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ADVANCED BIOMATERIALS FOR WOUND MANAGEMENT: A COMPREHENSIVE REVIEW OF PH-RESPONSIVE CHITOSAN HYDROGELS AND INTEGRATED PHYTOCHEMICAL THERAPIES

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ABSTRACT

The physiological process of wound healing is intricate and susceptible to disruption, often leading to chronic, non-healing wounds that impose a considerable global health and economic burden. Traditional wound dressings, while offering basic protection, frequently lack the capacity to actively modulate the complex wound microenvironment or address the underlying biological dysfunctions. This comprehensive review examines the significant advancements in wound care, focusing on the evolution from passive coverings to sophisticated, functional biomaterials. Particular emphasis is placed on chitosan-based hydrogels, which have garnered substantial interest due to chitosan's inherent biocompatibility, biodegradability, antimicrobial efficacy, and haemostatic capabilities. The advent of "smart" hydrogel systems, particularly those engineered to respond to specific physiological cues such as the pH fluctuations characteristic of different wound states, represents a paradigm shift towards targeted therapeutic interventions. This review critically analyses the rationale for employing pH as a trigger for controlled drug release within the wound bed. Furthermore, it explores the therapeutic potential of incorporating bioactive phytochemicals, notably Umbelliferone (UMB) and Resveratrol, into these advanced chitosan hydrogel matrices. These plant-derived compounds possess a spectrum of beneficial properties, including potent anti-inflammatory, antioxidant, and antimicrobial activities, which are directly relevant to mitigating the complex pathology of non-healing wounds. Strategies to overcome the inherent physicochemical limitations of these phytochemicals, such as poor solubility and instability, through hydrogel encapsulation techniques are discussed. The synergistic interplay between the pH-responsive chitosan delivery vehicle and the multifaceted therapeutic actions of encapsulated phytochemicals is highlighted as a promising frontier for developing more efficacious and targeted wound healing therapies. Finally, current research gaps are identified, and future perspectives for the clinical translation of these advanced wound management systems are presented.

KEYWORDS: Wound Healing, Chronic Wounds, Advanced Dressings, Chitosan, Hydrogels, pH- Responsive Drug Delivery, Smart Biomaterials, Phytochemicals, Umbelliferone, Resveratrol, Tissue Regeneration, Controlled Release.

1. INTRODUCTION

The ability of skin to repair itself following injury is a fundamental biological process, critical for maintaining organismal integrity and survival (Heimbuck et al., 2019). This process, known as wound healing, is a highly orchestrated cascade of cellular and molecular events. However, a multitude of factors, both local and systemic, can impede this natural reparative sequence, leading to the development of chronic, non-healing wounds. These wounds, such as diabetic foot ulcers, venous leg ulcers, and pressure sores, represent a significant and growing global health concern, causing substantial patient morbidity, reduced quality of life, and imposing an immense economic burden on healthcare systems worldwide (Yang et al., 2024). The limitations of traditional wound dressings, which often provide merely a passive barrier, have spurred extensive research into advanced wound care strategies designed to actively participate in and promote the healing process (Rasool et al., 2019).

Over the past few decades, the field of wound management has witnessed a paradigm shift from simple occlusive coverings to the development of sophisticated functional biomaterials. Among these, hydrogels have emerged as a particularly promising class of materials due to their unique physicochemical properties that mimic the natural extracellular matrix (ECM) and provide a moist, conducive environment for healing (Ding et al., 2020). Chitosan, a natural polysaccharide derived from chitin, has garnered considerable attention for hydrogel fabrication owing to its exceptional biocompatibility, biodegradability, inherent antimicrobial activity, and hemostatic properties (Rasool et al., 2019; Heimbuck et al., 2019).

A further advancement in this domain is the development of "smart" or "intelligent" biomaterials that can sense and respond to specific physiological cues within the wound microenvironment. The pH of a wound is a dynamic biomarker that changes predictably during the healing process and is significantly altered in chronic or infected states (Peng et al., 2023). Consequently, pH-responsive hydrogels, capable of modulating their properties or releasing therapeutic agents in response to specific pH triggers, offer an elegant approach for targeted and on-demand therapy (Yang et al., 2024).

This review aims to provide a comprehensive overview of the current landscape of advanced wound healing strategies, with a particular focus on the design, properties, and applications of pH-responsive chitosan hydrogels. It will begin by dissecting the intricate phases of normal wound healing and the complex pathophysiology of chronic wounds. Subsequently, the evolution of wound dressing technologies will be discussed, leading to a detailed examination of chitosan as a multifunctional biopolymer. The principles of pH-responsive drug delivery will be elucidated, followed by an exploration of the therapeutic potential of incorporating natural phytochemicals, such as Umbelliferone (UMB) and Resveratrol, into these smart hydrogel systems. These plant-derived compounds possess a wide array of pharmacological activities beneficial for wound healing, but their clinical utility is often hampered by challenges related to their stability and bioavailability (Mazimba, 2017; Mokhtari et al., 2020). Hydrogel encapsulation strategies to overcome these limitations will be reviewed. Finally, the synergistic benefits of combining pH-responsive chitosan hydrogels with these potent natural therapeutics will be discussed, highlighting current research gaps and outlining future directions for the development of next-generation wound management solutions.

2. The Wound Healing Cascade: An Orchestrated Biological Response

Wound healing is a sophisticated and highly regulated biological process aimed at restoring tissue integrity and function following injury. It is not a simple, linear sequence but rather a complex interplay of various cell types, growth factors, cytokines, and extracellular matrix components (Heimbuck et al., 2019). This dynamic process is traditionally

categorized into four distinct, yet overlapping and interdependent, phases: hemostasis, inflammation, proliferation, and remodelling.

