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Review

Plant-Derived Bioactive Hydrogels for Cutaneous Applications: Extract Standardization, Formulation Design, and Biological Evidence

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Abstract

Plant-derived hydrogels are promising topical delivery systems and wound dressings, but their performance depends on both the botanical preparation and the polymer matrix. This narrative review examines cutaneous formulations containing *Aloe vera*, *Matricaria chamomilla*, *Centella asiatica*, *Vitis vinifera* skin extracts, and curcumin associated with *Curcuma longa*, focusing on ingredient characterization, formulation design, release, and biological evidence. The reviewed studies show that hydrogel composition influences swelling, mechanical properties, and bioactive release. Biological findings include antioxidant and antimicrobial activity, cellular responses, and wound-healing-related outcomes in animal models. However, comparisons are limited by inconsistent extract characterization, incomplete dose reporting, heterogeneous biological models, and variable controls. Asiaticoside release does not represent the behavior of the entire *Centella* extract, while the contribution of chamomile cannot be isolated in formulations containing silver sulfadiazine. Similarly, the benefits of hydrogel incorporation over simpler formulations remain insufficiently established, and human evidence for the specific systems is limited. Future studies should prioritize reproducible extract characterization, accurate measurement of active content, appropriate component controls, and dose-matched comparisons linking release to biological outcomes. These steps are essential to determine the added value of hydrogel delivery and support clinical evaluation.

Keywords: hydrogels; botanical extracts; cutaneous delivery; wound healing; extract standardization; *Aloe vera*; *Matricaria chamomilla*; *Centella asiatica*; *Vitis vinifera*; curcumin

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Academic Editor: Jiantao Zhang

Received: 14 October 2026
Revised: 3 November 2026
Accepted: 5 November 2026
Published: 6 November 2026

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1. Introduction

Plant-containing hydrogels are being investigated as topical carriers and wound dressings because they combine a hydrated polymer matrix with constituents of potential therapeutic interest [1,2]. Their pharmaceutical value, however, depends on the finished formulation. An extract that is active in solution may behave differently after incorporation into a network, and favorable material properties do not establish a therapeutic effect [3].

The main challenge is to connect the composition of the botanical preparation with the dose delivered locally and the response measured in an appropriate biological model.

The literature considered here covers *Aloe vera* [2], *Matricaria chamomilla* [3], *Centella asiatica* [1], *Vitis vinifera* skin extracts [4], and curcumin associated with *Curcuma longa* [5].

These sources have been studied in substantially different systems: simple topical gels, chitosan carriers, reinforced dressings, gelatin–alginate networks, and patches [6] containing a nanosuspension. They also represent different types of active material. Curcumin is an isolated molecule; the other preparations contain mixtures whose composition depends on the plant material and extraction procedure. This distinction is fundamental to any comparison of loading, release, or biological activity.

Previous reviews have addressed plant-derived wound dressings and hydrogel-based delivery systems from broader or more specific perspectives. For example, some have examined herbal bioactive-loaded biopolymeric formulations or hydrogel dressings containing compounds from traditional Chinese herbs [7,8], whereas others have focused on the wound-healing evidence for a particular botanical source or on *Aloe vera*-based hydrogels [9,10]. Building on this literature, the present review offers a focused critical appraisal across five selected plant-derived or plant-associated ingredients: *Aloe vera*, *Matricaria chamomilla*, *Centella asiatica*, *Vitis vinifera* skin extracts, and curcumin. Its specific contribution is to examine these systems through a common pharmaceutical perspective, connecting botanical identity and extract characterization with active loading, hydrogel composition, release behavior, biological models, and comparator selection. Particular attention is given to whether the available experimental designs allow biological effects to be attributed to the botanical ingredient, the hydrogel matrix, or additional formulation components. This integrated approach is intended to identify shared methodological limitations and research priorities rather than simply catalogue wound-dressing materials or summarize the reported activities of individual plants.

For the purposes of this review, the core evidence concerns formulations in which a botanical preparation or a plant-associated phytochemical is incorporated into a hydrogel matrix. Systems such as composite patches are discussed when the hydrogel is an identifiable part of the delivery platform. Isolated curcumin is considered separately from whole-plant extracts, and non-hydrogel wound-dressing materials are included only as contextual comparators, not as direct evidence for hydrogel performance. This distinction is maintained when interpreting biological outcomes and comparing formulations.

The five materials were selected purposively to provide contrasting examples of plant-derived or plant-associated ingredients investigated in cutaneous hydrogel and related delivery systems. The selection includes complex extracts from *Aloe vera*, Matricaria chamomilla, *Centella asiatica*, and *Vitis vinifera* skin, alongside curcumin as an isolated phytochemical associated with *Curcuma longa*. Together, these examples allow discussion of different challenges in ingredient definition, chemical characterization, loading and release assessment, carrier design, and interpretation of biological outcomes. The selection also includes formulations with different levels of complexity, from extract-containing polymer networks to composite systems incorporating additional active agents or particulate carriers. These materials are not intended to represent the full diversity of plant-derived hydrogels or to provide a prevalence-based ranking of botanical ingredients. Rather, they form a focused set of examples through which to examine how the quality and scope of the available evidence depend on the ingredient, the finished formulation, and the experimental model.

The grape skin gelatin–alginate study provides an example of formulation-dependent behavior, discussed in Section 4.5. More generally, the same botanical preparation may behave differently when incorporated into networks with different compositions. Whether these changes improve wound repair requires biological evidence beyond release measurements alone [5].

The botanical source alone does not define the material incorporated into a hydrogel. Plant part, extraction procedure, processing, and chemical composition determine the preparation being tested. This is particularly important when comparing complex

extracts with isolated compounds, because their loading and release measurements are not directly equivalent.

Whole extracts, enriched fractions, and isolated compounds also require different analytical approaches. The concentration of curcumin can be expressed as the amount of a defined molecule. By contrast, a complex extract contains constituents that may partition into the network or leave it at different rates. A release curve based on one marker describes that marker; it does not describe the entire extract. Global assays provide complementary information, but their responses should not be interpreted as constituent-specific measurements.

The biological contribution of the carrier deserves equal attention. A comparison with untreated wounds establishes the performance of the complete product under the test conditions, but it does not separate the effects of the polymer and the plant preparation. An unloaded gel and, where feasible, a dose-matched free preparation are more informative comparators. In combined treatments, controls must also account for any additional drug or particulate carrier.

Evidence must be read at the level at which it was obtained. Radical-scavenging assays measure chemical antioxidant capacity; antimicrobial assays address specified organisms under defined exposure conditions. Cell migration, animal wound closure, and clinical epithelialization are different outcomes. Keeping these distinctions visible avoids turning a promising laboratory result into an unsupported claim of clinical effectiveness.

This narrative review examines how botanical characterization and hydrogel design influence the interpretation of cutaneous biological evidence. Rather than ranking the five botanical sources, it asks what the selected studies establish about each finished formulation and what remains unresolved. Particular attention is given to dose definition, release measurements, comparator selection, and the limits of translation from experimental models to human use.

Hydrogels are water-swollen polymer networks whose composition and structure influence solute transport and their suitability as biomedical carriers [11]. For cutaneous use, these material properties must be interpreted alongside the intended wound type and the functions required of a dressing, rather than treating all gel formulations as interchangeable [12].

Wound repair involves coordinated biological responses and can culminate in scar formation rather than complete tissue regeneration; consequently, wound closure alone is insufficient to demonstrate regeneration [13].

2. Literature Identification and Appraisal

The literature discussed in this critical narrative review was identified through targeted searches conducted between March and August 2026. The sources consulted included PubMed, PubMed Central, and publisher websites. The search strategy combined terms relating to the delivery system and intended application, including “hydrogel”, “wound healing”, and “skin”, with the names of the five selected botanical sources or plant-associated phytochemicals: “*Aloe vera*”, “*Matricaria chamomilla*”, “*Centella asiatica*”, “*Vitis vinifera*”, and “*curcumin*”. Searches focused on publications from the preceding 10 years (2016–2026).

Studies were considered relevant for inclusion when they addressed hydrogel-based formulations for cutaneous applications and involved at least one of the selected botanical ingredients or phytochemicals. Priority was given to reports providing information on botanical or phytochemical characterization, hydrogel composition and design, active loading, release behavior, or biological evaluation relevant to skin or wound healing. Selected clinical, mechanistic, and review publications were also considered when they provided relevant context for interpreting the formulation studies.

Publications were excluded when they did not concern cutaneous applications or wound healing, did not provide relevant evidence on hydrogel-based systems, did not involve any of the selected ingredients, or did not provide information relevant to ingredient characterization, formulation design, or biological evaluation. The selection was guided by the relevance of the available evidence to the review questions. As this is a critical narrative review rather than a systematic review, no formal systematic-screening process, PRISMA flow diagram, or quantitative study-selection counts are claimed. The resulting literature set is therefore focused and illustrative rather than exhaustive.

