# HYDROGEL DRESSING FOR WOUND HEALING

## Abstract

Wound healing technologies have witnessed a transformative shift with the advent of 3D printed hydrogels. This chapter explores the unique advantages offered by 3D printed hydrogels over traditional counterparts. By harnessing the power of additive manufacturing, these hydrogels allow for unparalleled customization and complexity in design, offering precise control over shape and architecture. The spatial control of bioactive agents within these hydrogels enables targeted and localized delivery of therapeutic compounds, enhancing their efficacy in wound healing applications. Moreover, the improved mechanical strength and stability of 3D printed hydrogels, achieved through innovative internal architectures, make them robust and adaptable for diverse clinical scenarios. Their patient-specific fit ensures optimal wound coverage and contact, while their multi-functionality, incorporating various components within a single structure, enhances their therapeutic potential. Additionally, the rapid prototyping and scalability of 3D printed hydrogels have revolutionized the speed and efficiency of production, paving the way for widespread clinical adoption. Although challenges such as biocompatibility and long-term stability persist, the evolution of 3D printed hydrogels represents a promising frontier in advancing wound care and tissue engineering, heralding a new era in medical innovation and patient-specific treatments.

**Keywords:** Hydrogels, Wound Healing, Additive Manufacturing, Bioactive Agents, Customization

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## I. WOUND AND WOUND HEALING

The skin is the largest organ of the body and serves as a protective barrier between the internal organs and the external environment. It plays a crucial role in regulating body temperature, preventing dehydration, and protecting against harmful pathogens **(Byrne, et al., 2008).** However, when the skin is damaged or injured, wound healing mechanisms come into action to restore its integrity and functionality. Wounds are not as simple as they appear many inherent factors and individual's health status makes it very complicated (**Diegelmann, et al., 2007).** Acute wounds are caused by traumatic injury, such as cuts, burns, or surgical incisions. These wounds typically go through a well-defined healing process, progressing through distinct stages. The normal wound is a definite sign of healing within 2–4 weeks whereas chronic wounds do not follow the sequential stages of healing and stagnant in one phase therefore fails to heal within 4 weeks or within an expected timeframe, often due to underlying factors such as poor blood circulation, infection, or underlying medical conditions. Examples of chronic wounds include pressure ulcers, diabetic foot ulcers, and venous leg ulcers. Chronic wounds represent a major health care burden including financial expenses and have a devastating impact on morbidity **(Enoch, et al., 2004).**

Acute and chronic wound are two broad categories of wound. Acute wounds heal normally in a very orderly and efficient manner. They are characterized by four distinct, but overlapping phases: haemostasis, inflammation, proliferation and remodeling (C**hhabr**a, **et al., 2023**). The wound healing process involves four overlapping phases:

1. **Homeostasis Phase:** Homeostasis stage is considered the initial phase of wound healing and occurs immediately after an injury. It is part of the inflammatory phase and involves the body's immediate response to the wound to control bleeding and establish a temporary barrier against pathogens (**Rodriguez, et al., 2019).** During the homeostasis stage, the body activates various mechanisms to achieve hemostasis, including:

   - ***Vasoconstriction:*** Immediately after an injury, blood vessels in the vicinity of the wound constrict to reduce blood flow and limit bleeding. Vasoconstriction helps minimize blood loss and create a localized environment conducive to wound healing (**Sheppard, et al., 2011**).

   - ***Platelet Aggregation:*** Platelets, small blood cells, are recruited to the site of injury. They adhere to the damaged blood vessels and form clumps or aggregates, creating a temporary platelet plug. This plug helps in sealing off the injured blood vessels and further limiting bleeding.

   - ***Coagulation Cascade:*** The coagulation cascade is a series of complex reactions involving clotting factors and platelets. It leads to the formation of a fibrin clot, which reinforces the platelet plug and stabilizes the wound. The clot prevents excessive bleeding and provides a scaffold for subsequent tissue repair. The homeostasis stage sets the foundation for subsequent stages of wound healing, such as the proliferation and remodeling phases (**Huang**, **et al., 2022**). It is a critical initial step that helps control bleeding and prepares the wound for subsequent repair processes.

2. **Inflammatory Phase:** The homeostasis stage also triggers an inflammatory response, characterized by the release of inflammatory mediators, such as cytokines and chemokines. These signaling molecules attract immune cells to the wound site, initiating the inflammatory phase of wound healing. The inflammatory response helps clear debris, remove pathogens, and initiate tissue repair processes (**Rohl, et al., 2015**). During this phase, blood vessels constrict to limit bleeding, followed by vasodilation to increase blood flow and deliver immune cells and growth factors to the wound area.

   - ***Vasodilation and Increased Vascular Permeability:*** Following the vasoconstriction that occurs during the homeostasis stage, blood vessels in the vicinity of the wound undergo vasodilatation, which leads to increased blood flow to the area. This increased blood flow brings immune cells, growth factors, and nutrients to the wound site. At the same time, vascular permeability is increased, allowing immune cells to migrate from the bloodstream to the site of injury.

   - ***Infiltration of Immune Cells:*** Various immune cells, including neutrophils and macrophages, are recruited to the wound site during the inflammatory phase. Neutrophils are the first responders and help clear the wound of any bacteria or debris. Macrophages, which arrive later, are responsible for phagocytosing (engulfing and digesting) bacteria, dead cells, and other foreign substances. Macrophages also release signaling molecules called cytokines that coordinate the wound healing process (**Kim, et al., 2019**).

   - ***Release of Inflammatory Mediators:*** Inflammatory mediators, such as cytokines, chemokines, and growth factors, are released at the wound site. These signaling molecules attract immune cells, stimulate angiogenesis (formation of new blood vessels), and initiate the proliferation and migration of various cell types involved in tissue repair. Inflammatory mediators also play a role in regulating the subsequent phases of wound healing ( **Pereir**a , **et al., 2008**).

   - ***Formation of Granulation Tissue:*** Granulation tissue, a delicate connective tissue composed of fibroblasts, new blood vessels, and extracellular matrix components, begins to form during the inflammatory phase. The angiogenic response stimulated by inflammatory mediators supports the development of new blood vessels within the wound bed (**DiPietro, et al., 2016**). Fibroblasts migrate into the wound and begin synthesizing collagen and other extracellular matrix components that provide structural support for the healing tissue.

   - ***Removal of Debris:*** The inflammatory phase is crucial for clearing the wound of debris, including dead cells, bacteria, and foreign particles. Immune cells, particularly macrophages, play a significant role in phagocytosing and removing these materials from the wound site. This debris clearance is essential for creating a clean environment that supports subsequent stages of healing (**Neumann, et al., 2016**).

   Overall, the inflammatory phase of wound healing is a dynamic and complex process that sets the stage for subsequent tissue repair. It is essential for initiating the recruitment of immune cells, the release of inflammatory mediators, and the clearance of debris. While inflammation is a necessary and beneficial response, excessive or prolonged inflammation can impede the healing process. Therefore, it is important to manage inflammation appropriately to ensure optimal wound healing outcomes.

3. **Proliferative Phase:** The proliferative phase is the third stage of wound healing, following the inflammatory phase (**Nissen**,**et al., 1998**). It is characterized by the active proliferation and migration of various cell types involved in tissue repair, leading to the formation of new tissue and wound closure. It promote angiogenesis (formation of new blood vessels), and restore the integrity of the wound. During the proliferative phase, several key events occur:

   - ***Fibroblast Proliferation and Extracellular Matrix (ECM) Production:*** Fibroblasts, which are specialized cells responsible for synthesizing collagen and other components of the extracellular matrix, play a central role in the proliferative phase. They migrate to the wound site, proliferate, and begin producing new collagen fibers, elastin, and proteoglycans. The newly formed ECM provides structural support and scaffolding for the developing tissue (**Badylak**.,**et al., 2002)**

   - ***Angiogenesis:*** Angiogenesis, the formation of new blood vessels, is a critical process during the proliferative phase. It is stimulated by various growth factors and cytokines released during the inflammatory phase. Endothelial cells, which line the blood vessels, proliferate and migrate to create new capillary networks in the wound bed. This process helps reestablish blood supply to the healing tissue and deliver oxygen and nutrients essential for proper healing.

   - ***Epithelialization:*** Epithelialization involves the migration and proliferation of epithelial cells from the wound edges and appendages, such as hair follicles and sweat glands, to cover the wound surface (**Fathke, et al., 2006)**. The leading edge of migrating epithelial cells gradually moves across the wound bed until complete coverage is achieved. This process helps restore the epidermal barrier and prevent infection.

