REVIEW

CHITOSAN AND HONEY-BASED HYDROGEL DRESSINGS FOR WOUND HEALING: A REVIEW OF THE CURRENT STATE OF KNOWLEDGE

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Abstract

Chronic wounds represent a rapidly growing challenge for global healthcare. Bacterial infections remain one of the most important factors contributing to the persistence of chronic wounds. In this context, chitosan and honey have regained prominence as promising natural supportive therapy agents. This article provides a comprehensive narrative review aimed at determining the effects of chitosan- and honey-based hydrogel dressings on the wound-healing process. The Scopus, Web of Science, and Medline (PubMed) databases were searched. The review included 19 basic and preclinical studies that met the established inclusion criteria. No clinical studies were found in this area of research. It was found that chitosan and honey, as components of hydrogel systems, exhibit combined antibacterial and wound-healing properties for the treatment of chronic wounds, including burns and ulcers. They exhibited high antibacterial activity against, among others, Staphylococcus aureus and Escherichia coli strains. Preclinical studies demonstrated favourable biocompatibility and low cytotoxicity toward skin cells.

Keywords: *chitosan, honey, hydrogel, polymer film, dressing, wound healing*

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1. Introduction

Chronic wounds represent a rapidly escalating global healthcare challenge, affecting millions of patients and placing a substantial economic burden on healthcare systems worldwide [1, 2]. Conditions such as diabetic foot ulcers, pressure ulcers, venous leg ulcers, surgical wounds, and burn injuries are particularly problematic due to delayed healing, frequent infections, and high recurrence rates [3]. This clinical burden is reflected in numerous experimental studies in which honey (HY)-based and chitosan (CS)-based hydrogel dressings have demonstrated accelerated healing in burn wound models [3, 4], full-thickness and excisional chronic wound models [5–7], and ulcer-relevant animal models characterised by delayed re-epithelialisation and persistent inflammation [8]. The increasing prevalence of diabetes, ageing populations, prolonged immobilisation, and trauma-related injuries has further intensified the global burden of chronic wounds, leading to prolonged hospitalisation, repeated medical interventions, and a reduced quality of life [9].

Acute wounds typically follow an orderly and predictable healing trajectory, progressing through haemostasis, inflammation, proliferation, and remodelling within a defined timeframe. In contrast, chronic wounds are characterised by a prolonged inflammatory phase, excessive protease activity, impaired fibroblast function, reduced angiogenesis, and dysregulated extracellular matrix deposition. Such factors prevent timely wound closure and functional tissue regeneration [1]. These pathological features create a hostile wound microenvironment that sustains microbial colonisation and further delays healing.

From a clinical perspective, chronic wounds present substantial management challenges due to their long duration, frequent need for debridement, repeated dressing changes, and high risk of infection. Diabetic foot ulcers and pressure ulcers, in particular, are associated with increased rates of hospitalisation, limb amputation, and mortality, placing an enormous financial burden on healthcare systems worldwide [2, 9]. Prolonged inpatient stays, the need for advanced wound dressings, and recurrent treatment failures further amplify the cost of chronic wound care.

Microbial infection remains one of the most critical factors contributing to the persistence of chronic wounds. Chronic wounds frequently harbour polymicrobial communities embedded within biofilms, which protect bacteria from host immune responses and significantly reduce their susceptibility to antibiotics [5, 6]. The widespread emergence of antibiotic-resistant pathogens, including methicillin-resistant *Staphylococcus aureus* and multidrug-resistant *Pseudomonas aeruginosa*, has further compromised the effectiveness of conventional antimicrobial therapies [5]. As a result, antibiotic-based approaches alone are often insufficient to eradicate infection or restore normal healing dynamics.

Antimicrobial resistance (AMR) has been identified by the World Health Organisation (WHO) as one of the leading global public health threats. Global burden analyses estimate that bacterial AMR was directly responsible for approximately 1.27 million deaths in 2019 and contributed to nearly five million additional deaths worldwide [10]. Surveillance data coordinated by the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) reveal persistently high resistance rates among clinically relevant wound-associated pathogens, particularly *S. aureus*, *Escherichia coli*, and *P. aeruginosa*, across multiple regions. The increasing ineffectiveness of first-line antibiotics in treating infected wounds underscores the urgent need for alternative, non-antibiotic antimicrobial strategies that can control infection without further accelerating resistance development.

Experimental wound infection models have demonstrated that conventional antimicrobial dressings, including silver sulfadiazine, often fail to fully eradicate the bacterial burden or restore normal healing dynamics, particularly in the presence of polymicrobial infections [5, 6]. On the contrary, HY-based and CS-HY composite dressings have shown superior antimicrobial efficacy and significantly accelerated wound closure in excision, incision, and burn wound models, even in heavily contaminated wounds [3, 5, 6].

The global crisis of AMR has further reinforced the search for therapeutic alternatives that do not rely solely on conventional antibiotics. In this context, HY has re-emerged as a promising natural therapeutic agent. HY has been used in wound care since antiquity and exhibits broad-spectrum antibacterial activity through multiple physicochemical mechanisms [1, 11]. These antimicrobial mechanisms act simultaneously, significantly reducing the likelihood of microbial resistance development.