2.1 Phases of Normal Wound Healing

A Step-by-Step Restoration

2.1.1 Hemostasis: The Initial Response to Injury

Occurring immediately after tissue damage, the primary objective of hemostasis is to arrest bleeding. This rapid response involves vasoconstriction of damaged blood vessels, facilitated by neural reflexes and vasoactive mediators. Platelets play a pivotal role by adhering to the exposed subendothelial collagen, becoming activated, and aggregating at the injury site. Activated platelets release a plethora of bioactive molecules, including growth factors (e.g., PDGF, TGF-β) and clotting factors, which initiate the coagulation cascade (Heimbuck et al., 2019). This cascade culminates in the conversion of fibrinogen to fibrin, forming a mesh-like fibrin clot. This clot not only provides a physical plug to stop hemorrhage but also serves as a provisional matrix or scaffold that facilitates the subsequent migration of inflammatory and regenerative cells into the wound bed (Heimbuck et al., 2019).

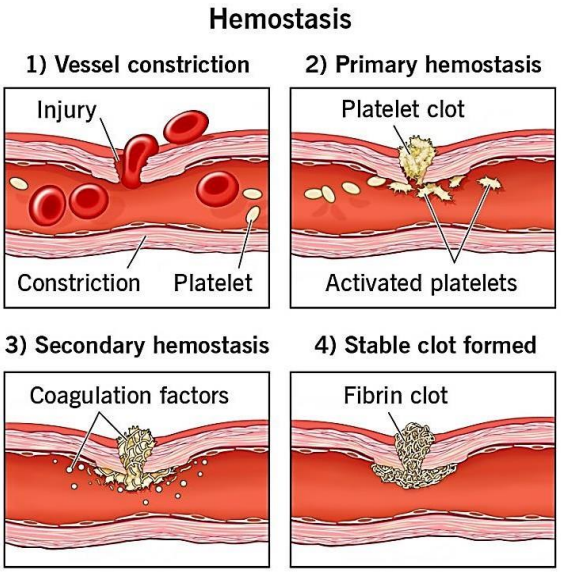

Fig. 1: A Step-by-Step Restoration.

2.1.2 Inflammation: Clearing Debris and Initiating Repair

The inflammatory phase typically commences within hours of injury and lasts for several days. The fibrin clot, along with damaged cells and activated platelets, releases chemoattractant molecules (chemokines and cytokines) that recruit various immune cells to the wound site.

Neutrophils are the first leukocytes to infiltrate the wound, usually within 24-48 hours. Their primary functions include phagocytosis of bacteria, foreign debris, and necrotic tissue, thereby cleansing the wound (Sun et al., 2023). Neutrophils also release proteolytic enzymes and reactive oxygen species (ROS) that contribute to debridement but can also cause damage to surrounding healthy tissue if uncontrolled.

Several days post-injury, neutrophils are gradually replaced by macrophages, which become the dominant inflammatory cell type (Zhang et al., 2025). Macrophages continue the phagocytic debridement process but also play a

critical immunomodulatory role by releasing a wide array of growth factors (e.g., TGF-β, VEGF, FGF) and cytokines (e.g., TNF-α, IL-1) that orchestrate the transition to the proliferative phase. They are essential for stimulating angiogenesis, fibroblast proliferation, and ECM deposition (Sun et al., 2023). While inflammation is a necessary component of normal healing, a prolonged, unresolved, or excessive inflammatory response is a key characteristic of impaired healing and chronic wound formation.

2.1.3 Proliferation: Rebuilding Lost Tissue

The proliferative phase, typically starting 3-5 days after injury and lasting for several weeks, is characterized by the formation of new tissue to fill the wound defect. This phase involves three main interconnected processes:

- **Angiogenesis:** The formation of new blood vessels from pre-existing ones is crucial for supplying oxygen, nutrients, and growth factors to the metabolically active cells in the healing wound. Endothelial cells migrate, proliferate, and differentiate to form new capillary networks, stimulated by factors like VEGF released by macrophages and keratinocytes (Zhou et al., 2022).
- **Fibroplasia and Granulation Tissue Formation:** Fibroblasts migrate into the wound, proliferate, and synthesize a new extracellular matrix, primarily composed of Type III collagen, fibronectin, and hyaluronic acid. This newly formed connective tissue, rich in new blood vessels, fibroblasts, and inflammatory cells, is known as granulation tissue. It appears bright red and granular, filling the wound space and providing a scaffold for re-epithelialization (Zhou et al., 2022).
- **Re-epithelialization:** Keratinocytes from the wound edges and surviving adnexal structures (hair follicles, sweat glands) migrate, proliferate, and differentiate to restore the epidermal barrier. This process involves the dissolution of cell-cell and cell-matrix adhesions, cellular motility, and subsequent re-establishment of a stratified epithelium over the granulation tissue.

2.1.4 Remodelling: Maturation and Scar Formation

The final and longest phase of wound healing is remodelling, which can begin several weeks after injury and continue for months or even years. During this stage, the newly formed granulation tissue matures into a scar. The cellularity of the wound decreases, and the ECM undergoes significant reorganization. The initially deposited, weaker Type III collagen is gradually replaced by the stronger, more organized Type I collagen through the action of matrix metalloproteinases (MMPs) and their inhibitors (TIMPs). This collagen remodelling increases the tensile strength of the wound, although the healed scar tissue rarely regains the full strength (typically 70-80%) or all the functional characteristics of the original, uninjured skin. Wound contraction, mediated by myofibroblasts, also occurs during this phase, reducing the size of the scar.