   - ***Contraction:*** Myofibroblasts, specialized cells with contractile properties, play a crucial role in wound contraction during the proliferative phase( **Davis, et al., 2014)**. These cells, derived from fibroblasts and other cell types, exert contractile forces on the wound edges, causing the wound to shrink in size. Contraction helps reduce the wound area, brings the wound edges closer together, and promotes faster closure.

   - ***Collagen Remodeling:*** During the proliferative phase, the newly synthesized collagen fibers undergo remodeling and maturation. The balance between collagen synthesis and degradation is regulated by various enzymes called matrix metalloproteinases (MMPs)( **Malemud**, **et al., 2006**).Collagen fibers are reorganized and realigned to provide increased tensile strength to the healing tissue. The process of collagen remodeling continues into the subsequent remodeling phase. The proliferative phase is crucial for the formation of granulation tissue, reepithelialization, and wound contraction. It involves the coordinated actions of different cell types, growth factors, and extracellular matrix components. Optimal wound care during this phase includes providing a moist environment, protecting the developing tissue, and supporting the activities of proliferating cells. Proliferative phase overlaps with the inflammatory phase, the duration of the proliferative phase varies depending on the size, depth, and characteristics of the wound.

4. **Remodeling Phase:** The remodeling phase, also known as the maturation phase or the resolution phase, is the final stage of wound healing (**Loiselle, et al., 2020**). It occurs after the inflammatory and proliferative phases and can last for several months to years, depending on the size and severity of the wound. During the remodeling phase, several key processes take place:

   - ***Collagen Remodeling and Maturation:*** Collagen, the main component of the extracellular matrix (ECM), undergoes remodeling and maturation during this phase. The balance between collagen synthesis and degradation shifts, with the gradual replacement of the initially deposited collagen with stronger, more organized collagen fibers. This process is mediated by enzymes called matrix metalloproteinases (MMPs) and their inhibitors (TIMPs). The remodeling of collagen helps improve the tensile strength and structural integrity of the healed tissue.

   - ***Scar Contraction:*** During the remodeling phase, the wound may continue to undergo contraction, albeit at a slower rate compared to the proliferative phase. Myofibroblasts, which are contractile cells derived from fibroblasts, contribute to the contraction process. The continuous contraction helps reduce the size of the scar and bring the wound edges closer together. However, excessive contraction can lead to functional impairments, particularly in large wounds.

   - ***Neovascularization and Vascular Maturation:*** Blood vessels formed during the proliferative phase undergo further maturation and stabilization in the remodeling phase. The newly formed vessels become more organized, acquire a hierarchical network, and establish connections with existing blood vessels in the surrounding tissue. This process helps improve blood supply and ensure proper oxygen and nutrient delivery to the healed tissue.

   - ***Scar Maturation and Remodeling:*** The scar tissue undergoes maturation and remodeling, leading to changes in its appearance and texture. The scar gradually becomes flatter, softer, and less red or pigmented over time. The process of scar maturation and remodeling can take several months to years, and the final appearance of the scar may vary depending on various factors such as wound type, location, and individual healing characteristics.

   - ***Functional Restoration:*** As the healing process progresses in the remodeling phase, the newly formed tissue gradually gains strength and flexibility. This allows the restoration of functional properties such as movement, sensation, and elasticity. However, complete functional restoration may not always be possible, especially in cases of extensive or deep wounds.

   Remodeling phase is a dynamic and ongoing process that can continue for an extended period after the wound appears to have healed externally. The remodeling process is influenced by factors such as mechanical stress, hormonal changes, and inflammatory responses. Proper wound care during this phase, including protection from excessive tension, UV radiation, and trauma, can help optimize the remodeling process and improve the final outcome of wound healing. Overall, the remodeling phase of wound healing is essential for the maturation and strengthening of the healed tissue. It involves the reorganization and maturation of collagen, scar contraction, vascular remodeling, and functional restoration. The duration and effectiveness of the remodeling phase can vary, and it is crucial to monitor and manage wounds during this phase to promote optimal healing outcomes.

Any disturbances or disruptions in the inflammatory and proliferative phases of wound healing can contribute to the development of acute and chronic wounds. Acute wounds typically follow a normal and timely progression through the different stages of wound healing. They are usually caused by a specific event, such as a surgical incision or a traumatic injury, and generally heal within the expected time frame. Acute wounds typically exhibit a well-orchestrated inflammatory response followed by appropriate cell proliferation, angiogenesis, and collagen synthesis, leading to wound closure and resolution.

On the other hand, chronic wounds are characterized by a prolonged or stalled healing process. They fail to progress through the normal stages of wound healing and may remain in the inflammatory or proliferative phase for an extended period. Chronic wounds often have underlying conditions that impede the healing process, such as diabetes, peripheral vascular disease, venous insufficiency, or immune system disorders. Factors contributing to the disturbance in these stages include:

- ***Persistent Inflammation****:* Chronic wounds often exhibit a persistent inflammatory response, with excessive levels of inflammatory mediators and prolonged infiltration of immune cells. This sustained inflammation can prevent the transition to the proliferative phase and impair the normal healing process.

- ***Impaired Cell Proliferation and Angiogenesis:*** In chronic wounds, the proliferation of fibroblasts, endothelial cells, and other cell types involved in tissue repair is often impaired **(Kalluri & Zeisberg, et al., 2006)**. This can lead to a reduced production of growth factors, ECM components, and new blood vessels, further hindering the progression of wound healing.

- ***Inadequate Extracellular Matrix (ECM) Formation:*** Chronic wounds may have deficiencies in the production and organization of ECM components, particularly collagen. The ECM provides the structural support necessary for tissue regeneration, and insufficient or abnormal ECM synthesis can result in weak, fragile tissue that is prone to breakdown.

- ***Persistent Infection:*** Chronic wounds are often susceptible to persistent or recurring infections, which can contribute to ongoing inflammation, delayed healing, and tissue damage. Bacterial biofilms, which form on the wound surface, create a protective environment for bacteria and can be difficult to eliminate **( Scalise, et al., 2015).**

- ***Excessive Matrix Metalloproteinase (MMP) Activity:*** Chronic wounds may have an imbalance between the production of MMPs, enzymes involved in ECM remodeling, and their inhibitors (TIMPs). Excessive MMP activity can lead to the degradation of newly formed ECM and impair the healing process.

Addressing the underlying causes and factors contributing to the disruption of the inflammatory and proliferative phases is crucial in the management of chronic wounds. This may involve optimizing wound care practices, addressing underlying health conditions, managing infection, promoting a healthy wound environment, and utilizing advanced wound therapies such as bioactive dressings, growth factors, or cellular therapies.

## II. DIFFERENT TYPES OF THE THERAPIES AVAILABLE FOR WOUND HEALING

1. **Debridement:** Debridement therapy is an important component of wound care, particularly for chronic wounds that have nonviable or devitalized tissue. Debridement involves the removal of necrotic, infected, or unhealthy tissue from the wound bed, which helps promote wound healing by facilitating the growth of healthy tissue. There are several methods of debridement therapy available, including:

   - ***Surgical Debridement*** is a procedure performed by a healthcare professional in an operating room or clinic setting. It involves the use of sharp instruments, such as scalpels or scissors, to surgically remove nonviable tissue, debris, and foreign materials from the wound bed. Surgical debridement allows for precise and thorough removal of necrotic tissue, and it may be necessary for large or complex wounds.

   - ***Mechanical Debridement*** t involves the use of external forces to remove nonviable tissue (**Broadus, , et al., 2013).**

     This can be achieved through various methods, including:

     - ***Wet-to-dry dressings:*** Wet dressings are applied to the wound and allowed to dry, forming a mechanical adhesion to the nonviable tissue. When the dressing is removed, the adhered tissue is pulled away.

     - ***Whirlpool therapy:*** *The wound is immersed in a whirlpool bath, and the mechanical force of the water helps dislodge necrotic tissue and debris.*

     - ***Pulse lavage:*** *A specialized device delivers a pressurized irrigation solution to the wound, helping to remove debris and nonviable tissue.*

     - ***Enzymatic Debridement:*** Enzymatic debridement involves the application of exogenous enzymes to the wound bed, which selectively break down necrotic tissue. Commonly used enzymes include collagenase, papain, and bromelain. These enzymes digest the nonviable tissue without affecting healthy tissue, promoting the removal of necrotic material from the wound.