The five botanical sources and plant-associated phytochemicals were selected to provide a focused yet diverse basis for examining cutaneous hydrogel systems. Selection was guided by the availability of published studies investigating their incorporation into hydrogel formulations for skin or wound-related applications, together with relevant information on formulation characteristics and biological evaluation. The selection also allowed consideration of different types of active materials, including complex botanical preparations (*Aloe vera*, *Matricaria chamomilla*, *Centella asiatica*, and *Vitis vinifera* skin extracts) and an isolated phytochemical (curcumin), for which different approaches to characterization and dose definition are required. Biological evidence relevant to cutaneous applications, including antioxidant and antimicrobial assays, cell-based studies, and animal wound models, provided an additional basis for inclusion. Other potentially relevant botanical hydrogel systems were not intended to be excluded on the basis of a lack of therapeutic potential; rather, the scope was deliberately restricted to these five selected sources to allow a more focused and consistent critical appraisal of ingredient characterization, formulation design, and biological evidence.

The appraisal considers ingredient identity, polymers and crosslinking agents, additional active substances, loading, release methods, biological models, and comparison groups. Isolated curcumin is considered separately from whole *Curcuma longa* extracts. Information absent from a report remains unreported; it is not reconstructed from customary botanical uses or from a different formulation.

Non-hydrogel wound-dressing systems were considered only when they provided a relevant contextual comparison for the selected botanical ingredients or illustrated an adjacent cutaneous delivery strategy. Their inclusion was restricted to discussing specific formulation features, such as carrier architecture, material reinforcement, or biological evaluation, that could inform the interpretation of hydrogel-based systems. These materials were not treated as part of the core hydrogel evidence, and their biological findings were not used to support conclusions regarding hydrogel performance. Accordingly, the review remains focused on botanical-containing hydrogel formulations for cutaneous applications, while non-hydrogel systems serve only as clearly identified contextual comparators.

3. Botanical Ingredients and Extract Standardization

3.1. Defining the Botanical Ingredient

A reproducible botanical hydrogel requires a reproducible starting material. Terms such as “herbal extract” or “polyphenol-rich preparation” leave too much uncertainty about composition. Even a correctly identified species may yield preparations with different properties when plant parts, extraction conditions, or subsequent processing differ. The ingredient therefore needs to be described as the material incorporated into the formulation, not merely by its botanical source.

An adequate description includes the botanical name, plant part, origin, extraction solvent and conditions, and physical form of the preparation [14]. Authentication and a voucher specimen support botanical identity, while extraction yield and batch identification

help relate the laboratory procedure to the material tested. Together, these details allow another investigator to judge whether a preparation can be reproduced.

Dose reporting is a frequent source of ambiguity. A volume of liquid extract cannot be converted into dry-extract loading without its solids content, and a nominal extract percentage does not specify the amount of an individual constituent. Original units should be retained whenever the necessary conversion data are missing. Apparent numerical precision is misleading if the quantities being compared are different.

3.2. Whole Extracts, Fractions, and Isolated Phytochemicals

The selected studies illustrate different analytical requirements for complex botanical extracts, enriched fractions, and isolated compounds. These distinctions are relevant because the measured dose and release profile depend on the active material incorporated into the formulation.

For whole extracts, chemical fingerprints and selected markers provide complementary information. In the *Centella asiatica* chitosan hydrogel study [1], asiaticoside release provides a quantitative measure of one constituent, but does not establish the release profile of the other extract components. Similarly, a general measure of phenolic content cannot identify the individual compounds contributing to the measured response.

Enriched fractions require sufficient compositional information to define what has been concentrated. Without such information, differences between formulations may reflect differences in the starting material rather than the hydrogel matrix. The selected studies do not provide a common basis for comparing all botanical preparations by enrichment level.

Isolated curcumin provides a more chemically defined example [4]. Its nominal loading can be expressed as the amount of a specific compound, but the amount incorporated into the nanosuspension should be distinguished from the actual curcumin content and release from the finished hydrogel patch.

These examples show that analytical claims should match the material measured: a marker assay describes the selected marker, a global assay describes the response measured by that assay, and compound-specific analysis describes the identified compound. None should be interpreted as a complete description of a complex extract without supporting compositional evidence.

3.3. Chemical Markers and the Interpretation of Release

The choice of marker depends on the analytical purpose. A constituent suitable for identity testing may not account for the biological response, while a constituent of biological interest may be unsuitable for routine quality control if its measurement is insufficiently robust [14,15].

The *Centella asiatica* chitosan hydrogel study illustrates this distinction: asiaticoside release provides a compound-specific measure of delivery, whereas total phenolic content offers a broader but non-specific assay response [1]. These measurements are complementary and should not be treated as interchangeable.

Marker-specific release quantifies the amount of a selected constituent released from the hydrogel and supports conclusions about that compound under the tested conditions. By contrast, total phenolic content (TPC) provides a global assay response, usually expressed relative to a reference standard, and does not identify or quantify the individual phenolic compounds contributing to that response. Other global measurements, such as radical-scavenging assays, indicate the functional response detected under the assay conditions rather than the release of specific molecules. Consequently, changes in TPC or antioxidant activity cannot, on their own, establish the release profile, compositional integrity, or chemical stability of a complex botanical extract. Such conclusions require complementary

compound-specific analyses and, where relevant, chemical fingerprinting before and after formulation or release testing.

Similarly, retained radical-scavenging activity after formulation indicates chemical antioxidant capacity under the assay conditions, but does not by itself establish the stability of individual extract constituents or antioxidant efficacy in living tissue. Release and functional measurements are therefore most informative when their analytical scope is clearly defined and their relationship to biological outcomes is assessed separately.

3.4. Extract–Hydrogel Compatibility

Extract–polymer compatibility concerns both sides of the formulation. Incorporation may alter the network, while mixing, crosslinking, or storage may alter the botanical preparation. A useful compatibility study examines these changes in the finished dosage form rather than inferring them from the starting ingredients.

Relevant changes include pH, swelling, mechanics, flow, and release. Their importance depends on use: a spreadable gel must be applied and retained satisfactorily, whereas a preformed dressing also needs sufficient integrity for handling and removal. No single combination of hydrogel properties is optimal for all cutaneous applications.

The selected studies illustrate different formulation-specific approaches, but they do not support a universal ranking of polymer systems. In the grape skin gelatin–alginate formulations, varying gelatin content and calcium chloride concentration was associated with changes in swelling, stiffness, and extract release [5]. This provides direct evidence that network composition and ionic crosslinking affected the measured properties within that particular system. The *Centella asiatica* formulation combined chitosan and extract, with rheological assessment considered alongside delivery measurements [1]. By contrast, the chamomile formulation combined an alginate/gelatin matrix, genipin and calcium chloride crosslinking, silver sulfadiazine, and reinforcing polyacrylonitrile fibres [3], while the curcumin hydrogel patch used a genipin-crosslinked chitosan/PVP network containing a curcumin nanosuspension [4]. These composite designs illustrate the range of polymer and processing strategies, but their complexity does not allow the independent contribution of each component to be established without suitable component-specific controls.

More generally, polymer composition and crosslinking can influence network density, swelling, mechanical integrity, rheological behavior, and the diffusion of incorporated substances. However, the direction and magnitude of these effects depend on the polymer system, crosslinking chemistry, extract composition, and processing conditions. pH is also relevant to polymer behavior and the chemical properties of botanical constituents, but its influence should be demonstrated for the formulation under study rather than assumed. Processing variables, including the order of ingredient addition, temperature, crosslinking time, and washing or drying steps, may further affect the final material. These are general formulation considerations, not effects established uniformly across the selected studies. Accordingly, comparisons should rely on measurements from the finished, extract-loaded formulations and, where possible, matched unloaded controls, with pH, solvent content, and other excipients appropriately controlled.

3.5. Assessing Standardization in the Finished Formulation

Standardization involves the starting plant material, the chemical composition of the preparation, and its behavior after incorporation. The following three levels organize this appraisal:

- Botanical definition: Whether the source material and extraction procedure are sufficiently described.

- Chemical definition: Whether the incorporated preparation is characterized by suitable analytical measurements.
- Formulation definition: Whether loading, retention, stability, and release are assessed in the final hydrogel.

This three-level framework is an analytical structure developed by the authors for the purposes of this review, rather than a formal standardization guideline or a newly proposed regulatory standard. It draws on established principles of botanical identity verification, phytochemical characterization, and pharmaceutical formulation assessment, but organizes them into a common appraisal structure for the selected studies. Each study is examined using the same three domains: (1) botanical definition, including species, plant part, source, and extraction procedure; (2) chemical definition, including fingerprints, quantified markers, and analytical methods, where reported; and (3) formulation definition, including loading, retention, compatibility, stability, and release in the finished hydrogel. The framework is applied according to the information available in each publication; missing data are recorded as limitations and are not inferred. For isolated curcumin, the botanical domain identifies its plant association, while chemical and formulation assessment focuses on the isolated compound and its delivery system rather than on a whole-plant extract.

Good characterization of an extract cannot compensate for an undefined finished product, just as reproducible rheology cannot compensate for an undefined ingredient. The scientific value lies in the connection between the two: the characterized material must be the material loaded, released, and tested biologically. The assessment domains and information required for this appraisal are summarized in Table 1.

Table 1. Information required to assess botanical ingredients in cutaneous hydrogels (source: authors' own analytical framework).

