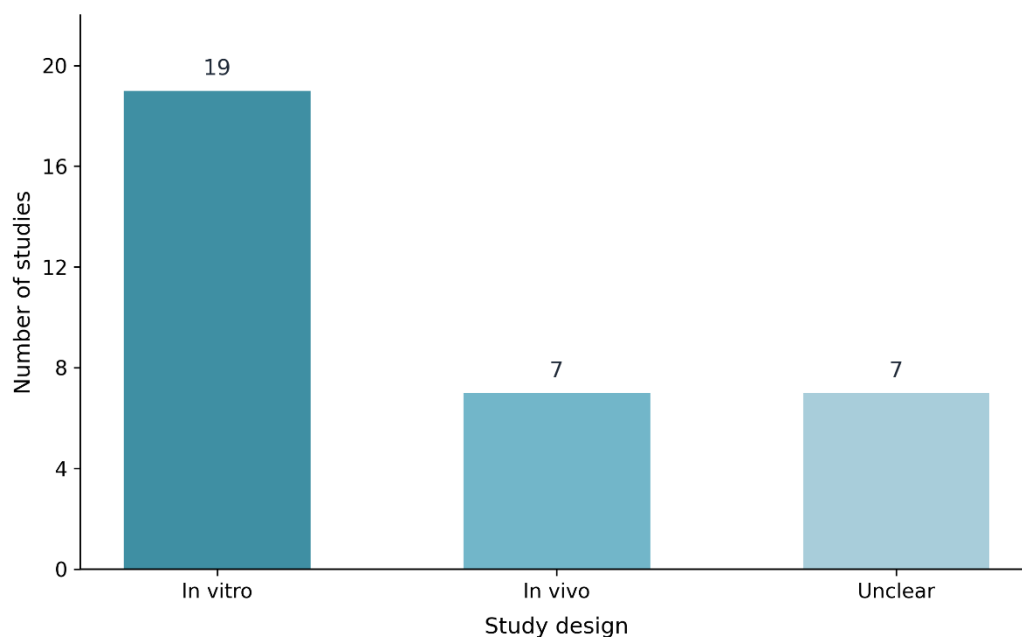


Figure 3.1. Distribution of experimental study designs among the 33 included studies

3.2. Methodological Reporting of the Included Studies

The preliminary methodological reporting assessment identified considerable variation in the completeness of reporting across the 33 included studies. Extraction or preparation methods were identifiable in 32 studies, whereas one study did not provide sufficient methodological detail for clear categorisation. Bioactive sources and investigated biological activities were generally reported, but information concerning independent replication, sample-size justification, randomisation, blinding, and other procedures used to minimise experimental bias was not consistently available. Furthermore, the experimental design

of seven studies could not be classified confidently from the reported information. Consequently, direct comparisons among studies and definitive judgements regarding methodological quality remain limited.

The principal characteristics of the 33 included studies are summarised in Table 3.1. The table presents the bioactive source, extraction or preparation method, reported biological activities, experimental study design, and reference for each study. Biological activities were standardised into broad wound-healing-related categories to support consistent descriptive synthesis across the heterogeneous evidence base.

Table 3.1. Characteristics of the 33 studies included in the systematic review

No	Bioactive Source	Extraction Method	Reported Bioactivity	Study Type	References
1	<i>Ipomoea pes-capre</i> leaf	Maceration	Anti-inflammatory, wound healing, and antiophidic properties.	Unclear	(Xavier-Santos et al., 2022)
2	<i>Woodfordia fruticosa</i> flowers	Distillation	Antioxidant; Antimicrobial; Anti-inflammatory	In vitro	(Maheshwari, 2024)
3	Propolis and honey	Heated ethanol extraction	Antioxidant; Antimicrobial; Anti-inflammatory	In vitro	(Abdelsattar et al., 2022)
4	Barley	High-power ultrasound (HPU)	Anti-inflammatory; Wound healing/regeneration	Unclear	(Di Michele et al., 2023)

