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Herbal bioactive-loaded biopolymeric formulations for wound healing applications

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Recent advancements in wound healing technologies focus on incorporating herbal bioactives into biopolymeric formulations. A biocompatible matrix that promotes healing is provided by biopolymeric wound dressings. These dressings use components such as ulvan, hyaluronic acid, starch, cellulose, chitosan, alginate, gelatin, and pectin. These natural polymers assist in three crucial processes, namely, cell adhesion, proliferation, and moisture retention, all of which are necessary for effective wound repair. Curcumin, quercetin, *Aloe vera*, *Vinca* alkaloids, and *Centella asiatica* are some of the herbal bioactives that are included in biopolymeric formulations. They have powerful anti-inflammatory, antibacterial, and antioxidant activities. Chitosan, cellulose, collagen, alginate, and hyaluronic acid are some of the biopolymers that have shown promise in clinical trials for wound healing. These trials have also confirmed the safety and functional performance of these materials. Their recent advancements in wound care can be understood by the increasing number of patents linked to these formulations. These innovative dressings improve healing outcomes in acute and chronic wounds while minimizing adverse effects by incorporating biopolymers with herbal bioactives in an efficient manner. This review emphasizes that the development of next-generation wound care products can be facilitated *via* the integration of natural materials and bioactive substances.

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1. Introduction

There are different types of wounds, which are described as breaches in the skin or underlying tissues, and they can range from open to closed, surgical to traumatic, and acute to chronic.[1] In contrast to chronic wounds, which are often linked to underlying diseases, such as diabetes or venous insufficiency, acute wounds caused by abrasions or lacerations heal predictably; chronic wounds can take longer to heal because of chronic inflammation or poor perfusion.[2] The biological reaction to injury or wound healing is intricate and multi-staged, including the stages of hemostasis, inflammation, proliferation, and remodeling. Factors such as the patient's age, nutritional status, comorbidities, and genetic predispositions play major roles in wound healing.[3] These factors impact cellular responses and tissue regeneration. Important extrinsic factors that might help or hinder healing include the local wound environment, moisture balance, infection control, and the use of proper dressings. Stress and mental health status are two examples of psychological elements that can have an indirect impact on healing through their effects on immunological function and general physiological resilience. Healthcare providers cannot improve wound care, increase patient satisfaction, and decrease healthcare expenditures related to chronic wound management without having a thorough comprehension of the complex relationship between various wound types and different factors impacting healing.[4]

Wound healing is a multifaceted biological process that occurs in response to injury to the body's structure and physiology. It encompasses several cellular and molecular mechanisms, both intracellular and extracellular, working together to accelerate the recovery of the damage.[5,6] It generally occurs in four major phases: hemostasis, inflammation (0 to 3 days), proliferation (2 to 12 days) and remodeling (3 to 6 months) (Fig. 1).[7] The two important types of wounds are acute (surgical, mechanical, thermal or chemical wounds) and chronic (bedsores, ischemia, venous stasis disorder, pressure or diabetic ulcers).[8,9] In the wound healing process, wound dressings have crucial roles, mainly in the chronic wounds that heal slowly.[10] Various properties such as non-toxic, protective, good absorption, and oxygen permeability properties are essential for wound healing as they prevent contamination and trauma and hasten the healing process.[11] Various medicinal systems (Ayurveda, Unani, Chinese, Siddha, *etc.*) are useful to treat skin

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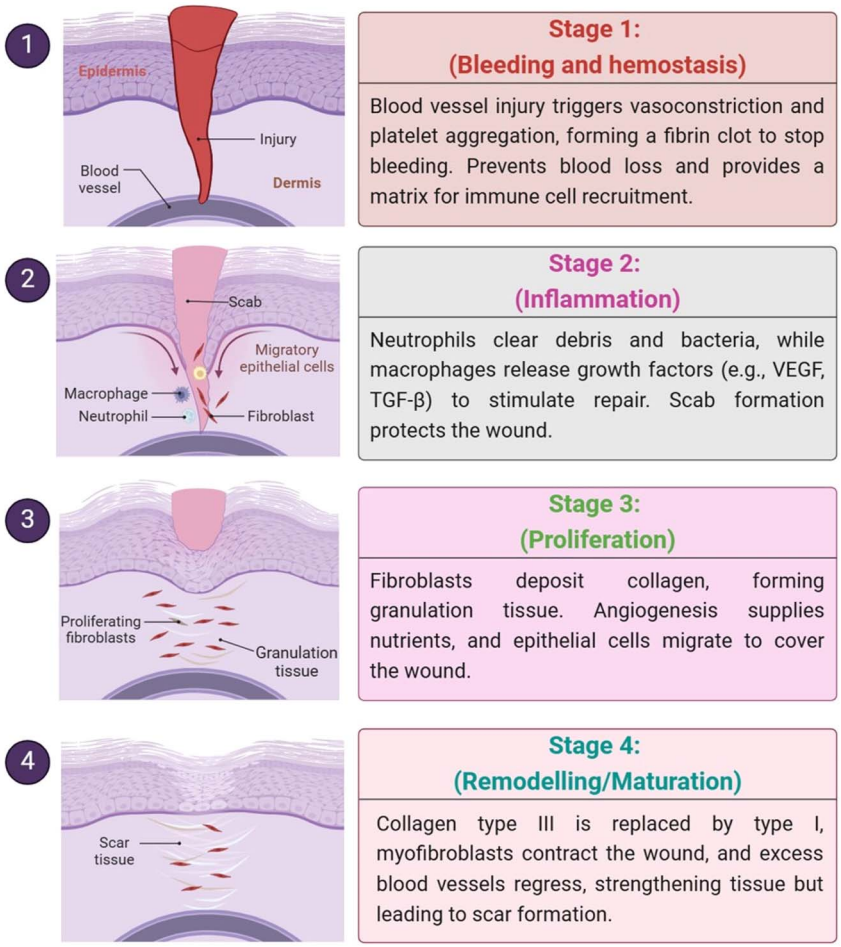

Fig. 1 Four major phases of wound healing.

damage.[12] For example, the seeds of *Moringa oleifera* are very popular due to their pharmacological and nutritional constituents, which contain all the vital phytochemical constituents necessary for wound healing.[13] Traditionally, wound dressing with herbal products (extract of plant/animal) plays an essential role in the development of modern wound healing.[14] Modern dressings consist of both synthetic and natural polymers (alginate, chitosan, starch, silicone and hydrocolloid gels, *etc.*) to boost the healing process because of the great anti-microbial-, anti-bacterial-, and growth factor (GF) properties.[15–17] Smart wound dressings (biopolymers + nanoparticles) provide numerous opportunities such as enhancing the wound healing by the drug delivery system (DDS), mimicking the lost natural intrinsic environment.[18] Active dressings are one of the trending modern wound healings that shows non-toxic, biodegradable, and biocompatible behaviours to fight against infections.[19] They have anti-oxidant properties that prevent extreme oxidation and regulate inflammation to support wound healing.[20] Hydrogels are promising wound dressing materials with interconnected porous structures that transfer oxygen and moisture vapor to simulate the physical and chemical properties of tissues and absorb liquid fluids.[21]

In addition to the capacity to develop gels when exposed to fluid, the greater the number of pores in porous dressings, the greater the rate of cell proliferation and tissue regeneration.[22] In underdeveloped nations, primarily in Africa and Asia, 70–80% of the population relies entirely on herbal therapy for various ailments, including wounds, metabolic disorders, and infectious infections. Consequently, traditional remedies primarily sourced from natural items (flora, fauna, sea organisms, and microorganisms) constitute a significant component of wound care for millions worldwide.[23,24] Natural polymers are increasingly significant because of their resource availability, compatibility, cost-effectiveness, and biodegradable properties. Nanofibers (NFs) are optimal materials for wound healing because of their exceptional properties, including porosity, surface-volume ratio, mechanical characteristics, and permeability.[25,26]

The management of chronic wounds, especially diabetic foot ulcers (DFUs), requires a thorough, multidisciplinary strategy because of their intricate characteristics and extended healing durations.[27] The initial assessment involves measuring wound size, depth, and exudate levels, succeeded by essential debridement methods, including sharp, enzymatic, or autolytic debridement to eliminate non-viable tissue and foster an optimal healing environment.[28,29] The use of advanced dressings, such as foam dressings, hydrocolloids, and alginates, is essential for preserving moisture balance, absorbing exudate,

and preventing infection.[30] Offloading treatments are crucial for diabetic foot ulcers, employing customized footwear or whole contact casting to reduce pressure on ulcerated regions. Infection therapy may necessitate the use of local or systemic antibiotics, particularly in instances of osteomyelitis.[31] Furthermore, managing underlying comorbidities *via* glycemic regulation and nutritional enhancement is essential for improving healing results. Interdisciplinary teamwork among healthcare professionals, such as endocrinologists, podiatrists, and nutritionists, facilitates comprehensive management, while patient education on foot care and self-monitoring contributes to the prevention of recurrence.[32] This methodical, evidence-based methodology is essential for efficient chronic wound treatment and enhancing patient's quality of life. In this review article, various herbal bioactives loaded with biopolymers and its formulation are discussed for wound healing applications.

2. Biopolymeric wound dressing

Biopolymers are polymers produced by living organisms that are made up of long chains of monomers (joined by polymerization), *e.g.*, alginate (ALG), chitosan (Cs), collagen (Col), and silk fibroin (SF).[33] These polymers have advantages over synthetic materials due to their biocompatibility, biodegradability, low antigenicity and reproducibility. They can exert antibacterial, anti-inflammatory, and proliferative effects or other targeted effects on specific cells to play important roles in the healing process.[34] Wound dressings (bandages) are used to cover a wound by adhering to the surrounding skin with wound dressing tape or glue. Wound dressings can be gel (hydrogel), foam, gauze or any other type of wound dressing patch. They aid in the prevention of infection, the promotion of healing, and the alleviation of pain.[35,36] The formulation of wound healing products entails the amalgamation of biocompatible materials to produce hydrogels, scaffolds, or nanogels that facilitate tissue regeneration, inhibit infection, and improve healing. Hydrogels are often synthesized from natural polymers like collagen, chitosan, or alginate, which are crosslinked by physical or chemical techniques to form water-saturated networks.[37] These hydrogels can be infused with antibacterial drugs, growth factors, or stem cells to promote healing and manage infections. Scaffolds are constructed from polymers such as chitosan or polycaprolactone, frequently integrated with nanoparticles and bioactive substances to enhance mechanical strength, porosity, and bioactivity, and are generally produced using methods like 3D bioprinting or electrospinning. Nanogels are diminutive, crosslinked polymer networks that are utilized to encapsulate pharmaceuticals or bioactive substances for regulated distribution, facilitating enhanced penetration into wound areas for targeted treatment (Fig. 2). These formulations can be augmented with supplementary bioactive agents, such growth factors, antibacterial agents, or anti-inflammatory chemicals, facilitating expedited healing and minimizing problems. The ultimate wound healing products undergo testing for mechanical characteristics, biocompatibility, and therapeutic efficacy before clinical application.[38] The summarized forms of various biopolymeric materials and their efficacy in wound healing applications, including their formulation, are provided in Table 1.

Bioactive properties such as antimicrobial, immune modulatory and angiogenic of the biopolymers create a microenvironment favourable for the healing process and contribute in the development of new systems based on nanotechnology for successful skin creation in chronic wounds.[51,52] The functional and structural characteristics of biopolymers can be improved to meet current wound care demands such as tissue repair, restoration of lost tissue integrity, and scarless healing due to technological advances in material science, regenerative medicine and bioengineering (scaffolds).[53,54]

2.1 Collagen

Collagen (mammalian protein) is a triple helix of collagen fibrils, with each fibril being a repeating polymer of amino acids linked by peptide bonds.[55] It can be extracted from cultures of *Clostridium histolyticum* and is commonly used in therapies to remove cellular debris and extracellular tissue necrosis.[56] MicroRNA-mediated MMP-2 (matrix metallopeptidase 2) upregulation creates a collagenolytic environment within the

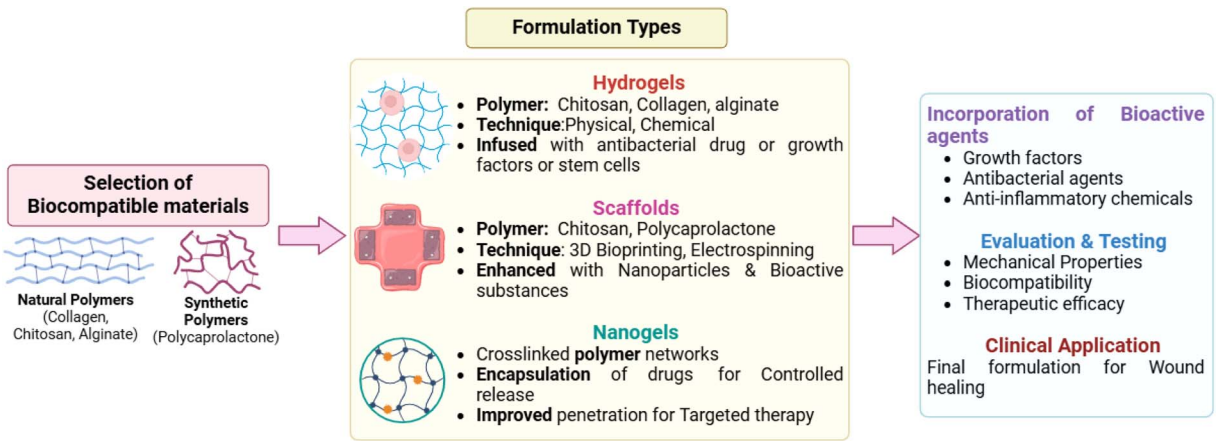

Fig. 2 Bioactive polymer-based formulations for wound repair.

Table 1 Summary of biopolymeric materials, and their efficacy in wound healing applications

Biopolymer	Formulation	Discussion	Reference
Chitosan (Ch) + acid soluble collagen (ASC)	Collagen–chitosan films (CChF)	CChF-treated rats showed a 95.75% ± 2.28% decrease in wound diameter, significantly higher than the control (22.25% ± 2.45%), CF (63.25% ± 2.08%), and ChF (52.67 ± 1.58%) groups. Higher hydroxyproline content (48.82 ± 1.25 mg g^{-1}) further supported wound healing efficacy	39
Ch + zein-methyl cellulose + curcumin (ZeinMCNPs)	Ch/ZeinMCNPs nanocomposite 1–3 films	Ch/ZeinMCNPs2 and Ch/ZeinMCNPs3 films showed 96% and 98% wound contraction, with reduced inflammation, improved re-epithelization, neovascularization, and increased collagen deposition. Higher SOD and lower MDA levels confirmed enhanced wound healing	40
Ulvan + chitosan + dopamine (DPA), silver nanoparticles (Ag NPs), human umbilical cord mesenchymal stem cell lyophilized powder (hUC-MSCs)	UC–DPA–Ag@hUC-MSC hydrogel	The UC–DPA–Ag@hUC-MSC hydrogel significantly accelerated wound healing in a type II diabetic mouse model, promoting cell proliferation, migration, and effective wound closure. It demonstrated strong antioxidant and antibacterial activity, and enhanced mechanical properties, making it a promising material for chronic diabetic wound management	41
Pectin (TFP), polyethylene glycol (PEG), montmorillonite (MMT), neomycin sulfate	Optimized nanocomposite film (ONCF)	The nanocomposite film showed no cytotoxicity (90% + C6 glioma cell survival), significant antioxidant activity, and enhanced *in vitro* wound healing. *In vivo* studies confirmed its efficacy in wound healing, making it a promising biomedical material	42
Polyvinyl alcohol (PVA) + tapioca pearl starch + α-terpineol	Electron beam crosslinked PVA/tapioca starch hydrogel	The α-terpineol-loaded PVA/tapioca starch hydrogel accelerated wound closure, promoted re-epithelialization, collagen and keratin deposition, and stimulated angiogenesis in full-thickness acid burn wounds. Histological analysis showed significant healing, including partial restoration of skin appendages, over 30 days. The hydrogel demonstrated good biocompatibility with 90% fibroblast viability and no inflammatory response *in vivo*	43
Komagataeibacter xylinus (K1G4) or *K. rhaeticus* (K2G46), *Lacticaseibacillus casei* UMCC 2535 (HA-producer), BNC (bacterial nanocellulose)	BNC–HA nanocomposites (C1–K1 and C2–K2)	The BNC–HA nanocomposites exhibited enhanced crystallinity, increased mechanical strength, higher moisture uptake, and water absorption compared to pure BNC. They were non-cytotoxic with >90% cell viability and promoted complete wound closure within 48 hours in scratch assays	44
Chitosan + polyherbal extracts (*Aloe vera*, *Azadirachta indica*, *Alternanthera brasiliana*), silver nanoparticles (AgNPs)	Polyherbal hydrogel integrated with AgNPs	The hydrogel significantly reduced wound size within 12 days, exhibited higher angiogenic potential, and showed strong antimicrobial activity against *E. coli* and *S. aureus*. It also demonstrated anti-inflammatory effects with reduced IL-6 and TNF-α levels, supporting its potential for enhanced wound healing	45