     - ***Autolytic Debridement:*** Autolytic debridement utilizes the body's own mechanisms to break down and remove necrotic tissue. It involves creating and maintaining a moist wound environment using dressings such as hydrogels or hydrocolloids. The moisture softens and liquefies the necrotic tissue, allowing the body's natural enzymes and white blood cells to gradually break it down and remove it.

- ***Biological Debridement:*** Biological debridement involves the application of sterile larvae, typically from medical-grade maggots, to the wound bed (**Wang, et al., 2022**).. These larvae feed on necrotic tissue, selectively debriding the nonviable material while leaving healthy tissue intact. This method of debridement, known as maggot therapy or larval therapy, has been used for centuries and has shown effectiveness in certain cases.

2. **Hyperbaric Oxygen Therapy:** Hyperbaric oxygen therapy (HBOT) is a medical treatment that involves breathing pure oxygen in a pressurized chamber. It is used as an adjunctive therapy for various medical conditions, including wound healing. HBOT provides the body with increased levels of oxygen, which can enhance the healing process in certain types of wounds **(Ortega, Fraile-Martinez, García-Montero, , et al., (2021)**).. HBOT delivers high concentrations of oxygen to the body, resulting in increased oxygen levels in the bloodstream. This increased oxygen supply helps promote angiogenesis (formation of new blood vessels) and enhances oxygen delivery to the wound site. Oxygen is essential for various cellular processes involved in wound healing, including cell proliferation, collagen synthesis, and antimicrobial activity. Oxygen plays a crucial role in the formation of new blood vessels (neovascularization) in the wound bed. HBOT stimulates the growth of new blood vessels, improving the blood supply to the wound site. Adequate blood flow is essential for providing oxygen and nutrients to support tissue repair and regeneration. HBOT exhibits direct antimicrobial effects by increasing oxygen tension, which creates an inhospitable environment for certain bacteria. Some bacteria, particularly anaerobic bacteria, thrive in low-oxygen environments. By increasing oxygen levels, HBOT can help inhibit the growth of anaerobic bacteria and enhance the effectiveness of the immune system in fighting infection. HBOT has been shown to help reduce edema (swelling) and inflammation in wounds. The increased oxygen levels promote the clearance of excess fluid and reduce tissue edema, which can impede the healing process. Additionally, HBOT can modulate the inflammatory response, leading to a reduction in inflammation and improved healing.

   Collagen is a key component of the extracellular matrix and provides structural support for wound healing. HBOT stimulates fibroblast activity and enhances collagen synthesis, leading to the formation of stronger and more organized collagen fibers in the wound bed. This can improve the tensile strength and integrity of the healed tissue. HBOT is typically administered as a series of treatments, with each session lasting around 60-120 minutes. The number of treatments required depends on the specific wound characteristics and individual patient factors. HBOT is often used in cases of non-healing or chronic wounds, such as diabetic foot ulcers, radiation-induced wounds, and compromised surgical wounds.

3. **Ultrasound and Electromagnetic Therapies:** Ultrasound therapy and electromagnetic therapies are two non-invasive modalities used in wound healing. While they operate through different mechanisms, both have been shown to have beneficial effects on the healing process.

Ultrasound therapy involves the use of high-frequency sound waves that are applied to the wound area using a handheld device. There are two main types of ultrasound therapy used in wound healing: LFU operates at frequencies between 20 kHz and 100 kHz. It is believed to stimulate wound healing by various mechanisms, including increased cellular activity, enhanced collagen synthesis, improved angiogenesis, and increased fibroblast migration and proliferation. LFU can also facilitate the penetration of topical medications or wound dressings into the wound bed. HFU operates at frequencies above 1 MHz. It is primarily used for diagnostic purposes to assess wound depth and tissue characteristics. HFU can help determine the extent of tissue damage and guide treatment decisions. Ultrasound therapy can promote wound healing by increasing blood flow, stimulating cell activity, reducing inflammation, and aiding in the removal of necrotic tissue. **(Elgohary & Jaouni, et al., 2018)**. It is commonly used for chronic wounds, such as pressure ulcers, diabetic foot ulcers, and venous leg ulcers.

Electromagnetic therapies involve the use of electromagnetic fields or currents to promote wound healing. There are several types of electromagnetic therapies used in wound care: ***Pulsed Electromagnetic Field*** (PEMF) therapy utilizes pulsed electromagnetic fields to stimulate tissue repair and regeneration. It is believed to promote wound healing by increasing cell proliferation, enhancing angiogenesis, modulating inflammation, and promoting collagen synthesis. ***Electromagnetic induction*** therapy utilizes electromagnetic fields to generate electrical currents within the tissue. This therapy can promote wound healing by stimulating blood flow, enhancing tissue oxygenation, and reducing inflammation. ***Electrostimulation*** therapy involves the application of electrical currents to the wound area **( Wainapel, et al., 1985**).. It can stimulate muscle contractions, improve blood flow, and enhance tissue regeneration. Various types of electrical stimulation, such as transcutaneous electrical nerve stimulation (TENS) or microcurrent therapy, may be used. Electromagnetic therapies have shown potential in promoting wound healing, particularly in chronic or non-healing wounds. They can enhance cellular activity, improve blood circulation, modulate the inflammatory response, and stimulate tissue repair processes.

4. **Negative Pressure Wound Therapy:** Negative pressure wound therapy (NPWT), also known as vacuum-assisted closure (VAC) therapy, is a specialized treatment technique used in wound healing. It involves the application of negative pressure or suction to a wound through a sealed dressing system. NPWT has been widely used in various types of wounds, including acute, chronic, traumatic, and surgical wounds. In this, foam or gauze dressing is applied to the wound bed, covering the entire wound surface. The dressing is connected to a tubing system that delivers negative pressure or suction. The tubing is connected to a collection canister that collects wound exudate and any debris. The negative pressure helps remove excessive wound exudate, which can contribute to swelling and inhibit healing. NPWT stimulates the wound edges to contract, reducing the wound size and promoting closure (**Huang, & Leavitt, et al., 2014**). It promotes increased blood flow to the wound bed, improving oxygen and nutrient delivery also reduces the tissue swelling and edema, facilitating the healing process. The negative pressure helps to remove infectious material and bacteria from the wound, reducing the risk of infection. NPWT creates a moist environment that is conducive to the formation of healthy granulation tissue, reduce the bacterial load in the wound bed, decreasing the risk of infection, stimulates the formation of new blood vessels (angiogenesis), improving

blood supply to the wound and facilitating healing. NPWT brings wound edges together, promoting wound closure and reducing the need for more invasive closure techniques, provides pain relief by reducing wound-related discomfort and minimizing dressing changes. NPWT typically applied for several days or weeks, depending on the wound characteristics and healing progress.

5. **Skin Grafts:** Skin grafting is a surgical procedure used in wound therapy to replace damaged or missing skin with healthy skin from another area of the body (donor site) or a donor source. Skin grafts can be classified into different types based on the source of the graft and the thickness of the skin used. The two main types of skin grafts are split-thickness grafts and full-thickness grafts: In a split-thickness graft, a thin layer of skin is harvested from the donor site, typically the thigh, buttock, or upper arm. The epidermis and a portion of the underlying dermis are removed. STGs consist of a thin outer layer of epidermis and a variable thickness of dermis. The thickness of the dermis can vary depending on the specific needs of the wound and the donor site. Split-thickness grafts are more versatile and can cover larger wound areas. They are less invasive and generally have better graft survival rates compared to full-thickness grafts. Commonly used for extensive burns, chronic wounds, and large defects that require coverage with healthy skin. Full-thickness grafts involve the removal of both the epidermis and the entire dermis from the donor site. The graft includes the complete thickness of the skin consisting of the epidermis, dermis, and subcutaneous fat. They are thicker and contain more blood vessels, nerves, and appendages compared to split-thickness grafts. Full-thickness grafts provide a more natural appearance and texture as they contain all layers of the skin. They are suitable for areas where aesthetic outcomes and function are important. FTGs are commonly used for reconstructive procedures, such as facial or hand reconstructions, where the goal is to restore both form and function.

   The choice of skin graft type depends on various factors, including the size, location, and characteristics of the wound, as well as the availability of suitable donor sites. Other specialized techniques, such as mesh grafting or dermal substitutes, may also be used in certain cases to maximize the coverage and healing of the wound.

   It's important to note that skin grafting is a surgical procedure that requires proper surgical techniques, anesthesia, and post-operative care. The procedure is typically performed by a trained healthcare professional, such as a plastic surgeon or a specialized wound care team, to ensure optimal outcomes and minimize the risk of complications.