2.2 The Complex Pathophysiology of Chronic Wounds

While the acute wound healing process is generally efficient in healthy individuals, numerous intrinsic and extrinsic factors can disrupt this delicate balance, leading to the development of chronic, non-healing wounds. These wounds are operationally defined as those that fail to proceed through the orderly and timely sequence of repair or fail to achieve functional integrity within three months (Yang et al., 2024). Common examples include diabetic foot ulcers, venous leg ulcers, and pressure ulcers, each with distinct underlying etiological factors but often sharing common pathological features.

A hallmark of chronic wounds is a prolonged and dysregulated inflammatory phase (Yang et al., 2024). There is a persistent influx of inflammatory cells, particularly neutrophils and macrophages, which release excessive levels of pro-inflammatory cytokines (e.g., TNF-α, IL- 1β) and proteolytic enzymes like MMPs (Sun et al., 2023). This chronic inflammatory state leads to continuous tissue damage, degradation of essential ECM components and growth factors, and impaired proliferation and migration of reparative cells like fibroblasts and keratinocytes.

Persistent microbial infection and biofilm formation are major impediments to healing in chronic wounds (Xiong et al., 2024). Biofilms are structured communities of microorganisms encased in a self-produced polymeric matrix, which adhere to the wound bed and are highly resistant to host immune responses and antimicrobial agents.

They contribute to sustained inflammation and impair cellular functions. Poor tissue perfusion and hypoxia (low oxygen levels) are also common in chronic wounds, particularly in diabetic and venous ulcers. Inadequate blood supply limits the delivery of oxygen, nutrients, and essential cells to the wound site, thereby impairing cellular metabolism, energy production, and collagen synthesis (Tang et al., 2023).

Systemic diseases, most notably diabetes mellitus, create a hostile microenvironment for wound healing. Hyperglycaemia leads to advanced glycation end-product (AGE) formation, oxidative stress, impaired neutrophil function, reduced growth factor production, and microvascular as well as macrovascular damage, all of which severely compromise the body's innate healing capacity (Tang et al., 2023; Zhao et al., 2017).

The management of these multifactorial non-healing wounds is a significant clinical challenge, necessitating the development of advanced therapeutic interventions that can address these underlying pathological mechanisms.

3. Evolution of Wound Dressing Technologies: From Passive to Active Modulators

The primary objectives of a wound dressing are to protect the wound from further trauma and microbial contamination, manage exudate, and create an environment that is conducive to the natural healing process. The design and material composition of wound dressings have undergone significant evolution over time, reflecting our expanding understanding of wound physiology and the complex cellular and molecular events involved in healing.

3.1 Traditional Wound Dressings: Basic Protection and Limitations.

For centuries, traditional wound dressings, such as cotton gauze, lint, and simple bandages, have been the mainstay of wound care. These dressings primarily function as absorptive materials and provide a basic physical barrier against external contaminants. While they are inexpensive and widely available, they possess several notable drawbacks (Rasool et al., 2019). Traditional dressings often fail to maintain a moist wound environment, which is now recognized as crucial for optimal healing. A dry wound bed can lead to tissue dehydration, scab formation (which can impede cell migration and re-epithelialization), and increased pain.

Their absorptive nature, while beneficial for heavily exuding wounds, can also wick away essential wound fluid containing growth factors, cytokines, and enzymes vital for the healing cascade.

Furthermore, traditional dressings like gauze can adhere to the wound bed, causing pain and trauma to newly formed granulation tissue and epithelium upon removal, thereby disrupting the healing process (Rasool et al., 2019).

Fig. 2: Traditional Wound Dressings.

3.2 Advanced Wound Dressings: Embracing Moist Wound Healing and Active Participation

The limitations of traditional dressings spurred the development of advanced wound dressings in the latter half of the 20th century. This new generation of dressings is largely based on the seminal work of Dr. George Winter in the 1960s, who demonstrated that wounds kept in a moist environment healed significantly faster than those exposed to air. The principle of moist wound healing posits that maintaining a hydrated wound bed facilitates cell migration, promotes autolytic debridement, enhances growth factor activity, and reduces pain. Advanced wound dressings are designed to be active participants in the healing process rather than just passive coverings.

They encompass a wide variety of materials and formulations, including:

- **Films:** Thin, transparent, semi-permeable polyurethane membranes that are permeable to gases (oxygen, carbon dioxide) and water vapor but impermeable to liquids and bacteria. They maintain a moist environment and allow for visual inspection of the wound.
- **Foams:** Polyurethane or silicone-based dressings with high absorptive capacity, suitable for moderately to heavily exuding wounds. They provide cushioning and thermal insulation.
- **Alginates:** Derived from seaweed, these dressings are composed of calcium and sodium alginate fibers that form a hydrophilic gel upon contact with wound exudate. They are highly absorbent and can promote hemostasis.
- **Hydrocolloids:** Occlusive or semi-occlusive dressings containing gel-forming agents (e.g., carboxymethylcellulose, gelatin, pectin) in an adhesive compound. They form a gel over the wound, maintain a moist environment, and support autolytic debridement.
- **Hydrogels:** These will be discussed in detail in the next section, as they represent one of the most promising platforms for creating an ideal wound healing environment and for advanced therapeutic delivery.