Table 1 (*Contd.*)

Biopolymer	Formulation	Discussion	Reference
Sodium alginate + allantoin, calcium chloride, citric acid	Enhanced alginate dressing	The S2 alginate dressing showed improved water absorption (363–442%), tensile strength (44.90–55.19 MPa), 52.71% cell migration, and 86.6% wound healing rate in mice, with low cytotoxicity and good biocompatibility	46
Chitosan + gum kondagogu (GKG), zinc oxide nanoparticles (ZnO NP), barbaloin (BB)	CS/GKG/BB-3 biocomposite film	The CS/GKG/BB-3 biocomposite film exhibited excellent mechanical strength (8.9 $\pm$ 0.30 MPa), high water absorption (451.1% $\pm$ 6.02%), strong antioxidant and antimicrobial activity, and facilitated rapid re-epithelialization *in vivo*. It promoted tissue regeneration with minimal scarring, offering a superior alternative to traditional wound dressings for effective wound care and tissue repair	47
Gelatin + oxidized lignosulfonate (OLS)	Gelatin/OLS wound dressing	The gelatin/OLS wound dressing significantly enhanced wound healing *in vivo*, as evidenced by improved re-epithelialization, collagen formation, reduced inflammation, and increased blood vessel density, outperforming untreated wounds	48
Oxidized carboxymethyl cellulose (OCMC), gelatin, polyvinyl alcohol (PVA)	Hybrid nanofibers	The OCMC/PVA–gelatin nanofibers showed 99.9% antibacterial activity, excellent biocompatibility (91–92% cell viability), and full degradation in 21 days, with promising applications for advanced wound healing	49
Sodium alginate + *Mentha aquatica* (MA) methanol extract	Hydrogel	The SA/MA hydrogel exhibited effective antibacterial activity with an MIC of 12.5 mg mL^{-1}. *In vivo* studies showed faster tissue regeneration, enhanced collagen recovery, and bacterial infection eradication in deep third-degree burn wounds, highlighting its potential as a promising wound dressing for infected and injured skin tissue	50

wound, significantly reducing the ratio of collagen I to collagen III, comprising the biomechanical properties of the repaired skin and repairing it. It may leave the affected skin vulnerable to wound recurrence and increase fibroblast production.[57] Because of its chemotactic properties, it attracts fibroblasts to the wound site. Collagen promotes the creation of new blood vessels, granulation tissue, wound debridement, and the ability of the wound to re-epithelize.[58] An injectable hydrogel was developed by Kim *et al.* (2022) by enzymatically cross-linking tyramine, alginate, and collagen using hydrogen peroxide and horseradish peroxidase. The potential for tissue regeneration was demonstrated by the 3D-bioprinted structures, which exhibited considerably greater cell proliferation and vitality (92.13% ± 0.70%) compared with ALG-TYR alone (68.18% ± 3.73%).[59] Similar to this, Wang *et al.* (2023) successfully eliminated bacterial infections by conjugating antimicrobial peptides with cypates and recombinant collagen-III to form a multifunctional hydrogel dressing. This dressing exemplifies the multipurpose properties of advanced hydrogels in tissue repair and infection management; it combines collagen, oxygen-carrying liposomes, and antimicrobial peptides to improve wound healing and fight multidrug-resistant infections in chronic wounds.[59,60] Yang *et al.* (2022), developed composite bioinks made of gelatin methacryloyl-recombinant human type III collagen (rhCol3). rhCol3-free bioinks fail to improve cell proliferation or more confluent spreading of epidermal keratinocytes compared with rhCol3-containing bioinks. Additionally, rhCol3 sped up skin wound healing in *in vivo* testing, which means it could be a useful bioink component for skin tissue engineering.[61] For 3D bioprinting bi-layer skin structures with fibroblasts and keratinocytes, Jiao *et al.* (2023) also investigated the biological properties of collagen/sodium alginate (Col/SA) and 1% collagen hydrogels. Their findings revealed improved cell spreading and proliferation, with Col/SA hydrogels showing the essential tunability for skin bioprinting with wound healing applications as bioinks.[61,62] The application of collagen-based formulations has been the primary focus of recent biomaterials research with the aim of enhancing wound healing and tissue regeneration. A non-denatured type I collagen (YCI) with a melting point of 42.7 °C was isolated from yak hide by Fu *et al.* (2023). The capacity of YCI to restore collagen integrity and promote skin regeneration was proven in a sunburn mouse model, where therapy considerably reduces the presence of denatured collagen in the skin. In addition to improving wound healing in burnt tissue, the non-denatured YCI shows enhanced biocompatibility and bioactivity.[63] At the same time, Kumar *et al.* (2024) synthesized a variety of NPs based on food-grade biopolymers, such as polylactic acid, collagen, chitosan, and alginate, which have antibacterial and wound-healing properties. This biopolymer therapy accelerates the healing process by stimulating tissue regeneration and reducing the amount of time it takes for wounds to close. These studies highlight the potential of collagen-based materials to enhance wound healing by repairing and regenerating tissues, whether in their native form or as composites.[63,64]

2.2 Cellulose

Cellulose (insoluble dietary fibre) found in plant cell walls is composed of repeating units of β-D-glucose linked by β-1,4-glycosidic bonds and is produced by bacteria belonging to *Acetobacter*, *Sarcina ventriculi* and *Agrobacterium* genera.[65,66] Cellulose has the chemical formula $(C_6H_{10}O_5)_n$, where n denotes the degree of polymerization and the quantity of glucose groups.[67] It acts as a primary matrix because of its strong structure and mechanical stability, it moisturizes the area around the wound, absorbs excess exudate, tissue repair, prevention of microbial infection, with the ability to stop bleeding and can be used to generate elastic gels with properties such as biocompatibility, low toxicity, and biodegradability to promote wound debridement.[68–70] Multifunctional hydrogels and scaffolds with improved therapeutic potential have been developed as a result of recent advances in biomaterials for wound healing. A hydrogel containing mesenchymal stem cell-derived exosomes (MSC-Exos) was developed by Geng *et al.* (2022) and used to treat chronic diabetic wounds. The hydrogel is composed of carboxyethyl chitosan (CEC) and dialdehyde carboxymethyl cellulose (DCMC). Hydrogels composed of CEC and DCMC possess antibacterial and self-healing characteristics. These hydrogels were produced using Schiff base reactions. The type 1 diabetic rats wound inflammatory microenvironment was much improved and wound healing was expedited by the MSC-Exos@CEC–DCMC hydrogel.[71] Similarly, Biranje *et al.* (2022) used bioprinting technology to develop a three-dimensional (3D) composite scaffold that included cellulose nanofibrils (TCNFs), chitosan, and casein to control bleeding and promote wound healing. The scaffold encourages the development and proliferation of NIH 3T3 fibroblasts, which are important for wound healing. When treated with cellulase, the scaffold shows considerable degeneration, with a weight loss of 80% ± 5%, suggesting that it might be used for fast wound closure.[72] Using NIR-responsive CNC, pH-responsive chitosan oligosaccharide, dynamic imine linkages, and temperature-responsive poly(*N*-isopropylacrylamide), He *et al.* (2022) developed an intelligent wound dressing based on cellulose nanocrystals. This versatile dressing demonstrates strong anticancer effects, effectiveness against methicillin-resistant *Staphylococcus aureus* (MRSA) and biofilm, and the ability to improve wound healing by photodynamic and photothermal therapies; thus, it can potentially treat drug-resistant infections. Taken as a whole, these studies highlight the potential of multifunctional biomaterials for improving long-term wound healing, infection prevention, and tissue regeneration.[71–73] According to Wang *et al.* (2025), a hydrogel made of hydroxyapatite (HA) and collagen considerably improves the rate of wound healing and bone regeneration. *In vivo* rat model experiments show that the hydrogel considerably prevails over control groups, accelerating wound closure to 93.5% in 14 days. Histological examination revealed enhanced skin regeneration and re-epithelialization at the wound location. New bone tissue was regenerated in bone defect models as a result of the HA–collagen hydrogel's stimulation of osteoblast proliferation and bone formation. Cells, especially fibroblasts

and osteoblasts, were able to migrate and proliferate in the hydrogel, which helped with cutaneous and skeletal tissue regeneration and repair. The hydrogel could be used for wound healing and bone regeneration at the same time.[74] Munhoz *et al.*, 2023 fabricated nanoscale silver compounds ($AgNO_3$), which are incorporated into CMs (bacterial cellulose membrane) for antimicrobial activity in wound healing. AgCM exhibits antibacterial effects *in vitro* without toxicity. Furthermore, AgCM offers balanced oxidative action, regulated inflammatory profile by reducing IL-1 and increasing IL-10 as well as improved angiogenesis and collagen synthesis *in vivo*. The results suggest that silver nanoparticles improve CM properties, antibacterial effects, modulate the inflammatory phase and promote healing in skin lesions to treat injuries.[75]

Novel materials have been developed to improve the therapeutic properties of biopolymeric wound healing formulations and to optimize the distribution of active chemical compounds. Patil and Wairkar (2024) formulated a mupirocin film-forming spray (MUP-FFS) utilizing chitosan and α-cellulose, optimized by the Box–Behnken design to enhance the sprayability and drying time. The MUP-FFS exhibits rapid application and releases 98.066% of mupirocin, indicating enhanced efficacy relative to commercial ointments and mupirocin API. In rat models, the spray markedly improves wound contraction and healing, while efficiently targeting *S. aureus* and *Escherichia coli*. This mixture offers a viable therapy for chronic wounds.[76] Similarly, Abaza *et al.* (2024) developed an innovative wound dressing by incorporating curcumin-loaded zein-methylcellulose (ZeinMCNPs) nanofillers into a chitosan matrix. The resultant Ch/ZeinMCNP nanocomposite film displays superior mechanical properties (Young's modulus, elongation, tensile strength) and enhanced antioxidant and antibacterial activity. This nanocomposite film may work as a versatile and effective wound dressing, facilitating wound healing due to its multifunctional characteristics. Collectively, these investigations highlight the future potential of biopolymer-based formulations, ranging from film-forming sprays to nanocomposite films, in improving wound healing therapies through enhanced drug delivery, antibacterial efficacy, and tissue regeneration.[77]

2.3 Chitosan

Chitosan (fibrous compound) is found in crustaceans, mollusks, and insects and is synthesized by some fungi, composed of *N*-acetylglucosamine held by β-1,4 bonds.[78,79] Chitosan promotes the wound healing process by stimulating inflammatory cells, macrophages, and fibroblasts reduces the inflammation phase, and initiates the proliferative phase earlier in wound healing.[80] Chitosan is a promising hemostatic agent for red blood cells and platelets, and it has various applications in medicine, drug delivery, and moisture permeability and in hydrogels and adhesives owing to its antioxidant, antifungal and antimicrobial activities.[81,82] Recent research has focused on developing advanced biopolymeric formulations for diabetic wound healing, integrating natural compounds with biocompatible polymers to improve therapeutic effectiveness. Zeng *et al.* (2023) developed a chitosan-based injectable hydrogel loaded with puerarin (C@P), a traditional Chinese medication, that enhances angiogenesis and suppresses the inflammatory response in diabetic wounds. C@P hydrogel controls the expression of miR-29a and miR-29b1, which in turn controls M1 polarization and pro-inflammatory cytokines (IL-1β and TNF-α) to facilitate wound healing.[83] In the same direction, Anushree *et al.* (2023) synthesized phosphorylated chitosan (PC) and investigated its antioxidant properties, revealing that PC-treated wounds display superior wound contraction (91.11%), elevated superoxide dismutase (SOD) activity, reduced lipid peroxidation, and enhanced tissue morphology, characterized by increased fibroblast activity, collagen deposition, and angiogenesis. These data indicate that PC may serve as a potential agent for the repair of diabetic wounds.[84] Le *et al.* (2023) examined chitosan-based hydrocolloid patches for wound healing, proving that these patches significantly reduce inflammation, inhibit pro-inflammatory cytokines, and facilitate skin regeneration by enhancing fibroblast proliferation and the expression of essential biomarkers (*e.g.*, vimentin, α-SMA, collagen I, and TGF-β1). Collectively, these investigations emphasize the efficacy of chitosan-based formulations independently and in conjunction with bioactive compounds such as puerarin and phosphorylated chitosan in expediting wound healing, mitigating inflammation, and promoting tissue regeneration in diabetic wounds.[85] Linju *et al.*, 2023 synthesized and characterized scaffolds of amino acid L-proline conjugated onto chitosan by FTIR and NMR that are characterized by swelling, dissolution, porosity and healing properties. The scaffold shows no cytotoxicity against L929 and HaCaT cells and improves wound healing potential in the L929 cell line, showing 53.35% ± 2.3%, 72.96% ± 2.2%, and 50.89% ± 0.3% wound closure with CS-P 200, 400, and 600, respectively compared to the native CS scaffold. Hence, the modified scaffold promotes collagen deposition, remodeling wound microenvironment and has potential as a wound dressing.[86] Moreira *et al.*, 2023 fabricated chitosan (CSF) and pentoxifylline films (PTX) for cutaneous wound healing, evaluating interactions, structural characteristics, *in vitro* release and morphometric aspects *in vivo* at two concentrations: F1 (2.0 mg mL^{-1}) and F2 (4.0 mg mL^{-1}). As a result, the release of films was proportional to concentration, with two phases: fast ≤2 h and slow >2 h. After 72 h, F2 shows faster healing, with wound reductions up to 60% on day 2 compared to CSF, F1, and the positive control. Therefore, CSF and PTX effectively form and incorporate, accelerating skin-wound reduction.[87]

Innovative hydrogels and nanogels possessing antibacterial and wound-healing capabilities have recently been the focus of biomaterial research and development. To aid in the healing of bladder wounds and to prevent urinary tract infections (UTIs), Yang *et al.* (2024) synthesized a nanogel (NA@CS) out of nalidixic acid and chitosan. The nanogel shows promising inhibitory effects on bacterial strains, lowering their pathogenicity and virulence, and it is well-tolerated by L929 fibroblast cells and an animal model of *Artemia salina*. The nanogel has potential as a treatment for urinary tract infections and for mending bladder wounds.[88] A biomimetic composite bioink

was developed for 3D bioprinting by Khoshmaram *et al.* (2024) using a similar strategy, combining gelatin methacrylate (GelMA) with chitosan nanoparticles (CSNPs). Nanoparticles with curcumin infused into them have better antibacterial and skin cell proliferation capabilities. Applying the composite hydrogel to Wistar rats shows potential for skin tissue engineering and wound healing since it promotes cell division and effectively blocks bacterial infections. Both studies show that advanced biomaterials can heal wounds in the skin and the urinary system, and that they are effective in managing infections and repairing tissues.[88,89]