6. **Wound Dressings:** There are various types of dressings available for the management of chronic wounds. The choice of dressing depends on factors such as the type and characteristics of the wound, the presence of infection, the amount and type of exudate (fluid) produced by the wound, and the desired therapeutic goals. Here are some commonly used dressings for chronic wound healing:

   - **Foam Dressings:** Foam dressings are absorbent dressings that can manage moderate to heavy exudating wounds. They are designed to absorb excess fluid while maintaining a moist wound environment. Foam dressings provide cushioning, protection, and insulation for the wound. They can also help minimize the risk of maceration (over hydration) of the surrounding skin.

- **Hydrocolloid Dressings:** Hydrocolloid dressings are occlusive dressings that contain hydrophilic particles that form a gel when they come into contact with wound exudate. These dressings create a moist environment and provide a barrier against external contaminants. Hydrocolloid dressings are commonly used for chronic wounds with minimal to moderate exudate and can promote autolytic debridement (removal of dead tissue) in the wound.

- **Hydrogel Dressings:** Hydrogel dressings are composed mostly of water and are used for wounds with minimal exudate or dry wounds. They provide moisture to the wound bed and help facilitate autolytic debridement. Hydrogel dressings can also provide a cooling and soothing effect, making them suitable for painful wounds (**McCarthy & Camci-Unal, et al., 2021)**. They are not recommended for heavily exudating wounds.

- **Alginate Dressings:** Alginate dressings are made from seaweed extracts and are highly absorbent. They are suitable for moderately to heavily exudating wounds. Alginate dressings form a gel when they come into contact with wound exudate, helping to maintain a moist wound environment. They can also promote autolytic debridement and are useful for packing deep or cavity wounds.

- **Transparent Film Dressings**: Transparent film dressings are thin, semipermeable dressings that provide a barrier against water, bacteria, and other contaminants (**Bainbridge, Blaser,& Hitschmann, et al., 2021)**. They are often used for superficial wounds or as a secondary dressing to secure other primary dressings. Transparent film dressings allow for wound visualization and provide a moist environment for wound healing.

- **Antimicrobial Dressings:** Antimicrobial dressings are designed to help manage chronic wounds that are infected or at risk of infection. These dressings contain agents such as silver, iodine, or antimicrobial peptides that can help reduce microbial colonization in the wound and prevent infection. Antimicrobial dressings are used in conjunction with other dressings based on the wound characteristics and severity of infection.

## III. HYDROGELS

Over the above mentioned wound dressing Hydrogels have emerged as promising materials in the field of wound healing due to their unique properties and capabilities. These three-dimensional, cross-linked networks of hydrophilic polymers can absorb and retain large amounts of water or biological fluids, giving them a gel-like consistency.

When it comes to wound healing, hydrogels offer several advantages. They create a moist environment at the wound site, which is conducive to the natural healing process. By providing hydration and preventing the wound from drying out, hydrogels promote cell migration, proliferation, and tissue regeneration. Additionally, they can act as a barrier against external contaminants, protecting the wound from infection. Hydrogels can be classified into different categories based on their composition, which can include synthetic polymers, natural polymers, or a combination of both. Synthetic hydrogels are typically made from materials like polyethylene glycol (PEG) or polyvinyl alcohol (PVA), while natural hydrogels can be derived from substances like chitosan, alginate, or collagen. The choice of hydrogel composition depends on factors such as the wound type, desired properties, and intended application.

These materials can be engineered to possess specific characteristics, such as porosity, mechanical strength, and degradation rate, to suit different wound types and stages of healing. Some hydrogels are designed to release bioactive compounds, such as growth factors or antimicrobial agents, which can further enhance the healing process. These properties make hydrogels versatile and adaptable to a wide range of wound management needs. Hydrogels can be applied directly to the wound site as dressings or incorporated into wound dressings, films, or patches. They provide a conformable and comfortable interface between the wound and the external environment. c. In addition to their direct application in wound healing, hydrogels have also found utility in other related areas. For instance, they can be used as scaffolds for tissue engineering, providing a supportive structure for the growth and organization of cells. Hydrogel-based systems are also being explored for drug delivery, enabling controlled release of therapeutic agents to the wound site (**Mirani, Currie & Hosseinzadeh, et al., 2017).**

1. **Synthetic Polymer based Hydrogel:** Synthetic polymer-based hydrogels possess several characteristics that make them beneficial for wound healing. Here are some key characteristics and their associated benefits:

   - **Tunable Physical Properties:** Synthetic polymer-based hydrogels offer the advantage of tunable physical properties, including mechanical strength, elasticity, and porosity. These properties can be adjusted during the hydrogel synthesis process to match the requirements of specific wound types. Tunability allows for the customization of hydrogels to provide appropriate support, conformability, and mechanical protection to the wound.

   - **High Water Absorption Capacity:** Synthetic polymer-based hydrogels can absorb and retain a significant amount of water or wound exudate relative to their dry weight. This high water absorption capacity helps to maintain a moist wound environment, which is known to facilitate wound healing. The hydrogels absorb excess exudate, preventing its accumulation in the wound bed and reducing the risk of bacterial colonization. The moisture also supports cell migration, proliferation, and the formation of granulation tissue.

   - **Controlled Drug Delivery:** Synthetic polymer-based hydrogels can be engineered to incorporate and release therapeutic agents, such as growth factors, antibiotics, or analgesics. The hydrogel matrix can act as a reservoir for these agents, allowing for controlled and sustained release over time. This controlled drug delivery system enhances the effectiveness of the therapeutic compounds, promoting wound healing, preventing infection, and managing pain at the wound site.

   - **Biocompatibility and Biodegradability:** Synthetic polymer-based hydrogels can be designed to be biocompatible, meaning they are compatible with living tissues and do not cause adverse reactions. They can also be engineered to be biodegradable, gradually breaking down into harmless byproducts over time. Biocompatibility ensures that the hydrogel does not induce inflammation or immune responses, while biodegradability allows for the natural clearance of the hydrogel as the wound heals, without the need for its removal (**Mohamad, Buang, & Mohd Amin, et al., 2017).**

- **Adhesive and Non-Adhesive Properties:** Synthetic polymer-based hydrogels can be formulated to exhibit adhesive or non-adhesive properties, depending on the specific wound requirements. Adhesive hydrogels adhere to the wound bed, providing stability and preventing the dressing from shifting or dislodging. Non-adhesive hydrogels, on the other hand, do not stick to the wound, allowing for easy and painless removal during dressing changes. The choice between adhesive and non-adhesive hydrogels depends on factors such as wound location, type, and patient comfort.

- **Enhanced Mechanical Strength:** Synthetic polymer-based hydrogels can be reinforced with fibers, nanoparticles, or other reinforcing agents to enhance their mechanical strength. This reinforcement improves the structural integrity of the hydrogel, making it more resistant to deformation and capable of withstanding mechanical forces. Enhanced mechanical strength is particularly beneficial for wounds that experience significant tension or require mechanical protection.

- **Versatile Formulations:** Synthetic polymer-based hydrogels offer versatility in their formulations, allowing them to be tailored to different wound types and conditions. They can be prepared as sheets, gels, films, injectable solutions, or spray formulations, enabling their application to various wound shapes, sizes, and depths. This versatility enhances the ease of use, conformability, and adaptability of the hydrogels in wound management.

Overall, synthetic polymer-based hydrogels possess desirable characteristics, including tunable physical properties, high water absorption capacity, controlled drug delivery capabilities, biocompatibility, adhesive/non-adhesive properties, enhanced mechanical strength, and versatile formulations.

2. **Natural Polymer based Hydrogel:** Natural polymer-based hydrogels have distinct characteristics that make them beneficial for wound healing. Here are some key characteristics and their associated benefits:

- **Biocompatibility:** Natural polymer-based hydrogels are derived from biologically sourced materials such as alginate, chitosan, collagen, gelatin, or hyaluronic acid. These polymers are inherently biocompatible, meaning they are well-tolerated by living tissues and do not typically cause adverse reactions or inflammation. Biocompatibility ensures that the hydrogel can be safely applied to the wound bed without causing additional harm or discomfort.

- **Biodegradability:** Natural polymer-based hydrogels are often biodegradable, meaning they can be broken down by biological processes over time. This characteristic allows the hydrogel to gradually degrade and be absorbed by the body as the wound heals. Biodegradability eliminates the need for manual removal of the dressing, reducing the risk of disrupting the wound and simplifying wound care.