Beyond its antimicrobial activity, HY actively modulates the wound microenvironment by reducing inflammation, stimulating angiogenesis, enhancing fibroblast proliferation, and supporting re-epithelialisation [3, 6]. These effects are supported by multiple *in vivo* studies showing that HY-containing dressings significantly accelerate wound closure and improve histological healing outcomes. For example, Rathinamoorthy and Sasikala [6] demonstrated that CS-Manuka HY dressings achieved over 94% wound contraction in rat excision models, accompanied by enhanced re-epithelialisation and collagen deposition compared with commercial dressings. Similarly, Movaffagh *et al*. [5] reported faster wound shrinkage, reduced inflammation, and superior antimicrobial efficacy in full-thickness rat wounds treated with CS-HY hydrogels.

Despite these advantages, direct application of HY to wounds presents several practical limitations, including uncontrolled flow from the wound bed, difficulty in maintaining effective concentrations, and patient discomfort [1, 8]. Owing to its high osmolarity and viscosity, HY rapidly dilutes upon contact with wound exudate and body fluids, leading to leakage from the wound site and reduced sustained antimicrobial efficacy [1, 12]. This necessitates frequent reapplication, increasing patient discomfort and the risk of wound contamination. Additionally, direct HY application offers limited mechanical protection, lacks structural integrity, and provides poor exudate management, particularly in highly exuding chronic wounds and burn injuries [3, 4]. Experimental studies have further shown that uncontrolled HY release can result in uneven distribution across the wound surface, reducing contact with deeper tissue layers and impairing sustained antimicrobial action [5, 6]. These inherent limitations have driven the development of HY-loaded hydrogel systems, in which polymeric matrices such as CS, gelatin, and polyvinyl alcohol (PVA) stabilise HY at the wound interface, enable controlled and sustained release, prevent leakage, and simultaneously provide moisture balance, mechanical support, and barrier protection [1, 7, 12].

2. The Potential of Hydrogels in Wound Treatment

Hydrogels are three-dimensional (3D), hydrophilic polymeric networks capable of absorbing and retaining substantial amounts of water or biological fluids while maintaining structural integrity. Owing to their physicochemical versatility and biological compatibility, hydrogels have emerged as one of the most promising wound dressing materials for chronic and complex wounds [1, 13]. Their structure closely resembles that of the extracellular matrix (ECM), providing both physical protection and biological support for regenerating tissue. Crucially, the advantages of hydrogel dressings are not

merely theoretical but have been consistently validated *in vitro* and *in vivo*. Studies have reported high swelling ratios, optimal water vapour transmission rates, and sustained mechanical integrity for CS-HY and composite hydrogels, confirming their suitability for managing exudative chronic wounds [7, 12, 14].

A critical requirement for effective wound healing is maintaining a moist wound environment. Hydrogels inherently fulfil this requirement due to their high-water content, which prevents wound desiccation, reduces pain, and supports cell migration and proliferation [7, 15]. Their cooling effect is particularly beneficial in burn wound management, where it alleviates pain and limits secondary tissue damage [3, 4]. Furthermore, hydrogels exhibit excellent exudate absorption capacity, enabling effective fluid management while preventing maceration of surrounding healthy tissue [8, 14].

From a biological standpoint, hydrogels are highly biocompatible and can be fabricated from natural/synthetic polymers or their composites to achieve optimal wound-dressing performance. Natural polymers, such as CS, gelatin, alginate (ALG), and hyaluronic acid (HA), confer biodegradability and intrinsic bioactivity, while synthetic polymers, such as PVA, provide mechanical stability and elasticity [7, 8]. Composite hydrogel systems combine these advantages, resulting in dressings that closely mimic the ECM while maintaining sufficient mechanical strength for clinical use [16, 17].

Experimental studies have consistently demonstrated the advantages of hydrogel-based wound dressings over conventional formulations. Wang *et al*. [4] reported that CS-HY-gelatin hydrogel sheets achieved complete re-epithelialisation of second-degree burn wounds in rabbits within 12 days while exhibiting near-complete antibacterial activity against *S. aureus* and *E. coli*. *In vivo* studies by El-Kased *et al*. [3] further confirmed that HY-based hydrogels enhanced epidermal regeneration and neovascularisation in burn wound models, outperforming standard treatments. More recent investigations have shown that the incorporation of HY into CS/PVA or CS/HA hydrogels improves swelling behaviour, biocompatibility, and wound closure rates in animal models, underscoring their suitability for chronic wound management [7, 8, 14].

Compared to conventional wound dressings such as gauze, foams, and simple polymeric films, hydrogels offer distinct advantages in maintaining a physiologically favourable wound environment. Traditional dressings often fail to maintain an adequate moisture balance, leading to either wound desiccation or excessive exudate accumulation, both of which negatively impact healing outcomes. Conversely, hydrogel dressings maintain continuous hydration while simultaneously absorbing excess wound fluid, thereby supporting optimal cellular activity and minimising tissue damage [7, 14].

The porous 3D structure of hydrogels plays a critical role in regulating wound healing processes. By facilitating oxygen diffusion and nutrient transport, hydrogels support fibroblast migration, keratinocyte proliferation, and angiogenesis, key events in effective tissue regeneration [8, 15]. In burns and highly inflamed wounds, the high water content of hydrogels provides a cooling effect that reduces pain, oedema, and secondary tissue injury, thereby improving patient comfort and compliance [3, 4].

Despite these advantages, conventional hydrogels may suffer from limitations such as insufficient mechanical strength, dehydration during prolonged application, or limited intrinsic antimicrobial activity. Consequently, recent research has focused on composite and multifunctional hydrogel systems that integrate natural and synthetic polymers to overcome these shortcomings [8, 16]. For example, incorporation of CS enhances antimicrobial activity and haemostatic properties, while polymers such as PVA and gelatin improve elasticity, tensile strength, and structural stability [7, 8, 17].