2.4 Alginate

Alginate (linear compound) is composed of repeating units of β-D-mannuronic acid and α-L-guluronic acid by α-1,4 glycosidic bonds derived from the sea and is extracted from brown algae such as *Laminaria*, *Macrocystis* and *Ascophyllum* species.[90,91] Alginate dressings are light, nonwoven textiles that are developed for moderately to heavily exuding wounds and possess highly absorbent properties, have modest hemostatic qualities, help to minimize bacterial infections, and can be left on the wound bed for days.[92] Various properties like nontoxicity, high mechanical strength, abundance, and high adsorption capacity have made the alginate-based polymeric systems a promising material.[93] Recent research shows favorable outcomes in the development of improved wound healing solutions utilizing biopolymers and bioactive compounds. Saraiva *et al.* (2023) reported that sodium alginate (SA) and polyvinyl alcohol (PVA) films, when crosslinked with Ca^{2+}, enhanced their physicochemical and biological properties, thereby augmenting their potential for wound healing through improved drug incorporation.[94] By crosslinking alginate, chitosan, and arginine–glycine–aspartate (RGD) with tannic acid (TA), Mndlovu *et al.* (2023) developed scaffolds that significantly increase the viability of mouse embryonic fibroblast cells and achieve an 86% encapsulation efficiency with a 57% burst release in 24 hours, showing the scaffolds' potential for acute and chronic wound healing.[95] Chen *et al.* (2023) synthesized SCTF cryogels by crosslinking sodium alginate with tannic acid and Fe^{3+} ions, showing significant hemostatic properties and improved bactericidal effectiveness *via* synergistic photothermal and chemodynamic mechanisms, thereby facilitating wound healing.[96] Cruz Sánchez *et al.* (2023) formulated chitosan and alginate membranes infused with lavender essential oil (LEO), revealing that the CHT/ALG + LEO membranes display a significant water absorption capacity (638% after 48 hours) with low cytotoxicity and regulated LEO release, rendering them appropriate for wound healing applications.[97] Ndlovu *et al.* (2024) developed SA/PVA/PLGA nanofibers loaded with *Capparis sepiaria* extract, exhibiting significant antibacterial properties against multiple bacterial species and displaying hemostatic potential, suggesting their possible application as burn wound dressings.[98] Sellappan *et al.* (2024) developed keratin–sodium alginate dressings infused with zinc oxide nanoparticles and herbal products, exhibiting superior antibacterial efficacy against *E. coli* and *Bacillus subtilis*, enhances biocompatibility, and increases collagen deposition, emphasizing their potential as antimicrobial wound dressings for enhanced healing. These studies collectively highlight the efficacy of biopolymer-based formulations in promoting wound healing by increasing antibacterial characteristics, biocompatibility, and regenerative potential.[99]

2.5 Starch

Starch (polysaccharide) is a soft, tasteless powder produced by green plants. It is a granular, organic chemical comprising glucose monomers joined in α-1,4 linkages. The linear polymer amylose is the most basic type of starch, and amylopectin is the branched form.[100,101] Starch hydrophilicity absorbs wound exudates, potentially causing bacterial infection, aiding in antimicrobial treatment for chronic wounds with the process of proliferation, differentiation and regeneration of cells.[102,103] Starch is an appealing polymer for wound healing applications because of its vast availability, low cost, biocompatibility, and biodegradability.[104] Wound dressing polysaccharides such as sago starch help facilitate and promote healing.[105] Recent studies have investigated numerous starch-based formulations and composites to improve wound healing capabilities using advanced biopolymeric scaffolds and hydrogels. Guo *et al.* (2023) engineered microcapsules comprising waxy maize starch (WMS) and modified waxy maize starch (EWMS), which were subjected to α-amylase and transglucosidase treatment to augment their self-healing capabilities. EWMS-16 shows a high degree of branching (21.88%), enhanced healing efficiency (58.33%), and self-healing abilities, exhibiting superior characteristics relative to WMS microcapsules.[106] Huang *et al.* (2023) developed a starch/natural rubber composite hydrogel that has tunable mechanical properties, significant elasticity, fatigue resistance, and self-healing abilities, along with exceptional durability and stability for tracking human movement, indicating its potential for wearable health monitoring applications.[107] Lopes *et al.* (2023) integrated the bioactive compound, porphyrin tetraiodide (TMPyP), into starch-based films, markedly enhancing their antibacterial efficacy and wound healing capacity. These films efficiently photoinactivate *E. coli* (>99.99%) and accelerate wound healing without light, highlighting TMPyP's potential in developing water-resistant, photosensitive biomaterials for wound care.[108] Finally, Joseph *et al.* (2024) utilized 3D bioprinting to develop scaffolds from gellan gum and starch derived from *Maranta arundinacea*, exhibiting superior cell survivability and improved performance relative to conventional monolayer cultures. This biocompatible and biodegradable scaffold exhibits potential for long-term wound healing by obstructing environmental pollutants. Collectively, these investigations highlight the adaptability and efficacy of starch-based formulations and composites in enhancing wound healing *via* superior antibacterial-, self-healing-, and biocompatible characteristics.[109] Khalid *et al.*, 2024 investigated the application of hydrogels as a possible remedy for full-thickness acid burn wounds when loaded with functional substances like α-terpineol and starch. The hydrogels encourage angiogenesis, re-epithelialization, the

deposition of keratin which results in the partial restoration of skin appendages and the repair of thick dermal and epidermal tissues. As a result, the hydrogels have potential as an economical and effective wound dressing, increasing the usefulness of the sheet hydrogel dressing made of natural polymers.[110]

2.6 Hyaluronic acid

Hyaluronic acid (hyaluronate) is a naturally produced gooey substance found in the body, particularly in eyes, joints, and skin. It acts as a cushion and lubricant, composed of polymeric disaccharides linked by a glucuronic β (1→3) bond.[111,112] It modulates specific HA receptors, inflammation (signaling the body to build more blood vessels in the damaged area), re-epithelization, scar tissue formation (promotes collagen and elastin production), cellular migration and angiogenesis, all of which are important phases of wound healing.[113] It has many unique properties including excellent biocompatibility, high viscoelasticity, biodegradability, hydrophilicity, moisture retention capacity and non-immunoreactivity.[114]

Modern research has focused on developing novel formulations for wound healing that make use of biodegradable substances and bioactive compounds. AlSalem *et al.* (2023) developed three biodegradable wound dressings utilizing collagen, hyaluronic acid (HA), silver nanoparticles (AgNPs), and gentamicin (GENT) by freeze-drying and assessment of physical properties. The findings revealed enhanced antibacterial efficiency against Gram-positive and Gram-negative bacteria, yeast, and fungi, with COL/HA/AgNPs/GENT displaying the greatest effectiveness in wound healing and antibacterial attributes. The membranes exhibit outstanding swelling characteristics, quick degradability, and cytocompatibility, with the exception of one formulation (COL/HA/AgNPs/GENT), which was considered unsafe for cellular application.[115] A multifunctional hydrogel made of oxidized hyaluronic acid (OHA) and gallic acid-grafted quaternized chitosan (GA-QCS) crosslinked by Schiff base chemistry was developed by Bai *et al.* in 2023. The GA-QCS/OHA hydrogels have injectable characteristics, efficient hemostasis, and regulated drug release, in addition to antioxidant and migration-enhancing activities. These hydrogels accelerate wound healing by suppressing TNF-α and enhancing CD31 expression, demonstrating their potential as an efficient, multifunctional approach for wound management, especially in cases of infection complications. Collectively, these studies illustrate the potential of bioactive and biodegradable wound dressings in improving wound healing *via* antibacterial-, anti-inflammatory-, and regenerative properties.[116] Lin *et al.*, 2023 developed a drug free hybrid hydrogel combining chitosan (CS) and hyaluronic acid (HA) for synergistic healing in MRSA-infected diabetic wounds. The CS/HA hydrogel exhibits broad-spectrum antibacterial activity, fibroblast proliferation, ROS scavenging, and cell-protection and promotes wound healing in diabetic mouse wounds, eliminating MRSA infection and enhancing epidermal regeneration, collagen deposition, and angiogenesis and has potential for clinical use in managing chronic diabetic wounds.[117] Eeckhout *et al.*, 2022 established hyaluronic acid gel after alveolar ridge preservation (ARP) in healthy patients showed changes in wound dimensions over time (patients with at least one neighboring tooth and >50% buccal bone were included). Three sites in the control group and six in the test group showed complete wound resolution at T2 ($p = 0.259$). HA did not affect analgesics, patient-reported outcomes, alveolitis, socket healing, soft tissue changes or mucosal scarring, while horizontal bone loss was significantly higher in the test group ($p \leq 0.025$). Thus, the hyaluronic acid gel trial evaluates wound healing and preservation.[118] Hyaluronic acid (HA) and other biopolymeric formulations have been investigated in recent studies for their potential to improve wound healing through a variety of mechanisms, including anti-inflammatory-, antimicrobial-, and regenerative characteristics. Lee *et al.* (2022) investigated the impact of HA films on oral wound healing in a rat model, revealing that the HA gel (84.4% ± 9.2%) and film (74.0% ± 15.0%) groups display significantly enhanced healing rates relative to controls, along with reduced inflammation, increased re-epithelialization, and reduced COL1α1 expression levels, thereby substantiating the efficacy of HA film in facilitating oral wound healing.[119] Mosawi *et al.* (2024) investigated the role of hyaluronic acid (HA) in drug delivery systems, emphasizing its biological functions that are dependent on molecular weight, including anti-angiogenic, wound-healing, and angiogenic properties, with potential applications in micro and nano-formulations containing antibacterial and anticancer agents.[120] Katiyar *et al.* (2024) formulated a hemocompatible hybrid material consisting of chitosan, gelatin, and hyaluronic acid infused with graphene oxide–silymarin (CGH–SGO), demonstrating improved biocompatibility, with antibacterial and antioxidant characteristics. The hybrid structures exhibit rapid blood coagulation and expedited healing of full-thickness burn injuries *in vivo*, positioning them as potential options for burn wound therapy. Collectively, these investigations underscore the adaptability and efficacy of HA-based formulations in enhancing wound healing *via* increased cellular responses, antimicrobial properties, and tissue regeneration.[121]

2.7 Gelatin

Gelatin (gelatine) is a translucent, colorless ingredient derived from collagen from animal body parts and used as a gelling agent in beverages, medications, drug or vitamin capsules, photographic films, *etc.* It is brittle when dry and rubbery when moist, also known as hydrolyzed collagen.[122] It is a protein with 98–99% protein content, with hydrolyzed collagen containing 19 amino acids, primarily glycine, proline, and hydroxyproline, affecting gelation properties.[123] Porous gelatin matrices absorb wound exudates and maintain moisture, cell migration, and support tissue development to promote the wound healing process.[124] Its water-binding, gel-, film-, and foam forming abilities, water vapour barrier, and emulsification propensity make it a promising material for wound healing.[125]

Mirjalili *et al.*, 2023 developed platelet-rich fibrin–chitosan (CH–PRF) nanoparticles integrated into gelatin–chitosan

hydrogel (Gel–CH/CH–PRF) for improved hydrogel dressing properties. Chitosan-containing hydrogels have the lowest scavenging capacity (83%) and highest DPPH radical scavenging activity and excellent cell viability and proliferation, with wound closure significantly higher on the Gel–CH/CH–PRF hydrogel which accelerates wound healing.[126]

Razack *et al.*, 2023 fabricated Oregano essential oil nanoemulsion and low-level laser therapy for diabetic wound healing using hydrogel-based patch by polymers (chitosan, gelatin, and polyvinyl pyrrolidone) with cellulose nanofibrils for enhanced stability. The drug concentration of 128 μg mL^{-1} showed viability of NIH/3 T3 fibroblasts after 24 hours. Hence, the combination of nanoemulgel and low-level laser therapy is a regimen for managing diabetic foot ulcers, resulting in rapid healing and minimal scar formation.[127]

Lu *et al.*, 2022 synthesized tilapia fish skin gelatin–fucose gum–tannic acid (Gel&Fuc–TA) hydrogel that promotes wound healing by combining with tannic acid, gelatin and fucoidan, offering excellent antibacterial-, antioxidant-, and hemostatic properties. As a result, Gel&Fuc–TA hydrogel is a green cross-linking reaction-based hydrogel that promotes the expression of VEGF, CD-31, and α-SMA, collagen deposition, wound repair, microbiome changes and regulates macrophage conversion.[128]

Asada *et al.*, 2022 showed that a dermal defect graft, Terudermis® Artificial Dermis (AD-T), was used as dressings on 100 mm^2 wounds with exposed bone in rats. The wound-healing efficacy of the treatment was compared between AD-T and GS (gelatin sponge) groups at 1, 2 and 4 weeks after surgery. AD-T achieves faster wound healing, accelerates bone remodeling, and increases the production of blood vessels, fibroblasts, and osteoblasts. This suggests that AD-T is better as a wound dressing material.[129]

Khoshmaram *et al.*, 2024 employed chitosan nanoparticles (CSNPs) and gelatin methacrylate (GelMA) to generate a biomimetic composite bioink for 3D bioprinting. Nanoparticles infused with curcumin enhance antibacterial activity and skin proliferation. The CSNPs demonstrate an efficient barrier against germs and regulate medication release. The biocomposite aids in wound healing, encourages cell division and lessens microbial infections in Wistar rats.[130]

Bessalah *et al.*, 2024 investigated the potential of gelatin–chitosan–*Moringa* leaf extract (G–CH–M) as a novel biomaterial for biomedical applications. Blood hemolysis, anti-inflammatory-, antioxidant- and antibacterial-properties against Gram-positive and Gram-negative bacterial isolates were evaluated for the wound-dressing G–CH–M biopolymer. Additionally, the biopolymer shields plasmid DNA from oxidative damage.[131]

The eco-friendly production of silver nanoparticles (AgNPs) using *Dactyloctenium aegyptium* extract as a capping and reducing agent can be used in wound healing.[132] Nanoparticles were subsequently integrated into PVA, Na-alginate, and gelatin-based hydrogel dressings to examine their *in vivo* wound healing efficacy in rats. The change in color of the reaction mixture and the surface plasmon resonance at 400 nm validated the synthesis of AgNPs. FT-IR research demonstrated the participation of phytochemicals from the plant extract in the capping and stability of nanoparticles. The nanoparticles display a crystalline structure, with an average crystal size of 28.03 nm, and show antibacterial efficacy against *S. aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *E. coli*, with zones of inhibition of 19 ± 0.0, 9 ± 0.0, 13 ± 0.0, and 13 ± 0.0 mm, respectively. Moreover, silver nanoparticle-embedded hydrogels demonstrate enhanced wound healing in rats relative to untreated animals and those administered a commercial product (Fig. 3). Consequently, the formulated hydrogel dressing exhibits promise for practical use in wound healing and infection management.