5	<i>Plumbago zeylanica</i> , <i>Datura stramonium</i> and <i>Argemone mexicana</i>	Methanolic extraction	Antimicrobial; Anti- inflammatory; Wound healing/regeneration	Unclear	(Dev et al., 2019)
6	<i>Curcuma longa</i> (turmeric)	Soxhlet	Antioxidant; Antimicrobial; Anti- inflammatory; Wound healing/regeneration	In vitro	(Abbas et al., 2019)
7	<i>Lansium domesticum</i> (duku)	Microwave- assisted extraction (MAE)	Antioxidant; Anti-inflammatory; Wound healing/regeneration	In vivo	(Febriani et al., 2024)
8	<i>Verbascum thapsus</i>	Maceration + liquid-liquid extraction	Antioxidant; Antimicrobial; Anti- inflammatory; Wound healing/regeneration	In vitro	(Razani et al., 2024)
9	<i>Moringa oleifera</i> flowers	Aqueous extraction	Antimicrobial; Wound healing/regeneration	Unclear	(Butt et al., 2024)
10	<i>Lawsonia inermis</i> and <i>Scrophularia striata</i>	Maceration	Antioxidant; Antimicrobial; Anti- inflammatory; Wound healing/regeneration	In vivo	(Akbarpour et al., 2024)
11	<i>Stachys byzantina</i>	Soaking	Antioxidant; Antimicrobial; Anti- inflammatory; Wound healing/regeneration	In vitro	(Abbasinia et al., 2024)
12	<i>Centella asiatica</i>	MAE + UAE	Anti-inflammatory; Wound healing/regeneration	In vivo	(Rachpirom et al., 2023)
13	<i>Lavandula stoechas</i>	Not clearly reported	Antioxidant; Antimicrobial; Anti- inflammatory; Wound healing/regeneration	In vitro	(Mutlu et al., 2023)
14	<i>Punica granatum</i> (pomegranate)	Hydroalcoholic percolation	Antimicrobial; Wound healing/regeneration	Unclear	(Costa et al., 2020)
15	<i>Punica granatum</i> (pomegranate)	Hydroalcoholic percolation	Antimicrobial; Wound healing/regeneration	Unclear	(Santoso et al., 2024)
16	<i>Centella asiatica</i> herb	Ultrasound- assisted extraction (UAE)	Wound healing/regeneration	In vivo	(Witkowska et al., 2023)
17	<i>Mauritia flexuosa</i>	Aqueous/ethanol extraction	Antioxidant; Antimicrobial; Anti- inflammatory	In vitro	(Ferreira et al., 2022)
18	<i>Tamarindus indica</i> seeds	Soxhlet	Antimicrobial	In vitro	(Yadav et al., 2024)
19	<i>Punica granatum</i> (pomegranate) and <i>Moringa oleifera</i>	Aqueous decoction	Antioxidant; Antimicrobial; Anti- inflammatory	In vitro	(Meghwar et al., 2024)
20	<i>Vernonia amygdalina</i> leaf	Percolation	Anti-inflammatory	Unclear	(Canh Pham et al., 2024)
21	<i>Acca sellowiana</i> (feijoa)	Hot-water, acid and alkaline extraction	Antioxidant; Wound healing/regeneration	In vitro	(Zhu et al., 2023)
22	<i>Tecoma undulata</i> (Sm.) seem, commonly known as "Rohira" or "Rohitaka"	Soxhlet + maceration	Antioxidant; Antimicrobial; Anti- inflammatory; Wound healing/regeneration	In vitro	(Sable et al., 2023)
23	<i>Strychnos</i> <i>camptoneura</i>	Maceration	Wound healing/regeneration	In vivo	(Moulari et al., 2023)
24	<i>Sophora japonica</i> flowers	Modified maceration	Antioxidant; Antimicrobial; Anti- inflammatory; Wound healing/regeneration	In vitro	(Đorđević et al., 2022)
25	<i>Olea europaea</i> and <i>Acacia dealbata</i>	Solid-liquid extraction, UAE, Soxhlet + MAE	Antioxidant; Antimicrobial	In vitro	(Borges et al., 2020)

26	<i>Ginkgo biloba</i>	Maceration, reflux, shaking + Soxhlet	Antioxidant; Antimicrobial; Wound healing/regeneration	In vitro	(Sati et al., 2019)
27	<i>Lepidium sativum</i>	Maceration, UAE, ASE + SFE	Antioxidant; Antimicrobial; Wound healing/regeneration	In vivo	(Rafińska et al., 2019)
28	<i>Mangifera indica</i> peel	Ultrasound-assisted extraction (UAE)	Antioxidant; Antimicrobial; Anti-inflammatory; Wound healing/regeneration	In vitro	(Guandalini et al., 2019)
29	<i>Pogostemon cablin</i>	Caprylic/capric triglyceride extraction	Anti-inflammatory; Wound healing/regeneration	In vivo	(Choo et al., 2024)
30	<i>Moringa oleifera</i>	Pressurised liquid extraction (PLE)	Antioxidant; Anti-inflammatory; Wound healing/regeneration	In vitro	(Chatzimita kos et al., 2024)
31	<i>Commiphora gileadensis</i>	Microwave-assisted extraction (MAE)	Other reported bioactivity	Unclear	(Bin Mokaizh et al., 2024)
32	<i>Citrus reticulata</i> (kinnow)	Ultrasound-assisted extraction (UAE)	Antioxidant	In vitro	(Kaur et al., 2023)
33	<i>Citrus amblycarpa</i> , <i>C. aurantiifolia</i> and <i>C. hystrix</i>	UAE with 70% ethanol	Antioxidant; Anti-inflammatory; Wound healing/regeneration	In vitro	(Desmiaty et al., 2024)