Significantly, hydrogels function not only as passive wound coverings but also as active therapeutic platforms. Their polymeric networks enable controlled loading and sustained release of bioactive agents, ensuring prolonged residence time at the wound site and consistent therapeutic action [1, 13]. In HY-loaded hydrogel systems, the hydrogel matrix mitigates the rapid dilution and leakage associated with direct HY application, allowing gradual release of antimicrobial and anti-inflammatory components while preserving moisture balance [5, 6].

Advances in hydrogel engineering have further expanded their functional capabilities. pH-responsive, multilayered, and crosslinked hydrogel architectures have been developed to dynamically adapt to wound conditions, enhance structural integrity, and optimise fluid management in complex and infected wounds [8, 16, 17]. These innovations reinforce hydrogels' role as versatile, highly effective platforms for advanced wound care, particularly when combined with bioactive components. Hydrogels also provide a non-adherent interface with the wound bed, reducing trauma and pain during dressing changes, a critical clinical advantage for patients with fragile or inflamed tissue [3, 4]. Their flexibility and conformability allow close contact with irregular wound surfaces, ensuring uniform coverage and effective barrier protection against microbial invasion [7, 17].

While hydrogels provide an optimal physical and biological platform for wound management, their therapeutic effectiveness can be significantly enhanced by incorporating bioactive components that actively modulate the wound-healing process. Among these, CS and HY have attracted considerable attention due to their complementary antimicrobial and regenerative properties [5, 8]. Rather than acting as passive dressings, CS-HY hydrogel systems interact dynamically with the wound microenvironment, influencing inflammation, microbial burden, and tissue regeneration [3, 6]. Understanding the biological activities of CS and HY and their influence on wound-healing processes is therefore essential for the rational design of advanced hydrogel dressings, as discussed in the following section.

3. Biological Role of Chitosan and Honey in Wound Healing

Chitosan and honey are natural bioactive compounds that have been widely investigated for their ability to modulate the wound-healing process. Both substances exhibit a wide range of biological activities that support wound healing, including antimicrobial, anti-inflammatory, and regenerative effects. When combined within hydrogel matrices, these natural compounds exert complementary effects in the wound microenvironment, promoting tissue regeneration while simultaneously controlling microbial colonisation [3, 6].

3.1. Properties of Chitosan

Natural polymers possess superior haemostatic, antimicrobial, biodegradable, biocompatible, and wound-healing-promoting qualities. This has led many researchers to show keen interest in using natural polymers to develop novel wound dressings that are easy to replace and possess haemostatic and antimicrobial properties [18]. Among various natural polymers, CS is the most preferred haemostatic material for the development of wound dressings. It is a polycationic natural polymer derived by total or partial *N*-deacetylation of chitin. It consists of D-glucosamine and *N*-acetyl-D-glucosamine units linked through β (1–4) glycosidic linkage. Its polyamine nature gives it pH-responsive behaviour. This means it's soluble at acidic pH levels, has a net positive charge, and can

adhere to surfaces. The cationic nature of CS is also responsible for its film-forming ability, making CS a popular, nontoxic, biodegradable biopolymer used in wound-healing applications [19]. Furthermore, CS is biocompatible with the skin, non-toxic and biodegradable, and also exhibits antibacterial and haemostatic properties, as well as the ability to absorb exudate. These make it effective for treating various wound types [20].

The antimicrobial properties of CS depend on the degree of deacetylation and its molecular weight. Low-molecular-weight CS exhibits antimicrobial activity against various microorganisms, including Gram-positive and Gram-negative bacteria and fungi, owing to its enhanced solubility and ability to interact with microbial cell surfaces [21]. The antimicrobial activity of CS is associated with several mechanisms, including electrostatic interactions between positively charged amino groups and negatively charged microbial cell membranes, which increase membrane permeability and lead to the leakage of intracellular constituents [22]. In addition, CS may interfere with nutrient transport, chelate essential metal ions required for microbial growth, inhibit biofilm formation, and interact with microbial DNA, thereby affecting transcriptional activity and cellular metabolism [22].

The haemostatic mechanism of CS differs from conventional coagulation. Several explanations have been proposed for its haemostatic properties, but the most widely accepted is electrostatic attraction between the cationic CS and anionic red blood cells (RBCs). Due to these electrostatic interactions, RBCs coagulate, and platelets bind to the wound site, stopping the bleeding. According to a study, CS interacts with plasma proteins to form a complex, thereby forming a plasma protein barrier membrane. Moreover, some researchers reported that CS facilitates wound healing by stimulating HA production at the wound site [2, 18]. Studies with CS films demonstrate their ability to stimulate tissue generation, inhibit microbial growth, reduce inflammation, and provide a moist environment that promotes wound closure [23].

3.2. Biological Activity of Honey in Wound Healing

Honey is a natural substance admired not only for its sweetness but also for its medicinal and nutritional value. It comprises sugars (80%) and moisture (20%) along with enzymes, organic acids, vitamins (B6, thiamine, niacin, riboflavin, and pantothenic acid), and minerals (calcium, copper, iron, magnesium, and potassium). It also contains bioactive components, such as carotenoids, proline, flavonoids, salicylic acid, naringin, and taxifolin, which significantly influence the nutritional value and health-promoting properties of HY [24]. It is well known for its wound-healing properties, owing to its chemical composition and physical properties. HY demonstrates antimicrobial, anti-inflammatory, and antioxidant properties due to its diversified nutritional components. Numerous studies have demonstrated the efficacy of natural HY in wound healing, including its ability to reduce scar formation, promote tissue growth, accelerate epithelialisation, and sterilise infected wounds [25, 26].