2.8 Pectin

Pectin (structural fiber) or gelatinous polysaccharide found in fruit is primarily present in the peel portion and becomes water-soluble during fruit ripening. It is a linear polymer with a backbone of galacturonic acid monomer units linked *via* α-(1→4)-glycosidic bonds.[133] Pectin is a hydrophilic substance that combines with wound fluid to generate a soft gel over the

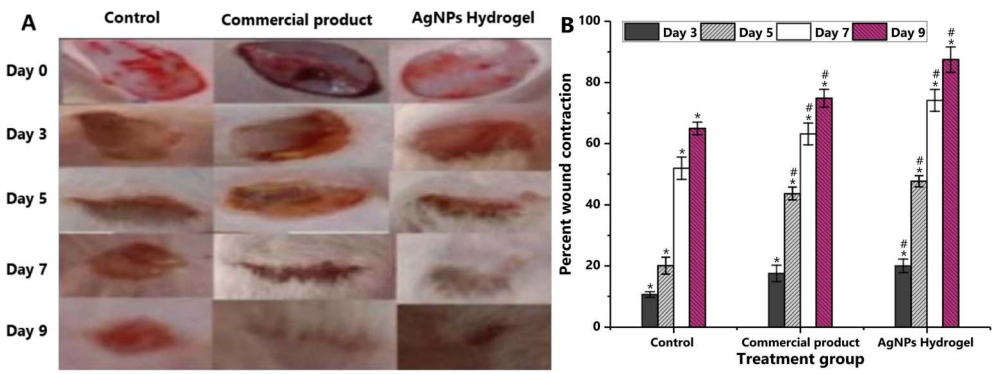

Fig. 3 Assessment of wound healing efficacy of AgNPs-loaded hydrogel compared with a control and a commercial product (A) Photographs of injuries of different animal groups on distinct measuring days. The control group received no therapy, the experimental group received commercial treatment (1% silver sulfadiazine), and another group received AgNPs–DA-loaded (1%) hydrogel dressing. (B) Percentage of wound contraction. Data are presented as mean ± standard deviation (SD). * signifies statistical comparison between the control group and the standard group, as well as the AgNP–DA hydrogel group, whereas # indicates a comparison between the standard group and the AgNPs–DA hydrogel group. Reproduced from ref. 132 with permission from [Elsevier], copyright [2024].

wound bed, which aids in the removal or management of exudates.[134] During pectin solubilization, the acidity of the resultant pectin solution improves the system's bacterial or virus barrier characteristics.[135] Pectin binds to intestines, adds bulk to stools, and reduces cholesterol absorption, aiding in mitigating high cholesterol, diabetes, heartburn, and diarrhea and functions in cell adhesion and wall hydration.[136]

Chanmontri *et al.*, 2023 used quaternized chitosan (QCS) and oxidized pectin (OPEC) to improve antibacterial activity and enhance solubility, with self-healing hydrogels enhancing ionic interactions through co-injection. The hydrogel displays self-healing, fast gelation, storage modulus and compressibility and has no cytotoxicity to NCTC clone 929 cells. The extraction media lacks antibacterial characteristics, while QCS has a MIC50 of 0.04 mg mL^{-1} against *E. coli* and *S. aureus*. Hence, injectable self-healing QCS/OPEC hydrogel has potential for wound management.[137]

Song *et al.*, 2023 designed a pectin–chitosan (PEC–CS) hydrogel with a bioadhesive micelle containing ciprofloxacin for wound healing. PEC–CS hydrogels have high water content (>95%), strong absorption, good water retention, and no cytotoxicity, making them suitable for wounds. Thus, dopamine-modified carriers improve solubility, retention time, and antibacterial activity. *In vitro* and *in vivo* pharmacodynamics experiments show that they resist bacteria, promote wound healing and possesses anti-infective properties.[138]

Saucedo-Acuña *et al.*, 2023 synthesized allantoin-enriched pectin hydrogel and showed that it improves surgical wound healing in rat models with hydrophilic behavior and healing efficacy. Hydrophilic behavior (11.37°) and functional groups like carboxylic acid and amine groups are found in the amorphous pectin hydrogel. As a result, allantoin promotes wound drying and interaction with cells, reducing healing time by 71.43% and achieving total closure in 15 days in female Wistar rats.[139]

Phonrachom *et al.*, 2023 investigated quaternized chitosan (QCS) and pectin (Pec) blended to enhance water solubility and antibacterial activity in hydrogel films. Propolis was loaded for wound healing, mechanical properties, adhesiveness, and biological activities. Blending QCS and Pec enhances hydrogel films, tensile strength, stability, and controls propolis release. These films show antioxidant activity (~21–36%), bacterial growth inhibition, non-toxicity to mouse fibroblast cells, and support wound closure. Thus, propolis-loaded QCS/Pec hydrogel films are promising wound dressing materials.[140]

Alsakhawy *et al.*, 2022 encapsulated NAR in Arabic gum (AG)/pectin hydrogel which showed excellent EE% (99.88% ± 0.096%) and DL% (16.64% ± 0.013%) characterized using FTIR, DSC, SEM and EDS%. NAR-loaded AG/pectin hydrogel accelerates wound healing by enhancing angiogenesis, re-epithelialization and collagen deposition. It significantly down-regulates inflammatory mediators and apoptosis ($P < 0.001$) and has potent antioxidant activity, enhancing SOD and GSH levels.[141]

Elsherif *et al.*, 2024 evaluates how nebivolol hydrochloride and pectin affect wound healing. The formulation containing pectin nanoparticles loaded with NBV demonstrated a particle size of 572 nm and an encapsulation effectiveness of 70.68%. The formulation encourages collagen deposition, tissue proliferation and wound healing *in vivo*. This implies that it is a potentially useful substance for tissue regeneration and wound healing.[142]

Kapoor *et al.* examined formulation tactics and crosslinking approaches to improve drug entrapment and controlled release, 2024 s. Pectin hydrogels could deliver medicinal drugs in clinical trials, wound healing, tissue engineering and oral and transdermal administration. Thus, pectin hydrogels appears to have a bright future, notwithstanding issues with standardization and regulatory compliance.[143]

2.9 Ulvan

Ulvan are sulfated heteropolysaccharides from marine macroalgae (sea lettuce) used in food, medicine, and agriculture. They consist of L-rhamnose, D-xylose, D-glucose, and D-glucuronic acid, with aldobiuronic acid (4-*O*-β-D-glucuronosyl-L-rhamnose) being a unique component.[144,145] It is a biopolymer with antioxidant-, antiviral-, anti-inflammatory-, and anticoagulant properties, and it is valuable for wound dressing development. It reduces cholesterol, LDL, and triglycerides, which are risk factors for coronary disease.[146,147] Adding uncommon carbohydrates into its backbone structure, such as iduronic acid and sulfated rhamnose, keeping the wound wet, and increasing its ability to absorb wound exudate can improve wound healing activity.[148,149] Ulvan protects cells from free radical damage and boosts our immunity.[150]

Kikionis *et al.*, 2022 fabricated nanofibrous patches made from ulvan and polyethylene oxide (PEO) for anti-inflammatory and antioxidant properties for use in keloid (fibroproliferative disorder) treatment and cryosurgery (treatment for keloids, causes skin traumas). The ulvan/PEO patch demonstrates significant wound healing, skin inflammation elimination and biophysical restoration after 21 days of cryosurgery. It is the first wound dressing that heals skin trauma after cryosurgical treatment of keloids without discomfort.[151]

Ren *et al.*, 2022 prepared *Ulva fenestrata* green macroalgae polysaccharide to create a hydrogel for chronic diabetic wound healing (UC–DPA–Ag hydrogel) containing hUC-MSCs for enhanced healing. The hydrogel with UC–DPA–Ag exhibits mechanical properties, swelling capability, adhesiveness, antioxidant, antibacterial ability and promotes cell proliferation and migration. Thus, it accelerates wound healing in diabetic mellitus mice and offers a new route for Ulva biomaterial production.[152]

Don *et al.*, 2022 developed crosslinked ulvan/chitosan complex films with or without the addition of glycerol and chlorophyll. The ulvan/chitosan complex films shows high tensile strength and elongation at break (2.23–2.48 MPa), with water vapor transmission rates of 1791–2029 g per m^2 per day. Biocompatibility studies show that glycerol and chlorophyll-added films promote migration, protection, wound healing, regeneration and collagen production in NIH 3T3 and HaCaT cells.[153]

Sulastri *et al.*, 2023 successfully fabricated a novel hydrogel film wound dressing combining ulvan and silver nanoparticles, with silver nitrate concentrations of 0.5 mM and 1 mM to produce ulvan–silver nanoparticle hydrogels. Physicochemical characteristics were evaluated using various techniques. Ulvan–

silver nanoparticle hydrogel films show potential as wound dressings for second-degree burn healing, with UHF–AgNP0.5 showing the highest antimicrobial activity and accelerated healing in Wistar rats.[154]

Mariia *et al.*, 2021 incorporated chitosan–ulvan hydrogel with cellulose nanocrystals (CNCs) loaded with epidermal growth factor for improved morphological features, mechanical stress curve and swelling behavior through a freeze-drying process. As a result, nanocomposites exhibit non-toxic behavior, cell proliferation, and enhanced epidermal growth factor delivery (15 days from 100% wound contraction) with CS–U–CNC–EGF hydrogels showing faster wound healing efficiency, faster tissue formation and collagen deposition, potentially enhancing wound dressing applications.[155]

Foroughi *et al.*, 2024 described a novel technique for employing ulvan hydrogel to create 3D biomaterials for wound healing applications. Wet-spinning and additive manufacturing were used to create 3D printed hydrogel structures and wet-spun ulvan fibers. The ulvan solution improves mechanical characteristics and cell survival with a viscosity of 110 Pa s and surpasses 180 Pa s on day four. Because ulvan fibers are naturally biocompatible, they act as a potential remedy for wound healing.[156]

Statha *et al.*, 2024 examined the marine sulfated polysaccharide carrageenan's and ulvan's capacity to promote wound healing in gels. The 10% w/w carrageenan gel considerably accelerates wound healing in female SKH-hr2 mice without hair and with burn-inflamed skin, particularly in the initial phases. The 5% w/w ulvan gel shows effectiveness in accelerating the healing process, particularly in the later phases. These results imply that ulvan and carrageenan gels may be able to increase the effectiveness of wound healing in second-degree burn injuries.[157]

Wound dressings were synthesized from alginate and pectin, integrated with mangosteen extract (ME), and encapsulated in niosomes (ME-loaded niosomes).[158] Researchers subsequently analyzed the *in vitro* release and physical properties of ME-loaded niosomes. The agar diffusion method quantifies the extent of a substance's antibacterial inhibition. The size of the zone of inhibition increased with antibacterial efficacy. The NCs contained identical components to the tested samples, except ME. MEs at doses of less than 0.15 mg and 0.3 mg did not inhibit *S. aureus* and *Staphylococcus epidermidis*, respectively. Meanwhile, 20 mg of ME suppressed *S. aureus* and *S. epidermidis*, yielding zones of inhibition (ZOIs) of 17 ± 1.1 mm and 16 ± 1.2 mm, respectively (Fig. 4). The findings indicated that the ME concentration rose in conjunction with antibacterial activity. Excessive

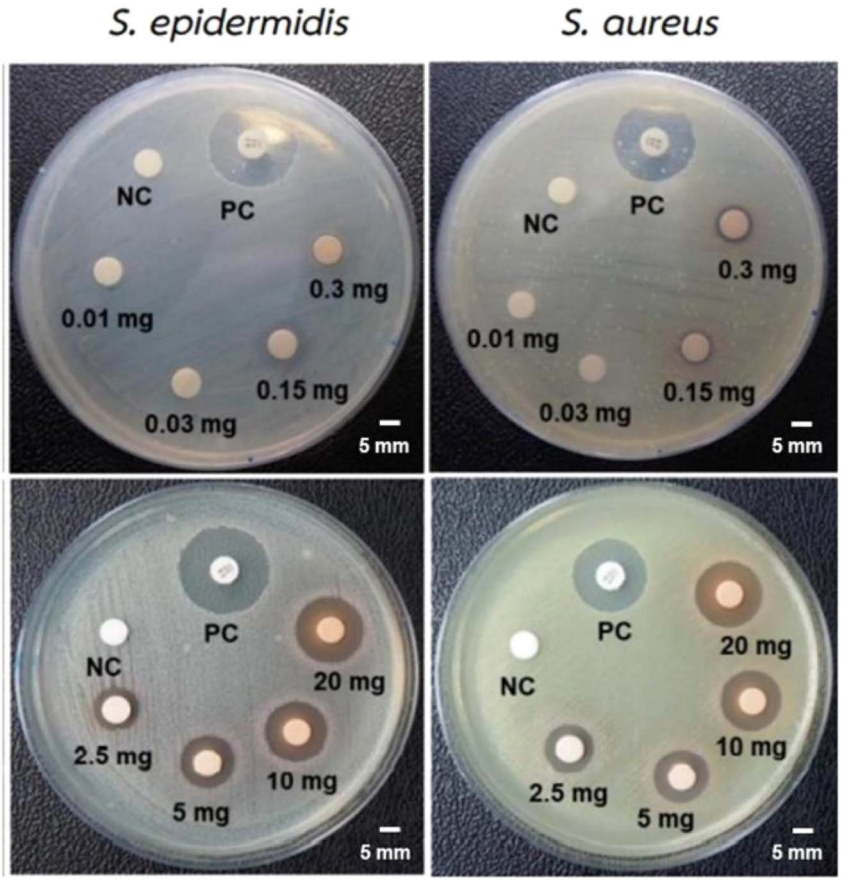

Fig. 4 Results of disk diffusion (zone of inhibition) for *S. epidermidis* (left) and *S. aureus* (right) vancomycin as the positive control (PC), normal saline solution as the negative control (NC), and various doses of ME were used. Reproduced from ref. 158 with permission from [CellPress], copyright [2024].

levels of ME adversely affect fibroblasts (L929). Reduced concentrations of ME were most effective for inhibiting bacterial growth. Furthermore, researchers analyzed the swelling ratio and biological properties of the hydrogel film. The maximum swelling ratios of patches with 0.5% and 1% Ca^{2+} crosslinking were 867 wt% and 1025 wt%, respectively, after 30 min. A medium dose (15 mg) of niosomal ME incorporated in a hydrogel film provides better bacterial inhibition, cell migration, and cell adhesion in an *in vitro* model. Additionally, no toxicity is observed in the fibroblasts and red blood cells. Consequently, this product may serve as a viable option for wound dressing applications.

3. Herbal bioactive loaded formulations

An abundant number of medicinal plants are being therapeutically used for skin and wound treatment (Fig. 5 and 6).[159] The natural products promote the healing process as a result of the active chemical constituent's existence, *e.g.*, flavonoids, alkaloids, triterpenes, and other biomolecules.[160]

3.1 Curcumin

Curcumin (Cur or diferuloylmethane) is an herbal plant with a low molecular weight poly-phenolic flavonoid, *i.e.*, extracted from the rhizomes of *Curcumin longa*, family *Zingiberaceae*.[161] The molecular formula of Cur is $C_{21}H_{20}O_6$.[162] Curcumin (77%) is a bio-active constituent of turmeric rhizomes, with 17% demethoxycurcumin, 3% cyclocurcumin, and 3% bisdemethoxycurcumin.[163] It is an ideal therapeutic biomolecule for the treatment of various inflammatory diseases (Alzheimer's, rheumatoid arthritis, diabetes, multiple sclerosis, inflammatory bowel, atherosclerosis, *etc.*) and wound healing due to its strong anti-infective, anti-inflammatory, antibacterial, and antioxidant properties.[164] Various *in vitro* and *in vivo* studies prove that it can accelerate skin, excision and chronic wound healing.[165,166] Novel drug delivery systems (nano DDS) are required to increase its restricted therapeutic efficacy, *e.g.*, poor oral absorption bioavailability, water solubility, chemically unstable, rapid metabolism and elimination, short shelf life, *etc.*[167,168] Cur has also gained attention as a local drug due to its pharmacological properties: non-toxic, good tolerance, *etc.*[169] It also helps forms anti-scars by reducing inflammatory factors secretion and inducing apoptosis.[170] Curcumin hydrogels are promising tools for drug delivery to the epidermis and dermis to enhance the drug concentration at the site of treatment and they also reduce adverse reactions in systemic circulation.[171,172] WHO confirmed that the daily consumption of Cur as a food preservative has extraordinary wound healing properties by stimulating proliferation and remodeling phases of the skin regeneration

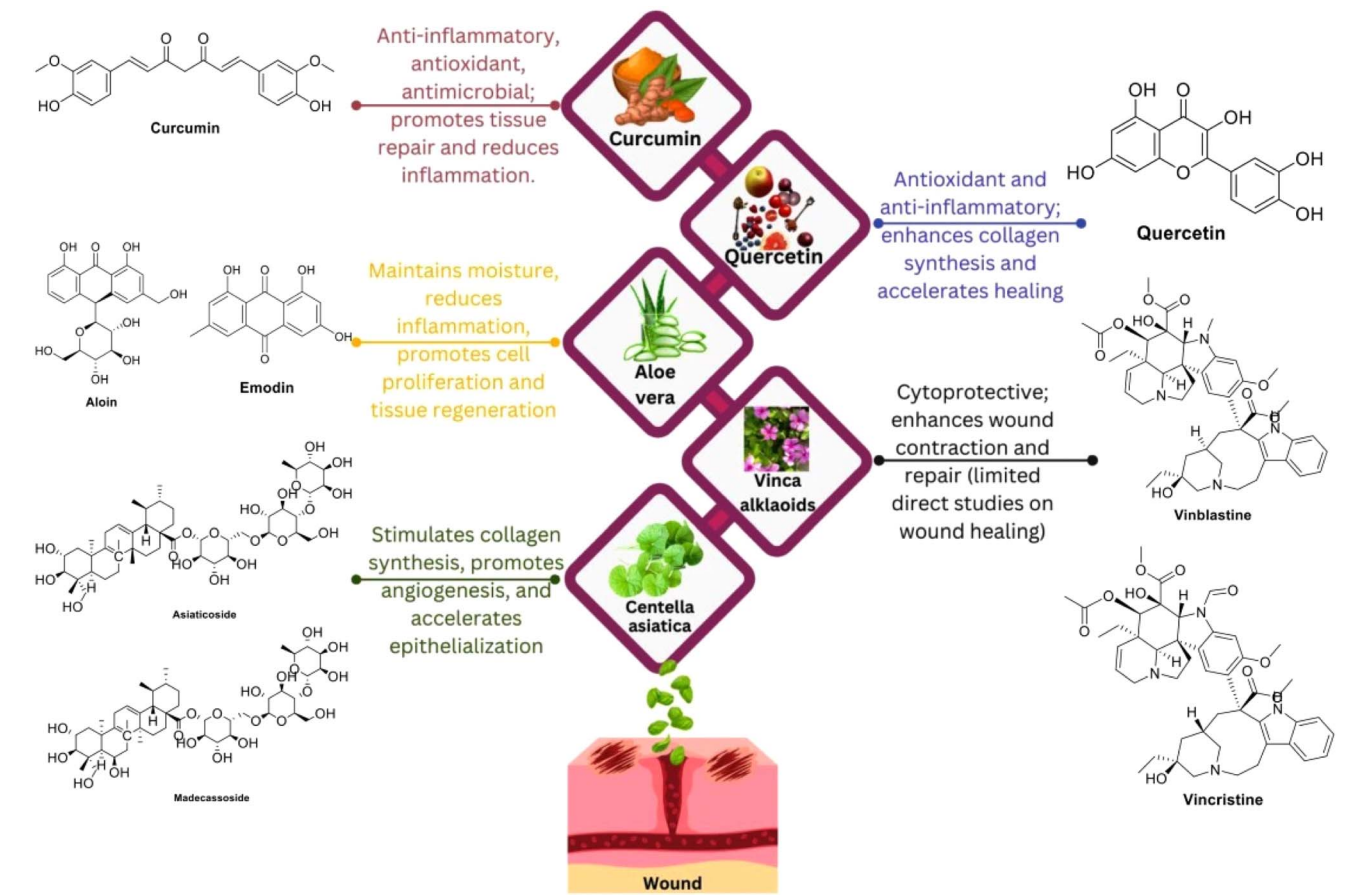

Fig. 5 Medicinal plants, with their chemical structures and bioactivities, utilized in wound treatment.