Assessment Domain	Information to Extract from Each Study	Purpose in the Review
Botanical identity	Species, plant part, authentication and source	Establish the identity of the starting material
Extraction	Solvent, extraction conditions, yield and extract form	Define the preparation incorporated
Chemical characterisation	Fingerprint, quantified markers and analytical methods	Assess compositional definition
Loading	Dry-extract or compound concentration, units and basis of calculation	Compare doses without conflating unlike measurements
Processing retention	Measurements before and after manufacture	Distinguish nominal loading from retained content
Formulation compatibility	pH, homogeneity, swelling, rheology and mechanical properties	Identify changes associated with incorporation
Release	Analytes, medium, sampling conditions and analytical method	Determine what the release measurements represent
Stability	Storage conditions, duration and chemical or functional endpoints	Assess preservation of the finished formulation
Biological comparison	Unloaded hydrogel, free ingredient and other relevant controls	Examine the contribution of the carrier and ingredient

The three-level framework is applied throughout the following sections to distinguish the identity of the botanical material, its chemical definition, and the characteristics of the finished formulation. For each selected system, the discussion considers what is established at each level and identifies missing information where the available reports do not provide sufficient characterization. This approach also distinguishes evidence concerning the starting extract from evidence concerning the formulated product and its biological performance.

The present section establishes the criteria for defining and characterizing the botanical starting material. The following section applies these criteria to the selected formulation studies, focusing on the composition of each delivery system and its formulation-specific properties. Broader design principles governing hydrogel performance and local delivery are considered separately in Section 5, whereas Section 6 evaluates the biological outcomes and the extent to which the available controls support attribution of these outcomes to the botanical ingredient, the carrier, or their combination.

4. Formulation Studies of the Selected Botanical Sources

4.1. Centella Asiatica: Connecting Extract Characterisation with Delivery Performance

The *Centella asiatica* study links extraction optimization with chitosan hydrogel development and marker-based release analysis [1]. Its design-of-experiments approach connects the characterization of the asiaticoside-rich extract with the performance of the resulting formulation. However, asiaticoside release describes the behavior of this selected marker and does not establish the release profile of the extract as a whole.

These findings highlight the importance of evaluating the combined contribution of the botanical extract and the chitosan carrier [1].

Additional studies provide broader context for *Centella asiatica*, including comparisons of aqueous-extract ointment, cream, and gel formulations in open wounds in rats, as well as reviews of hydrogel delivery systems and clinical evidence [7–9,16]. However, these studies involve different formulations and outcome measures and should not be interpreted as direct evidence of the efficacy of the specific hydrogel discussed here.

4.2. Aloe Vera: Distinguishing the Botanical Preparation from the Finished Hydrogel

In *Aloe vera* research, the word "gel" can refer to the botanical material or to a manufactured topical dosage form. These uses should be separated. A polymer formulation containing Aloe material is not defined adequately by the name "Aloe gel".

The selected experimental studies used substantially different preparations. One study investigated an *Aloe vera* hydrogel formulated with propanediol and triethanolamine in female Wistar rats [2], whereas another evaluated chitosan–*Aloe vera* gels, including formulations loaded with zinc oxide nanoparticles, in a rat wound-healing model [17]. Their excipients and polymer matrices differ, so their outcomes cannot be attributed to a common formulation. Representative histological findings from the Aloe vera hydrogel study are shown in Figure 1.

Interpretation of the botanical contribution depends on the characterization of the Aloe preparation and the use of suitable controls. In chitosan-based systems, comparisons with an unloaded carrier are particularly relevant because the polymer may also contribute to the observed biological response.

A dedicated review of *Aloe vera*-based hydrogels describes multiple synthesis approaches and discusses diffusion, swelling, and degradation as contributors to release [10]. A more recent Aloe polysaccharide–collagen system containing *Aloe vera* expands the range of carrier chemistries explored for this ingredient [18]. Such diversity strengthens the rationale for reporting the polymer network and botanical preparation separately.

Ingredient-level evidence also includes an isolated *Aloe vera* glycoprotein fraction investigated through cell-based and wound-healing assays [19]. Because this is a fraction rather than a whole botanical preparation, its biological findings cannot be assigned automatically to an uncharacterized *Aloe* gel or to a finished polymer hydrogel.

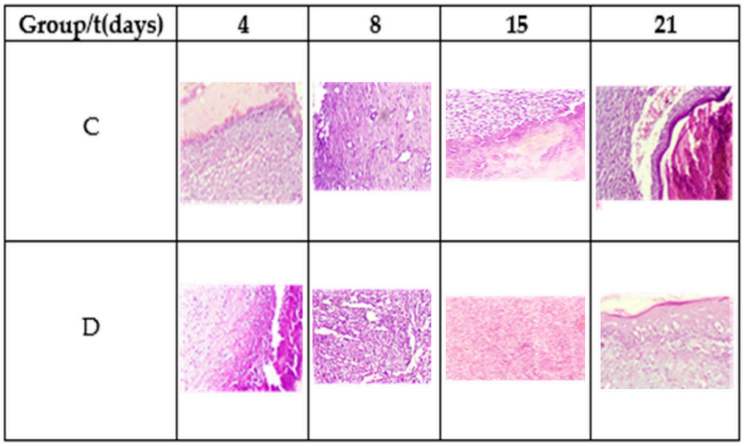


Figure 1. Tissue morphology during healing in the *Aloe vera* hydrogel study, assessed using hematoxylin and eosin staining (20×) [2]. Reproduced from Meza-Valle et al. under the CC BY 4.0 license.

4.3. Matricaria Chamomilla: Interpreting Multicomponent Formulations

The chamomile composite described in the review combines *Matricaria chamomilla* extract with silver sulfadiazine in an alginate/gelatin hydrogel reinforced with polyacrylonitrile fibers. Genipin and calcium chloride contribute to its crosslinking strategy [3,20].

Because the formulation contains both chamomile extract and silver sulfadiazine, its biological performance should be interpreted at the level of the complete dressing. Unless the underlying study includes suitable component-specific comparisons, the contribution of chamomile cannot be separated from those of the drug and carrier [3].

Chamomile evidence extends beyond the selected composite hydrogel. Valmy et al. discuss an earlier small double-blind clinical study involving 14 patients that assessed epithelialization and drying of wounds after tattoo dermabrasion [21]. This is contextual clinical evidence for chamomile extract, rather than confirmation of the current hydrogel formulation. Melnyk et al. summarize a comparative in vitro and animal study that examined *Chamomilla recutita* against corticosteroid treatments [22]; its experimental ulcer model should not be treated as direct evidence for a cutaneous hydrogel.

Electrospun chamomile-containing polycaprolactone/polystyrene mats [23] and multilayer carboxyethyl-chitosan/poly(vinyl alcohol)–polycaprolactone patches [24] illustrate adjacent wound-dressing strategies. These nanofibrous materials are included as formulation comparators, not classified as hydrogels. Their release and biological observations support discussion of carrier-dependent performance but cannot substitute for hydrogel-specific validation.

4.4. Curcumin: An Isolated Phytochemical Within a Composite Delivery System

Curcumin offers a chemically defined counterpart to the complex extracts. Its dose and release can be assigned to an isolated molecule, but that advantage should not be extended to claims about a whole *Curcuma longa* extract. The botanical origin and the pharmaceutical ingredient are different levels of description.

The 2024 hydrogel patch study combined a curcumin nanosuspension with genipin-crosslinked chitosan/polyvinylpyrrolidone and evaluated the product in an excisional wound model [4]. Both particle formulation and the surrounding network may influence local delivery.

Interpretation of this formulation depends on distinguishing the nanosuspension fraction added during preparation from the actual curcumin content of the finished patch. Active-content measurement, recovery after manufacture, and the analytical basis of release are therefore important for dose comparison. In addition, without suitable component-

specific controls, the contribution of the nanosuspension cannot be separated fully from that of the hydrogel network [4].

Curcumin has also been incorporated into poloxamer-based thermosensitive hydrogels [24], micelle-containing thermosensitive systems [25], and biodegradable dextran hydrogels containing curcumin nanomicelles [26,27]. These systems illustrate alternative strategies for delivering isolated curcumin, but differences in carrier composition, loading, and release conditions limit direct comparisons with the selected patch formulation.

Other studies investigated curcumin in chitosan–PVA films through in vitro and computational assays [28], in guar gum hydrogels incorporating curcumin-stabilized silver nanoparticles, with in vitro scratch assays performed on the nanoparticles and wound-healing-related gene-expression analyses conducted in treated rat wounds [29], and in PVA hydrogels with antibacterial tests and rat wound-healing experiments [30]. The differences in evidence level are substantial: molecular docking, cell responses, and animal wound closure answer different questions and should not be combined into a single clinical-efficacy claim.

4.5. Vitis Vinifera-Derived Preparations: Linking Network Composition with Measured Functionality

The grape skin gelatin–alginate study combines material characterization with release and functional testing [5]. Changing gelatin and calcium chloride concentrations affected swelling and stiffness; antioxidant, antimicrobial, and cytocompatibility measurements extended the assessment beyond mechanics. This makes the study useful for examining how network design and extract performance are related.

The measurements still answer separate questions. Mechanics describe the carrier, antioxidant assays describe chemical activity, and antimicrobial tests describe responses of the organisms tested. None of these laboratory endpoints, alone or in combination, demonstrate clinical wound healing.

The release profile provides additional information on the extract's availability from the hydrogel under the tested conditions. Figure 2 presents the experimental release behavior; its interpretation should account for the sampling period and the intended application. The selected botanical and phytochemical formulations discussed in this section are summarized in Table 2.