- **Moisture Retention:** Natural polymer-based hydrogels have high water retention capabilities. They can absorb and retain large amounts of wound exudate or water, creating and maintaining a moist environment at the wound site. This moist environment is essential for optimal wound healing, as it promotes cell migration, proliferation, and the formation of new tissue. Additionally, moisture retention helps prevent wound drying and the formation of a dry scab, which can impede healing.

- **Bioactive Properties:** Natural polymers often possess inherent bioactive properties that can benefit wound healing. For example, chitosan has antimicrobial properties, while collagen and hyaluronic acid can promote cell proliferation and tissue regeneration. The bioactive properties of natural polymers can support the wound healing process by enhancing antibacterial activity, promoting angiogenesis, and modulating cellular behavior **(Zhang & Guo, et al., 2022).**

- **Extracellular Matrix (ECM) Mimicry:** Natural polymer-based hydrogels can be engineered to mimic the structure and composition of the extracellular matrix (ECM) found in native tissues. The ECM provides a supportive environment for cells and plays a critical role in tissue regeneration. By mimicking the ECM, natural polymer-based hydrogels can provide a favorable microenvironment for cell attachment, migration, and proliferation, facilitating the formation of new tissue and wound closure.

- **Controlled Drug Delivery:** Natural polymer-based hydrogels can serve as carriers for controlled drug delivery. The hydrogel matrix can be loaded with bioactive molecules such as growth factors, antimicrobial agents, or anti-inflammatory compounds. These molecules can be released gradually from the hydrogel, providing sustained exposure to the wound bed. Controlled drug delivery enhances the effectiveness of therapeutic agents in promoting wound healing, reducing infection, and managing inflammation.

- **Easy Application and Removal:** Natural polymer-based hydrogels are generally easy to apply and remove from the wound site. They can be prepared as gels, films, sheets, or other formats, allowing for convenient application to wounds of different sizes and shapes. Easy application and removal minimize patient discomfort and facilitate regular dressing changes for wound management.

Overall, natural polymer-based hydrogels offer characteristics such as biocompatibility, biodegradability, moisture retention, bioactive properties, ECM mimicry, controlled drug delivery, and ease of application/removal.

3. **Natural Polymer based Hydrogels Synthetic Polymer:** Both natural polymer-based hydrogels and synthetic polymer-based hydrogels have their own advantages and applications in wound healing. It's important to note that the choice between natural and synthetic polymer-based hydrogels depends on various factors, including the specific wound characteristics, desired properties of the dressing, and individual patient considerations. Here are some reasons why natural polymer-based hydrogels are often preferred:

- **Biocompatibility:** Natural polymers are derived from biological sources and are generally well-tolerated by the body. They exhibit inherent biocompatibility, meaning they are less likely to cause adverse reactions, inflammation, or immune responses. Natural polymer-based hydrogels are therefore suitable for a wide range of wounds, including sensitive or compromised skin, and can be safely applied without significant risks of allergic reactions or toxicity.

- **Bioactivity:** Natural polymers often possess inherent bioactive properties that can positively influence wound healing. For example, substances like chitosan, collagen, or hyaluronic acid found in natural polymer-based hydrogels can promote cell proliferation, angiogenesis, and tissue regeneration. These bioactive properties can help accelerate the healing process and support the natural wound repair mechanisms.

- **ECM Mimicry:** Natural polymer-based hydrogels can mimic the composition and structure of the extracellular matrix (ECM), which is a vital component of native tissues. This mimicry provides a favorable microenvironment for cells, enabling enhanced cell attachment, migration, and proliferation. By closely resembling the ECM, natural polymer-based hydrogels can better support tissue regeneration and wound closure.

- **Biodegradability:** Natural polymer-based hydrogels are typically biodegradable, meaning they can be broken down by the body's natural processes over time. Biodegradability eliminates the need for manual removal of the dressing, reducing the risk of disturbing the wound bed and simplifying wound care. The gradual degradation of natural polymer-based hydrogels aligns with the healing process, allowing for a seamless transition as the wound progresses through various stages of healing.

- **Moisture Retention:** Natural polymer-based hydrogels have excellent water retention properties, enabling them to create and maintain a moist environment at the wound site. A moist wound environment is crucial for optimal wound healing, as it promotes cell migration, proliferation, and the formation of granulation tissue. Natural polymer-based hydrogels can effectively retain moisture, preventing wound drying and promoting faster healing.

- **Controlled Drug Delivery:** Natural polymer-based hydrogels can serve as carriers for controlled drug delivery. The hydrogel matrix can be loaded with bioactive molecules such as growth factors, antimicrobial agents, or anti-inflammatory compounds. These molecules can be released gradually from the hydrogel, providing sustained exposure to the wound bed. Controlled drug delivery enhances the effectiveness of therapeutic agents in promoting wound healing, reducing infection, and managing inflammation.

- **Easy Application and Removal:** Natural polymer-based hydrogels are generally easy to apply and remove from the wound site (**Zhong, Xiao & Seidi, , et al., 2020).** They can be prepared as gels, films, sheets, or other formats, allowing for convenient application to wounds of different sizes and shapes. Easy application and removal minimize patient discomfort and facilitate regular dressing changes for wound management.

Synthetic polymer-based hydrogels also offer distinct advantages, such as tunable physical properties, controlled drug delivery capabilities, and enhanced mechanical strength. These properties can be advantageous for specific wound types or clinical situations. Additionally, the availability, cost, and ease of synthesis may also influence the selection of the hydrogel type for wound healing.

Both natural polymer-based hydrogels and synthetic polymer-based hydrogels have their own advantages and applications in wound healing. It's important to note that the choice between natural and synthetic polymer-based hydrogels depends on various factors, including the specific wound characteristics, desired properties of the dressing, and individual patient considerations. Natural polymer-based hydrogels are often preferred for wound healing due to their biocompatibility, bioactivity, ECM mimicry, biodegradability, and moisture retention properties.

In general, natural hydrogels and synthetic hydrogels exhibit differences in porosity, mechanical strength, and degradation rate.

4. **Porosity:** Natural hydrogels often have a higher porosity compared to synthetic hydrogels. The structure of natural polymers, such as collagen, chitosan, or alginate, allows for the creation of interconnected pores within the hydrogel matrix. This porosity facilitates the exchange of oxygen, nutrients, and waste products between the wound bed and the surrounding environment, promoting cell infiltration and tissue regeneration (**McArthur & Kingshott, , et al., 2014**). Whereas Synthetic hydrogels can also be engineered to have controlled porosity, but their pore structure is generally more uniform and less interconnected compared to natural hydrogels. The porosity of synthetic hydrogels can be adjusted during the synthesis process, but it typically requires the incorporation of porogens or other additives.

5. **Mechanical Strength:** Natural hydrogels typically have lower mechanical strength compared to synthetic hydrogels. The mechanical properties of natural polymers can vary, but they are generally softer and more flexible. While natural hydrogels provide good conformability to irregular wound surfaces, they may lack the robustness required for wounds that experience significant mechanical stress or tension. Whereas Synthetic hydrogels offer the advantage of tunable mechanical properties. They can be engineered to have a wide range of mechanical strengths, from soft and flexible to rigid and strong. Synthetic polymers provide greater control over the mechanical properties of the hydrogel, allowing for customization based on the specific wound requirements.

6. **Degradation Rate:** Natural hydrogels are often biodegradable, meaning they can degrade over time through enzymatic or hydrolytic processes. The degradation rate of natural hydrogels can be influenced by factors such as the choice of natural polymer, crosslinking density, and environmental conditions. Natural hydrogels can be designed to degrade at a rate that matches the wound healing timeline, gradually breaking down and being absorbed by the body. Whereas Synthetic hydrogels can be engineered to have different degradation rates, ranging from fast to slow degradation. The degradation kinetics of

synthetic hydrogels can be controlled by modifying the polymer structure, crosslinking density, or incorporating specific cleavable linkages. This allows for customization of the hydrogel's degradation rate to match the wound healing process.

7. **3D Structure of Hydrogels:** The 3D structure of hydrogels plays a crucial role in their benefits for wound healing. Hydrogels are formed by cross-linking polymer chains, resulting in a network-like structure that can hold a significant amount of water or biological fluids. This unique structure provides several advantages in the context of wound healing:

   - ***Moist Wound Environment:*** Hydrogels maintain a moist environment at the wound site, which is considered ideal for wound healing. This moisture helps to prevent the wound from drying out, reducing scab formation and promoting the migration of cells involved in the healing process, such as fibroblasts and keratinocytes. Moisture also supports angiogenesis, the formation of new blood vessels, which is crucial for delivering nutrients and oxygen to the wound.