Note: Reported biological activities were standardised into broad wound-healing-related categories. Extraction method and biological-activity categories were not mutually exclusive because individual studies could report more than one method or activity. UAE, ultrasound-assisted extraction; MAE, microwave-assisted extraction; ASE, accelerated solvent extraction; PLE, pressurised liquid extraction; SFE, supercritical fluid extraction.

3.3. Extraction Technologies

As summarised in Table 3.1, both conventional and intensified extraction methods were represented across the included studies. Maceration was the most frequently reported method, appearing in nine studies, followed by ultrasound-assisted extraction in eight studies. Soxhlet extraction was reported in five studies and microwave-assisted extraction in four studies, whereas pressurised or accelerated solvent extraction and supercritical fluid extraction were reported in two studies and one study, respectively. As several studies evaluated or combined multiple techniques, these frequencies represent method occurrences and should not be interpreted as mutually exclusive study categories.

Overall, conventional extraction methods remained widely represented, while green and intensified techniques were also evident within the current evidence base. However, meaningful comparisons of extraction performance remain challenging because of substantial differences in feedstock characteristics, solvent systems, operating conditions, extraction-yield

definitions, and analytical methods across the included studies. The reported frequencies therefore indicate the prevalence of method use rather than the relative effectiveness of each extraction technology.

The reported biological activities were also quantitatively synthesised using the standardised categories presented in Table 3.1. Wound-healing or regenerative outcomes were reported in 23 studies (69.7%), followed by anti-inflammatory activity in 21 studies (63.6%). Antimicrobial and antioxidant activities were each reported in 20 studies (60.6%). These categories were not mutually exclusive because most studies evaluated more than one biological activity. The distribution indicates that the evidence primarily focuses on wound-regenerative, anti-inflammatory, antimicrobial, and antioxidant outcomes rather than clinical measures of treatment effectiveness.

Figure 3.2 provides a conceptual synthesis of the research pathway identified across the included studies, beginning with the selection of natural waste- or plant-derived bioactive sources and progressing through extraction, chemical composition, formulation, and reported wound-

healing-related activities. Conventional and intensified extraction techniques were used to recover phenolic compounds, flavonoids, terpenoids, and other bioactive constituents. These extracts or bioactive materials were subsequently incorporated into hydrogels, gels, films, nanofibrous dressings, and related delivery systems associated with antioxidant, antimicrobial, anti-inflammatory, and wound-regenerative activities. The framework

highlights that the potential performance of a wound-care formulation depends on interconnected factors, including source characteristics, extraction conditions, recovered chemical composition, and formulation design. However, not every included study investigated all stages of this pathway, and the framework should therefore be interpreted as an integrated conceptual synthesis rather than a causal mechanism validated within a single study.



Figure 3.2. Conceptual framework illustrating the pathway from natural waste- or plant-derived bioactive sources through extraction and formulation to reported wound-healing-related biological activities. Created with BioRender.com.

3.4. The Formulation Strategies, Their Advantages and Challenges

Table 3.2 summarises the representative formulation strategies identified among the included studies. The formulations comprised topical gels, chitosan-based hydrogels, polysaccharide-based hydrogels, polyherbal gels, and composite delivery systems containing natural products or plant-derived extracts. Chitosan and plant-derived polysaccharides

were frequently employed as formulation matrices because of their biocompatibility, gel-forming properties, and suitability for incorporating bioactive constituents. However, the formulations differed substantially in polymer composition, extract concentration, preparation method, physicochemical characterisation, and biological assessment, limiting direct comparisons of their performance.

Table 3.2. Representative formulation strategies reported among the included studies.