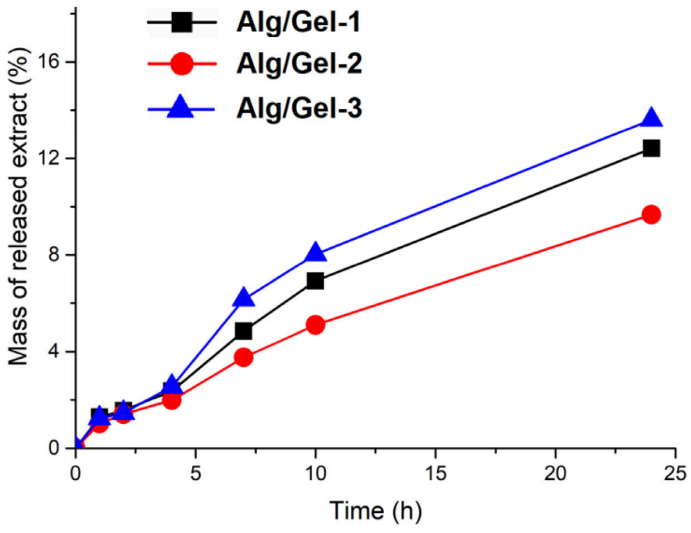


Figure 2. Release of grape skin extract from the investigated gelatin–alginate formulations [5]. Reproduced from Bradić et al. [5], under the CC BY 4.0 license.

Table 2. Selected botanical and phytochemical formulations. Source: authors' synthesis of references [1–5,16]. The chamomile formulation is described through the secondary review [3].

Source	Ingredient Investigated	Hydrogel Example	Key Interpretative Consideration
Centella asiatica	Asiaticoside-rich extract	Chitosan-based hydrogel	The contribution of the extract should be distinguished from that of the carrier.
Aloe vera	Botanical preparation	Topical hydrogel; chitosan-containing hydrogel	The incorporated botanical preparation requires adequate characterization to support comparisons.
Matricaria chamomilla	Extract combined with silver sulfadiazine	Composite alginate/gelatin system	The contribution of chamomile cannot be isolated from that of silver sulfadiazine and the other formulation components.
Curcuma longa	Isolated phytochemical	Nanosuspension-containing chitosan/PVP patch	The respective contributions of the curcumin nanosuspension and hydrogel matrix require appropriate controls.
Vitis vinifera	Complex extract	Gelatin–alginate hydrogel	Changes in network composition should be interpreted in relation to measured release and biological activity.

5. Hydrogel Design and Local Delivery

Whereas Section 4 describes the selected formulations individually, this section considers the broader design principles that influence hydrogel performance and local delivery. The discussion focuses on relationships between matrix composition, crosslinking, swelling, mechanical properties, ingredient retention, and release. Individual botanical systems are referred to only when they illustrate a specific formulation principle; their biological outcomes are evaluated separately in Section 6.

5.1. Defining the Intended Cutaneous Application

A spreadable gel for intact skin, an open-wound dressing, and a repair scaffold face different pharmaceutical requirements [31]. Tissue condition, contact time, and application method should therefore guide formulation selection before individual material properties are optimized [11].

Skin penetration, surface retention, and release into a wound environment should also be distinguished. Disrupted skin presents a different delivery situation from an intact barrier, and a result obtained in one setting cannot automatically support an application in the other.

The chitosan/Centella study used a Skin PAMPA assay, which measures the apparent permeability of active compounds across a lipid-impregnated artificial membrane designed to mimic selected aspects of the skin barrier [1]. This model can provide comparative information on membrane permeability under controlled in vitro conditions, but it does not reproduce the full structure of human or animal skin. Its results should therefore be distinguished from permeation studies using excised skin, which provide ex vivo evidence, and from measurements of active-compound concentrations in skin tissue, which are needed to demonstrate local deposition or retention. In the absence of these additional data, the Skin PAMPA findings indicate potential permeability across a model membrane but do not establish enhanced skin penetration, tissue retention, or local drug concentrations. Further ex vivo and, where appropriate, in vivo studies are required to validate these aspects of cutaneous delivery.

5.2. Polymer Selection and the Contribution of the Carrier

Polymer selection must serve the dosage form. The carrier needs to accommodate the botanical preparation, permit reproducible application, and maintain suitable contact with tissue. Its properties should be assessed after loading, because the extract may change a network that behaved satisfactorily when empty.

A blank gel is an informative comparator because it helps distinguish changes associated with the active ingredient from the behavior of the carrier [32].

Several polymers, an extract, an antimicrobial drug, and particles create several possible explanations for an observed effect. More elaborate formulations need controls suited to those explanations. Otherwise, added complexity increases uncertainty about which component contributes to the response.

Comparator formulations should allow the proposed advantage to be tested directly. Improvement over an untreated group may justify further work, but it does not establish that a complex carrier outperforms a simpler formulation at a comparable active dose.

5.3. Network Composition and Experimentally Demonstrated Effects

Network behavior must be measured in the finished material. Swelling, mechanical tests, rheology, and release each describe a different aspect of performance [6]. Their interpretation is stronger when the measurements refer to the same formulation and relevant conditions of hydration.

These relationships should be established experimentally for each formulation, because the effects of polymer composition and crosslinking depend on the specific network and processing conditions. The grape skin gelatin–alginate study provides a formulation-specific example, discussed in Section 4.5 [5]. In this system, changes in gelatin content and calcium chloride concentration were associated with differences in swelling, stiffness, and extract release. These measurements should therefore be interpreted together: swelling and network stiffness characterize the hydrated matrix, while the release profile indicates the availability of extract constituents under the tested conditions. However, the reported association does not by itself establish that a particular mechanical property caused a specific biological outcome.

Processing deserves the same attention as composition. Ingredient-addition order, temperature, crosslinking, washing, and drying or rehydration may distinguish formulations with otherwise similar ingredient lists. Reporting these conditions helps explain discrepancies between studies and supports reproducibility.

Spectroscopic or structural observations may support a proposed extract–polymer interaction. The consequences for delivery remain a separate question, requiring release or biological measurements rather than an inference from interaction alone.

5.4. Rheology, Handling, and Contact with the Application Site

Handling requirements differ between spreadable gels and preformed dressings. The former must spread acceptably and remain at the intended site; the latter must also withstand placement and removal without losing integrity. Rheological or mechanical measurements are useful only when related to those practical functions. The highest viscosity, stiffness, or swelling value is not inherently the best result. A property that favors one function may hinder another. Formulation selection should therefore explain the required balance rather than identify an optimum from a single measurement.

The *Centella*/chitosan investigation considered rheology together with delivery measurements [1]. This is a useful formulation approach because application behavior and active availability are examined together. Practical performance during repeated human use still requires separate evaluation.

Comparing loaded and unloaded gels shows whether extract incorporation alters flow or handling. Concentration-series experiments can then examine the extent of the change, provided other components remain comparable.

5.5. Loading, Retention, and Release as Separate Measurements

Nominal loading describes the amount added during manufacture. A delivery claim becomes clearer when each is reported explicitly, rather than using "loading" to describe all three.

Nominal loading describes what entered manufacture. Recovery measurements establish what remains after processing, and release tests establish what is detected outside the gel under specified conditions. None directly measures the concentration reaching a biological target.

For complex extracts, release also depends on what is measured. A marker profile should be named as such; a global assay should retain its analytical limitations. These approaches may complement one another but do not produce equivalent descriptions of extract release.

Medium composition, sampling, analytical method, and observation time all affect release comparisons. When these conditions differ, a qualitative comparison is often more defensible than a numerical ranking. A fitted model summarizes the data; assigning a physical mechanism requires supporting evidence beyond the fit.

5.6. Composite Systems Containing Particles and Phytochemicals

Particle-containing hydrogels introduce two stages of formulation: preparation of the particulate carrier and its incorporation into the polymer network. Both stages can influence the dose available outside the gel.

The curcumin nanosuspension patch is an example of this arrangement [4]. Its wound-model findings concern the complete chitosan/polyvinylpyrrolidone composite. They cannot by themselves determine whether nanosuspension preparation, gel incorporation, or their combination accounts for the observed performance.

Appropriate component controls can help resolve this issue. Without them, interpretation should remain at the level of the tested product, avoiding claims of a specific delivery mechanism that the design did not isolate.

The final active concentration is the relevant basis for dose comparison. The amount of nanosuspension mixed into a gel is insufficient unless its curcumin content and the resulting product content are known.

5.7. Connecting Physicochemical Performance with Biological Evidence

Material characterization becomes biologically useful when it helps explain exposure or tissue response. A list of favorable physical properties is insufficient if the link to the biological experiment remains unspecified.

For example, a different release profile may be compatible with faster wound closure without establishing its cause. Chemical antioxidant activity does not demonstrate tissue modulation of oxidative stress, and mechanical integrity does not establish clinical suitability. Each proposed connection needs evidence appropriate to that question.

A convincing link requires the same formulation, comparable doses, and observation periods compatible with the proposed delivery effect. Otherwise, physical and biological results may remain parallel findings rather than a demonstrated explanation of performance. The most informative studies connect a characterized ingredient to a reproducible product and then to biological tests with relevant controls. An incomplete sequence can still provide useful findings, but the conclusion must identify which connection remains unresolved.

The questions used to connect hydrogel characterization with biological interpretation are summarized in Table 3.

Table 3. Questions linking hydrogel characterization to biological interpretation. Source: authors' own analytical framework.