   - ***Wound Exudate Management:*** Hydrogels have the capacity to absorb and retain wound exudate, which is the fluid that is naturally secreted by the wound. Excessive exudate can hinder the healing process, while inadequate moisture can lead to wound desiccation. Hydrogels strike a balance by absorbing excess exudate and maintaining an optimal moisture level in the wound bed, promoting a favorable environment for healing.

   - ***Protection and Barrier Function:*** Hydrogels act as a protective barrier over the wound, shielding it from external contaminants, bacteria, and other harmful agents. This barrier function helps reduce the risk of infection and minimizes the chance of complications during the healing process.

   - ***Drug Delivery Capability:*** Hydrogels can be designed to incorporate and release various therapeutic agents, such as growth factors, antimicrobial agents, or pain relievers. These bioactive compounds can be incorporated into the hydrogel matrix or loaded into nanoparticles embedded within the hydrogel structure. This drug delivery capability enables controlled release of therapeutic agents at the wound site, enhancing the healing process by promoting tissue regeneration or preventing infection (**Saghazadeh & Kashaf, et al., 2018**).

   - ***Conformability and Ease of Application:*** Hydrogels can be formulated into various forms, such as sheets, gels, films, or injectable solutions. This versatility allows them to conform to different wound shapes and sizes, providing a comfortable and adaptable interface between the wound and the external environment. Hydrogel dressings are generally easy to apply, remove, and change, which facilitates wound care management.

   - ***Biocompatibility and Tissue Integration:*** Hydrogels can be engineered using biocompatible and biodegradable materials, making them suitable for use in contact with biological tissues. They are designed to minimize adverse reactions, inflammation, and allergic responses, ensuring compatibility with the wound environment. Some hydrogels can also support cell adhesion and tissue integration, promoting the regeneration of damaged tissues.

8. **Hydrophillic Nature of Hydrogel:** The hydrophilic nature of hydrogels, which refers to their ability to attract and retain water or biological fluids, offers several benefits in wound healing:

   - ***Moisture Retention:*** Hydrogels have a high water content and are capable of absorbing and retaining large amounts of fluid. This property helps to create and maintain a moist environment at the wound site, which is known to promote optimal wound healing. The moisture in the hydrogel provides hydration to the wound bed, preventing it from drying out ( **Lan & Shoga, et al., 2023).** This moist environment supports various cellular processes involved in wound healing, including cell migration, proliferation, and the formation of granulation tissue.

   - ***Facilitates Gas Exchange:*** Hydrogels allow for efficient gas exchange between the wound and the external environment. Oxygen is crucial for cellular metabolism and tissue regeneration, and carbon dioxide removal is necessary for maintaining a healthy wound environment. The hydrophilic nature of hydrogels facilitates the transport of oxygen and carbon dioxide through the gel structure, ensuring an adequate oxygen supply to the wound and facilitating the removal of waste gases.

   - ***Debridement and Autolytic Debridement:*** In the context of wound healing, debridement refers to the removal of non-viable tissue or foreign material from the wound bed. Hydrogels can assist in this process through autolytic debridement. Autolytic debridement occurs when the hydrogel absorbs excess wound exudate, creating a moist environment that facilitates the breakdown of devitalized tissue by the body's own enzymes. This process helps to promote the removal of necrotic or sloughy tissue, allowing for the growth of healthy granulation tissue.

   - ***Minimizes Wound Trauma:*** Hydrogels possess a soft and gel-like consistency, making them gentle and non-adherent to the wound bed. This property reduces the risk of trauma and damage to the delicate newly formed tissue during dressing changes. The hydrophilic nature of hydrogels also minimizes the need for frequent dressing changes, as they can retain moisture for extended periods, reducing disruption to the wound healing process.

   - ***Enhanced Drug Delivery:*** The hydrophilic nature of hydrogels allows them to serve as effective drug delivery vehicles. Hydrogels can be loaded with therapeutic agents such as growth factors, antimicrobial agents, or pain relievers, which can be released slowly and continuously into the wound bed. This controlled release mechanism ensures sustained exposure of the wound to the therapeutic compounds, enhancing their effectiveness in promoting healing, preventing infection, or managing pain.

   - ***Cooling and Soothing Effect:*** Hydrogels with a high water content possess a cooling and soothing effect when applied to the wound. This can provide relief to patients experiencing pain or discomfort associated with the wound. The hydrophilic nature of the gel allows it to absorb heat from the wound surface, providing a cooling sensation that can help alleviate pain and inflammation.

Overall, the hydrophilic nature of hydrogels contributes to creating a moist and favorable wound environment, supporting key processes in wound healing such as cell migration, proliferation, tissue regeneration, and autolytic debridement. Additionally, their ability to facilitate gas exchange, minimize trauma, and provide sustained drug delivery further enhances their benefits in wound healing applications.

9. **Moist environment and Conductive nature:** The moist environment and conductive nature of hydrogels are advantageous for wound healing. Here's how these properties contribute to the healing process:

- **Moist Environment:** Hydrogels create a moist environment at the wound site, which is crucial for optimal wound healing. This moist environment helps to prevent the wound from drying out and promotes cell migration, proliferation, and tissue regeneration. Moisture also facilitates the exchange of oxygen and nutrients between the wound and the surrounding tissues, supporting cellular metabolism and the growth of new blood vessels (angiogenesis). Moreover, a moist environment aids in the autolytic debridement process, which involves the breakdown and removal of non-viable tissue from the wound bed.

- **Conductive Nature:** Hydrogels have a conductive nature, meaning they can facilitate the movement of electrical signals. This property is particularly relevant in chronic or non-healing wounds where the wound bed often exhibits an impaired electrical potential. Hydrogels with conductive properties can help restore the normal electrical balance at the wound site. Electrical stimulation has been shown to enhance wound healing by promoting cell migration, collagen synthesis, angiogenesis, and antibacterial activity. By acting as conductive substrates, hydrogels can facilitate these electrical signaling processes, further supporting the healing cascade.

Together, the moist environment created by hydrogels and their conductive nature work synergistically to enhance wound healing outcomes. The moist environment promotes cellular activities and tissue regeneration, while the conductive nature supports electrical signaling processes that stimulate the healing process. These properties make hydrogels valuable tools in wound management, especially for chronic wounds that require additional assistance to overcome healing barriers.

10. **Mechanism of Wound healing through Hydrogel**

- **Moisture Retention:** Hydrogels have the ability to absorb and retain moisture, creating a moist environment at the wound site. This moisture is essential for cell migration, as it helps to keep the wound bed hydrated and supports the movement of cells across the wound surface. Hydration is particularly important for the migration of keratinocytes, fibroblasts, and endothelial cells, which are critical for re-epithelialization and angiogenesis ( **Amiri, & Ghahary, et al., 2022).**

- **Scaffold for Cell Attachment:** Hydrogels can serve as a scaffold or support structure for cells to attach and proliferate. The three-dimensional structure of hydrogels provides a physical framework for cell adhesion and migration. Cells can anchor themselves to the hydrogel matrix, extending protrusions and forming focal adhesions. This attachment allows cells to migrate, proliferate, and organize within the hydrogel, promoting tissue regeneration.

- **Biocompatibility and Bioactivity:** Hydrogels can be designed to be biocompatible and bioactive, meaning they are compatible with living tissues and can interact with cells to influence their behavior. Some hydrogels are engineered to mimic the natural extracellular matrix (ECM), providing a supportive microenvironment that resembles the native tissue. These hydrogels can contain bioactive molecules, such as growth factors or peptides, that promote cell migration, proliferation, and differentiation, further enhancing tissue regeneration.

- **Release of Bioactive Molecules:** Hydrogels can be designed to incorporate and release bioactive molecules, such as growth factors or cytokines, to the wound site. These molecules can be directly loaded into the hydrogel matrix or encapsulated within nanoparticles embedded within the hydrogel structure. The controlled release of these bioactive molecules from the hydrogel provides a localized and sustained delivery, creating a favorable microenvironment that stimulates cell migration, proliferation, and tissue regeneration.

- **Modulation of Cellular Behavior:** Hydrogels can be tailored to have specific physical and biochemical properties that can influence cellular behavior. For example, the mechanical properties of the hydrogel, such as stiffness or elasticity, can impact cell behavior, including migration and proliferation. Additionally, the incorporation of bioactive cues, such as cell adhesion ligands or extracellular matrix components, into the hydrogel can guide cellular behavior and promote tissue regeneration.