Bioactive source or material	Formulation strategy	Reported purpose or biological activity	Reference
<i>Ipomoea pes-caprae</i> phenolic-rich leaf extract	Topical gel	Anti-inflammatory, wound-healing and antiophidic activities	(Xavier-Santos et al., 2022)
Asiaticoside-rich <i>Centella asiatica</i> extract	Chitosan-based hydrogel	Controlled delivery and wound-healing activity	(Witkowska et al., 2023)
<i>Mauritia flexuosa</i> oil	Chicha gum–chitosan gel	Potential wound-healing activity	(Ferreira et al., 2022)
Carboxymethyl tamarind kernel gum and ciprofloxacin	Hydrogel containing synthetic polymers	Antimicrobial drug delivery	(Yadav et al., 2024)
<i>Plumbago zeylanica</i> , <i>Datura stramonium</i> and <i>Argemone mexicana</i> extracts	Polyherbal gel	Antimicrobial, anti-inflammatory and wound-healing activities	(Dev et al., 2019)
Honey, propolis and bee venom	Chitosan-based hydrogel	Antimicrobial, anti-inflammatory and wound-healing activities	(Abdelsattar et al., 2022)

Note: The reported purposes and biological activities are based on the outcomes described in the individual studies and should not be interpreted as evidence of comparative clinical effectiveness. The table presents representative formulation-focused studies from the final dataset.

Among the six formulation-focused studies summarised in Table 3.2, five employed gel- or hydrogel-based delivery systems, while one investigated a hydrogel-based antimicrobial drug-delivery system. This distribution indicates that gel-forming polymeric matrices predominated among the selected formulation studies. Nevertheless, the limited number of studies and substantial differences in polymer composition, bioactive concentration, preparation method, and outcome assessment prevent conclusions regarding the superiority of any formulation type.

The therapeutic activities reported for the reviewed formulations were associated with

several structurally diverse plant-derived constituents. Phenolic compounds and flavonoids were frequently reported, while more specifically identified constituents included asiaticoside from *Centella asiatica*, ellagic acid and punicalagin from pomegranate, and curcumin from turmeric. Figure 3.3 presents the representative chemical structures of these selected constituents, which belong to different chemical classes and therefore possess distinct physicochemical characteristics that may influence their extraction, formulation, stability, and biological performance.

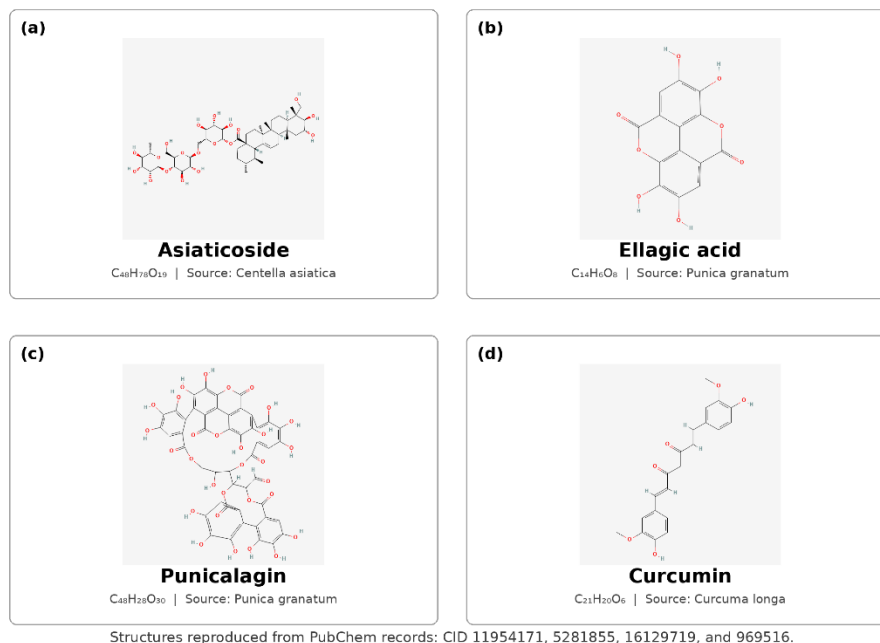


Figure 3.3. Representative chemical structures of selected bioactive constituents reported among the included studies: (a) asiaticoside, (b) ellagic acid, (c) punicalagin, and (d) curcumin. Chemical structures were reproduced from PubChem records (CID 11954171, 5281855, 16129719, and 969516, respectively).

As illustrated in Figure 3.3, the selected constituents differ considerably in molecular size and structural complexity. Asiaticoside is a relatively large triterpenoid glycoside containing multiple sugar moieties, whereas ellagic acid is a smaller polyphenolic compound. Punicalagin is a structurally complex hydrolysable tannin with numerous hydroxyl groups, while curcumin possesses a comparatively flexible diarylheptanoid structure. These structural differences may affect compound polarity, solvent compatibility, extraction behaviour, formulation requirements, and susceptibility to degradation. Nevertheless, the reviewed studies did not evaluate these compounds under standardised extraction, concentration, formulation, and biological-assay conditions. Consequently, Figure 3.3 should be interpreted as an illustration of the chemical diversity within the evidence base rather than as a direct comparison of biological potency or wound-healing effectiveness.