Fig. 3: Advanced Wound Dressings.

4. Hydrogels: A Superior Platform for Modern Wound Management.

Among the diverse array of advanced wound dressings, hydrogels have emerged as a particularly versatile and promising platform for creating an optimal wound healing environment and for the delivery of therapeutic agents.

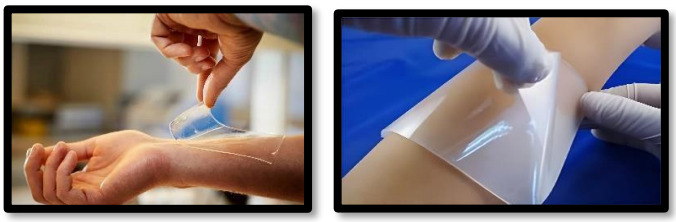

Fig. 4: Hydrogels.

4.1 Definition and Unique Properties of Hydrogels

Hydrogels are three-dimensional, crosslinked networks of hydrophilic polymers that possess the ability to absorb and retain large volumes of water or biological fluids—often exceeding 90% of their total weight—without dissolving (Ding et al., 2020). This high water content endows them with a soft, flexible, and often elastic consistency that closely mimics the turgidity and mechanical properties of natural soft tissues, making them exceptionally biocompatible (Heimbuck et al., 2019).

Key advantages of hydrogels as wound dressings include:

- **Moisture Regulation:** They can donate moisture to dry, desiccated wounds, preventing dehydration and promoting autolytic debridement of necrotic tissue. Conversely, some hydrogels can also absorb a moderate amount of wound exudate, helping to prevent maceration of the surrounding healthy skin.
- **Non-Adherence:** Due to their smooth, moist surface, hydrogels are generally non- adherent to the wound bed, minimizing pain and trauma during dressing changes.
- **Gas Permeability:** Their porous structure typically allows for the exchange of oxygen and other gases, which is vital for cellular metabolism and viability in the healing tissue.
- **Soothing and Cooling Effect:** The high-water content provides a cooling and soothing sensation upon application, which can significantly alleviate wound pain and discomfort.
- **Barrier Function:** The hydrogel matrix can act as a physical barrier against external microbial contaminants, reducing the risk of secondary infections.
- **Conformability:** Their flexible nature allows them to conform well to irregular wound contours, ensuring good contact with the wound bed.
- **Drug Delivery Vehicle:** The porous network of hydrogels can be effectively utilized to load and deliver a wide range of therapeutic agents—such as antimicrobial drugs, anti- inflammatory agents, growth factors, or phytochemicals—directly to the wound site in a controlled and sustained manner (Peng et al., 2023; Sun et al., 2023).

4.2 Chitosan: A Multifunctional Biopolymer for Hydrogel Fabrication in Wound Healing

Hydrogels can be synthesized from a wide variety of natural and synthetic polymers. While synthetic polymers (e.g., polyethylene glycol (PEG), polyacrylamide) offer tunable mechanical properties and controlled degradation rates, natural polymers are often preferred for biomedical applications due to their inherent biocompatibility, biodegradability, and often, specific biological activities (Bala Vigneswaran et al., 2025; Zhou et al., 2022).

Among natural polymers, chitosan has garnered significant attention and is extensively investigated for its exceptional suitability in creating advanced wound dressings and hydrogel systems (Rasool et al., 2019).

Chitosan is a linear polysaccharide derived from the alkaline N-deacetylation of chitin, which is the second most abundant natural polymer on Earth (after cellulose), found primarily in the exoskeletons of crustaceans (e.g., crabs, shrimp) and insects, as well as the cell walls of fungi. Its structure is composed of randomly distributed β-(1→4)-linked D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit).

The key characteristics that make chitosan particularly attractive for wound healing applications include:

- **Biocompatibility and Biodegradability:** Chitosan is generally non-toxic, non- immunogenic, and well-tolerated by the human body. In the physiological environment, it can be gradually broken down by bodily enzymes, such as lysozyme, into non-toxic oligosaccharides that can be safely absorbed. This biodegradability eliminates the need for surgical removal of the dressing, which can otherwise disturb the delicate healing tissue (Ding et al., 2020; Heimbuck et al., 2019).
- **Inherent Antimicrobial Activity:** One of the most significant advantages of chitosan is its broad-spectrum antimicrobial activity against a wide range of bacteria (both Gram- positive and Gram-negative) and fungi. The primary mechanism is believed to be the electrostatic interaction between the positively charged (protonated) primary amino groups (-NH3+) on the chitosan backbone (at physiological pH or lower) and the negatively charged components (e.g., teichoic acids, phospholipids, lipopolysaccharides) of microbial cell membranes. This interaction disrupts membrane integrity, leading to leakage of intracellular contents and ultimately, cell death (Sun et al., 2023; Xiong et al., 2024). This property is invaluable for preventing or treating wound infections, a major cause of healing impairment.
- **Hemostatic Properties:** The positive charge of chitosan also allows it to interact with negatively charged red blood cells and platelets, promoting their aggregation and accelerating the formation of a blood clot. This makes chitosan-based dressings particularly useful for managing bleeding wounds (Ding et al., 2020).
- **Acceleration of Healing:** Beyond its passive roles as a scaffold and barrier, chitosan actively promotes several stages of the healing cascade. It has been shown to stimulate the migration and proliferation of key regenerative cells, including fibroblasts and keratinocytes. It also enhances the production of collagen and other essential extracellular matrix components and can modulate the local immune response, helping to transition the wound from the inflammatory to the proliferative phase (Heimbuck et al., 2019; Zhou et al., 2022).
- **Film-Forming and Gel-Forming Ability:** Chitosan can be easily processed into various physical forms, including films, fibers, sponges, and hydrogels, making it highly versatile for dressing fabrication. Its abundant amino and hydroxyl groups allow for easy chemical modification and crosslinking to form hydrogels with tailored properties (Din et al., 2023; Wu et al., 2024; Zhou et al., 2022). These chitosan-based hydrogels have been engineered to be injectable for minimally invasive application (Zhang et al., 2025), to possess self- healing properties that maintain their structural integrity (Ding et al., 2020), and, most importantly for this review, to respond to specific stimuli in the wound environment.