It exhibits antimicrobial properties and is effective against various pathogens, bacteria, and fungi due to several factors. Numerous bacteria, including *Escherichia coli*, *Streptococcus pyogenes*, *Salmonella* spp., and *Pseudomonas aeruginosa*, as well as several yeasts, are effectively inhibited by HY. Its acidic nature, owing to the presence of a diverse range of organic acids, coupled with high osmolarity, high viscosity, and its ability to generate hydrogen peroxide enzymatically, primarily contributes to its antimicrobial properties. Moreover, the presence of flavonoids and non-peroxide activity further supports the antimicrobial properties of HY. It mainly hinders biofilm formation, quorum-sensing mechanisms, and the expression of virulence genes essential for bacterial

resistance and infection [24]. The wide range of phytochemicals in HY provides antioxidant and anti-inflammatory properties that enable it to effectively scavenge the free radicals, thereby preventing cell damage and decreasing inflammation. HY's potential to influence inflammatory pathways is crucial in wound healing. This involves either promoting or inhibiting the production of inflammatory mediators, such as interleukin-6 (IL-6). These phytochemicals not only prevent oxidative stress in wound cells but also promote angiogenesis and the formation of new blood vessels. HY prevents the wound from drying and minimises pain and wound exudate due to its high moisture content.

Moreover, HY helps maintain a moist wound environment, which supports autolytic debridement and facilitates the removal of necrotic tissue and wound debris. Its high sugar content creates a hyperosmotic environment that promotes fluid movement from deeper tissues toward the wound surface, thereby supporting wound cleansing and helping limit microbial colonisation [25–27]. Additionally, HY modulates inflammatory processes and supports tissue regeneration through its antioxidant and anti-inflammatory properties.

4. Materials and Methods

4.1. Focused Questions

Do chitosan and honey-based hydrogel dressings have a beneficial effect on wound healing?

4.2. Eligibility Criteria

A literature review was conducted using the databases Scopus, Web of Science, and Medline (PubMed). The following MeSH subject headings were used: "chitosan", "honey", "polymer", "hydrogel", "dressing", "polymer film", "wounds", "wound healing", "chronic wound", "burn wound", "diabetic wound", "skin ulcers", and "biopolymer". Given the narrative nature of the review, the articles were selected based on the authors' opinions. The review included studies published between 2000 and February 2026. The following inclusion criteria were adopted: articles reporting original results from basic, preclinical, and clinical research on chitosan-based hydrogel systems containing honey to support wound-healing processes. Publications that contained only one component (chitosan or honey) and indicated a therapeutic purpose other than wound closure were excluded from the analysis. Letters to the editor, non-peer-reviewed studies, and popular science texts were not included.

Clinical trials were one of the inclusion criteria; however, no such trials were found, confirming that the current state of knowledge is limited exclusively to preclinical in vitro and in vivo models.

5. Review of Research on the Chitosan and Honey-based Hydrogel Dressings for Wound Healing

An important area of research at present is the design of hydrogel matrices that not only protect the wound but also stimulate tissue repair processes. The key challenge is to develop an optimal formulation that accounts for the specific characteristics of the wound, the level of exudate, and the risk of bacterial infection. The following summary (Table 1) provides an overview of the literature, focusing on the therapeutic potential of honey- and chitosan-based hydrogel systems. An analysis of the articles included in the review enables comparison of the mechanical, protective, and therapeutic properties of the developed hydrogel dressings, thereby guiding planning for future clinical trials.

Table 1. Review of studies investigating CS-HY hydrogel dressings for wound healing (2012–2026).

Hydrogel components	Study phase / model	Main findings	Interpretation / clinical relevance	[Ref] Year
chitosan: 1, 2, and 3% (w/v) solvent: acetic acid 1% (v/v) PVA: 1, 2, and 3% (w/v) gum arabic: 8% (w/v) honey: 5% (v/v) piper longum aqueous extract: 65–75% (v/v)	*in vitro* assays; male rabbits (n = not specified), wound excision model	maximum antibacterial activity observed for formulations containing 1% chitosan and 1% PVA; improved wound-healing ability and re-epithelialisation; enhanced hemocompatibility and cell proliferation	enhanced antibacterial activity and hemocompatibility may support tissue regeneration and reduce microbial colonisation during wound healing	[28] 2026
chitosan: 0.5% (w/v) solvent: acetic acid 5% (v/v) alginate: 2% (w/v) calcium chloride: 20% (w/v) blackcurrant extract: 1% (w/v) hyaluronic acid: 0.3% (w/v) honey: 5, 10, and 15% (w/v)	*in vitro* assays	high swelling ratio (22.11 ± 0.25); high water content ($95.48 \pm 0.05\%$); structural stability across pH variations; controlled WVTR (~34503850 g/m²/day)	high swelling and hydration support exudate absorption and the maintenance of a moist wound environment; controlled WVTR may help prevent wound dehydration and maceration	[16] 2025
chitosan: 1% (w/v) solvent: acetic acid 1% (v/v) PVA: 5% (w/v) citric acid: 5% (w/v) honey: 9–12% (w/v) aloe vera gel: 6–8% (w/v)	preformulation studies; *in vitro* assays	water-retention capacity: 218%; moisture content: 99%; broad-spectrum antibacterial activity against *S. aureus*, *E. coli*, and *K. pneumoniae;* low cytotoxicity (≤ 11% haemolysis)	high water-retention capacity and moisture content may improve exudate management and hydration of chronic wounds; low haemolysis suggests favourable haemocompatibility	[17] 2025

Table 1. (continued) Review of studies investigating CS-HY hydrogel dressings for wound healing (2012–2026).