3.5. Reported Efficacy, Stability, and Safety of Natural Waste-Derived Wound-Healing Products

Across the included studies, natural waste- and plant-derived extracts demonstrated multiple wound-healing-related biological activities. Pomegranate-derived extracts were associated with antimicrobial and wound-regenerative activities (Costa et al., 2020), while turmeric-derived curcuminoids demonstrated antioxidant, antimicrobial, anti-inflammatory, and wound-healing-related effects (Abbas et al., 2019). Duku leaf extract was also associated with antioxidant, anti-inflammatory, and wound-regenerative activities (Febriani et al., 2024). These findings suggest that natural bioactive extracts may act through several complementary mechanisms, including the reduction of oxidative stress, modulation of inflammation, inhibition of microbial growth, and support of tissue regeneration.

Nevertheless, the available evidence does not establish that natural waste-derived formulations are equivalent or superior to established synthetic wound-care products. Most of the reported outcomes were obtained from in vitro or preclinical in vivo investigations, and direct comparisons were limited by differences in formulation composition, extract concentration, experimental model, treatment duration, and outcome assessment. Therefore, the findings

should be interpreted as evidence of therapeutic potential rather than confirmation of comparative clinical effectiveness.

The principal mechanisms through which the reported bioactive constituents may contribute to wound healing are conceptually summarised in Figure 3.4. The framework links the antioxidant, antimicrobial, and anti-inflammatory activities identified across the included studies with their potential cellular and tissue-level effects.

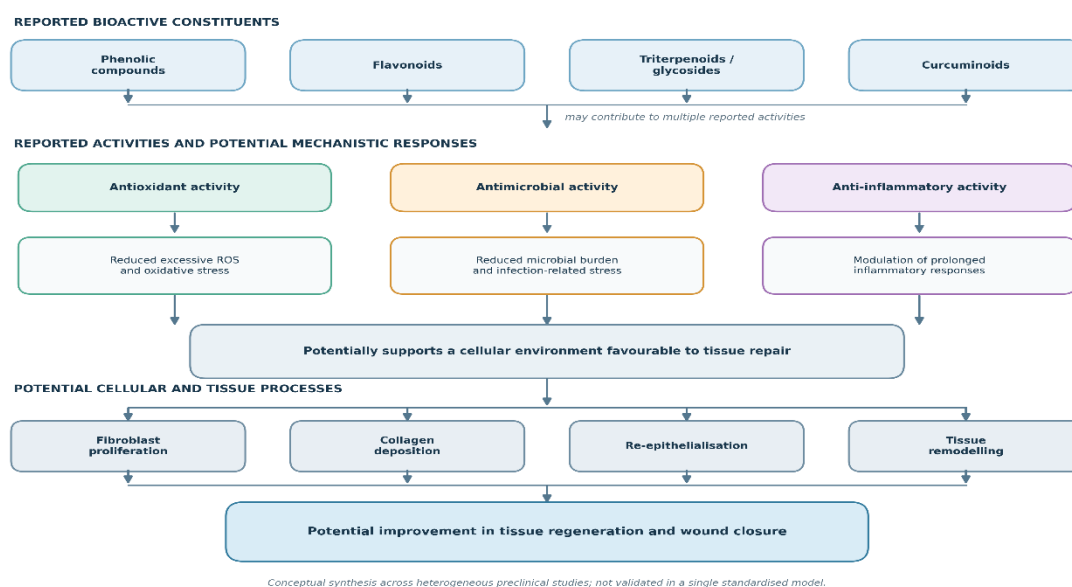


Figure 3.4. Conceptual mechanistic pathway linking the reported bioactive constituents and biological activities to potential cellular and tissue processes involved in wound healing. The pathway represents a synthesis across heterogeneous preclinical studies and was not validated using a single standardised experimental model.

As illustrated in Figure 3.4, the wound-healing potential of the reported bioactive constituents may involve several complementary pathways. Antioxidant activity may reduce excessive reactive oxygen species and oxidative stress, while antimicrobial activity may decrease microbial burden and infection-related stress. Anti-inflammatory activity may help modulate prolonged inflammatory responses. Collectively, these effects may create conditions that support fibroblast proliferation, collagen deposition, re-epithelialisation, and tissue remodelling, potentially improving tissue regeneration and wound closure. However, the pathway represents a conceptual synthesis of

findings obtained from different studies rather than a mechanism validated within a single experimental model. It should therefore be interpreted cautiously because the included studies differed in bioactive sources, extraction methods, formulations, concentrations, biological models, and outcome measures.