Domain	Question for Assessment	Implication for Interpretation
Intended use	Was the formulation tested on intact skin, an open wound, or an artificial model?	Defines the application supported by the experiment
Carrier contribution	Was an unloaded formulation included?	Helps distinguish material effects from ingredient effects
Manufacture	Were processing conditions adequately described?	Supports reproducibility and comparison
Handling	Were rheological or mechanical properties connected to intended use?	Supports the rationale for formulation selection
Active content	Was retained content measured or only nominal loading reported?	Clarifies the dose present in the finished formulation
Release	Which constituents were measured, and under what conditions?	Defines what the release profile represents
Composite delivery	Were particle and hydrogel contributions investigated separately?	Limits attribution to individual delivery elements
Biological linkage	Was the same formulation assessed across characterization and biological tests?	Strengthens the connection between design and outcome

6. Biological Evidence Across the Selected Formulations

This section synthesizes the biological evidence reported for the selected systems rather than repeating their formulation details. The emphasis is on the type and relevance of each biological endpoint, the suitability of the experimental model, the comparators used, and the extent to which the reported effects can be attributed to the botanical ingredient, the hydrogel matrix, or additional formulation components. Findings from chemical assays, cell-based experiments, animal wound models, and clinical investigations are interpreted as distinct levels of evidence. To avoid repeating formulation details and general design considerations discussed in Sections 4 and 5, this section focuses on the biological outcomes and their interpretation.

Wound contraction, re-epithelialization, tissue repair, and tissue regeneration describe related but distinct aspects of the wound-healing process. Wound contraction refers to the reduction in wound size through the movement of surrounding tissues. Re-epithelialization refers to the restoration of the epidermal surface through epithelial cell migration and proliferation. Tissue repair encompasses the processes that restore tissue continuity, which may involve granulation tissue formation, extracellular matrix deposition, and scar formation. Tissue regeneration implies restoration of the original tissue architecture and function and therefore requires evidence beyond macroscopic wound closure, such as appropriate histological, structural, or functional findings. Accordingly, wound-area reduction alone is not considered evidence of complete tissue regeneration in this review.

6.1. Aloe Vera: Wound Closure and Tissue-Level Observations

Meza-Valle and colleagues reported complete wound closure after 15 days with the tested *Aloe vera* hydrogel in female Wistar rats. The study also reported tissue observations concerning inflammation, angiogenesis, and wound contraction [2]. These findings describe separate macroscopic and tissue-level outcomes; wound closure should not, by itself, be interpreted as evidence of complete tissue regeneration.

The study's microscopy also concerned dried hydrogel specimens [2]. That state should be distinguished from the hydrated material at the application site. Structural images can characterize the specimen examined, but they do not directly measure the network during wound contact [32].

Human evidence for *Aloe vera* is limited and specific to the preparations and procedures investigated. Sánchez et al. summarize a randomized, double-blind study involving 12 patients and 24 skin-graft donor sites, in which *Aloe vera* gel was compared with placebo. Complete epithelialization occurred sooner in the *Aloe vera* group, whereas pain scores did not differ significantly between groups [33]. Vogler and Ernst describe an earlier split-face study in patients undergoing dermabrasion, in which stabilized *Aloe vera* in a polyethylene oxide gel dressing was evaluated against the study comparator [34]. The summary cited here does not provide sufficient information to report the sample size or all outcome estimates for that study. These clinical observations apply to the specific preparations, comparators, and procedures investigated; they do not establish the efficacy or safety of the experimental *Aloe vera* hydrogels reviewed here. Differences in formulation composition, concentration, application conditions, and patient population limit extrapolation without formulation-specific clinical evaluation.

6.2. Matricaria Chamomilla: Botanical Activity Within a Combined Treatment

The chamomile dressing includes silver sulfadiazine and reinforcing fibres in addition to the extract and alginate/gelatin matrix [3,20]. Its biological findings therefore concern a combined intervention.

Separating extract-associated effects from drug-associated effects would require corresponding component formulations and the unloaded matrix. These comparisons matter particularly for antimicrobial outcomes, where more than one ingredient may plausibly contribute.

The formulation is consequently treated here as a botanical–drug combination. Positive results may support its development, but they cannot establish the performance of a chamomile-only hydrogel.

6.3. Grape Skin Extracts: Distinguishing Functional Assays from Animal Evidence

The initial grape skin formulation study assessed material properties, release, antioxidant and antimicrobial activity, and cytocompatibility [5]. These endpoints describe laboratory performance of the formulations tested.

A separate investigation examined grape skin extract hydrogels in diabetic wound repair and reported tissue findings related to collagen synthesis and matrix deposition [34]. This adds preclinical biological evidence, but it should be distinguished from the functional assays in the formulation study.

The phrase "antioxidant hydrogel" can conceal this distinction. Radical-scavenging capacity, tissue biochemical responses, and wound repair are different observations. Consistency among them may strengthen a rationale, yet none proves the others.

The two publications should be connected only to the extent that their extracts, loading, processing, and final products are comparable. Shared botanical and polymer names do not establish formulation equivalence.

6.4. Curcumin: Evaluating a Defined Phytochemical in a Composite Carrier

The excisional-wound study reported over 80% wound recovery by day 7 with the curcumin nanosuspension-loaded hydrogel patch, comparable to the commercial hydrocolloid comparator [4]. This finding represents preclinical evidence for the complete tested

formulation. These findings concern isolated curcumin and should not be extrapolated to whole *Curcuma longa* extracts.

6.5. Cross-Study Interpretation

Cross-study comparison identifies differences in the type and strength of evidence rather than establishing a ranking of botanical efficacy. The selected studies address distinct questions and use different experimental models, formulations, and outcome measures. The *Centella asiatica* study links asiaticoside release from a chitosan hydrogel with fibroblast-related observations, providing a connection between formulation characterization and a cellular endpoint; however, marker release does not establish the exposure or behavior of the complete extract [1]. A separate rabbit wound study compared a *Centella*-containing hydrogel with a blank carrier, a reference cream, and untreated wounds [33]. Although these comparators support interpretation within the animal model, the findings do not establish effectiveness in human chronic wounds.

These endpoints should be interpreted as distinct categories of evidence rather than as successive levels in a single hierarchy of therapeutic effectiveness. Antioxidant assays assess chemical radical-scavenging or reducing capacity, whereas antimicrobial assays measure activity against specified microorganisms under defined experimental conditions. Cell migration assays examine cellular responses associated with wound repair, while cytocompatibility tests primarily assess whether a formulation adversely affects cell viability under the tested conditions. Animal wound-closure studies provide integrated preclinical evidence in a living organism, but their outcomes remain dependent on the model and experimental design. Clinical outcomes, in turn, address responses in human patients and cannot be inferred from laboratory or animal findings alone. Accordingly, positive results in one endpoint should not be taken as evidence of success in another.

The *Aloe vera* study reports wound closure and tissue-level findings in an animal model, but these outcomes apply to the tested preparation and do not establish that the hydrogel is superior to a dose-matched free preparation or other carriers [2].

The chamomile-containing composite presents a different interpretative challenge because silver sulfadiazine and the reinforced polymer matrix are part of the same dressing. Without suitable component-specific comparisons, the contribution of chamomile cannot be isolated [3]. In the grape skin studies, formulation-level measurements—including swelling, release, antioxidant and antimicrobial assays, and cytocompatibility—address different properties from tissue-level outcomes reported in a separate diabetic wound model [5,35]. These publications therefore provide complementary rather than directly interchangeable evidence.

Taken together, the main limitation is not simply that the studies use different methods, but that the available evidence does not consistently connect ingredient composition and delivered dose to formulation performance and biological outcomes within comparable experimental designs. Dose-matched comparisons with the free preparation and unloaded carrier, together with controls that isolate additional active ingredients or delivery components, would help determine whether the hydrogel itself provides a measurable advantage. The available studies support further investigation, but do not permit a reliable ranking of the five botanical or phytochemical systems or broad conclusions about their clinical effectiveness.

Quantitative results provide useful context for interpreting individual formulations. For example, the *Centella asiatica* H12 hydrogel achieved 73.4% and 99.0% scratch closure after 24 and 48 h, respectively, in a fibroblast model, whereas the curcumin nanosuspension-loaded hydrogel showed over 80% wound recovery by day 7 in a rat excisional-wound model [1,4]. The *Aloe vera* formulation achieved complete wound closure by day 15 in its an-

imal model [2]. These values describe different endpoints and experimental conditions and should not be interpreted as a direct comparison of efficacy. For the grape skin formulations, the reported 24 h release profile characterizes delivery behavior rather than wound-healing efficacy [5]. Quantitative findings are therefore interpreted within the model, formulation, and observation period in which they were obtained.

Applying the assessment dimensions in Table 1 across the selected studies reveals several recurring limitations, although not every limitation applies equally to every formulation. The most consequential cross-study challenge is the incomplete connection between the identity and chemical characterization of the starting material, the amount incorporated into the finished formulation, and the biological response observed. Botanical preparations are not consistently characterized to the same level, and nominal loading does not always establish the amount of a defined constituent retained in or released from the final product. Release data also differ in the analyte measured and the experimental conditions, limiting direct comparison between studies. A further recurring challenge is comparator selection: where an unloaded carrier, a dose-matched free ingredient, or suitable component-specific controls are absent, the independent contribution of the botanical ingredient or hydrogel matrix cannot be established confidently. By contrast, formulation properties and biological endpoints are reported in some studies but are not measured uniformly across the selected systems. Stability during storage and the relationship between chemical retention and biological activity also remain insufficiently documented where these assessments were not reported. Overall, the principal evidence gap is not a single missing test, but the lack of a consistently reported chain linking botanical identity, chemical definition, formulation performance, and biological outcome. These gaps should be interpreted study by study, rather than assumed to be present to the same extent in every formulation.