Hydrogel components	Study phase / model	Main findings	Interpretation / clinical relevance	[Ref] Year
chitosan:2% (w/v) solvent: acetic acid 1% (v/v) honey: 1–6% (w/w) hyaluronic acid: 1–6% (w/v)	Sprague-Dawley rats (n = 30), wound excision model	reduced hydrogel viscosity after honey incorporation; enhanced fibroblast proliferation and adhesion; accelerated wound healing; complete wound closure on day 21	enhanced fibroblast activity may support tissue regeneration and re-epithelialisation during wound healing	[8] 2023
chitosan: 3.5% (w/v) solvent: glacial acetic acid 1% (v/v) honey: 28% (v/v) propylene glycol: 6% (v/v)	*in vitro* assays; Albino Wistar rats (n = 36), dorsal wound model	improved elasticity and adhesiveness of hydrogel; enhanced wound-healing activity *in vivo*	improved elasticity and adhesiveness may facilitate dressing adherence and conformability to wound surfaces	[9] 2022
chitosan: 0.25–2% (w/v) solvent: acetic acid 3% (v/v) PVA: 5% (w/v) honey: 1% (w/w)	preformulation studies; *in silico* analysis	significant swelling and moisture uptake; appropriate mechanical properties; in-silico interaction of honey components with wound-healing proteins	high swelling capacity may support exudate absorption, while suitable mechanical properties may improve dressing stability during application	[13] 2022
chitosan: 0.86% (w/v) solvent: 0.86% (v/v) acetic acid PVA: 5% (w/v) honey: 0.9% (w/v)	*in vitro* assays	good thermal and mechanical stability; antibacterial activity against *S. aureus* and *E. coli*	mechanical stability may improve the structural integrity and durability of wound dressings	[29] 2021

Table 1. (continued) Review of studies investigating CS-HY hydrogel dressings for wound healing (2012–2026).

Hydrogel components	Study phase / model	Main findings	Interpretation / clinical relevance	[Ref] Year
chitosan: 1.5% (w/v) solvent: 0.5% (v/v) acetic acid PVA: 10% (w/v) chitosan/PVA: 30/70 (v/v) honey: 5% (w/w) allantoin: 4% (w/v)	*in vitro* assays; male Wistar rats (n = 6), second-degree burn wound model	good mechanical strength and swelling properties; long-term biocompatibility; antibacterial activity against *E. coli* and *S. aureus;* enhanced burn wound healing	appropriate swelling behaviour may facilitate exudate absorption and the maintenance of moisture balance in burn wounds	[14] 2021
chitosan: 3% (w/v) solvent: 3% (v/v) acetic acid PVA: 10% (w/v) gelatin: 5% (w/v) chitosan/PVA/gelatin 2/1/1 (v/v) honey: 10 or 20% (v/v)	*in vitro* assays; male Wistar rats (n = 18), wound excision model	increased mechanical strength and antibacterial activity after honey incorporation; increased cell growth in MTT assay; accelerated wound healing	improved mechanical properties and cell proliferation may support tissue regeneration and dressing durability	[7] 2021
chitosan: 2% (w/v) solvent: acetic acid honey: 20% (v/v) sodium alginate: 2% (w/v) aloe vera: 2.5% (v/v)	preformulation studies; *in vitro* assays	porous structure suitable for cell adhesion and migration; favourable biocompatibility and hemocompatibility; antibacterial activity against *S. aureus* and *P. aeruginosa*	porous architecture may facilitate oxygen diffusion, nutrient transport, and cell proliferation within the wound environment	[15] 2021

Table 1. (continued) Review of studies investigating CS-HY hydrogel dressings for wound healing (2012–2026).

Hydrogel components	Study phase / model	Main findings	Interpretation / clinical relevance	[Ref] Year
chitosan: 0.25, 0.5, 0.75, and 1% (w/v) solvent: acetic acid 2.5% (v/v) gelatin: 10, 20, and 30% (w/v) honey: 10 or 20% (w/v)	preformulation studies; *in vitro* assays	high water absorption and retention capacity; inhibition of bacterial (*E. coli*) and fungal growth	water-retention capacity may support hydration and exudate management in chronic wounds	[12] 2020
chitosan: 2% (w/v) solvent: glacial acetic acid 1% (v/v) honey: 25, 50, and 75% (v/v)	*in vitro* assays; male Wistar rats (n = 105), wound excision model	antibacterial activity against *S. aureus*, *B. cereus*, *E. coli*, *P. aeruginosa*, and *C. albicans*; accelerated wound healing and tissue regeneration	broad-spectrum antimicrobial activity may help reduce wound colonisation and support tissue repair	[5] 2019
chitosan: 25% (w/v) solvent 1% (w/v) lactic acid sodium bicarbonate: 0.5% (w/v) glicerol: 13% (w/v) honey: 15% (w/v)	female Wistar rats (n = 35), excision, incision, and burn wound models	superior wound-healing performance compared with commercial dressing; complete healing in excision and incision models by day 18; complete burn wound healing by day 21	improved wound closure and re-epithelialisation suggest potential usefulness in burn and chronic wound management	[6] 2019

Table 1. (continued) Review of studies investigating CS-HY hydrogel dressings for wound healing (2012–2026).