By providing a moist and supportive environment, serving as a scaffold for cell attachment, releasing bioactive molecules, and modulating cellular behavior, hydrogels effectively promote cell migration, proliferation, and tissue regeneration in wound healing. These properties make hydrogels valuable tools in wound management, facilitating the complex and dynamic processes involved in wound healing and tissue repair.

11. **Hydrogel work as barrier against the external contamination:** Hydrogels can act as a barrier against external contamination, helping to protect the wound from infection.

Hydrogels form a physical barrier between the wound and the external environment. The gel-like structure of hydrogels creates a protective layer over the wound, preventing direct contact with contaminants such as dirt, bacteria, or other microorganisms. This barrier helps to reduce the risk of infection by minimizing the entry of harmful agents into the wound (**Wright, Hansen & Burrel, , et al., 1999).** Hydrogels have the capacity to absorb and retain wound exudate, which is the fluid naturally produced by the wound. Excessive exudate can provide a breeding ground for bacteria and prolong the inflammatory phase of wound healing. By absorbing and retaining exudate, hydrogels help to manage the moisture level at the wound site, preventing the accumulation of excess fluid that could promote bacterial growth. As mentioned earlier, hydrogels create a moist environment at the wound site, which is conducive to wound healing. While this moist environment supports cell migration and tissue regeneration, it also helps to prevent the formation of a dry scab. A dry scab can impede the healing process and create a favorable environment for bacterial colonization. By keeping the wound moist, hydrogels discourage the formation of a scab and reduce the risk of infection. Some hydrogels can be engineered to possess inherent antimicrobial properties or incorporate antimicrobial agents into their matrix. These antimicrobial hydrogels release active compounds that can inhibit the growth of bacteria or other microorganisms in the wound environment. This feature helps to reduce the risk of infection and prevent the proliferation of bacteria that could impede the healing process. Hydrogel dressings are generally easy to apply and remove, which is beneficial in wound management. Their conformable nature allows for easy application to various wound shapes and sizes. This ease of use minimizes the potential for contamination during dressing changes and ensures that the wound is protected throughout the healing process.

12. **Direct and indirect application of hydrogel for Wound Healing:** Hydrogels can be applied directly or indirectly to wounds, depending on the specific requirements and characteristics of the wound.

    - **Direct Application:** Direct application involves directly applying the hydrogel dressing onto the wound bed. This method is suitable for wounds where direct contact between the hydrogel and the wound surface is desired. Direct application of hydrogel can be achieved through various forms, including gels, films, sheets, or injectable formulations. Some common direct application methods include: Hydrogel gels can be applied directly to the wound bed as a gel or gel-like dressing. The gel adheres to the wound surface, creating a moist environment, promoting wound healing, and providing a protective barrier against external contaminants. Hydrogel sheets or films can be cut to the appropriate size and placed directly onto the wound. These sheets adhere to the wound surface, conforming to the contours of the wound and maintaining a moist environment. They provide protection, prevent dehydration, and promote healing. Hydrogel formulations can be injected directly into the wound site. Injectable hydrogels can fill irregular-shaped wounds, adapt to the wound surface, and provide a moist environment for healing (**Ren, hang &.Chang, , et al., 2021).** They can also deliver therapeutic agents or promote cell infiltration and tissue regeneration.

    - **Indirect Application:** Indirect application involves using a secondary material or carrier to deliver the beneficial properties of the hydrogel to the wound site. This method is suitable when direct contact between the hydrogel and the wound is not desired or when the hydrogel needs to be applied in combination with other treatment modalities. Some common indirect application methods include:

        - **Impregnated Dressings:** Hydrogel can be impregnated into other dressings, such as foam or non-woven dressings. These dressings act as carriers, delivering the benefits of the hydrogel to the wound while also providing additional functionalities such as absorption, protection, and exudate management.

- **Composite Dressings:** Hydrogel can be combined with other materials, such as antimicrobial agents, silver nanoparticles, or growth factors, to create composite dressings. These dressings combine the advantages of hydrogel with other therapeutic agents, providing targeted treatment and enhanced wound healing properties.

- **Coatings:** Hydrogel coatings can be applied to other wound dressings or medical devices to impart moisture-retention properties or facilitate wound healing. The hydrogel coating serves as a barrier, preventing wound dehydration, reducing friction, and promoting a favorable wound environment.

The choice between direct and indirect application of hydrogel depends on factors such as the wound type, size, depth, location, presence of exudate, desired functionalities, and treatment goals.

13. **Advancement in the Hydrogel Dressings:** Hydrogel dressings have undergone advancements and innovations in recent years to improve their effectiveness in wound healing. Here are some notable advancements in hydrogel dressings:

- **Smart Hydrogel Dressings:** Smart hydrogel dressings are designed to respond to specific wound conditions or stimuli (**Dong, & Guo, et al., 2021).** These dressings can change their properties in response to factors like pH, temperature, or wound exudate. For example, they can absorb excess exudate and maintain a moist environment in the wound while releasing bioactive agents or antimicrobial substances.

- **Biodegradable Hydrogel Dressings:** Biodegradable hydrogel dressings are designed to degrade over time, eliminating the need for dressing removal or frequent changes. These dressings are typically made from natural polymers or synthetic materials that can be broken down by the body's natural processes. Biodegradable hydrogels reduce patient discomfort during dressing changes and minimize disruption to the wound bed.

- **Antibacterial Hydrogel Dressings:** Antibacterial hydrogel dressings incorporate antimicrobial agents or nanoparticles that help prevent or manage wound infections. These dressings can provide sustained release of antimicrobial substances, such as silver nanoparticles or antimicrobial peptides, to inhibit bacterial growth and reduce the risk of infection.

- **Hybrid Hydrogel Dressings:** Hybrid hydrogel dressings combine the benefits of hydrogels with other materials to enhance their functionality. For example, hydrogels can be combined with fibrous scaffolds or nanofibers to improve mechanical strength, promote cell adhesion, and support tissue regeneration. Hybrid dressings can provide a supportive structure while maintaining the beneficial properties of hydrogels (**Xue, & Xiong, et al., 2019).**

- **Drug Delivery Hydrogel Dressings:** Hydrogel dressings can be used as drug delivery systems to release therapeutic agents directly into the wound site. They can encapsulate bioactive compounds, growth factors, or medications and release them in a controlled manner to promote wound healing. Drug delivery hydrogel dressings enable targeted and localized delivery of therapeutic agents, enhancing their effectiveness.

- **Nanotechnology-based Hydrogel Dressings:** Nanotechnology has been employed to develop advanced hydrogel dressings with unique properties. Nanoparticles or nanofibers can be incorporated into hydrogels to improve mechanical strength, enhance drug delivery capabilities, and provide a high surface area for cell adhesion and proliferation. Nanotechnology-based hydrogel dressings offer improved wound healing outcomes through their unique nanoscale features.

- **3D printed Hydrogels:** The 3D structure of hydrogels plays a crucial role in their benefits for wound healing. Hydrogels are formed by cross-linking polymer chains, resulting in a network-like structure that can hold a significant amount of water or biological fluids. This unique structure provides several advantages in the context of wound healing:

  3D printed hydrogels offer several advantages over other types of hydrogels, providing unique benefits in various applications. Here are some benefits of 3D printed hydrogels:

  - **Customization and Complexity:** 3D printing allows for precise control over the design, shape, and architecture of hydrogel structures. This level of customization enables the creation of complex geometries and structures that closely mimic the natural tissue environment. It allows for the fabrication of patient-specific hydrogel scaffolds tailored to individual wound needs, promoting better wound healing outcomes.

  - **Spatial Control of Bioactive Agents:** 3D printing enables the incorporation of bioactive agents, such as growth factors or drugs, into the hydrogel matrix with spatial precision. By precisely placing bioactive agents within the hydrogel structure, 3D printed hydrogels can deliver controlled and localized release of therapeutic compounds, enhancing their effectiveness in promoting wound healing and tissue regeneration.

  - **Mechanical Strength and Stability:** 3D printed hydrogels can be engineered to possess improved mechanical strength and stability compared to traditional hydrogels (**Abdollahiyan, , et al., 2020).**

    The ability to control the internal architecture and composition of the hydrogel structure allows for the incorporation of reinforcing materials, such as fibers or nanoparticles, to enhance mechanical properties. This enables the development of robust hydrogel constructs that can withstand mechanical stress and provide better support to the wound site.