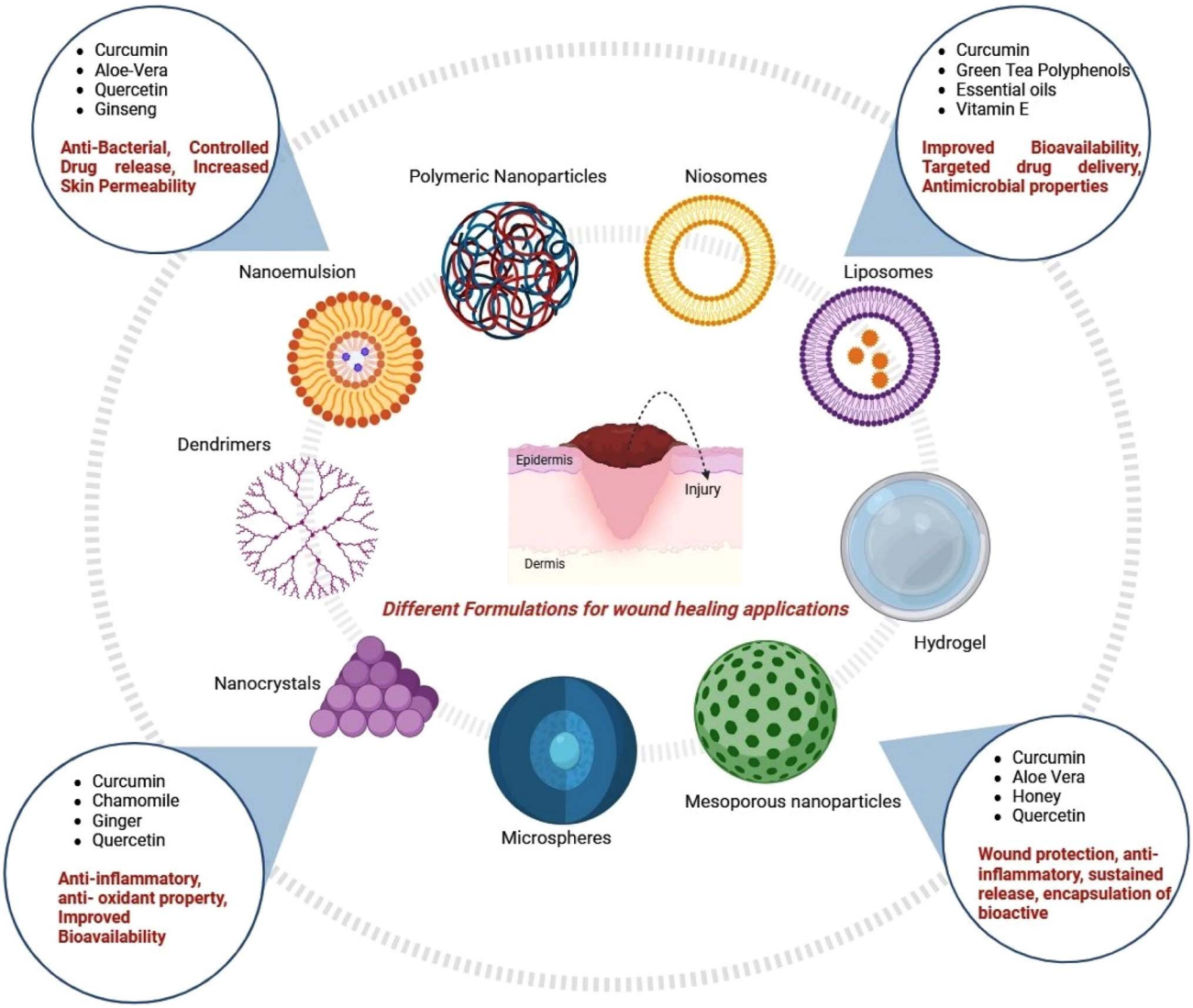

Fig. 6 Nano-formulations loaded with herbal bioactives for enhanced therapeutic efficacy.

process.[173,174] It enhances the contraction rate of wounds, boosting the wound healing process.[175] Cur also binds with COX-2 protein, which ultimately reduces its expression, as well as prostaglandin and thromboxane synthesis. It increases the wound area by up to 20%.[176] During inflammatory reactions, Cur blocks the activity of the two crucial cytokines *i.e.*, tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1), which are generated by macrophages and monocytes that regulate inflammatory responses.[177] It enhances PPAR-γ activity, which ultimately inhibits vascular smooth muscle cell proliferation and decreases angiotensin-II induced inflammatory reactions.[178] Curcumin has an effective protective function against oxidative stress, a complex element which limits tissue regeneration in the process of wound healing through modulating lipoxygenases (LPx) by scavenging free radicals.[179] Curcumin treatment causes fibroblast infiltration into wound sites.[180] It enhances granulation tissue formation and ultimately facilitates re-epithelialization by providing a stable foundation for epithelial cells for migration and healing of wound gaps.[181] Cur enhances collagen and synthesis of the extracellular matrix to accelerate the wound healing process.[182] Gels, films, sponges, synthetic polymers (polyurethane and polyester) and natural biopolymers membranes (*e.g.*, chitosan, hyaluronic acid, and collagen) are used for wound treatment.[183] Curcumin with CNP results in enhanced maturation of the wound, collagen content, cell proliferation and granulation tissue development.[184,185] The applications of curcumin-loaded formulations are summarized in Table 2, highlighting their applications in various wound healing scenarios.

Al-Arjan *et al.*, 2022 fabricated pH-responsive hydrogels by blending bacterial cellulose (BC) with polyvinyl alcohol (PVA) and graphene-oxide (GO) dressing materials by crosslinking with tetraethyl orthosilicate (TEOS). The formulated hydrogels show good, controlled curcumin release (at pH 6.4, 7.4, and 8.4) in a controlled form. As curcumin loaded-BSG-4 shows antibacterial ($p < 0.05$, $p < 0.01$, and $p < 0.001$) and anti-tumor

Table 2 Applications of curcumin-loaded formulations

Components	Formulation	Applications	Reference
Curcumin + chitosan	Nanoparticles, nanofibers, nanotubes	Bacterial infection	186
Curcumin + succinyl chitosan-fish	Hydrogel	Subcutaneous wounds	187
Cur + chitosan + carboxy methyl cellulose (CMC)	Injectable hydrogels	Diabetic wound regeneration	188
Curcumin + pectin + chitosan	Nanofilms	Antibacterial, wound dressing material	189
Curcumin + fenugreek essential oil (FEO) + polylactic acid (PLA)	Films	Antibacterial, antioxidant	190
Cur + dextran + sodium alginate	Wafer dressings	Enhances the healing rate	191
Curcumin + alginate + carrageenan + poloxamer	Hydrogel films	Transdermal wound healing	192
Curcumin + alginate + carrageenan + poloxamer + diclofenac	Films	Antibacterial, transdermal dressings	193
Cur + chitosan + methylcellulose	3D-biocomposite scaffolds	Diabetic wound healing	194
Cur + hyaluronic acid + pullulan	Injectable hydrogel	Diabetic wound repair	195
Curcumin + silk fibroin + HA	Hydrogels	Cell therapy, scaffolding	196
Indole curcumin analogue (ICA) + folic acid conjugated chitosan	Nanoparticles	Antibacterial, anti-inflammatory, anticancer	197
Liposomal CUR + hyaluronic acid (HA) + polyvinyl alcohol (PVA)	Hydrogel	Skin recovery, wound dressings	198

properties (against U87 cell lines), these hydrogels act as a potent biomaterial for chronic wound healing.[199]

Velmurugan *et al.*, 2022 formulated chitosan-based curcumin loaded carbon nanospheres (CNS) on polypropylene (PP) non-woven fabric support. CNS and Cur both contribute to feasible water and moisture absorption by scaffolds and the wound dressing shows maximum wettability (475.37% ± 8.98%). About 96.5% of wound contraction was measured, hence it is effective in skin regeneration.[200]

Singh *et al.*, 2022 developed sustainable extracellular matrices (ECMs) containing Cur and decellularized goat small intestine submucosa (DG-SIS). The scaffolds scavenge free radicals (DG-SIS: 8.6%, DG-SIS/C1: 65.8%, DG-SIS/C2: 71.7%, DG-SIS/C3: 79.9%) and exhibit antioxidant and antibacterial properties. The porosity% and large pore size are 87–94% and 50–357 μm, respectively, which results in enhanced water uptake. DG-SIS/C3 containing 1 wt% Cur shows free radical scavenging of about 80%, which is beneficial for wound healing. Therefore, the system is a promising biomaterial for skin tissue engineering and wound healing.[201]

Wu *et al.*, 2023 encapsulated Cur and Cur-chitosan nanoparticles (CCNP) into chitosan collagen vanillin scaffold by the freeze-drying method. The CCNP + VC and Cur NP + VC nanoscaffolds have particle sizes of 110.6 nm and 195.9 nm, respectively. These nanoscaffolds also have release profiles >60%, improved anti-oxidant properties (>80%) and enhanced wound healing capacity (85.62% and 77.05%, respectively) in a murine cell line. Hence, they are effective and biodegradable drug delivery system for topical use to heal wounds and stop bacterial infection.[202]

Kenawy *et al.*, 2023 prepared cross-linked antimicrobial membrane comprising PVA–*Aloe vera* hydrogels by propanol to transform PVA into a highly crystalline structure. Cur and gentamycin incorporation enhances biological and antimicrobial activities. Cur/gentamicin-loaded hydrogel membranes show the highest angle of contact values (78.2° decreased to 27.7°) after encapsulating the *Aloe vera* to 80% in membranes. *In vivo* studies and the wound dressed histological test reveals the reduced size of the fully thickened wound and re-epithelialization. Therefore, it can be a preferred biomaterial for skin regeneration and wound healing.[203]

Li *et al.* (2024) investigated the use of decellularized caprine small intestine submucosa (D-CIS) encapsulated with nanoformulations of cerium oxide and curcumin for enhancing burn wound healing. The study highlighted the bioactive gel's properties, including antimicrobial-, antioxidant-, and anti-inflammatory effects, along with the sustained release of active components. The combination of cerium oxide and curcumin in the gel accelerates burn wound healing by mitigating oxidative stress, reducing inflammation, and supporting cell recruitment for epithelial and vascular regeneration. These findings underscore curcumin's role as a key component in promoting tissue repair through its antioxidant properties, establishing it as a promising candidate in wound healing applications.[204]

Miele *et al.* 2024 conducted a comparative study on electrospun nanofibers made of collagen and polycaprolactone (PCL) loaded with curcumin (Cur) or resveratrol (Rsv) to evaluate their biocompatibility and effects on wound healing and angiogenesis. Curcumin-loaded fibers exhibit hydrophobic properties, support cell adhesion, and maintain structural integrity, indicating potential for wound dressing applications. Both Cur and Rsv display anti-angiogenic effects in the chick embryo chorioallantoic membrane assay, suggesting suitability for anticancer uses but posing challenges for wound healing where angiogenesis is critical. This highlights the importance of optimizing curcumin concentration to balance its antioxidant and anti-inflammatory benefits while avoiding reduced vascularization in healing tissues.[205]

3.2 Quercetin

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is an endogenous antioxidant from the flavonoid group of polyphenols found in many fruits, vegetables, leaves, seeds, red wines, onions and capers (Liliaceae).[206] It exists as a glycoside, glycone (sugar attached) or aglycone (no sugar attached). It takes many forms in nature, but the form found in plant is quercetin-3-*O*-glucoside (iso-quercetin).[207] The molecular formula of quercetin is $C_{15}H_{10}O_7$ (302.236 g mol^{-1}).[208] Quercetin minimizes fibrosis and scar formation during wound healing, boosts fibroblast cell proliferation, limits immune cell infiltration, and cause changes in fibrosis-related signaling pathway.[209] It has potent antibacterial, anticancer, anti-inflammatory and antioxidant effects, which benefits inflammatory diseases like asthma, arthritis, lung damage, and diabetic angiopathy. In addition, quercetin can reduce inflammation in the acute and chronic phases.[210,211] QCN protects skin from dehydration and inhibits collagen deterioration during inflammatory feedback.[212] It is a great reactive oxygen and nitrogen species and reactive nitrogen species scavenger, making it a suitable option to reduce oxidative stress.[213] QCN is crucial for wound healing due to its free radical scavenging and histamine inhibition, reducing skin swelling.[214] Quercetin has been produced in a variety of dermatological preparations including gel, emulgel, and microemulsion gel.[215] Nanoformulations offer advantages like increased bioavailability, targeted tissue targeting, and controlled release behavior, but also face long-term instability, complex preparation, and high costs, making them less accessible to patients.[216] The application of QCN-loaded gels leads to a significant improvement in wound healing compared with other groups, highlighted by enhancement and reduction of fibroblasts and inflammatory cells, respectively.[217] The levels of inflammatory factors such as tumour necrosis factor, interleukin-1, and interleukin-6 were dramatically lowered.[218] Prodrugs and liposomes are some of the ways to facilitate topical/transdermal delivery of Qu through the skin. The production of quercetin-3-*O*-acyl esters results in a potential topical prodrug.[219,220] QCN has antiaging properties on middle-aged keratinocytes and supports regeneration of terminally senescent cells. It promotes wound recovery, regulates VEGF, TGF-β1, IL-10, slow-modulates TNF-α, and improves wound care by inhibiting the MAPK pathway.[221,222] The wound healing capacity of quercetin and curcuminoid combinations were tested using a scratch experiment, and show faster wound closure and reduced immune cell infiltration (cell migration).[223] *In vitro* studies reveal that quercetin enhances keratinocyte proliferation and migration by increasing β-catenin expression.[224,225] Activation of the ER accelerates re-epithelialization during wound healing *in vivo*. As a result, we believe that quercetin may promote EpSC proliferation *via* the ER.[226] Polymeric drug delivery systems, including nanoparticles, offer promising strategies for disease prevention and treatment.[227,228] Nanoparticles can enhance tumor-targeted delivery by regulating surface ligands, transport various agents *via* antitumor mechanisms, and accumulate higher tumor-encapsulated drugs through permeability and retention.[229] Quercetin's effect on cancer cells includes cell growth inhibition, apoptosis induction, and metastasis inhibition (activates caspase-3, inhibits Akt, mTOR, ERK, reduces β-catenin, and stabilizes HIF-1α).[230] Quercetin stability is affected by antioxidant concentrations, pH, temperature, and metal ions. Encapsulating it in a strong carrier protects it from oxidation, isomerization, and degradation, increasing shelf stability and enabling effective administration.[231] Hence, quercetin therapy enhances wound healing by modulating cytokines and growth factors.[232] Table 3 provides a comprehensive summary of the formulations and applications of quercetin-loaded systems, emphasizing their therapeutic potential in various wound healing scenarios.