Stability represents an important limitation in the development of natural waste- and plant-derived wound-healing products. Bioactive constituents may undergo oxidation, hydrolysis, thermal degradation, or loss of biological activity during processing and storage, while differences in extract composition and formulation conditions may further affect

product reproducibility. Formulations containing aqueous extracts or natural polymers may also be susceptible to microbial contamination if appropriate preservation and packaging systems are not employed. However, storage stability, shelf life, microbial quality, and the retention of bioactivity over time were not consistently evaluated across the included studies (Gościński et al., 2025; Sharifi & Bahrami, 2024). Future investigations should therefore incorporate standardised stability testing under defined temperature, humidity, light, and storage-duration conditions. Strategies such as encapsulation, freeze-drying, antioxidant protection, appropriate preservation systems, and moisture- or oxygen-barrier packaging may be investigated, but their effectiveness and compatibility with the final formulation must be experimentally validated.

Safety evidence was similarly limited across the included studies. Natural origin should not be interpreted as evidence that an extract or formulation is inherently safe, because biological responses may vary according to chemical composition, bioactive concentration, impurities, residual solvents, formulation components, and duration of exposure agents (Rezvani Ghomi et al., 2019; Yousefian et al., 2023). Although some included studies reported cytocompatibility or preclinical biological activity, information concerning irritation, sensitisation, systemic toxicity, repeated exposure, and long-term safety was not consistently available (Ferreira et al., 2022; Witkowska et al., 2023). Standardised dose-response, cytotoxicity, irritation, sensitisation, and biocompatibility assessments are therefore required before these formulations can progress towards clinical evaluation.

The incorporation of natural bioactive constituents into polymeric delivery systems may offer a means of combining biological activity with improved handling, protection, and controlled release at the wound site (Razani et

al., 2024). Nevertheless, hybrid natural-synthetic formulations should be evaluated as complete products because interactions between the extract, polymer matrix, preservatives, and other formulation components may influence stability, safety, release behaviour, and biological performance (Sharifi & Bahrami, 2024). Direct comparisons with established wound-care products under standardised experimental conditions are required before claims of equivalent or superior efficacy, stability, or safety can be supported.

3.6. Technological Advances and Sustainability of Extraction Processes

Recent advances in the recovery of bioactive compounds from natural waste- and plant-derived materials have increasingly focused on intensified extraction technologies. Among the included studies, ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), pressurised or accelerated solvent extraction (PLE/ASE), and supercritical fluid extraction (SFE) were investigated as alternatives or complements to conventional extraction methods. These techniques offer potential advantages, including shorter extraction times, improved mass transfer, reduced solvent consumption, and greater control over operating conditions. However, their performance varied according to the feedstock, solvent system, temperature, pressure, extraction time, liquid-to-solid ratio, and analytical response employed. Consequently, the available evidence does not establish that any single intensified extraction technique is universally superior. Representative operating conditions and study-specific outcomes reported for selected intensified extraction techniques are summarised in Table 3.3. The table illustrates the variation in process parameters and analytical responses among the included studies rather than providing a direct performance comparison between extraction methods.

Table 3.3. Representative operating conditions and reported outcomes of intensified extraction methods among the included studies.

Extraction method	Bioactive source	Reported operating conditions	Principal reported outcome	Reference
Ultrasound-assisted extraction (UAE)	<i>Citrus reticulata</i> (kinnow) peel	Amplitude: 31%; liquid-to-solid ratio: 30:1 mL/g; temperature: 41 °C; extraction time: 15 min	TPC: 36.17 mg GAE/g extract; DPPH radical-scavenging activity: 64.70%	(Kaur et al., 2023)
Microwave-assisted extraction (MAE)	<i>Commiphora gileadensis</i> leaf	Microwave power: 300 W; solvent-to-sample ratio: 10 mL/g	Recovery and characterisation of phenolic constituents; the reported outcome was method-specific and was not directly comparable with the UAE or PLE studies	(Bin Mokaizh et al., 2024)
Pressurised liquid extraction (PLE)	<i>Moringa oleifera</i> leaves	Liquid-to-solid ratio: 70 mL/g; pressure: 1700 psi; temperature: 150 °C; extraction time: 15 min	TPC: 24.28 mg GAE/g dry weight; TFC: 17.20 mg RtE/g dry weight	(Chatzimitakos et al., 2024)

Note: The values are reproduced as reported in the individual studies. They should not be compared directly because the studies differed in plant material, solvent system, extraction scale, analytical method, and response definition. TPC, total phenolic content; TFC, total flavonoid content; GAE, gallic acid equivalents; RtE, rutin equivalents; DPPH, 2,2-diphenyl-1-picrylhydrazyl.