5. Smart Hydrogels: Engineering Responsiveness for Enhanced Wound Therapy

The concept of a "smart" or "intelligent" biomaterial refers to a system that can sense changes in its surrounding environment and respond in a predictable, controlled, and therapeutically useful manner. In the context of wound

dressings, smart hydrogels are designed to respond to specific physiological cues within the wound bed, such as changes in temperature, the presence of specific enzymes (e.g., MMPs), glucose concentration, or, most relevant to this review, pH (Peng et al., 2023; Rasool et al., 2019). This responsiveness can be harnessed to trigger a desired action, most commonly the on-demand and site-specific release of an encapsulated therapeutic agent. This approach offers a significant advantage over conventional dressings that release drugs passively (e.g., via simple diffusion), as it allows for targeted therapy precisely when and where it is needed, potentially enhancing efficacy, reducing systemic side effects, and minimizing the risk of drug resistance (Yang et al., 2024).

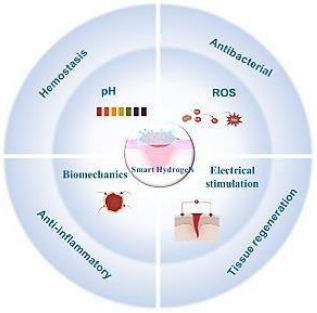

Fig. 5: Smart Hydrogel.

5.1 Wound pH: A Critical Biomarker and Trigger for Smart Delivery

The pH of the wound surface is a dynamic and reliable indicator of its healing status and overall physiological condition. The skin of a healthy individual maintains a naturally acidic pH, typically ranging between 4.5 and 6.0. This "acid mantle" is crucial for maintaining skin barrier function, controlling the growth of pathogenic microorganisms, and regulating the activity of skin-resident enzymes (Khadem et al., 2023).

During the normal healing of an acute wound, the pH profile undergoes characteristic changes. Initially, following injury and hemostasis, the wound pH may become transiently alkaline due to exposure to blood and other bodily fluids. However, as healing progresses through the inflammatory and proliferative phases, the pH gradually returns to an acidic state, reflecting successful re-epithelialization and restoration of the acid mantle. In sharp contrast, chronic and infected wounds are consistently characterized by a shift to a persistently alkaline environment, with pH values often exceeding 7.4 and sometimes reaching pH 8-9 (Su et al., 2024; Yang et al., 2024). This alkaline milieu is now recognized as being detrimental to the healing process. It promotes the activity of tissue-degrading proteases (like MMPs), inhibits the proliferation and migration of essential cells like fibroblasts and keratinocytes, and creates a favourable environment for the growth and virulence of pathogenic bacteria, such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* (Sun et al., 2023; Zheng et al., 2021).

This distinct and often sustained pH differential between healthy/healing wounds (acidic) and chronic/infected wounds (alkaline) presents an ideal and clinically relevant opportunity for designing smart, triggerable drug delivery systems. A dressing that can sense the pathological alkaline pH of a non-healing wound and respond by releasing a therapeutic agent would represent a highly targeted and efficient treatment strategy.

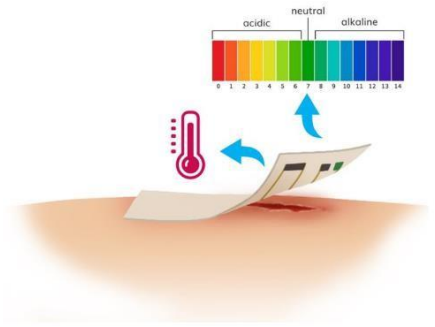

Fig. 6: Wound pH.

5.2 Chitosan's Intrinsic pH-Responsiveness: A Natural Advantage for Smart Hydrogels

Chitosan is uniquely suited for the development of pH-responsive hydrogels due to the inherent acid-base properties of its primary amino groups (-NH2) present on the D-glucosamine units. These amino groups have a pKa (acid dissociation constant) value of approximately 6.2-6.5, depending on the degree of deacetylation and environmental conditions. In acidic solutions, where the pH is below chitosan's pKa (e.g., pH < 6.5), a significant proportion of these amino groups become protonated, acquiring a positive charge (-NH3+).

The resulting electrostatic repulsion between adjacent positively charged polymer chains causes the chitosan molecules to extend and the hydrogel network to swell, becoming more porous and permeable (Zhu & Bratlie, 2018).

Conversely, in neutral or alkaline environments, where the pH is above chitosan's pKa (e.g., pH > 6.5), the amino groups are predominantly deprotonated and thus neutral (-NH2). This reduction in electrostatic repulsion, coupled with increased hydrophobic interactions and hydrogen bonding between polymer chains, causes the chitosan chains to aggregate or collapse, leading to shrinkage of the hydrogel network and reduced porosity (Qu et al., 2017; Yu et al., 2020).