Nalini *et al.*, 2023 created gel formulations of quercetin-loaded alginate (Q-ALG)/chitosan nanoparticles (CSNP) incorporated into carbopol encoded as Q-ALG/CSNP-G1 and Q-ALG/CSNP-G2. Q-ALG/CSNP-G2 gel effectively releases quercetin (62.51% ± 0.72%) for 24 h, promotes wound healing, enhances antioxidant and antibacterial effects, and improves the healing quality in Wistar albino rats.[246]

Chaturvedi *et al.*, 2023 explored nano-encapsulated quercetin formulations (lipid-based nanocarriers, nanocrystals, polymeric, mesoporous silica nanoparticles, nanofibers, and scaffolds) to overcome the shortcomings of quercetin. Owing to low aqueous solubility (0.48 g mL^{-1}), membrane permeability (1.8), and high gut wall metabolism (93.3%), a 5% bioavailability enhances quercetin permeability and retention for diabetic foot ulcer treatment efficacy.[247]

Saleh *et al.*, 2023 synthesized quercetin/selenium nanoparticles (Qu/SeNPs) mixed in various ratios into the produced hydrogel to enhance the biological performance and revealed antibacterial-, cell viability-, and anti-inflammatory properties. Qu is used as a reducing agent in SeNP manufacturing since it reduces cytotoxicity against HFB4 and enhances erythrocyte protection, suggesting potential tissue engineering applications with low harmful effects.[248]

Li *et al.* 2024 developed an SF/SPI-Q hydrogel by incorporating quercetin into a silk fibroin and soybean protein isolate hydrogel. The SF/SPI-Q hydrogel combines excellent biocompatibility, biodegradability, and cell migration promotion with the antibacterial and antioxidant properties of quercetin. It accelerates wound healing in an infected burn wound model by promoting epidermal regeneration, collagen deposition, angiogenesis, and reducing inflammation, making it a promising treatment for wound care.[249]

Kumar *et al.* 2024 synthesized a $CaCO_3/SiO_2$ nanocomposite using the sol–gel method and characterized it using XRD, FTIR, and TEM. They combined this nanocomposite with quercetin and incorporated it into a PLGA/gelatin patch to enhance wound healing. The patch promotes cell proliferation, exhibits antibacterial efficacy against four major wound-associated bacterial strains, and demonstrates excellent water retention, making it an ideal material for diabetic wound healing. *In vivo* trials confirm the enhanced wound healing potential of the patch, highlighting its effectiveness in treating diabetic foot ulcers.[250]

3.3 *Aloe vera*

Aloe vera (*Aloe barbadensis miller*, family-Liliaceae) is a perennial, stem-less, xerophytic and succulent green herb, which is

Table 3 Applications of quercetin-loaded formulations

Components	Formulation	Applications	Reference
Sodium alginate + poly(vinyl) alcohol (PLA) + quercetin	Hydrogel	Skin ageing and inflammation	233
Quercetin + oleic acid	Nano-hydrogel	Diabetic foot ulcer	234
Quercetin + silver nanoparticles (AgNPs)	Hydrogel matrices	Diabetic wounds	235
Pectin + chitosan NP + quercetin	Beads	Antibacterial, antioxidant	236
Quercetin + chitosan	Nanotube	Promote moist environment	237
Asparagus cellulose + quercetin	Films	Antimicrobial	238
Quercetin + H_2S	Conjugates	Diabetic wounds	239
Quercetin + lactoferrin + chitosan nanofiber	Nanofiber	Biodegradability, antioxidant	240
Chitosan + PLGA + quercetin	Scaffolds	Oral lesions	241
Quercetin + ZnO + CuO + chitosan	Nanocomposite	Wound recovery	242
Quercetin + PLA + graphene oxide (GO)	Scaffold matrices	Anti-infection	243
Quercetin + *Prunus armeniaca* gum exudate (PAGE)	Green nanoparticles	Antibacterial	244
Quercetin + carboxymethyl cellulose (CMC)	Nanogel	Anticancer	245

found in the desertic region of Asia, Europe, America, Africa and is also cultivated in India.[251] *Aloe vera* (AV) is a plant extract that is widely used for therapeutic purposes as it consists of polysaccharides (pectic acid and glucomannans) and enzymes (bradykinase, carboxypeptidase, peroxidase, lipase, cellulase, and catalase).[252] AV leaves consist of three layers: inner (transparent gel containing 99% water + 1% of lipids, glucomannans, vitamins, amino acids, and sterols), middle (bitter yellow juice with anthraquinones and glycosides) and outer (contains carbohydrates and proteins) layers.[253] It is known for its antioxidant-, anti-diabetic-, immunostimulatory-, neuro-protective-, anti-bacterial-, anti-viral-, wound healing-, anti-tumor-, antiseptic-, analgesic-, anti-fungal-, anti-hyperlipidemic-, anti-rheumatoid-, anti-arthritis-, and skin protectant properties.[254] Also, AV leaves contain various chemical constituents such as anthraquinones (treat burns + wound healing), minerals (essential in wound healing), amino acids (reconstruct damage tissues), hormones (wound healing), salicylic acid (analgesic), steroids (anti-inflammatory), saponins (antiseptic), sugars (antiviral), vitamins (anti-oxidant), and protein (cell proliferation).[255] It promotes healing by affecting different factors involved in the process of wound healing.[256] AV is widely used for chronic wounds, *e.g.*, psoriasis, surgical, burn wounds, pressure ulcers and genital herpes.[257] Various polymeric wound dressing materials including non-fibers, hydrogels, foams, transdermal patches, membranes, films, and wafers are used to improve the wound healing properties.[258] They prevents the formation of scar during skin injury by promoting and stimulating the regeneration process and production of cells respectively at hypodermis layer.[259] AV enhances the migration of epithelial cells, maturation of collagen and reduces swelling by keeping the wound moist.[260] The active constituent in the AV gel is a polymer (acemannan), which helps activate macrophages and T-cells to stimulate cytokine production and accelerates the process of wound healing by inducing pro-inflammatory mRNA transcription.[261,262] Additionally, when acemannan is applied topically, it acts through Cyclin-D1 and AKT/mTOR signaling pathways, resulting in reducing the time for wound closure.[263] Also, magnesium lactate as its constituent helps to stop histamine production, which ultimately results in skin itching and irritation.[264] *Aloe vera* enhances the wound healing process due to its inhibiting activity on thromboxane, IL-6 and IL-8 and reduces the levels of TNF-α.[265] AV is responsible for enhancing the cross-linkage of collagen and its composition.[266] It also consists of mannose, which enhances macrophage activity by increasing collagen production.[267] Table 4 provides a summary of the formulations and applications of *Aloe vera*-loaded systems, emphasizing their therapeutic effectiveness in enhancing wound healing in diverse clinical contexts.

Chakraborty *et al.*, 2021 synthesized *Aloe vera* topical gel + nanoemulsion loaded with insulin using polyethylene glycol-400 (PEG), oleic acid, and Tween-80, and evaluated wound healing in diabetic rats. The anti-diabetic effect was found to be $P < 0.0001$ and the biochemical shows greater wound contraction, *i.e.*, about 75 percent in 15 days. Hence, the nanoemulsion acts as a promising tool in rounds of treatment in diabetic patients.[281]

Valizadeh *et al.*, 2022 developed a nanoemulsion gel based on *Aloe vera* loaded erythromycin (AVNE) to improve the process of wound healing. The size of the nanoemulsion particles were 21.2 $\pm$ 5.7 nm. There was great anti-bacterial activity and a reduction in the epithelization period, wound contraction and inflammatory cells. Therefore, AVNE acts as a potential candidate in healing wounds as it enhances collagen synthesis.[282]

Wang *et al.*, 2021 designed a hydrogel wound dressing using AV, dopamine (DA), sodium hyaluronate (SH) and chitosan with the help of deep eutectic solvent (DES). The hydrogel shows great cell compatibility and promotes the regeneration of skin tissues within 12 days. The developed hydrogels has potential as a potent wound dressing.[283]

Ijaz *et al.*, 2022 formulated herbal cream containing AV-gel and tomato powder. The amount of AV-gel was 2.0 mL, 4.0 mL, 6.0 mL, 8.0 mL and of tomato powder was 0.2 g, 0.4 g, 0.6 g, and 0.8 g in four different formulations (F1 to F4, respectively). The pH of the creams is 7.3 to 7.6, so it is safe for human skin and the spreadability is between 9 to 13. Hence, the herbal creams are effective against any skin injury due to the economical and moisturizing behaviour.[284]

Ghorbani *et al.*, 2020 synthesized the nano-fibers (NFs)-zein/polycaprolactone (PCL)/collagen loaded with zinc oxide NPs +

Table 4 Applications of *Aloe vera*-loaded formulations

Components	Formulation	Applications	Reference
Arabic gum + *Aloe vera* + gelatin powder + polyurethane	Bio-based wounds	Bedsore	268
Aloe vera-acetate/polyvinylpyrrolidone (AVAc/PVP)	Electrospun fibres	Anti-bacterial and anti-inflammatory	269
Alginate + *Aloe vera* + honey + cellulose	Nanocrystals	Scratch wound and anti-bacterial	270
Thymol + *Aloe vera* + chitosan	Films	Anti-oxidant	271
Tetracycline hydrochloride (TCH) + poly(caprolactone) + gelatin + *Aloe vera*	Hybrid nanofibers	Anti-microbial	272
Chitosan + *Aloe vera*	Hydrogels	Cell adhesion, reduce inflammation, better re-epithelization	273
Aloe vera + honey + sodium alginate + chitosan	Wound dressings	Repair tissue	274
Xanthan gum (XG) + *Aloe vera* extract (AVE) + bimetallic Ag/MgO NPs	Nanocomposite	Anti-bacterial	275
AV + gum Arabic (GA) + silver (Ag)	Nanocomposites	Anti-biofilm	276
Chitosan + *Aloe vera* + mesenchymal stem cells (MSCs)	Gel	Grade-II burn injuries	277
Aloe vera + copaiba + chitosan	Nanofilms	Wound closure	278
Alginate/gelatin + nanosilver + AV + CUR + plantain peel + *Calendula* flower petal	Hydrogel	Antioxidant, antimicrobial, anti-inflammatory	279
Zinc oxide (ZnO) + *Aloe vera* + cellulose	Nanoparticles	Antimicrobial, antioxidant	280

AV (ZnO NPs AV) for tissue engineering. The ZnO (1 wt%), AV (8 wt%) and zein/PCL (70 : 30) show mechanical properties and thermal stability. Also, the water contact angle of NFs is enhanced by reducing the zein/PCL. The formulated NFs inhibited *E. coli* and *S. aureus* bacteria with ZOIs of 15.38 ± 1.12 mm and 19.23 ± 1.35 mm, respectively. Therefore, NFs act as a promising active scaffold for the process of wound healing.[285]

Vajrabhaya *et al.*, 2022 synthesized toothpaste containing *Aloe vera* + sodium chloride for enhancing healing as well as oral hygiene. The cytotoxicity of 0.2% (96.44%) or 0.02% (99.07%) toothpaste solution was checked: of the human fibroblast cell line shows good cell migration for the 0.2% concentration. The herbal formulation also enhances cell migration compared with control medium ($p = 0.02$). Also, the anti-microbial effect on *Porphyromonas gingivalis* planktonic form is lower than 0.12% chlorhexidine (38.22 + 9.13%) and *P. gingivalis* biofilm inhibition is enhanced. Therefore, it is an effective and promising formulation for oral health purposes.[286]

Kenawy *et al.* 2024 developed physically crosslinked PVA membranes blended with *Aloe vera* extract using a solution-casting method. These membranes were loaded with caffeine and vitamin C and evaluated for their wound healing potential in Wistar albino rats. *In vitro* results show improved wound healing through enhanced tissue platelet aggregation and appropriate release behavior. *In vivo* studies reveal that PVA/*Aloe vera*/vitamin C membranes significantly reduce the wound area, while the PVA/*Aloe vera*/caffeine membranes show faster wound closure. Membranes containing both caffeine and vitamin C result in the most significant healing, including hair re-growth. Histological analyses confirm effective re-epithelialization, demonstrating the strong wound healing and skin regeneration properties of these membranes.[287]

Aizaz *et al.* 2024 developed a biocompatible, biodegradable biopolymeric gel based on Agar–agar (AA) and gelatin (G) infused with hyaluronic acid (HA) and *Aloe vera* (AV) for burn treatment and wound healing. The gel exhibits therapeutic effects due to its hydrating-, antibacterial-, and angiogenic properties. Characterization through SEM shows a porous structure, allowing the release of AV and HA, while FTIR analysis confirms crosslinking between AA and G. The gels display rapid release of AV and HA, with high antibacterial activity against *E. coli* and *S. aureus*. *In vivo* studies using the chorioallantoic membrane assay confirmed enhanced angiogenic potential, with a significant increase in the number of branched vessels in the AA/G/HA/AV gel. The results suggest that the AA/G biopolymeric gels infused with AV and HA are effective for burn treatment and wound healing.[288]

3.4 *Vinca* alkaloids

Vinca alkaloids (*Cape periwinkle*) are organic compounds derived from the Madagascar periwinkle plant *Catharanthus roseus G*, containing carbon, hydrogen, nitrogen, and oxygen with hypoglycemic and cytotoxic effects.[289] *Vinca* alkaloids including vinblastine (VBL), vinorelbine (VRL), vincristine (VCR) and vindesine (VDS), which prevent mitosis of cancerous cells by inhibiting microtubule formation.[290,291] *Vinca* alkaloids have dimeric structures with an indole nucleus (catharanthine) and dihydroindole nucleus (vindoline) which are linked together with complex systems.[292] *Vinca* alkaloid treats various diseases, including leukemia, lymphoma, Hodgkin's disease, neuroblastoma, and breast and testicular cancer.[293] It possesses various activities, like antioxidant, antimicrobial, antitumor, antidiabetic, antineoplastic, *etc.*[294] *Vinca* alkaloids prevent spindle formation during the M-phase of the cell cycle. At low doses, they disrupt microtubular function, but cell cycle arrest and apoptosis occur at higher doses.[295] Cell cycle arrest is caused by B-cell lymphoma BCL-2 protein phosphorylation and increased BAX protein levels. Microtubules are involved in transcellular transport, motility, and cytoskeleton stability.[296] *C. roseus* wet flowers and leaf extracts are used as a paste for wounds and tea for Ayurvedic treatment of skin issues,

dermatitis, eczema, and acne.[297] The juice of *Vinca rosea* leaves is more successful in lowering total cholesterol, LDL-C, and VLDL in serum levels, triglycerides, and histology of the liver, kidney, and atherosclerotic activity.[298,299] Bioactive compounds are heat-, light-, and oxygen sensitive, and drying procedures have a substantial impact on the retention of bioactive components in *C. roseus* material.[300] The investigation of ex vivo applications of the nanoformulation to assess the increased deliverability of *Vinca* alkaloids *via* nano-vectors creates a novel drug delivery system based on nanosized particulate particles, known as niosomes, to improve the bioavailability.[301,302] *Vinca* alkaloids and anti-microtubule agents affect nonmalignant and malignant cells in the nonmitotic cell cycle, making them commonly used in combination chemotherapy regimens without DNA cross-resistance.[303,304] Cancer remains a significant challenge, with vincristine and vinblastine being highly beneficial agents but their exorbitant and inefficient production persists.[305,306] Due to the diverse qualities and applications, *Vinca* alkaloids are an effective herbal bioactive in the treatment of a variety of ailments.[307] The therapeutic potential of *Vinca* alkaloid-loaded systems to enhance wound healing across various clinical scenarios is highlighted in Table 5.