Hydrogel components	Study phase / model	Main Ffndings	Interpretation / clinical relevance	[Ref] Year
chitosan: 2% (w/v) solvents: 1% (w/v) lactic acid glycerol: 15% (w/v) coagulant: 5 ml of a 5% sodium bicarbonate solution honey: 13% (w/v)	preformulation studies; *in vitro* assays	WVTR: 1598 g/m²/day; swelling ratio: 207%; antibacterial activity against *S. aureus* (29 mm) and *E. coli* (22 mm); folding endurance: 253 cycles; tensile strength: 46 N	appropriate WVTR and swelling ratio may support moisture balance and exudate absorption; tensile strength and folding endurance may improve dressing handling and durability	[30] 2018
chitosan: 3.5% (w/w) solvents: glacial acetic acid 1% (w/w) methyl paraben: 0.1% (w/w) honey: 75% (w/w)	*in vitro* assays; albino mice (n = 10), burn wound model	enhanced epidermal regeneration and neovascularisation; antibacterial activity against *P. aeruginosa*, *S. aureus*, *K. pneumoniae*, and *S. pyogenes;* improved burn wound healing	enhanced neovascularisation and epidermal regeneration may support tissue repair in burn wounds	[3] 2017
chitosan: 2% (w/v) glycerol: 15% (w/v) honey: 13% (w/v)	*in vitro* assays; female Wistar rats (n = 8), excision wound model	greater bacterial inhibition compared with blank chitosan film; approximately 95% wound healing after 18 days	antibacterial activity may contribute to reduced microbial burden and improved wound healing	[31] 2017

Table 1. (continued) Review of studies investigating CS-HY hydrogel dressings for wound healing (2012–2026).

Hydrogel components	Study phase / model	Main findings	Interpretation / clinical relevance	[Ref] Year
chitosan: 2% (w/v) solvent: 1% (w/v) lactic acid honey: 8% (w/v)	*in vitro* assays; Wistar rats (n = not specified), dorsal wound model	antibacterial activity against *S. aureus* and *E. coli*; approximately 94.4% wound closure after 12 days	rapid wound closure suggests a favourable regenerative potential in preclinical wound models	[32] 2015
chitosan: 2% (w/v) solvents: 1% (w/v) acetic acid and 1% (w/v) lactic acid coagulant: 5 ml of a 5% sodium bicarbonate solution honey: 6 or 10% (w/v)	preformulation studies; *in vitro* assays	water absorption: 668%; WVTR: 9984 g/m²/day; tensile strength: 38 N/mm²; elongation: 28.99%; antibacterial activity against *S aureus* and *E. coli*	water absorption and WVTR influence moisture balance and exudate management, while tensile strength and elongation affect dressing flexibility and integrity	[33] 2013
chitosan: 0.5% (w/w) solvent: glacial acetic acid 0.5% (w/w) gelatin: 20% (w/w) honey: 20% (w/w)	*in vitro* assays; Kunming mice (n = 20); New Zealand rabbits (n = 4), second-degree burn wound model	up to 100% antibacterial activity against *S. aureus* and *E. coli*; non-toxic and non-irritating to skin; complete epidermal repair by day 12	antibacterial activity and favourable biocompatibility may support application in infected burn wounds	[4] 2012

Several studies have reported favourable physicochemical properties of chitosan-honey hydrogel systems, including high swelling capacity, appropriate water vapour transmission rates (WVTR), porous microstructures, and adequate mechanical strength. These characteristics are particularly important for wound-healing applications because they support moisture balance, facilitate exudate absorption, enable oxygen exchange, and help maintain structural stability at the wound site. Appropriate WVTR values may help prevent excessive wound dehydration or maceration, while high swelling capacity contributes to efficient exudate management in chronic and highly exuding wounds.

Sasikala *et al.* [30–33] conducted a series of *in vitro* and *in vivo* studies on the development of a CS-HY hydrogel film. The optimal dressing consisted of CS (prepared from 1% lactic acid) and Manuka HY [33]. It exhibited high mechanical strength and inhibited the growth of *S. aureus* and *E. coli* bacteria (the most common wound-infecting bacteria). Studies using a rat back surgical wound model confirmed that the CS-HY film reduced the wound area by 94.4% on day 12 [32] and by 95% on day 18 [31]. During this time, 36% of the control wounds remained open, compared with 15% of those treated with standard ointment. The CS-HY film supported collagen synthesis and cell proliferation. Using gas chromatography–mass spectrometry (GC-MS), the authors [31] confirmed that the antibacterial activity of Manuka HY is due, among other things, to the presence of methyl syringate, methylglyoxal, and 5-hydroxymethylfurfural (HMF). In addition, HY's low pH (3.5–4.5) inhibits the growth of microorganisms. The MIC95 of Manuka HY against *S. aureus* was 10% and against *E. coli*, 12.5%. Recent research by the authors [30] on improving the composition of CS-HY film has led to the development of an optimal formulation: 2% CS, 13% HY, and 15% glycerol. The hydrogel film exhibited a swelling ratio of 207%, a water vapour permeability of 1598 g/m²/day, a tensile strength of 46 N/mm², and an elongation of 52%. As part of their ongoing work on the effectiveness of CS-HY polymer film, Rathinamoorthy and Sasikala [6] conducted studies in a rat model with induced excision, incision, and burn wounds. The authors confirmed the effectiveness of the developed formulation in comparison with a commercial polyurethane film (Tegaderm).