Table 3.3 presents representative operating conditions and outcomes for selected intensified extraction techniques among the included studies. UAE achieved phenolic recovery from kinnow peel under moderate temperature and a relatively short extraction period, while PLE employed elevated temperature and pressure to recover phenolic and flavonoid compounds from *Moringa oleifera* leaves. MAE was also applied to the recovery and characterisation of phenolic constituents from *Commiphora gileadensis* leaves. Although these findings demonstrate the potential of intensified extraction technologies, the reported outcomes cannot be used to rank the methods directly. Differences in feedstock composition, solvent system, operating scale, extraction conditions, yield definition, and analytical response prevent a reliable determination of whether UAE, MAE, or PLE provides superior extraction performance.

Beyond the recovery of bioactive compounds, the valorisation of fruit peels and other plant-derived residues may contribute to waste reduction and circular-resource

utilisation. Converting these materials into potentially useful extracts and wound-care formulations could reduce the disposal of bioactive-rich residues while generating products with possible biomedical value. This approach is conceptually aligned with Sustainable Development Goal 12, particularly the reduction of waste through prevention, recycling, and reuse, and may also support Sustainable Development Goal 3 through the development of wound-care materials with potential health applications (Sorooshian, 2024). Nevertheless, the environmental advantages of these extraction processes should not be assumed solely from their classification as green or intensified technologies. Their sustainability depends on solvent toxicity, energy consumption, extraction yield, equipment requirements, waste generation, process scalability, and the overall life cycle of the resulting formulation. Future studies should therefore incorporate quantitative environmental and techno-economic assessments before definitive sustainability claims are made.

3.7. Limitations and Future Directions

Despite the promising biological activities reported across the included studies, several limitations currently restrict the translation of natural waste- and plant-derived wound-healing products into clinical practice. The evidence base remains predominantly preclinical, and the studies differed substantially in bioactive source, extraction method, formulation composition, treatment concentration, experimental model, and outcome assessment. Variability in plant origin, harvesting conditions, post-harvest processing, and extraction parameters may also affect the chemical composition and biological activity of the resulting extracts. In addition, the limited reporting of sample-size justification, independent replication, randomisation, blinding, and other procedures used to minimise experimental bias reduces confidence in direct comparisons among studies. Standardised extraction, compound-characterisation, formulation, and biological-testing protocols are therefore required to improve reproducibility and facilitate the validation of promising wound-care products.

Stability represents another important limitation in the development of natural waste- and plant-derived wound-healing products. Bioactive constituents may undergo oxidation, hydrolysis, thermal degradation, or loss of biological activity during processing and storage. Formulations containing aqueous extracts or natural polymers may also be susceptible to microbial contamination if appropriate preservation and packaging systems are not employed. However, storage stability, shelf life, microbial quality, and the retention of bioactivity over time were not consistently evaluated across the included studies. Future investigations should therefore incorporate standardised stability testing under defined temperature, humidity, light, and storage-duration conditions. Strategies such as encapsulation, freeze-drying, antioxidant

protection, appropriate preservatives, and moisture- or oxygen-barrier packaging may be investigated, but their effectiveness and compatibility with the final wound-care formulation must be experimentally validated.

The principal limitations identified across the included studies and the corresponding priorities for future research are summarised in Table 3.4. These limitations encompass extraction standardisation, variability in bioactive composition, formulation characterisation, stability and safety assessment, methodological reporting, clinical translation, scalability, and environmental sustainability. The table links these recurring evidence gaps with appropriate assessment strategies rather than attributing every limitation to each study. As summarised in Table 3.4, the future development of natural waste- and plant-derived wound-healing products requires improvement across the entire research pathway, from raw-material control and extraction standardisation to formulation characterisation, stability testing, safety assessment, and clinical validation. These limitations are interconnected. Variability in feedstock and extraction conditions may alter bioactive composition, which subsequently affects formulation behaviour, biological activity, reproducibility, and shelf life. Similarly, promising *in vitro* activity alone does not establish product safety or clinical effectiveness. Future studies should therefore adopt integrated development strategies that combine chemical standardisation, robust experimental design, formulation-performance testing, and staged translational evaluation.

Future research should adopt a staged translational pathway rather than focusing solely on improvements in extraction yield or short-term biological activity. Initial studies should establish raw-material specifications, validated chemical markers, reproducible extraction procedures, and complete formulation characterisation.

Table 3.4. Current limitations and recommended future directions for natural waste- and plant-derived wound-healing products.