Aldawsari *et al.*, 2022 synthesized vinpocetine (VNP) to improve cerebrovascular disease management but it faces limitations due to reduced bioavailability and brain levels. The study evaluated the drug delivery effectiveness of surface-tailored intranasal emulsomes using 3221 factorial design and optimization methods. Rat pharmacokinetic assessment improves bioavailability and higher brain levels in surface-tailored VNP emulsomal formulations. Thus, surface-tailored emulsomes are promising for generating high VNP levels in the brain.[319]

Barnett *et al.*, 2023 used photochemical internalization (PCI) to improve the anticancer drug therapeutic index and develop novel nanoformulations against breast and pancreatic cancer cells. Frontline drugs, *Vinca* alkaloids, taxanes, antimetabolites, and nano-sized formulations were tested in a 3D PCI *in vitro* model. PCI technology enhances therapeutic activity in drug molecules (up to 5000–170 000-fold) with *Vinca* alkaloids and nanoformulations showing potency, efficacy, and synergy.[320]

Bluette *et al.*, 2021 developed a nanoparticle vincristine (VCR) formulation to alleviate chronic ischemic neuropathy (CIPN) in nonclinical animals. Nano-VCR and empty nanoparticles do not affect gait parameters, while solution-based VCR reduces run speed and increases step cycle ($P < 0.05$), with no sciatic nerve degeneration. Hence, nano-VCR formulation alleviates behavioral changes in the peripheral nerve without structural improvements; hence optimization is needed for better observation.[321]

Wang *et al.*, 2021 fabricated liposome polymeric micelles (PMs) loaded with vinorelbine (NVB) and cisplatin (CDDP) for NSCLC treatment, addressing high mortality and poor prognosis. CoNP-lips, with a spherical shape and uniform size distribution (162.97 ± 9.06 nm), show synergistic cytotoxicity in NSCLC cell lines, a higher plasma half-life than NP solution, antitumor efficacy in C57BL/6 mice and enhanced permeability and a retention effect in tumors.[322]

Mohsen *et al.* (2024) developed a polyelectrolyte complex (PEC) carrier system for vinorelbine tartrate used in cancer treatment. The PEC was prepared by entrapping vinorelbine tartrate using gum kondagogu and chitosan as polymers. Various formulations were optimized by adjusting the ratios of these polymers. The highest PEC output was achieved with gum kondagogu concentrations exceeding 80%. The PEC demonstrates reduced drug release in 0.1 N HCl compared to phosphate buffer (pH 6.8), with increased drug release and swelling as the gum kondagogu concentration rose. The formulation with a higher chitosan content (PEC 1 : 3) shows 98% drug release in 4.5 h. These findings suggest that the gum kondagogu/chitosan-based hydrogels offer significant potential for controlled drug delivery by reducing the dosing frequency for drugs like vinorelbine tartrate.[323]

3.5 *Centella asiatica*

Centella asiatica (CA) or Gotu Kola or Jalbrahmi or Indian pennywort or tiger grass is a medicinal herbal perennial plant

Table 5 Applications of *Vinca* alkaloid-loaded formulations

Components	Formulation	Applications	Reference
Polyesteramide (PEA) + *Vinca* alkaloids + polyvinylpyrrolidone, polyvinyl alcohol + surfactants	Nanoparticles	Cytotoxic activity	308
VNR + propylene glycol + melanoma cell	Hydrogel	Treatment of skin cancer	309
Vinca alkaloid + niosomes	Nano niosomal	Cell growth and strong cytotoxic activity	310
Vinpocetine (VIN) tablets + poloxamer–chitosan + carbopol–HPMC–alginate	Hydrogel	Chronic disorders	311
Ag–MnO_2 + *Vinca* minor extracts + *Chelidonium majus*	Nanoparticles	Chemotherapeutic and cytotoxicity	312
Curcumin + *Vinca* alkaloids, + taxanes + camptothecin + anthracyclins	Nanocarriers	Cancer therapy and improved bioavailability	313
Monoterpene indole alkaloids (*Vinca*) + MS + HRMS + acetylcholinesterase	Scaffolds	Antioxidant	314
Vincristine + vinorelbine + cyclopropane ring	Conjugates	Antitumor, chemotherapeutic agent	315
Uracil + paclitaxel + *Vinca* alkaloids + doxorubicin (DOX)	Nanotool	Enhanced permeation and retention (cancer)	316
Manganese-doped copper NPs + *Vinca rosea* leaf	Nanoparticles	Antioxidant, antibacterial	317
ZnO + V-doped ZnO + *Vinca* plant leaf	Nanoparticles	Antidiabetic, antioxidant	318

and a culinary vegetable belonging to the Umbelliferae family which is available in Southeast Asian countries.[324–326] Traditionally, it is popular for skin condition therapy such as leprosy, ulcers, eczema, lupus, *etc.*, due to its anti-hepatotoxic, antioxidant, anti-inflammatory, anti-microbial, neuroprotective and wound-healing properties.[327,328] CA extracts have positive action on the wound healing process as it enhances the synthesis of collagen as well as micro-circulatory functions.[329,330] Also, it contains asiatic acid (AA) which has a great potential for keloid (occurs due to collagen deposition and high proliferation, *i.e.*, fibro-proliferative lesions) management, because of abnormal healing beyond wound margins.[331] CV induces collagen formation, plays an important role in Transforming Growth Factor-β1 (TGF-β1) and prevents plasminogen activators action by Plasminogen Activator Inhibitor-1 (PAI-1).[332] CV is responsible for preventing blood loss and is important for clot dissolution by sealing the blood vessels and protecting them.[333] Various triterpenes/centelloids are present in CA, *i.e.*, asiaticoside (AS), madecassoside (MS), AA, madecassic acid (MA), brahmoside, brahminoside, brahmic acid, madasiatic acid, centic acid, cenellic acid, centelloside, isothankuniside, thankiniside, *etc.*[334,335] *C. asiatica* reduces inflammation by bringing up the lessening proteinase and inhibiting lipoxygenase (LOX) activity to inhibit protein denaturation, which can improve rheumatoid arthritis.[336] Other phytoconstituents in CA include flavonoids, saponins, sesquiterpenes, eugenol, catechin, epicatechin, kaempferol, quercetin and plant sterols.[337] AA is one of the most important chemical constituents with a pivotal role in the wound healing process.[338] CA has potential therapeutics in respiratory, endocrine, digestive, neurological, cardiovascular and dermatological diseases.[339] AS promotes cell migration, attachment and growth of normal human skin.[340] CA is very effective for the treatment of wound burns, wound infections and hyper-trophic scars.[341] It accounts for the rapid epithelization and induces angiogenesis that promotes the wound healing process.[342] It is also used as a brain-tonic.[343] It is rich in niacin, carotene, and vitamins (C, B1, B2, and A).[344] Table 6 provides a comprehensive analysis of *Centella asiatica*-loaded formulations, highlighting their therapeutic efficacy in promoting wound healing across multiple clinical applications.

Sukmawan *et al.*, 2021 determined wound healing activity of *Ageratum conyzoides* L. leaf ethanolic extract + CA + astaxanthin gel. The wound healing activity are 69.36%, 72.51%, 70.14%, 81.70%, 86.54% and 80.21% for the six-treatments: positive (bioplacenton) control, negative (placebo) control, BP5, BU5, BU10 and BP10, respectively. Therefore, BU10 acts as a promising tool that provides the best and highest wound healing activity ($p < 0.05$).[358]

Camacho-Alonso *et al.*, 2019 evaluated the effect of porcine acellular urinary bladder matrix (AUBM) + CA extract for healing tongue wounds. For this, four groups were created: Group 1 (Control with no product), Group 2 (CAE), Group 3 (AUBM + orabase), and Group 4 (Orabase). Based on CD31 and histological wound repair, they were arranged as Group 3 > 2 > 4 > 1 and tongue wound % were arranged as least to greatest: 3 < 2 < 4 < 1. Group3 containing AUBM shows a vast difference compared with the other groups. Therefore, CAE and AUBM are effective for the oral tissues and oral mucosa regeneration, respectively.[359]

Bozkaya *et al.*, 2022 produced antimicrobial nanofiber wound dressing using CA coated silver NPs. The size and zeta potential of NPs are 14.8 ± 7.3 nm and −30.4 mV, respectively. The 12% polycaprolactone (PCL) and 3.5% polyethylene oxide (PEO) solutions were also prepared. *In vitro* and silver release profile shows that nanofibers show great potential, with cytotoxic and anti-microbial studies indicating that the nanofibers are effective against *Staphylococcus*, *E. coli* and *Candida albicans*, with good biocompatibility for L929 fibroblast cells. Hence, the nanofibers have a promising potential for wound healing.[360]

Wang *et al.*, 2021 designed sandwich like nanocomposite hydrogel dressing using non-woven fabrics (NF) in the middle, with gelatin + chitosan hydrogel + CA as the base. The hydrogels showed a uniform microporous structure with high water absorbency, and *in vitro* study also showed sustained release with goof anti-bacterial activity against *S. aureus* and *E. coli*. Therefore, the hydrogels show excellent biocompatibility and have a potential in wound healing.[361]

Liu *et al.*, 2022 fabricated a topical gel by combining CA, nitric oxide (NO), and hydroxyethyl cellulose for diabetic cutaneous ulcers (DCU) for promoting wound healing. This combination accelerates the healing speed of the DCU wounds. The 8% CA total glycoside nitric oxide gel (CATGNOG) shows the best headlining effect on ulcers by inhibiting the bacterial growth on the surface of wounds, thereby relieving the inflammation reaction and promoting DCU healing.[362]

Tanga *et al.*, 2022 evaluated the efficacy and biocompatibility of CA using CMC on methanol based extract for wound healing progression. The concentrations were prepared as: 0.0%, 0.25%, 0.5% and 1% of CA extract; out of which 0.5% extract showed the highest wound contraction ($p < 0.05$) in terms of tissue deposition and polymorphonuclear cell infiltration. Therefore, 0.5% CA extract in CMC shows great wound closure progression by enhancing collagen-II and III expression and reducing TGFβ1 expression.[363]

Wang *et al.* 2024 developed a PLX/ZnO nanocomposite incorporated with *Centella asiatica* extract (CAE) for diabetic wound healing. The ZnO nanoparticles are evenly distributed within the PLX framework, as confirmed by XRD, FTIR, and TEM analyses. The nanocomposite is biocompatible with mouse fibroblast (L929) cells and exhibits key properties, such as rapid self-healing and effective antibacterial activity against Gram-positive and Gram-negative bacteria. The formulation significantly improves cell proliferation, migration, and tube formation in skin fibroblast and HUVEC cell lines. This CAE@PLX/ZnO nanoformulation offers a promising approach for multi-functional diabetic wound healing treatment.[364]

4. Clinical trials

4.1 Chitosan

Abdollahimajd *et al.*, 2022 compared the clinical safety and efficacy of chitosan dressing and nano-silver (Anticoat™) dressings for the treatment of refractory diabetic wounds. The dressings were applied on wounds and examined every week.

Table 6 Applications of *Centella asiatica*-loaded formulations

Components	Formulation	Applications	Reference
Chitosan-sodium tripolyphosphate + polyvinyl alcohol (PVA) + *Centella asiatica*	Nanocomposite	Bacterial penetration	345
PVA + *Centella asiatica*	Nanofibers	Antibacterial	346
Gelatin/chitosan + *Centella asiatica* + *Phellodendron amurense*	Patches	Accelerate skin fibroblast cell viability	347
PVA + *Centella asiatica* (CA) + NH_4I	Polymer electrolytes	Wound healing	348
Chitosan + *Centella asiatica* + ethanol extract	Microneedles	Wound healing	349
Poly(hydroxybutyrate-*co*-hydroxyvalerate) and carboxymethylcellulose (CMC) + *Centella asiatica*	Nanocomposite	Anti-proliferative	350
Centella asiatica + hyaluronic acid	Hydrogel	Self-healing	351
Collagen + gelatin + *Centella asiatica*	Nanocomposite	Tissue repair	352
CMC + gelatin + *Centella asiatica*	Nanofilm	Antioxidant	353
CA + polyurethane + asiaticoside + silver nanoparticles + CMC	Dressings	Traumatic dermal wound	354
CA + CMC + polyethylene oxide + cellulose	Nanofiber	Anti-bacterial	355
CA + chitosan + PVA	Nanogel	Anti-inflammatory, antioxidant, antibacterial	356
C. asiatica (pegagan) + chitosan	Nanoparticles	Diabetic wounds	357

The mean% reduction of the 10-item-Diabetic-Foot-infection (DFI) score were 74.2% and 78.1% in nano-silver and chitosan, respectively; with no toxic events. The above data proves that the chitosan dressing as more effective and safer for diabetic wounds than nano-silver.[365]

Radhakrishna *et al.*, 2023 evaluated wound healing and hemostatic efficacy of chitosan dressing compared with cotton pressure pack after extraction of tooth in anti-thrombotic patients. Out of 54 subjects, 36 patients were on single anti-thrombotics whereas 19 patients were on dual anti-thrombotics. The time taken to achieve homeostasis by the chitosan dressing was shorter compared with cotton pressure packs (96 ± 4 and 797 ± 23 seconds; $P < 0.001$). The chitosan group took a similar time to achieve homeostasis of single (90 ± 6 seconds)/dual therapy (109 ± 8 seconds). On the other hand, patients on single therapy in the cotton pressure pack group have less time to achieve homeostasis (726 ± 26 seconds; $P < 0.001$) compared with the time taken by dual therapy (940 ± 20 seconds). Also, the alveolar healing index was better in chitosan (88.9%) compared with the cotton pressure pack (3.7%). Hence, the chitosan dressing has a future potential in patients with post-operative bleeding either with single or dual anti-thrombotic therapy.[366]

Slivnik *et al.*, 2024 assessed the efficacy of a chitosan-based gel (ChitoCare) for treating non-healing diabetic foot ulcers (DFUs). Forty-two patients with chronic DFUs were randomized to receive either ChitoCare or a placebo gel for 10 weeks, followed by a 4-week follow-up. At week 10, the ChitoCare group showed 16.7% complete wound closure compared to 4.2% in the placebo group ($p = 0.297$). The ChitoCare group also had a significantly greater median relative reduction in wound surface area (92% *vs.* 37%, $p = 0.008$) and a 4.62-fold higher likelihood of achieving 75% wound closure ($p = 0.012$). Additionally, the Bates-Jensen Wound Assessment Tool revealed significantly better wound conditions in the ChitoCare group. These findings suggest that the ChitoCare gel significantly enhances the healing of DFUs and offers promising results for chronic wound management.[367]

4.2 Cellulose

Oliveira *et al.*, 2021 investigated the effectiveness of human recombinant-Epidermal Growth Factor (h-EGF) compared with 2% carboxymethyl cellulose (CMC) in diabetic wound healing. For this, 25 subjects (14: rh-EGF and 11: CMC) were taken with Type-II diabetes. The %reduction in wound area was higher in the intervention group (reduce slough) compared with the control group ($p = 0.049$). The observations were enhanced granulation and epithelial tissues with reduction in exudate levels in both groups. h-EGF is considered to be effective and feasible as no toxic effects are observed, it causes significant reduction in the wound area and is the safest therapy for chronic wounds.[368]

Koivuniemi *et al.*, 2020 evaluated the performance of nanofibrillar cellulose (NFC) wound dressing (FibDex®) for donor site treatment against polylactide-based copolymer dressing. About 24 patients were enrolled for skin grafting with mean age of 49 ± 18, and the results showed enhanced skin elasticity properties; therefore, it has potential for the treatment of wounds.[369]

4.3 Collagen

Miyab *et al.*, 2020 assessed the effect of cheaper, oral collagen-based supplement for the healing process in 31 patients with about 30% body surface area burn. The patients were assigned to receive a collagen supplement or isocaloric placebo. After changes, the concentrations were higher in the collagen group at week 2 (from 29.7 ± 13.6 *vs.* 17.8 ± 7.5 mg dL^{-1}, $P = 0.006$ to 13.9 ± 9.8 *vs.* −1.9 ± 10.3 mg dL^{-1}, $P < 0.001$) than that of week 4 (from 35.1 ± 7.6 *vs.* 28.3 ± 8.2 mg dL^{-1}, $P = 0.023$ to 19.2 ± 7.5 *vs.* 8.5 ± 10.1 mg dL^{-1}, $P = 0.002$). Also, the ratio of wound healing was 3.7 times in collagen as that of control group (95% CI: 1.434–9.519, $P = 0.007$). Therefore, hydrolysed collagen

supplement improves the healing of wounds and clinically reduces 20–30% of burns in patients.[370]