This reversible pH-dependent swelling-shrinking behaviours of chitosan hydrogels can be ingeniously exploited for controlled drug release. A therapeutic agent can be loaded into the chitosan hydrogel network. In the acidic environment characteristic of a healthy or normally healing wound, the hydrogel can remain in a relatively stable, less swollen (or more swollen, depending on the specific design and loading mechanism) state, retaining its therapeutic cargo. However, upon exposure to the pathologically alkaline pH of a chronic or infected wound, the chitosan hydrogel structure can undergo a conformational change (e.g., shrink if loaded in an acidic state, or swell differently if crosslinked to respond this way), triggering the enhanced release of the encapsulated drug precisely at the site of pathology (Bala Vigneswaran et al., 2025; Jiang et al., 2023; Xiong et al., 2024).

This mechanism allows the dressing to act as a "smart bomb," delivering its therapeutic payload in a targeted manner. Numerous studies have successfully demonstrated this principle, loading chitosan hydrogels with various agents like antimicrobial peptides, anti-inflammatory drugs, and growth factors for pH-triggered release (Sun et al., 2023; Wu et al., 2024; Zhang et al., 2025).

6. Phytochemicals: Nature's Bioactive Compounds for Therapeutic Intervention in Wound Healing

The effectiveness of any smart drug delivery system is contingent not only on the sophistication and responsiveness of the carrier vehicle but also critically on the therapeutic potency and suitability of the encapsulated payload.

Phytochemicals, or plant-derived secondary metabolites, offer a rich and diverse source of bioactive molecules with multifaceted pharmacological profiles that are highly relevant to the complex pathology of wounds, particularly chronic wounds. Many traditional medicine systems have long utilized plants for wound treatment, and modern science is increasingly validating these uses by identifying and characterizing the active compounds.

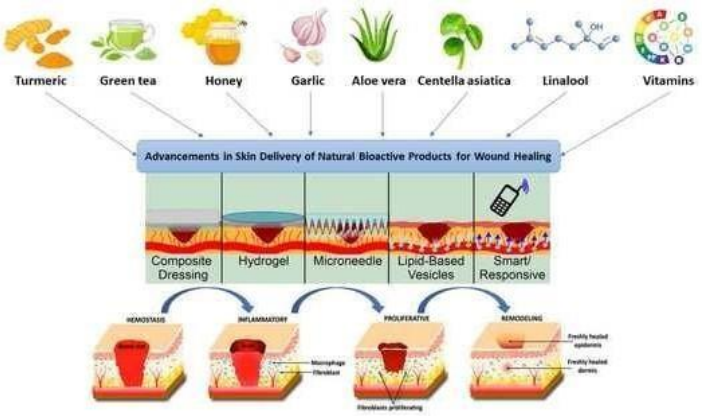

Fig. 7: Phytochemicals.

6.1 Umbelliferone (UMB): A Multifunctional Coumarin with Significant Wound Healing Potential

Umbelliferone (UMB), also known as 7-hydroxycoumarin, is a natural phenolic compound belonging to the coumarin family. It is widely distributed in the plant kingdom, found in many edible plants and traditional medicinal herbs, particularly those from the Apiaceae (Umbelliferae) and Rutaceae families (Mazimba, 2017). UMB has attracted considerable scientific interest due to its broad spectrum of pharmacological activities, many of which are directly relevant to addressing the challenges of non-healing wounds.

- **Potent Anti-inflammatory Activity:** As previously discussed, chronic wounds are often trapped in a state of persistent, unresolved inflammation. Umbelliferone has demonstrated potent anti-inflammatory properties by modulating key inflammatory signalling pathways. It has been shown to suppress the production of pro-inflammatory cytokines (e.g., TNF-α, IL-6) and to inhibit pathways such as the Wnt/β-catenin signalling pathway, which is implicated in skin inflammation and arthritic models (Cai et al., 2022). Furthermore, UMB can inhibit the NLRP3 inflammasome, a multiprotein complex that plays a critical role in sensing danger signals and driving the production of potent pro-inflammatory cytokines IL-1β and IL-18 (Luo et al., 2017). By dampening this excessive and prolonged inflammatory response, umbelliferone can help shift the wound microenvironment from a chronic, stalled state toward a productive healing trajectory.
- **Significant Antioxidant Properties:** The inflammatory milieu of a chronic wound is invariably associated with high levels of oxidative stress, characterized by an overproduction of reactive oxygen species (ROS) by activated inflammatory cells (e.g., neutrophils, macrophages). Excessive ROS can cause damage to healthy cells (lipids, proteins, DNA), impair cellular function, and further perpetuate inflammation, thereby hindering the healing process. Umbelliferone acts as a powerful antioxidant through multiple mechanisms. It can directly scavenge harmful free radicals and also bolster the body's endogenous antioxidant defense systems by activating the Nrf2 (Nuclear factor erythroid 2-related factor 2) signalling pathway. Nrf2 is a master regulator of antioxidant gene expression, upregulating enzymes like heme oxygenase-1 (HO-1) and glutathione S-transferases (Yin et al., 2018; Allam et al., 2021).

- This reduction in oxidative stress helps to protect cells from damage and create a more favourable environment for tissue regeneration.