Wound healing in the excision and incision wound model was observed after 18 days of treatment (94%) compared with the control group (51%) and the commercial group (90%), $p < 0.05$. The CS-HY preparation significantly supported re-epithelialisation. The tensile strength of the dressing was 2.27 MPa (compared to 2.02 MPa for the commercial preparation), $p < 0.05$. In burn wounds, the wound-contracture rate with the CS-HY preparation was 96% on the 21st day of observation. At the same time, the effectiveness of the commercial preparation was 85% ($p < 0.05$). Histopathological examination confirmed that the CS-HY Manuka-based dressing supports blood vessel proliferation and epithelial regeneration. El-Kased *et al.* [3] confirmed that HY incorporated into a CS hydrogel matrix plays an important role in modulating wound healing. A dressing containing 75% HY and CS showed high antimicrobial activity against *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Streptococcus pyogenes*. The combination of HY and CS in a polymer matrix increased the effectiveness of burn wound treatment in a rat model compared to pure HY and a commercial preparation ($p < 0.0001$). The authors observed epidermal tissue regeneration and the formation of new capillaries. Movaffagh *et al.* [5] confirmed that a 1:3 CS/HY hydrogel was effective against *S. aureus*, *Bacillus cereus*, *Escherichia coli*, *P. aeruginosa*, and *Candida albicans*, and effective in wound healing, tissue regeneration, and repair ($p < 0.01$).

Other authors have incorporated gelatin into the CS-HY matrix. This polymer facilitates the formation of hydrogels at room temperature. It increases the mechanical

strength of the hydrogel and slows down its biodegradation. Wang *et al.* [4] developed a dressing composed of CS, HY, and gelatin in a 0.5:20:20 (w/w) ratio. They reported enhanced antibacterial activity of the combined CS-HY system, achieving up to 100% inhibition of *S. aureus* and *E. coli*. The dressing was non-toxic. No skin irritation was observed 1, 24, and 48 hours after application (statistically insignificant differences; ns). The effectiveness of the dressing was tested in the treatment of burn wounds in a rabbit model (vs MEBO® ointment). Burns treated with the CS-HY-gelatin preparation healed quickly, achieving 80% wound closure on the 8th day of observation and complete healing with epidermal regeneration on the 12th day. At the same time, the MEBO®-treated and control groups showed a significantly slower rate of regeneration, leaving 15% and 37% of the wound surface unclosed, respectively ($p < 0.005$). The authors note the low water-absorption capacity of the developed hydrogel as a disadvantage, limiting its use to wounds with little exudate. Kosimaningrum *et al.* [12] reported that the optimal matrix composition was a 0.5:20:20 (w/w) mixture of CS, HY, and gelatin. The resulting matrix was characterised by a gel fraction content of nearly 60% and a swelling degree of 300%. The authors confirmed that, in the absence of CS, bacterial colony growth in the gelatin-HY hydrogel was approximately 4 times faster. The addition of CS to the matrix significantly reduces *E. coli* growth by approximately 75%. CS is therefore a key factor in determining the antibacterial activity of the preparation.

Shamloo *et al.* [7] developed a hydrogel comprising CS, PVA, and gelatin (2:1:1 (v/v)), with the addition of HY. The hydrogels exhibited a microporous structure with an average pore size ranging from 37 ± 7 μm to 45 ± 7 μm, similar to the ECM of human skin tissue. The tensile strength ranged from 0.54 ± 0.08 kPa to 1.51 ± 0.16 kPa, while the elastic modulus ranged from 1.3 ± 0.36 kPa to 6.8 ± 0.82 kPa. A decrease in the elastic modulus and tensile strength of the hydrogels was observed with increasing HY concentration (0, 5, 10, and 20%). The highest antibacterial activity against *S. aureus* and *P. aeruginosa* (8 ± 0.8 mm and 14 ± 1 mm, respectively) was observed for the hydrogel containing 20% HY, which the authors attribute to hydrogen peroxide, flavonoids, the high sugar content, and the pH. In a rat model, the wound was shown to have shrunk by 95% after 12 days. This is probably due to HY's ability to promote cell proliferation, stimulate angiogenesis, and enhance fibroblast growth.

Koosha *et al.* [14] developed CS/PVA hydrogels containing HY and allantoin. PVA improves the mechanical properties of hydrogels. Allantoin, in turn, has a moisturising effect, stimulates epidermal granulation, and supports wound healing processes. The authors confirmed that allantoin incorporated into a CS/PVA/HY-based hydrogel matrix increased antibacterial activity against *S. aureus*. Treatment of second-degree burn wounds with the developed preparation closed the wound area by 98% on the 21st day of observation (vs. 89% closure of the control wound). No significant effect of the type of HY contained in the hydrogel matrix on the therapeutic efficacy of the preparation was found. Studies by Radoor *et al.* [29] indicated that the antibacterial efficacy of the CS/PVA/HY membrane can be regulated by HY concentration, with an optimal value of 15%. The matrix containing 15% HY showed inhibition zones of 8 mm (*E. coli*) and 14 mm (*S. aureus*). Studies conducted by Chopra *et al.* [13] demonstrated that the CS/PVA/HY polymer films exhibited favourable mechanical properties, a high swelling capacity, and efficient exudate absorption. The developed films also showed antimicrobial and bacteriostatic activity against wound-associated microorganisms. These considerations are complemented by the work of Shahzad *et al.* [17, 28], who supplemented a CS-PVA-HY hydrogel with aloe vera gel. Citric acid was used as a cross-linking agent. Aloe vera supports skin regeneration, induces cell proliferation, and reduces