The cellular findings reported for the *Centella asiatica* formulation illustrate the importance of comparing the extract, the polymer, and the complete hydrogel, as shown in Figure 3 [1].

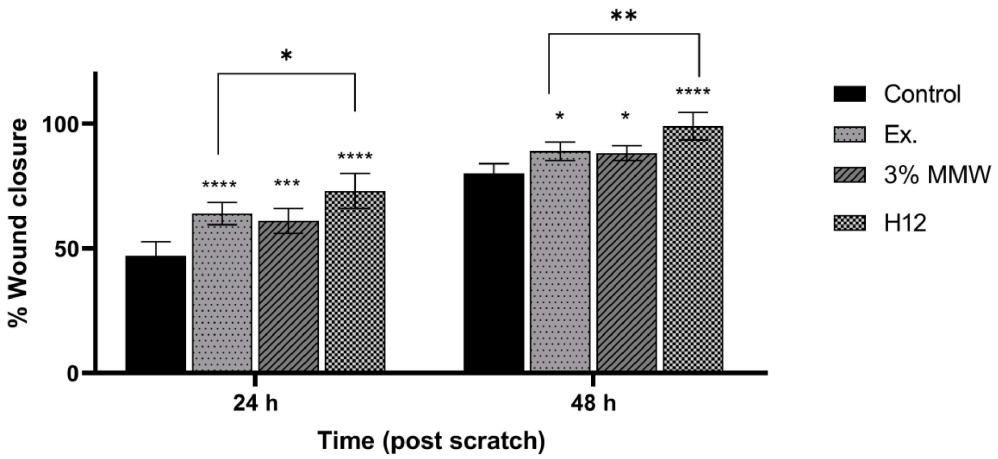


Figure 3. Post-scratch wound closure in human skin fibroblasts (Hs27) after 24 and 48 h of exposure to *Centella asiatica* extract (Ex.), 3% medium-molecular-weight chitosan (3% MMW), or H12 hydrogel [1]. Reproduced from Figure 9 of Witkowska et al. [1], under the CC BY 4.0 license. Statistical significance was designated as follows: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.001$ (vs. control or vs. Ex. at the respective time points), as reported in the original study.

The three-level framework also helps explain why the strength of evidence differs across the selected systems. Botanical definition determines which preparation was investigated; chemical definition establishes what is known about its composition or measured markers; and formulation definition identifies the product through which the ingredient

was delivered. These levels are related but not interchangeable. A well-characterized marker does not establish the composition of an entire extract, and evidence of favorable biological activity does not by itself demonstrate that the finished hydrogel provides an advantage over an appropriate comparator. The studies are therefore interpreted according to the information available at each level, with gaps in characterization treated as limitations rather than filled by inference.

Four questions are particularly useful when reading these studies:

1. Was the botanical ingredient adequately characterized?
2. Was the finished formulation characterized at the dose used biologically?
3. Did the controls distinguish ingredient effects from carrier effects?
4. Did the conclusion remain within the experimental model and measured endpoints?

A relatively simple formulation that answers these questions can offer a clearer development pathway than a complex system with unresolved component effects. Added delivery elements should be justified by evidence of their contribution.

The main interpretative limitations identified across the selected studies are summarized in Table 4. The table links each botanical or phytochemical system to the evidence that requires particular scrutiny, highlighting the need to distinguish ingredient-related effects from those of the carrier or additional active components and to assess whether the available biological findings support the conclusions drawn.

Table 4. Comparative evidence and main interpretative limitations. Source: authors' synthesis of References [1–5,34]. Interpretative limitations were formulated by the authors.

Plant Source	Example of Identified System	Evidence to Assess	Main Limitation to Examine
Aloe vera	Topical hydrogel	Animal model, wound closure, histology	Relative contributions of the plant preparation and the formulation
Matricaria chamomilla	Composite hydrogel containing silver sulfadiazine	Evaluation of the combined system	Distinguishing the effect of the extract from that of the drug
Vitis vinifera—grape skin	Gelatin–alginate hydrogel containing extract	Characterization, functional tests, and separate animal studies	Comparability of formulations across publications
Curcumin, associated with *Curcuma longa*	Nanosuspension incorporated into a hydrogel	Excisional wound model	Relative contributions of the nanosuspension and the hydrogel
Centella asiatica	Hydrogel containing an asiaticoside-rich extract	Release studies and biological evaluations	Relative contributions of the extract and chitosan

To facilitate comparison across the selected botanical and phytochemical formulations, Table 5 summarizes the investigated ingredients, hydrogel matrices, loading characteristics, biological models, comparators, and principal findings. The comparison also highlights differences in experimental design and evidence level that limit direct ranking of the formulations. Where quantitative formulation details or component-specific controls were not available, these limitations are explicitly identified.

Table 5. Comparative overview of selected plant-derived hydrogel formulations and their biological evidence. Source: authors' synthesis of references [1–5,20,35,36].

Evaluation Dimension	Botanical/Phytochemical System				
	Centella asiatica	***Aloe vera***	***Matricaria chamomilla***	**Curcumin Associated with *Curcuma longa***	***Vitis vinifera***
Extract characterization and standardization	Optimized water/alcohol extract; lyophilized extract characterized by its asiaticoside-rich profile.	Commercial *Aloe vera* hydrogel; the independent contribution of the botanical ingredient cannot be isolated from the complete formulation.	Chamomile (*Matricaria chamomilla* L.) extract; detailed chemical characterization and quantitative extract loading were not specified in the information available for this review.	Isolated curcumin formulated as a nanosuspension; this is a defined phytochemical system rather than a whole *Curcuma longa* extract.	Grape skin extract obtained from Cabernet Sauvignon skins, a by-product of rosé wine production, using ultrasound-assisted extraction with ethyl acetate. Total phenolic content was determined using the Folin–Ciocalteu method.
Hydrogel composition and active loading	H12 chitosan hydrogel containing 3% extract and 3% medium-molecular-weight chitosan.	Commercial Restauder® *Aloe vera* hydrogel containing 1,2-propanediol and triethanolamine; the *Aloe vera* concentration and its independent contribution were not established in the study.	Alginate/gelatin hydrogel crosslinked with genipin and $CaCl_2$, containing chamomile extract and silver sulfadiazine, and reinforced with electrospun polyacrylonitrile (PAN) nanofibers. The combined formulation does not allow the independent contribution of chamomile to be established.	Genipin-crosslinked chitosan/PVP hydrogel patch, with a 70:30 chitosan:PVP ratio, 2% *w*/*w* genipin solution, and 5% *w*/*w* curcumin nanosuspension incorporated into the hydrogel.	Gelatin–alginate hydrogels prepared with 0.3 g alginate and 0.1, 0.2, or 0.3 g gelatin, crosslinked using 0.5 M or 1 M $CaCl_2$. Extract was incorporated at 8 mg/mL; lower and higher extract concentrations (4 and 8 mg/mL) were also evaluated in the biocompatibility tests.
Biological model and sample size	In vitro scratch assay using human skin fibroblasts (Hs27); culture-medium control, extract alone, 3% chitosan solution, and H12 hydrogel. Experiments performed at least in duplicate. In vivo incisional wound model in six male New Zealand White rabbits, with four treatment conditions: asiaticoside-rich PVA/PEG hydrogel, Madecassol® cream (positive control), blank hydrogel, and untreated wounds (negative control). A 1 cm incision was used, and wound healing was monitored for 12 days.	In vivo full-thickness excisional wound model in 27 female Wistar rats (2 cm diameter): untreated control group (n = 15) and Restauder® hydrogel-treated group (n = 12).	In vitro cytocompatibility and antibacterial assays; in vivo full-thickness wound model in mice. The animal sample size and comparator groups are not specified in the information available for this review.	In vitro cell-viability assay using normal human fibroblasts; in vivo excisional wound model in 18 Wistar rats allocated to three groups (n = 6 each): gauze (negative control), Nexcare® hydrocolloid dressing (positive control), and curcumin nanosuspension-loaded hydrogel patch.	Study 1: In vitro biocompatibility assays using MRC-5 human lung fibroblasts, together with antioxidant and antimicrobial assays; no animal wound model was included. Study 2: In vivo diabetic excisional wound model in male Wistar rats, with four groups (20 animals per group): untreated control, 1% silver sulfadiazine, blank hydrogel, and grape skin extract-loaded hydrogel.