Chandler *et al.*, 2020 evaluated the comparison of diabetic foot ulcer (DFUs) outcomes with a daily saline-moistened gauze dressing: standard of care (SOC) or collagen wound conforming matrix (WCM), made up of 2.6% fibrillar bovine dermal collagen. There is a faster healing rate of the WCM compared with the SOC. Over 4 weeks, the wound area decreased to ≥75% in about 50% patients with WCM compared with 13% for the SOC treatment. Due to the non-toxic, well-tolerated and feasible nature of WCM, it has a potential to treat modality to accelerate the healing rates of DFU.[371]

Beinz *et al.*, 2024 evaluated the progression of wound healing using three different collagen-based wound dressings—Mucograft® (MG), Mucoderm® (MD), and Fibro-Gide® (FG)—compared to a control (C) group for palatal defects. The study involved 20 participants, each with four palatal defects randomly assigned to the treatment groups. All groups achieved complete wound closure by day 14. At day 7, the control group showed the least remaining open wound (49.3%) compared to FG (70.1%), MD (56.8%), and MG (62.2%), with statistically significant differences between FG and C ($p = 0.01$) and MD and FG ($p = 0.04$). Pain levels remained low across all groups, with no participant rating pain higher than 4 out of 10. The results indicate that collagen-based dressings aid in covering open defects but do not significantly accelerate wound closure or reduce pain. FG exhibits slower wound closure than C and MD, despite not being designed for open oral wounds.[372]

4.4 Alginate

Zhao *et al.*, 2022 explored the timing of change in first dressing with alginate dressing, used after peripherally inserted central catheter (PICC) line insertion in patients with a tumor. About 286 patients with tumors and alginate dressing after PICC were then divided into the control (10) and observation group 1 or OG1 (9) and 2 or OG2 (10); out of which 29 have +ve bacterial cultures. The condition of each patient after 96 h of PICC placement promotes wound healing.[373]

Loera-Valencia *et al.*, 2022 developed calcium-alginate dressings with ZnO nanoparticle dressings (CAZnODs) for DFU therapy and it was tested on 26 Type 2 diabetes patients for its efficacy. Patients were grouped as G1 (CA NPs), $n = 16$ and G2 (without NPs), $n = 10$. In G1, about 75% of wound closure was achieved whereas it was about 71% in G2 ($p = 0.011$). The average time of healing is 48 days in G1 and 72 days in G2. Hence, the NP dressings avoid the secondary or T2D infection and induce better tissue regeneration.[374]

Wang *et al.* (2024) conducted a randomized clinical trial to compare the effectiveness of electrospun poly(L-lactide-*co*-caprolactone) and formulated the porcine fibrinogen (PLCL/Fg) dressing with alginate dressing for treating diabetic foot ulcers (DFUs). The study included 52 patients with DFUs of 1–20 cm^2 and Wagner grade 1 or 2. The participants were randomized to receive PLCL/Fg ($n = 26$) or alginate dressing ($n = 26$) for 12 weeks. The results show that 91.7% of patients in the PLCL/Fg group achieve complete healing, compared with 63.6% in the alginate group ($p = 0.003$). Both groups experience some treatment-related adverse events (20.8% in the PLCL/Fg group and 18.1% in the alginate group). The PLCL/Fg dressing is more effective at promoting wound healing and regulating the wound microenvironment in DFUs.[375]

4.5 Hyaluronic acid (HA)

Kartika *et al.*, 2021 evaluated autologous platelet rich fibrin (A-PRF) + HA, A-PRF + NaCl 0.9% as a control for the treatment of DFU. Patients with DFU with a wound time of 3 months were randomly arranged into A-PRF + HA, A-PRF and Control groups and examined on day 0, 3 and 7. ARF + HA has an enhanced VEGF from day 0 (232.8 pg mg^{-1}) *vs.* day 7 (544.5 pg mg^{-1}) and day 3 ($p = 0.022$) *vs.* day 7 ($p = 0.001$). Also, there is decrease in IL-6 in this group from day 0 (106.4 pg mg^{-1}) *vs.* day 7 (88.7 pg mg^{-1}) compared with the other groups, where it was enhanced. Therefore, the A-PRF + HA group enhances angiogenesis and reduces inflammation in patients with DFU.[376]

Ibraheem *et al.*, 2022 evaluated the efficacy of 0.01% HA spray Gengigel® and 0.2% HA gel Gengigel® in the extraction wound healing through ruler and digital planimetry method. About 30 healthy females (20–60 years old) were grouped into Test Group A (gel), test Group B (spray) and a control group (without HA). The results in the ruler method in terms of wound closure in the control group, gel group and spray group were 43.01%, 67.01% and 65.82%, respectively. On the other hand, it was 47.97%, 69.08% and 66.94% for control, gel and spray group respectively with the digital planimetry method. Therefore, HA gel has greater potential than the spray due to its better wound closure properties.[377]

Graziani *et al.* (2024) conducted a single-center, randomized clinical trial to evaluate the effect of chlorhexidine (CHX)-based mouth rinses on periodontal surgical wound healing. Patients were randomly assigned to one of three groups: (i) CHX + anti-discoloration system (ADS) + hyaluronic acid (HA), (ii) CHX + ADS, or (iii) no treatment (control). Wound healing was assessed using the plaque score, gingival inflammation, and the early healing index (EHI) at 3, 7, and 14 days post-surgery. At 3 days, the CHX + ADS group has significantly improved healing, with lower EHI scores compared to the control ($p < 0.01$). The CHX + ADS + HA group exhibits enhanced healing, with improved EHI, plaque containment, and reduced gingival inflammation at all-time points ($p < 0.01$). The study concluded that CHX–ADS mouth rinses improve early wound healing and the addition of HA further promotes soft tissue closure following periodontal surgery.[378]

4.6 Pectin

Sabando *et al.*, 2020 evaluated and assessed hydrocolloid films by crosslinking pectin/starch blend-loaded with bioactive extracts of *Ugni molinae* and *Gunnera tinctoria* leaves to check the healing property on pressure ulcers. The formed films show good water-uptake capacity (100–160%) and inhibit about 50% of topical edematous responses due to the incorporation of leaf extract. The topical application of films shows complete closure of pressure ulcers after 17 days without any toxic effect;

therefore, the hydrocolloid matrix exhibits physiochemical properties, which can be used as plant extract carriers with wound healing properties.[379]

Alsakhawy *et al.*, 2022 utilized Arabic gum (AG)/pectin hydrogel to encapsulate naringin (NAR) for wound healing potential. The hydrogel shows 99.88% ± 0.096% encapsulation efficiency with 16.64% ± 0.013% drug loading%. NAR-loaded hydrogel accelerates the healing of wounds, and increases angiogenesis and collagen deposition due to its potent antioxidant property. Also, the hydrogel down regulates ($P < 0.001$) TNF-α and apoptosis mRNA expression. Hence, the NAR-loaded AG/pectin hydrogel is effective and potent for wound healing purposes.[380]

Gou *et al.*, 2024 developed a multifunctional carboxymethyl chitosan-based hydrogel dressing (EGF@PDA–CMCS–PE) for diabetic wound healing. The hydrogel incorporates pectin (PE) and polydopamine (PDA) to enhance its mechanical properties, tissue adherence, and water retention. Loaded with recombinant human epidermal growth factor (rhEGF), it exhibits significant antioxidant capacity, scavenging harmful radicals and increasing antioxidant enzyme levels *in vivo*. The hydrogel demonstrates good biocompatibility, antimicrobial properties, and a sustained EGF release over 120 h. *In vivo* studies in diabetic mice show a 97.84% wound contraction rate by day 14, with histopathology confirming fibroblast proliferation, neovascularization, and improved wound healing. The EGF@PDA–CMCS–PE hydrogel holds promise as a therapeutic tool for chronic diabetic wounds and future clinical applications.[381]

4.7 Gelatin

Ehab *et al.*, 2020 compared the effects of Alvogyl *vs.* an absorbable gelatin sponge for the first time as palatal dressings on post-surgical bleeding, post-operative pain and wound re-epithelization. For this, 36 healthy patients were randomized to receive Alvogyl (18 patients, intervention group) or absorbable gelatin sponge (18 patients, control group). Higher visual analogue scale (VAS) pain scores were reported in the control compared with the intervention group up to 12 days after surgery (from (median [range]) 8.5 [2–10] to 1 [0–2] and from 6 [0–10] to 0 [0–2] respectively), with higher analgesics consumption (from 2 [1–3] to 1 [0–3] and from 1 [0–3] to 0 [0–2] tablets, respectively). At 4 weeks, about 22.2% patients in the intervention group *vs.* 11.1% patients in the control group showed complete re-epithelization and no post-surgical bleeding of the palatal engraftment site. Therefore, absorbable gelatin sponge has more potential due to its low cost, haemostasis, pain-reduction and re-epithelization properties.[382]

Li *et al.*, 2022 compared the healing and its outcomes of gelatin sponge patch, ofloxacin otic solution for large traumatic tympanic membrane perforation and healing. About 136 patients with the perforation were included and were divided into three groups: G1 (ofloxacin otic solution), G2 (gelatin sponge patch) and G3 (spontaneous healing). The following closure rates were found: G1-97.6% with a mean time of 13.12 ± 4.61 days, G2-87.2% with a mean time of 16.47 ± 6.24 days and G3-79.2% ($P = 0.041$) with a mean time of 49.51 ± 18.22 days ($P < 0.001$). Therefore, G1 and G2 are effective methods for traumatic large tympanic membrane peroration.[383]

Hussein *et al.*, 2024 evaluated the effect of a melatonin-loaded gelatin sponge on palatal wound healing after graft harvesting. Twenty-six patients were divided into two groups: the test group received the melatonin-loaded sponge, while the control group received a placebo-loaded sponge. Wound healing was assessed clinically using photo-digital planimetry at 7 and 14 days, and histological specimens analyzed. At 7 days, the test group shows significantly reduced raw wound area and increased immature epithelial area compared to the control group. Histologically, melatonin treatment accelerates healing and improves maturation. Pain scores show no significant differences according to the VAS. The study concluded that melatonin-loaded gelatin sponges enhance wound healing, offering a promising new approach to improve palatal wound recovery and reduce morbidity.[384]

4.8 Ulvan

Mariia *et al.*, 2021 evaluated chitosan–ulvan hydrogel encapsulated with cellulose nanocrystals + Epidermal Growth Factor (CS–U–CNC–EGF) by the freeze drying method for wound healing. The NC encapsulation modifies the porous microstructure (size: 237 ± 59 μm to 53 ± 16 μm) and enhances the curve of mechanical stress (0.57 MPa to 1.2 MPa), and swelling behaviour. The nanocomposites show the best cell proliferation and non-toxic effect and the hydrogel shows sustained release of EGF. Hence the hydrogel enhances the EGF delivery at the site of the wound for 15 days from the 100% wound contraction treated group. Therefore, the study proved that the hydrogel has faster wound healing efficiency.[385]

Kikionis *et al.*, 2022 evaluated and investigated the non-woven nanofibrous patches with a ulvan + polyethylene oxide (PEO) patch for anti-inflammatory properties for keloid treatment. Twenty-four patients volunteered for cryosurgery or to apply the ulvan/PEO patch for about 21 days. The results showed significant wound healing, skin inflammation elimination, and biological–physical parameter restoration with no side effects. Hence, the designed patches potentially heal skin trauma after keloid cryo-surgical treatment.[386]

5. Patents

S. no.	Patent number	Biopolymer	Goal	Reference
1	CN113372585A (2021)	Hyaluronic acid + chitosan	Hydrogel having self-healing capacity	387
2	EP3801654A1 (2021)	Chitosan + sodium alginate	Film showing tissue adhesive and healing property	388
3	CN118718059A (2024)	Chitosan	Chronic wounds, anti-inflammatory effects	389

(*Contd.*)

S. no.	Patent number	Biopolymer	Goal	Reference
4	DE102018009781A1 (2020)	Chitosan + gelatin	Aerosol-forming bubble for high absorption used for wound healing treatment and other skin conditions	390
5	CN118236541A (2024)	Hyaluronic acid	Accelerates healing of diabetic wounds, manages bacterial infection, reduces inflammation, promotes angiogenesis and collagen deposition	391
6	CN112957521A (2022)	Alginate–silk fibroin	Hydrogel carrying artemisinin liposome that promotes wound tissue healing	392
7	US11571492B2 (2023)	Starch, chitosan + alginate	Gel used to enhance adhesive properties	393
8	JP2023090744A (2023)	Alginate + hyaluronate + collagen	Hydrogel preventing scarring after surgery	394
9	CN112741929B (2022)	Chitosan + sodium alginate	Composite dressing used as base material and a vacuumizing mode	395
10	BR122021015641B1 (2023)	Cellulose + hyaluronic acid	Composition used for chronic wound treatment	396

6. Conclusion

The integration of herbal bioactives into biopolymeric formulations has marked a significant progress in wound healing, merging the advantages of natural substances with modern biomedical engineering methods. Biopolymers, including ulvan, hyaluronic acid, collagen, chitosan, cellulose, alginate, starch, gelatin, and pectin, have inherent qualities that facilitate wound healing by maintaining moisture, protecting cells from microbial intrusion, and enhancing cell adhesion and proliferation. The incorporation of herbal bioactives such as curcumin, quercetin, *Aloe vera*, *Vinca* alkaloids, and *Centella asiatica* significantly improves the therapeutic efficacy of these formulations, providing anti-inflammatory, antibacterial, and antioxidant properties that mitigate numerous limitations of traditional wound care treatments. Biopolymeric dressings infused with herbal bioactives can expedite wound healing, reduce infection risk, and lessen consequences such as delayed wound closure. Nonetheless, significant research gaps and limitations persist despite these encouraging developments. A challenge is the inconsistency in the efficacy of herbal bioactives, as their biological activity can be affected by factors such as extraction techniques, doses, and formulation stability. Furthermore, the scalability of production and the standardization of these biopolymeric formulations for extensive clinical application necessitate additional research. A further challenge pertains to the necessity for more extensive clinical research to determine long-term safety and efficacy profiles, especially with chronic wounds. Notwithstanding these limitations, the rising quantity of patents pertaining to these advanced formulations reflects the escalating interest in the commercialization of biopolymeric dressings infused with herbal bioactives. These advances possess significant potential to enhance patient care and quality of life by providing a comprehensive approach to wound healing, integrating ancient herbal remedies with advanced biomedical engineering to meet acute and chronic wound healing requirements.

7. Future perspective

Ongoing research and innovative technology are driving the future of herbal bioactive-loaded biopolymeric formulations in wound healing, which is expected to see transformational advancements. One promising approach is to develop multifunctional dressings that can adapt to different wound microenvironments in real time, considering factors like temperature, pH, and the presence of particular biomarkers. By allowing the controlled release of bioactive chemicals suitable to the particular healing phase of the wound, such responsive materials would improve the therapeutic efficacy. Furthermore, careful investigation of synergistic interactions among various herbal bioactives within single formulations may produce improved therapeutic results. Research endeavors must focus on determining the ideal mixtures and concentrations that enhance bioactive characteristics while reducing potential cytotoxicity or adverse effects. The incorporation of nanotechnology offers a significant opportunity for enhancing the mechanical characteristics and bioactivity of these biopolymeric dressings. Utilizing nanoparticles could lead to improved drug delivery methods or the development of coatings with supplementary antibacterial properties. Longitudinal clinical trials are necessary for these novel formulations to be proven as safe, effective, and standardized across diverse patient demographics and wound types. Artificial intelligence (AI) and machine learning (ML) are progressively employed to develop more efficient wound healing therapies by facilitating the analysis of extensive datasets to forecast ideal biomaterial combinations, formulation methodologies, and healing outcomes. These technologies enhance the optimization of drug delivery systems, personalized treatments, and the discovery of novel bioactive compounds by examining patterns in cellular behavior, inflammatory responses, and tissue

regeneration processes, thereby expediting the advancement of more targeted and efficient wound care solutions. Additionally, regulating the development of protocols for the clinical application of these sophisticated dressings will require coordinated efforts among regulatory authorities, academia, and industry. Future developments anticipate more emphasis on sustainability. In line with worldwide sustainability efforts and patient care needs, biopolymeric dressings that prioritize the use of biodegradable and eco-friendly materials are being developed. Overall, next-generation wound care solutions that improve healing trajectories and the patient's quality of life will be made possible by the convergence of advanced materials science, herbal pharmacology, and clinical practice.

Data availability

No new data sets were generated during the study.

Conflicts of interest

There are no conflicts to declare.

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