scar tissue formation. HY, in combination with aloe vera, increased the formulation's elasticity and improved water retention capacity to 218% and moisture content to 99%, thereby significantly increasing the dressing's ability to absorb exudate [17]. The hydrogel was a spongy, porous structure. The dressing was biodegradable (93%) and biocompatible, with low haemolytic activity, indicating its safety for use in wound treatment. The hydrogel enriched with HY and aloe vera showed significant potential against *S. aureus* and *K. pneumoniae*, which the authors attribute to the complementary effects of CS, HY, and aloe vera. In subsequent studies by this team [28], *Piper longum*, with strong anti-inflammatory and antibacterial properties, was introduced into the CS/PVA/HY dressing matrix. The film (PLAE/CS/HY/GA) showed strong antibacterial activity against *S. aureus* and *E. coli*. The developed dressing demonstrated high efficacy in treating puncture wounds in a rabbit model. Almost complete healing was observed after 14 days. The films provided a moist wound environment, proper re-epithelialisation, and better haemolytic parameters, and they also promoted cell proliferation and migration. This effect may result from the combined antibacterial and regenerative properties of CS, HY, and the aqueous extract of Piper longum. Saberian *et al.* [15] confirmed the anti-inflammatory and antibacterial properties of aloe vera in wound healing. The authors prepared a hydrogel of CS and alginate (as a polymer base) and HY and aloe vera (as biocomponents accelerating wound healing). They determined the inhibitory activity of the preparation against *S. aureus* (inhibitory zone 23 mm) and its high biocompatibility and porosity of 60.29% (the desired degree of porosity should be 60–90%). This ensured suitable conditions for cell adhesion, migration, and proliferation. The water vapour transmission rate was 573.3 (g/m²/day).

Ciarleglio *et al.* [16] developed a multilayer, pH-sensitive dressing with the following composition: alginate /Manuka honey (2 wt.% ALG, 10 wt.% MH), alginate/hyaluronic acid (2 wt.% ALG, 0.3 wt.% HA), and alginate/blackcurrant extract (2 wt.% ALG, 1 wt.% RN) and 0.5 wt.% CS. The preparation was characterised by high water uptake (swelling ratio up to 22.11 ± 0.25; water content 95.48 ± 0.05%) and controlled WVTR (~3450–3850 g/m²/day). The hydrogel's high hydration was due to the natural hydrophilicity of alginate and the presence of functional groups that form hydrogen bonds. The authors suggest that the dressing is a promising alternative in the treatment of burn wounds. Şalva *et al.* [8] developed a CS/HA hydrogel containing HY. Hyaluronic acid has good gelling properties, biodegradability, and biocompatibility. The addition of HY to the CS/HA hydrogel decreased hydration and porosity while improving fibroblast proliferation and adhesion to the dressing surface. In a rat wound excision model, the CS/HA/HY hydrogel accelerated healing on day 7 of observation compared with the control groups. Complete wound closure occurred on day 21. The authors suggest that HY accelerated wound closure through re-epithelialisation, while CS enhanced this effect by increasing cell migration and proliferation. Abraham *et al.* [9] incorporated HY and nanosilver into a CS hydrogel matrix. The most effective formulation for wound healing contained 3.5% CS and 40% HY. The authors reported enhanced antibacterial activity of CS (a bioadhesive and biodegradable polymer) and nanosilver (with broad-spectrum antiseptic and antibacterial activity), which accelerated healing (90–95% reduction in wound size, $p < 0.05$).

6. Limitations in Modelling and Monitoring Tissue Regeneration

The literature review indicates that research on the development of chitosan- and honey-based hydrogel dressings is at the preclinical stage. The authors evaluated the wound-

healing process using animal models, particularly rodents (rats and mice) and lagomorphs (rabbits). The proposed *in vivo* models are universal, albeit imperfect, research tools that allow for a preliminary assessment of the safety and efficacy of the developed preparations. Wound healing in rodents is primarily driven by wound contraction rather than by re-epithelialisation and granulation tissue formation, which only partially reflects the pathophysiology of wound healing in humans. It has been suggested that other animals, such as pigs, exhibit greater similarity to human skin physiology, thereby enabling more accurate simulation of the wound-healing process [6, 34, 35].

Another limitation in wound-healing research is the lack of well-defined quantitative parameters that would enable an objective assessment of tissue regeneration dynamics. Currently, wound-healing progress is mainly determined by qualitative analyses, i.e., visual assessment of the wound and histopathological examinations, which rely on the researcher's subjective judgment [6].

7. Conclusions

Chitosan- and honey-based hydrogel systems demonstrated promising antibacterial and wound-healing properties in preclinical studies, including *in vitro* assays and animal models of chronic wounds, burns, and ulcers. These hydrogel dressings exhibited antibacterial activity against *S. aureus* and *E. coli.* At the same time, the addition of honey helped maintain a moist wound environment and a low pH, which may help limit microbial colonisation in the wound bed. The developed dressings were characterised by porous structures and appropriate mechanical properties and displayed favourable biocompatibility and low cytotoxicity in preclinical evaluations involving skin cells and animal models. Current findings suggest that chitosan-honey hydrogel systems are promising biomaterials for wound-healing applications and may also serve as carriers for the delivery of active substances to wound sites. However, due to limitations in modelling and monitoring tissue regeneration, further preclinical studies using more advanced, standardised experimental models are required to evaluate their regenerative potential and biological performance better.

8. Author Contributions

Conceptualisation, A.O.-C.; literature search, A.O.-C., S.R., and A.T.; writing—original draft preparation, A.O.-C., S.R., and A.T.; data analysis and curation, A.O.-C. and S.R.; writing—review and editing, A.O.-C. and S.R. All authors have read and agreed to the published version of the manuscript.

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