Current limitation	Evidence pattern identified in the included studies	Recommended future direction	Suggested assessment or approach
Heterogeneous extraction conditions	Studies differed in feedstock preparation, solvent system, liquid-to-solid ratio, temperature, pressure, power, and extraction time	Develop standardised and reproducible extraction protocols for specific bioactive sources	Design of experiments, response-surface methodology, extraction mass balance, and reporting of complete operating parameters
Variability in extract composition	Bioactive composition may vary according to plant origin, processing conditions, extraction method, and analytical procedure	Establish chemical specifications and marker compounds for each extract	Validated HPLC, LC–MS, GC–MS, or spectroscopic fingerprinting and batch-to-batch comparison
Incomplete formulation characterisation	Formulation composition, extract concentration, mechanical properties, and release behaviour were not consistently reported	Standardise formulation preparation and physicochemical characterisation	Rheology, swelling, porosity, mechanical strength, moisture transmission, degradation, and controlled-release testing
Limited stability and shelf-life evidence	Storage stability, microbial quality, and retention of bioactivity over time were infrequently or inconsistently evaluated	Conduct stability testing under defined storage and packaging conditions	Accelerated and real-time stability studies, microbial-limit testing, bioactivity-retention analysis, and packaging evaluation
Limited methodological reporting and risk-of-bias control	Replication, sample-size justification, randomisation, blinding, and other bias-minimisation procedures were not consistently reported	Adopt study-design-specific reporting and quality-assessment procedures	Appropriate in vitro and animal-study reporting guidelines, preregistered protocols, randomisation, blinding, and justified sample sizes
Predominantly preclinical evidence	Most studies employed in vitro or animal models, with no full clinical trials identified	Progress from standardised preclinical testing to carefully designed clinical investigations	Cytotoxicity, irritation, sensitisation, dose–response, validated animal models, and phased clinical evaluation
Uncertain scalability and sustainability	Laboratory-scale extraction and formulation processes were rarely supported by scale-up, energy, cost, or life-cycle data	Evaluate technical, economic, and environmental feasibility before commercial translation	Pilot-scale processing, solvent-recovery assessment, energy analysis, techno-economic assessment, and life-cycle assessment

Note: The limitations represent patterns identified across the 33 included studies rather than deficiencies attributed to every individual study.

Promising formulations should subsequently undergo standardised stability, cytotoxicity, irritation, sensitisation, and dose–response testing before evaluation in validated in vivo models. Only formulations supported by reproducible efficacy and safety evidence should progress to clinical investigation. In parallel, pilot-scale production, solvent recovery, energy demand, manufacturing cost, and life-cycle impacts should be assessed to determine whether the proposed products are technically, economically, and environmentally feasible.

4. Conclusion

This systematic review synthesised evidence from 33 original research studies on extraction technologies and formulation strategies for natural waste- and plant-derived wound-healing products. The evidence base was dominated by preclinical studies, comprising 19 in vitro studies, seven in vivo studies, and seven studies whose experimental designs could not be classified confidently from the reported information. Conventional extraction methods remained widely represented, while intensified techniques, particularly ultrasound-assisted extraction, microwave-assisted extraction, pressurised or accelerated solvent extraction, and supercritical fluid extraction, demonstrated potential for recovering bioactive compounds under method-specific operating conditions. The recovered extracts were incorporated into gels, hydrogels, films, nanofibrous dressings, and other delivery systems associated with antioxidant, antimicrobial, anti-inflammatory, and wound-regenerative activities.

Nevertheless, the available evidence does not establish that these extraction techniques or natural-product-based formulations are superior to conventional extraction processes or established wound-care products. Direct comparisons were limited by substantial heterogeneity in feedstock characteristics, extraction conditions, analytical procedures, formulation composition, bioactive concentration, experimental models, and outcome measures. Methodological reporting

was also incomplete, particularly regarding independent replication, sample-size justification, randomisation, blinding, stability, safety, and procedures used to minimise experimental bias. Consequently, the reported findings should be interpreted as evidence of preclinical potential rather than confirmation of clinical effectiveness.

Future research should prioritise standardised raw-material specifications, validated extraction and analytical procedures, complete formulation characterisation, and reproducible biological-testing protocols. Promising formulations should undergo systematic stability, safety, dose–response, and validated in vivo evaluation before progressing to clinical investigation. Pilot-scale processing, techno-economic assessment, solvent recovery, energy consumption, and life-cycle impacts should also be evaluated to determine whether these technologies are practically and environmentally sustainable. Addressing these limitations is essential for translating natural waste- and plant-derived bioactive materials into reliable, safe, and clinically relevant wound-care products.

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