Table 5. *Cont.*

Evaluation Dimension	Botanical/Phytochemical System				
	Centella asiatica	***Aloe vera***	***Matricaria chamomilla***	**Curcumin Associated with *Curcuma longa***	***Vitis vinifera***
Component controls and conclusions permitted by the study design	Study 1: The in vitro scratch assay included culture-medium control, extract alone, 3% chitosan, and the extract-loaded H12 hydrogel. These comparisons allow the effects of the extract, polymer, and their combination to be examined in the cell-based model. Study 2: The rabbit wound model included the asiaticoside-rich extract-loaded hydrogel, blank hydrogel, Madecassol® cream, and untreated wounds. This permits comparison of the loaded hydrogel with its blank carrier and reference treatment in the animal model. However, neither study establishes clinical efficacy in humans, and Study 2 did not include a free-extract treatment arm.	No unloaded-carrier, free *Aloe vera* preparation, or dose-matched free-ingredient control was reported. The study compared the Restauder® hydrogel with untreated wounds only. Therefore, the findings support an effect of the complete tested hydrogel product under the study conditions, but do not isolate the contribution of *Aloe vera* or establish an advantage of hydrogel delivery over the free ingredient.	The use of component-specific controls could not be established from the information available for this review. The reported formulation combines chamomile extract with silver sulfadiazine in an alginate/gelatin matrix, with additional crosslinking and fibre components. Accordingly, any observed biological effects should be attributed to the complete composite dressing; the independent contribution of chamomile, silver sulfadiazine, the hydrogel matrix, or the fibre cover cannot be determined from the available information.	The in vivo study included gauze as a negative control and a commercial Nexcare® hydrocolloid dressing as a positive comparator, but did not include an unloaded chitosan/PVP hydrogel or a free-curcumin/nanosuspension treatment group. Therefore, the findings support the performance of the complete curcumin nanosuspension-loaded hydrogel patch relative to the tested dressings, but do not allow the separate contributions of curcumin, the nanosuspension, and the polymer carrier to be determined.	Study 1: The available information does not clearly establish whether an unloaded hydrogel was included as a biological control, and no free-extract comparator is documented. Therefore, conclusions are limited to the tested gelatin–alginate formulations and the reported in vitro assays; the independent contribution of the extract cannot be fully separated from that of the formulation. Study 2: The diabetic wound model included untreated control, 1% silver sulfadiazine, blank hydrogel, and grape skin extract-loaded hydrogel groups. The blank-carrier comparison allows the additional effect associated with extract incorporation to be assessed in this model. However, the absence of a free-extract group does not permit assessment of whether hydrogel delivery offers an advantage over the extract administered separately.
Key quantitative findings and endpoints	H12 produced 73.4% scratch closure at 24 h and 99.0% at 48 h. The study also assessed asiaticoside release, membrane permeability, antimicrobial activity, and hyaluronidase inhibition. In the separate rabbit study, the asiaticoside-rich PVA/PEG hydrogel showed a mean epithelialization period of 5.33 ± 0.52 days, compared with 6.50 ± 0.55 days for Madecassol® cream, 8.33 ± 0.52 days for blank hydrogel, and 9.67 ± 0.82 days for untreated wounds.	Complete wound closure was reported by day 15, together with a 29% reduction in total healing time. Histological observations concerned inflammation, angiogenesis, and wound contraction. These findings apply to the complete commercial Aloe vera hydrogel tested in the rat model [2].	Elastic modulus: 2.4 ± 0.2 MPa; tensile strength: 6.2 ± 0.5 MPa; elongation at break: 21.8 ± 1%. The study also reported antibacterial activity, sustained silver sulfadiazine release, wound closure, re-epithelialization, and collagen deposition.	The optimized unloaded hydrogel showed 486% swelling. The curcumin-nanosuspension-loaded patch achieved over 80% wound recovery by day 7, comparable to the commercial hydrocolloid product. Curcumin release followed a Korsmeyer–Peppas Fickian-diffusion model.	Cell viability remained above 80% after 24 h of direct contact across the tested formulations. Extract release showed an initial rapid phase followed by sustained release over 24 h. Antioxidant capacity was assessed using DPPH, ABTS, and FRAP assays; selective antimicrobial activity was particularly observed against *E. coli*. In the separate diabetic wound study, the grape skin extract-loaded hydrogel was evaluated for its effects on wound repair and tissue regeneration in vivo. These findings complement, but are not directly interchangeable with, the in vitro formulation and release data reported in the other study.

Table 5. *Cont.*

Evaluation Dimension	Botanical/Phytochemical System				
	Centella asiatica	***Aloe vera***	***Matricaria chamomilla***	**Curcumin Associated with *Curcuma longa***	***Vitis vinifera***
Evidence gaps and limitations	The scratch assay is an in vitro endpoint and does not establish wound-healing efficacy in animals or humans. The relative contribution of the extract and chitosan should be interpreted in the context of the study's comparator design.	Animal-model findings do not establish clinical efficacy in humans. The untreated control does not isolate the contribution of Aloe from that of the complete commercial formulation.	The multicomponent dressing does not allow the effect of chamomile to be isolated unless suitable component-specific comparators were included. Animal findings do not establish clinical efficacy in humans.	The 5% *w*/*w* value refers to the incorporated nanosuspension, not necessarily to pure curcumin content in the final patch. The study does not establish clinical efficacy in humans or independently quantify the contribution of each formulation component.	The study provides physicochemical and in vitro biological evidence but does not demonstrate wound closure or healing in an animal model or in humans. Antioxidant, antimicrobial, and cytocompatibility endpoints should not be interpreted as direct evidence of wound-healing efficacy. Study 1 provides physicochemical and in vitro biological evidence, without an animal wound model. Study 2 adds evidence from a diabetic rat wound model, but does not establish clinical efficacy in humans. The comparability of the extracts and finished formulations across the two studies remains to be demonstrated.
References	[1,35]	[2]	[3,36]	[4]	[5,35]

To provide a clearer overview of the breadth and maturity of the evidence, the studies discussed in this review are further summarized according to the type of biological model and the availability of human evidence (Table 6). The overview distinguishes studies directly investigating hydrogel formulations containing the selected ingredients from clinical studies evaluating related botanical preparations in other pharmaceutical forms. This distinction is important because clinical findings obtained with a botanical preparation cannot be considered direct evidence for a hydrogel formulation containing the same ingredient.

Table 6. Overview of the biological models and human evidence discussed for the selected botanical hydrogel systems.

Botanical/Phytochemical Source	Direct Hydrogel Studies Discussed	Biological Models Used in Direct Hydrogel Studies	Human Evidence
Centella asiatica	2	In vitro scratch assay using Hs27 human skin fibroblasts; in vivo incisional wound model in six male New Zealand White rabbits, with four treatment conditions (asiaticoside-rich hydrogel, Madecassol® cream, blank hydrogel, and untreated wounds).	No human clinical evidence identified in the studies discussed in this review
Aloe vera	1	Full-thickness wound model in Wistar rats (n = 27)	Two clinical studies of related *Aloe vera* preparations are discussed: a donor-site study involving 12 patients and 24 donor sites, and a split-face dermabrasion study. These findings are indirect evidence for the specific hydrogel formulations reviewed.
Matricaria chamomilla	1	In vitro cytocompatibility and antibacterial tests; full-thickness wound model in mice	No human clinical evidence identified in the studies discussed in this review
Curcumin	1	In vitro human fibroblast cell-viability assay; rat excisional wound model (n = 18)	No human clinical evidence identified in the studies discussed in this review
Vitis vinifera (grape skin)	2 related hydrogel studies	In vitro cytocompatibility using MRC-5 human lung fibroblasts, antioxidant and antimicrobial assays; a separate preclinical diabetic wound model	No human clinical evidence identified in the studies discussed in this review

Counts refer only to the studies discussed in this critical narrative review and do not represent an exhaustive count of all publications. Human-derived cell lines are in vitro models and should not be interpreted as clinical evidence. The clinical studies summarized for Aloe vera concern related preparations and provide indirect context; they do not establish the clinical efficacy of the specific hydrogel formulations reviewed. The two *Vitis vinifera* hydrogel publications are treated as related evidence, but comparability between their formulations is not assumed.

7. Safety and Clinical Translation

7.1. Safety Should Be Assessed at the Formulation Level

Safety must be assessed for the product applied to tissue. Polymers, botanical constituents, excipients, drugs, and particulate components determine the exposure; knowledge of the source plant alone cannot define the tolerability of their combination.

The five groups considered here include quite different pharmaceutical products. An *Aloe*-containing topical gel, a chamomile–drug composite, a *Centella*/chitosan carrier, a grape skin network, and a curcumin patch should each retain their own safety evidence. Transfer between them requires a demonstrated basis for comparability.

Ingredient identity, compatibility in the biological test system, and suitability for the intended use are related questions. They require different evidence, especially when application to wounded skin or repeated exposure is proposed.

7.2. Finished-Product Stability and Reproducibility

Translation requires consistent manufacture as well as a defined botanical preparation [10]. The finished gel must retain the attributes relevant to its intended use across batches and storage conditions.

Appearance, pH, viscosity, marker content, and retained functional activity measure different aspects of stability [20]. An unchanged appearance cannot establish chemical preservation, while preserved marker content cannot by itself establish acceptable handling or microbiological quality.

Physical, chemical, and functional stability should be reported with storage conditions, duration, packaging, and the batches examined [37]. An unreported measurement is a development gap; it is not evidence that instability has occurred.

This requirement applies to isolated curcumin as well as complex extracts. A chemically defined ingredient still needs to be assessed within the product in which it will be delivered.

7.3. Preclinical Evidence and Attribution of Biological Effects

Cell-based assays provide an initial view of formulation–cell interactions. Cell type, contact method, dose, exposure duration, and endpoint determine the scope of the result.