- **Moderate Antimicrobial Effects:** While not as potent as conventional antibiotics, umbelliferone exhibits moderate broad-spectrum antimicrobial activity against a range of pathogenic bacteria and fungi that commonly infect wounds (Mazimba, 2017; Kornicka et al., 2023).
  - This intrinsic antimicrobial activity can complement that of the chitosan carrier, helping to control the bioburden in infected wounds and prevent or disrupt the formation of biofilms, which are a major barrier to healing.
- **Other Relevant Bioactivities:** Beyond these primary effects, umbelliferone has also been investigated for its potential in other areas, including its ability to inhibit abnormal cell proliferation and induce apoptosis (programmed cell death) in various cancer cell lines (Aslantürk & Çelik, 2023; Vijayalakshmi & Sindhu, 2017). While not directly targeting wound healing processes like cell migration or proliferation (in a positive sense for healing), these findings underscore its potent bioactivity and its capacity to modulate fundamental cellular processes. A comprehensive review by Kornicka et al. (2023) highlights the vast therapeutic potential of umbelliferone and its derivatives, solidifying its status as a promising candidate for drug development in various fields, including wound care.

6.2 Resveratrol: A Well-Studied Polyphenol with Wound Healing Attributes and Delivery Hurdles

Resveratrol, a natural stilbenoid polyphenol found in sources like grapes, berries, and peanuts, has been extensively studied for its wide range of health benefits, including potent effects relevant to wound repair. It is recognized as a powerful agent capable of addressing multiple barriers to healing simultaneously.

- **Powerful Antioxidant Capability:** Chronic wounds are characterized by high levels of oxidative stress due to an excess of ROS, which damages healthy cells and stalls the healing process (He et al., 2021). Resveratrol effectively neutralizes these harmful free radicals, protecting essential cells like fibroblasts and keratinocytes and creating a more favourable environment for tissue regeneration.
- **Potent Anti-inflammatory Action:** While inflammation is a necessary initial step in healing, prolonged or chronic inflammation is a hallmark of non-healing wounds. Resveratrol helps to downregulate key pro-inflammatory signalling pathways (e.g., NF- κB), allowing the wound to progress from the deleterious chronic inflammatory phase to the constructive proliferative phase (Li et al., 2022).
- **Promotion of Angiogenesis and Collagen Production:** Studies have demonstrated that resveratrol actively promotes angiogenesis, the formation of new blood vessels, which is critical for delivering oxygen and nutrients to the injury site (Gao et al., 2022). It also stimulates fibroblasts to produce collagen, the main structural protein of the skin, thereby improving the strength and quality of the newly formed tissue (Hashemikia et al., 2022).

However, despite its significant therapeutic potential, the practical clinical application of resveratrol is hindered by several major challenges related to its inherent physicochemical properties. Firstly, resveratrol has very poor water solubility, making it difficult to formulate into aqueous topical solutions or gels suitable for even application to a wound bed (Mokhtari et al., 2020). Secondly, resveratrol is chemically unstable and highly susceptible to degradation when exposed to light, oxygen, and certain pH levels, quickly losing its bioactivity. Finally, its bioavailability is low due to poor absorption and rapid metabolism (Mokhtari et al., 2020). These limitations mean that simply adding pure resveratrol to a standard dressing is an inefficient and unreliable strategy.

Fig. 8: Resveratrol.

6.3 Hydrogel Encapsulation: A Viable Strategy to Stabilize and Deliver Phytochemicals like Resveratrol

To overcome the inherent limitations of phytochemicals such as resveratrol, researchers have increasingly turned to advanced drug delivery platforms, with hydrogels being a prominent example. By encapsulating resveratrol within a hydrogel polymer matrix, its key challenges can be directly addressed. The hydrogel can act as a protective shield, sequestering the resveratrol molecules from degradative environmental factors like light and oxygen, thus enhancing its stability (Aksu et al., 2021). Encapsulation also improves its dispersion within an aqueous-based formulation, ensuring that the otherwise poorly soluble compound can be distributed more evenly across the wound.

Most importantly, the hydrogel serves as a reservoir for controlled and sustained release. Instead of delivering a single, large bolus dose that is quickly metabolized or degraded, the hydrogel can release resveratrol slowly and continuously over an extended period at the wound site (Wang et al., 2018).

This sustained delivery ensures that a therapeutically effective concentration of resveratrol is maintained locally, maximizing its antioxidant and anti-inflammatory actions where they are needed most. When chitosan is used as the hydrogel polymer, its natural antimicrobial and hemostatic properties can work synergistically with resveratrol's effects (Li et al., 2022).

Furthermore, designing such a chitosan-resveratrol hydrogel to be pH-responsive could allow for triggered release in response to the wound's specific pH, further enhancing targeted delivery (Zhang et al., 2021).

7. Rationale for Developing pH-Responsive Chitosan Hydrogels Loaded with Umbelliferone for Wound Healing

The comprehensive review of the literature clearly establishes several key points that form the rationale for the development of advanced wound healing systems:

(1) Chronic wounds, characterized by a hostile microenvironment including persistent inflammation and oxidative stress, represent a major unmet clinical need requiring targeted therapeutic interventions (Yang et al., 2024).

(2) Advanced hydrogel dressings, particularly those fabricated from the natural biopolymer chitosan, offer a superior platform for wound management due to their inherent biocompatibility, biodegradability, moisture-regulating properties, and intrinsic bioactivities like antimicrobial and hemostatic effects (Ding et al., 2020; Rasool et al., 2019).

(3) The distinct and sustained alkaline pH characteristic of chronic and infected wounds provides a reliable and clinically relevant physiological trigger that can be exploited for smart, on-demand drug delivery systems (Su et al., 2024; Khadem et al., 2023).
(4) Umbelliferone (UMB) is a natural phytochemical possessing a powerful and multifaceted combination of anti-inflammatory, antioxidant, and antimicrobial properties that are ideally suited to address the complex underlying pathology of non-healing wounds (Mazimba, 2017; Cai et al., 2022; Yin et al., 2018; Kornicka et al., 2023).