The grape skin gelatin–alginate study included an MTT assay [5]. The resulting measurements concern cellular metabolic activity under the reported conditions. They are useful cytocompatibility data, but they do not establish tolerability during repeated skin application.

The available safety evidence differs substantially across the selected formulations. For the grape skin extract-loaded alginate–gelatin hydrogels, direct-contact testing with MRC-5 human lung fibroblasts showed cell viability above 80% after 24 h across the tested formulations. Exposure to hydrogel extracts at 25%, 50%, and 100% also did not reduce viability below 80%, although a mild concentration-dependent decline was observed for some samples at the highest concentration [5]. These findings support in vitro cytocompatibility under the reported conditions, but do not establish skin-specific tolerability or safety during repeated application.

For the other selected systems, the available evidence must be interpreted according to the specific formulation and biological model reported. Wound closure or tissue-level improvement in an animal model should not be treated as a substitute for dedicated tolerability testing. Likewise, findings for a combined dressing containing chamomile extract and silver sulfadiazine cannot establish the independent safety of either component. For the Centella-containing chitosan hydrogel and the curcumin nanosuspension–hydrogel patch, safety conclusions should be limited to the endpoints and exposure conditions explicitly evaluated in the respective studies. Where dedicated irritation, sensitization, or repeated-exposure data are not reported, this should be identified as an evidence gap rather than interpreted as evidence of safety. The direct-contact microscopy and MTT results for the grape skin extract-containing hydrogels are presented in Figure 4.

Direct contact, material extracts, and released fractions expose cells differently. These approaches should be described separately, with the botanical dose reaching the cells reported whenever it is known.

Activity is more useful when observed at a dose compatible with repair-related cells. An antimicrobial effect at an intolerable concentration would have limited pharmaceutical value. Conversely, satisfactory viability in one cell line cannot exclude irritation or sensitization.

Colored or chemically reactive preparations also require suitable controls in optical assays. This is a methodological question to check in each report; it should not be taken as proof that interference occurred.

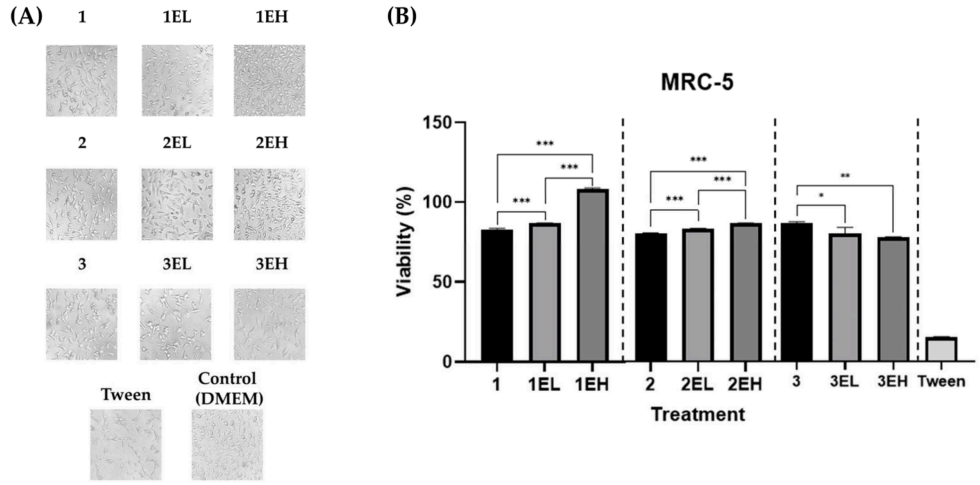


Figure 4. Direct-contact cytocompatibility assessment of grape skin extract-containing hydrogels in MRC-5 cells. (**A**) Bright-field microscopy images (20× objective) of MRC-5 cells after 24 h of direct exposure to hydrogel formulations (1, 2, and 3), grape skin extract-enriched formulations with lower (EL) and higher (EH) extract concentrations, Tween 20 (positive control), and DMEM (untreated negative control). (**B**) MTT assay results showing cell viability expressed as a percentage of the untreated control. Data are presented as mean ± SD. Statistical significance: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Reproduced from Figure 6 of Bradić et al. [5] under the CC BY 4.0 license.

The chamomile–silver sulfadiazine composite illustrates why safety attribution is difficult in combined treatments [3]. Tolerability concerns the finished combination, just as antimicrobial or repair-related effects do.

An absence of adverse findings with that combination does not establish the safety of each component in other products. If an adverse response occurs, identifying its cause likewise requires appropriate comparisons [38].

The same reasoning applies to the curcumin nanosuspension patch [4]. The phytochemical, particle preparation, and hydrogel form a single exposure system, and safety conclusions should name that system.

Additional drugs and delivery components are therefore explicit in the appraisal. Their presence affects both the interpretation of activity and the evidence needed for tolerability.

Animal experiments allow tissue responses to be examined during wound repair [39]. Their relevance depends on the species, wound model, application schedule, follow-up period, and outcomes assessed.

The *Aloe vera* rat study provides wound-closure and tissue observations for the preparation investigated [2]. It supports further development but does not establish effectiveness across human wound types or tolerability during prolonged application.

The *Centella* rabbit study is informative because it includes a blank carrier and reference treatment [36]. Those controls strengthen interpretation within the model without changing the preclinical status of the findings.

For grape skin systems, the diabetic-wound publication adds tissue-level observations to the laboratory evidence [35]. Clinical relevance still requires assessment in the intended patient population with a sufficiently comparable formulation.

Closure should therefore be read alongside tissue organization, inflammatory findings, and later observations where available. Earlier closure alone does not establish the quality or durability of repair [12].

7.4. Clinical Translation and Development

A credible development sequence links a defined ingredient to reproducible manufacture, controlled biological evaluation, and studies relevant to the intended exposure. Progression to clinical use requires evidence for the finished formulation, not merely for its botanical source.

8. Research Priorities

Further research should address common challenges that currently limit the interpretation and comparability of botanical hydrogel studies. A first priority is the reproducible characterization of the active material. Botanical preparations should be described in terms of plant identity, plant part, extraction procedure, and relevant chemical markers, while isolated phytochemicals should be distinguished clearly from whole-plant extracts. The amount of extract or active compound incorporated into the finished formulation should also be reported in a way that permits comparisons across studies. The physical, chemical, and functional stability of the finished formulation should also be assessed under defined storage conditions, including changes in marker content and, where relevant, retained biological activity.

A second priority is to establish whether hydrogel incorporation provides a measurable advantage over the free botanical preparation or a simpler carrier. Dose-matched comparisons should evaluate the effects of incorporation on release, local exposure, tolerability, and relevant biological outcomes. Measurements of marker release should, where possible, be connected to biological exposure and response rather than interpreted as evidence of therapeutic activity on their own.

Appropriate experimental controls are also essential. Studies of multicomponent systems should include comparisons that allow the contributions of the botanical ingredient, additional active agents, and unloaded carrier to be distinguished. This is particularly important when a hydrogel contains drugs, reinforcing materials, or specialized delivery components. The complexity of a formulation should be justified by evidence that each added component contributes to a relevant functional or biological advantage.

Finally, greater consistency in biological evaluation is needed to support meaningful comparisons. Studies should report the biological model, dose, exposure conditions, comparators, and outcome measures in sufficient detail. In vitro findings, animal-model outcomes, and clinical observations should be interpreted as distinct levels of evidence. Clinical studies should evaluate the specific finished formulation in the intended patient population, using appropriate comparators and outcome measures relevant to the proposed cutaneous application.

Where different studies are intended to support a common development pathway, comparability of the botanical preparation, loading, and finished formulation should be demonstrated rather than assumed.

Addressing these priorities would improve reproducibility, clarify the contribution of hydrogel delivery, and provide a stronger basis for selecting formulations for further preclinical and clinical evaluation [40,41].

9. Conclusions

The selected literature supports continued investigation of *Aloe vera*, *Matricaria chamomilla*, *Centella asiatica*, *Vitis vinifera* skin preparations, and isolated curcumin in cutaneous hydrogels. It shows a range of carrier designs and encouraging experimental observations, but the evidence is heterogeneous in ingredient definition, controls, dose reporting, and biological model.

The principal pharmaceutical issue is the relationship between the characterized ingredient and the product tested. A botanical name does not establish equivalence between preparations, and a favorable response to a multicomponent dressing does not isolate the plant's contribution. Marker-based release, global chemical assays, cell responses, and animal wound repair should each retain their own analytical and biological meaning.

Small human studies provide relevant context for some preparations, particularly *Aloe vera*, but they do not validate all hydrogel designs discussed here. The next useful step is formulation-specific evaluation with dose-matched comparators and outcomes relevant to the intended cutaneous use. This would establish whether the carrier provides a measurable benefit and give a firmer basis for clinical development.

Author Contributions: Conceptualization, A.D.R.; methodology, A.D.R. and C.E.M.; validation, A.D.R. and C.E.M.; formal analysis, A.D.R.; investigation, A.D.R.; resources, A.D.R.; data curation, A.D.R.; writing—original draft preparation, A.D.R.; writing—review and editing, A.D.R.; visualization, A.D.R. and C.E.M.; supervision, A.D.R. and C.E.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new datasets were generated or analyzed in this narrative review. The information discussed is derived from previously published studies and is presented in the main text and summary tables.

Conflicts of Interest: The authors declare no conflict of interest.

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