A significant body of research has focused on developing pH-responsive chitosan hydrogels for wound healing applications, typically loading them with various synthetic drugs, antibiotics, or growth factors (Ding et al., 2020; Sun et al., 2023; Xiong et al., 2024; Zhang et al., 2025). Similarly, the individual therapeutic benefits of umbelliferone have been well- documented in a variety of disease models, highlighting its potential (Cai et al., 2022; Luo et al., 2017; Yin et al., 2018).

However, a clear research gap exists at the intersection of these promising fields. To date, there has been comparatively limited investigation into the specific design, formulation, and evaluation of a pH-responsive chitosan hydrogel system intelligently incorporating the natural, multi-action phytochemical umbelliferone for targeted wound therapy. The potential synergistic benefits arising from the combination of a "smart" delivery vehicle (the pH- responsive chitosan hydrogel capable of sensing and reacting to the wound environment) and a multifaceted therapeutic payload (umbelliferone, addressing multiple pathological targets simultaneously) have not yet been fully explored or optimized for wound healing applications. Therefore, the rationale for focusing research in this area is to bridge this existing gap by developing and thoroughly evaluating a novel smart hydrogel system. Such research endeavors would typically involve engineering a chitosan-based hydrogel specifically designed to sense the alkaline pH characteristic of chronic or infected wounds and, in response, trigger the enhanced release of encapsulated umbelliferone directly at the site of pathology. It is hypothesized that this targeted and on-demand delivery mechanism will maximize the local therapeutic efficacy of umbelliferone, leading to a more effective resolution of chronic inflammation, a significant reduction in detrimental oxidative stress, improved control of microbial bioburden, and an overall acceleration of the healing process compared to passive delivery systems or the application of UMB alone. This line of research aims to contribute a novel, effective, and potentially nature-inspired solution to the pressing and complex clinical challenge of chronic wound management.

8. CONCLUSION AND FUTURE PERSPECTIVES

The journey of wound dressing development from simple passive coverings to sophisticated, intelligent biomaterials represent a significant paradigm shift in modern wound care. Chronic wounds, with their complex and often recalcitrant nature, continue to pose a formidable challenge to clinicians and researchers alike. However, the advent of advanced hydrogel systems, particularly those fabricated from the versatile biopolymer chitosan and engineered for responsiveness to physiological cues like pH, offers new avenues and renewed hope for more effective treatments. Chitosan's inherent biocompatibility, biodegradability, antimicrobial properties, and its ability to promote various stages of healing make it an exemplary candidate for constructing these advanced therapeutic platforms.

The incorporation of potent natural phytochemicals, such as Umbelliferone and Resveratrol, into these smart hydrogel systems further amplifies their therapeutic potential. These plant- derived compounds often target multiple facets of wound pathology—including inflammation, oxidative stress, and microbial invasion—offering a holistic approach to

treatment that can be more effective than single-target therapies. Overcoming the inherent delivery challenges associated with many phytochemicals (e.g., poor solubility, instability) through innovative strategies like hydrogel encapsulation and controlled, stimulus-responsive release is key to unlocking their full clinical utility.

While the individual components of these systems—chitosan as a biomaterial, pH- responsiveness as a smart mechanism, and phytochemicals as therapeutic agents—have shown considerable merit in numerous studies, their integrated and optimized application for wound healing warrants further intensive investigation. Specifically, the development and thorough evaluation of pH-responsive chitosan hydrogels for the targeted delivery of Umbelliferone represent a particularly promising, yet underexplored, area.

Future research in this field should focus on several critical aspects

- **Optimization of Hydrogel Formulations:** Fine-tuning the degree of chitosan deacetylation, molecular weight, crosslinking density, and incorporation of other synergistic polymers to achieve optimal mechanical properties, swelling behaviours, pH- sensitivity, drug loading capacity, and release kinetics.
- **In-depth Mechanistic Studies:** Elucidating the precise molecular mechanisms by which these combination therapies (chitosan-phytochemical hydrogels) exert their effects on various cell types and signalling pathways involved in wound healing.
- **Advanced Preclinical Evaluation:** Conducting robust *in vivo* studies using relevant animal models of acute and chronic wounds (e.g., diabetic wound models, infected wound models) to assess the safety, efficacy, and biocompatibility of these novel hydrogel systems.
- **Exploration of Combination Phytochemical Therapies:** Investigating the potential for co-encapsulating multiple phytochemicals with complementary or synergistic activities to achieve enhanced therapeutic outcomes.
- **Development of Multifunctional Systems:** Integrating other functionalities, such as real- time wound status monitoring (e.g., pH sensors integrated into the dressing), with therapeutic delivery.
- **Addressing Clinical Translation Challenges:** Focusing on scalability of production, sterilization methods that do not compromise hydrogel integrity or drug activity, regulatory approval pathways, and cost-effectiveness to facilitate the transition from laboratory research to clinically available products.

Ultimately, the goal is to develop nature-inspired, intelligent wound management solutions that are not only highly effective but also personalized to the specific needs of the patient and the dynamic state of their wound. The continued exploration and refinement of pH-responsive chitosan hydrogels incorporating bioactive phytochemicals represent a significant and exciting step towards achieving this objective and alleviating the substantial burden imposed by problematic wounds.

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