  - **Patient-Specific Fit:** 3D printing allows for the creation of hydrogel scaffolds that precisely match the size and shape of the wound or defect. This patient-specific fit ensures better coverage and contact with the wound bed, facilitating optimal wound healing. It also minimizes the need for extensive modification or trimming of the hydrogel, improving efficiency and reducing treatment time.

- **Multi-Functionality:** With 3D printing, it is possible to create multi-functional hydrogel constructs that incorporate multiple components within a single structure. For example, the hydrogel scaffold can contain different types of cells, bioactive agents, or even sensors for real-time monitoring of wound healing progress. This multi-functionality enhances the therapeutic potential of 3D printed hydrogels and allows for more comprehensive wound healing strategies.

- **Rapid Prototyping and Scalability**: 3D printing enables rapid prototyping of hydrogel constructs, facilitating iterative design and testing. It allows for quick adjustments and modifications in the design to optimize the performance of the hydrogel for specific wound healing applications. Additionally, 3D printing offers scalability, allowing for the production of hydrogel constructs in various sizes and quantities to meet the demand in clinical settings.

## REFERENCE

[1] Lim, C. L., Byrne, C., & Lee, J. K. (2008). Human thermoregulation and measurement of body temperature in exercise and clinical settings. *Annals Academy of Medicine Singapore*, *37*(4), 347.
[2] Menke, N. B., Ward, K. R., Witten, T. M., Bonchev, D. G., & Diegelmann, R. F. (2007). Impaired wound healing. *Clinics in dermatology*, *25*(1), 19-25.
[3] Enoch, S., & Price, P. (2004). Cellular, molecular and biochemical differences in the pathophysiology of healing between acute wounds, chronic wounds and wounds in the aged. *World Wide Wounds*, *13*, 1-17.
[4] Chhabra, J., Chopra, H., Pahwa, R., Raina, N., Wadhwa, K., Saini, S., ... & Emran, T. B. (2023). Potential of nanoemulsions for accelerated wound healing: innovative strategies. *International Journal of Surgery (London, England)*.
[5] Rodrigues, M., Kosaric, N., Bonham, C. A., & Gurtner, G. C. (2019). Wound healing: a cellular perspective. *Physiological reviews*, *99*(1), 665-706.
[6] Sheppard, L. W., Vuksanović, V., McClintock, P. V. E., & Stefanovska, A. (2011). Oscillatory dynamics of vasoconstriction and vasodilation identified by time-localized phase coherence. *Physics in Medicine & Biology*, *56*(12), 3583.
[7] Huang, J., Heng, S., Zhang, W., Liu, Y., Xia, T., Ji, C., & Zhang, L. J. (2022, August). Dermal extracellular matrix molecules in skin development, homeostasis, wound regeneration and diseases. In *Seminars in Cell & Developmental Biology* (Vol. 128, pp. 137-144). Academic Press.
[8] Rohl, J., Zaharia, A., Rudolph, M., & Murray, R. Z. (2015). The role of inflammation in cutaneous repair. *Wound Practice & Research: Journal of the Australian Wound Management Association*, *23*(1).
[9] Kim, S. Y., & Nair, M. G. (2019). Macrophages in wound healing: activation and plasticity. *Immunology and cell biology*, *97*(3), 258-267.
[10] Pereira, L. M., Hatanaka, E., Martins, E. F., Oliveira, F., Liberti, E. A., Farsky, S. H., ... & Pithon‐ Curi, T. C. (2008). Effect of oleic and linoleic acids on the inflammatory phase of wound healing in rats. *Cell Biochemistry and Function: Cellular biochemistry and its modulation by active agents or disease*, *26*(2), 197-204.
[11] DiPietro, L. A. (2016). Angiogenesis and wound repair: when enough is enough. *Journal of Leucocyte Biology*, *100*(5), 979-984.
[12] Neumann, H., Kotter, M. R., & Franklin, R. J. (2009). Debris clearance by microglia: an essential link between degeneration and regeneration. *Brain*, *132*(2), 288-295.
[13] Nissen, N. N., Polverini, P., Koch, A. E., Volin, M. V., Gamelli, R. L., & DiPietro, L. A. (1998). Vascular endothelial growth factor mediates angiogenic activity during the proliferative phase of wound healing. *The American journal of pathology*, *152*(6), 1445.
[14] Badylak, S. F. (2002, October). The extracellular matrix as a scaffold for tissue reconstruction. In *Seminars in cell & developmental biology* (Vol. 13, No. 5, pp. 377-383). Academic Press.

[15] Fathke, C., Wilson, L., Shah, K., Kim, B., Hocking, A., Moon, R., & Isik, F. (2006). Wnt signaling induces epithelial differentiation during cutaneous wound healing. *BMC cell biology*, *7*(1), 1-9.
[16] Davis, J., & Molkentin, J. D. (2014). Myofibroblasts: trust your heart and let fate decide. *Journal of molecular and cellular cardiology*, *70*, 9-18.
[17] Malemud, C. J. (2006). Matrix metalloproteinases (MMPs) in health and disease: an overview. *Frontiers in Bioscience-Landmark*, *11*(2), 1696-1701.
[18] Best, K. T., Nichols, A. E., Knapp, E., Hammert, W. C., Ketonis, C., Jonason, J. H., ... & Loiselle, A. E. (2020). NF-κB activation persists into the remodeling phase of tendon healing and promotes myofibroblast survival. *Science signaling*, *13*(658), eabb7209.
[19] Kalluri, R., & Zeisberg, M. (2006). Fibroblasts in cancer. *Nature reviews cancer*, *6*(5), 392-401.
[20] Scalise, A., Bianchi, A., Tartaglione, C., Bolletta, E., Pierangeli, M., Torresetti, M., ... & Di Benedetto, G. I. O. V. A. N. N. I. (2015, September). Microenvironment and microbiology of skin wounds: the role of bacterial biofilms and related factors. In *Seminars in vascular surgery* (Vol. 28, No. 3-4, pp. 151-159). WB Saunders.
[21] Broadus, C. (2013). Debridement options: BEAMS made easy: learn how the various debridement methods promote wound healing. *Wound Care Advisor*, *2*(2), 15-19.
[22] Song, M., Zong, J., Zou, L., Fu, Z., Liu, J., & Wang, S. (2022). Biological debridement combined with stem cell therapy will be a convenient and efficient method for treating chronic wounds in the future. *Medical Hypotheses*, *166*, 110905.
[23] Ortega, M. A., Fraile-Martinez, O., García-Montero, C., Callejón-Peláez, E., Sáez, M. A., Álvarez-Mon, M. A., ... & Canals, M. L. (2021). A general overview on the hyperbaric oxygen therapy: applications, mechanisms and translational opportunities. *Medicina*, *57*(9), 864.
[24] Elgohary, H. M., Al Jaouni, S. K., & Selim, S. A. (2018). Effect of ultrasound-enhanced Nigella sativa seeds oil on wound healing: An animal model. *Journal of Taibah University medical sciences*, *13*(5), 438-443.
[25] Wainapel, S. F. (1985). Electrotherapy for acceleration of wound healing: low intensity direct current. *Arch Phys Med Rehabil 19S5*, *66*, 443-6.
[26] Huang, C., Leavitt, T., Bayer, L. R., & Orgill, D. P. (2014). Effect of negative pressure wound therapy on wound healing. *Current problems in surgery*, *51*(7), 301-331.
[27] He, J. J., McCarthy, C., & Camci-Unal, G. (2021). Development of Hydrogel- Based Sprayable Wound Dressings for Second- and Third- Degree Burns. *Advanced NanoBiomed Research*, *1*(6), 2100004.
[28] Bainbridge, P., Browning, P., Bernatchez, S. F., Blaser, C., & Hitschmann, G. (2021). Comparing test methods for moisture-vapor transmission rate (MVTR) for vascular access transparent semipermeable dressings. *The Journal of Vascular Access*, 11297298211050485.
[29] Mirani, B., Pagan, E., Currie, B., Siddiqui, M. A., Hosseinzadeh, R., Mostafalu, P., ... & Akbari, M. (2017). An advanced multifunctional hydrogel- based dressing for wound monitoring and drug delivery. *Advanced healthcare materials*, *6*(19), 1700718.
[30] Mohamad, N., Buang, F., Mat Lazim, A., Ahmad, N., Martin, C., & Mohd Amin, M. C. I. (2017). Characterization and biocompatibility evaluation of bacterial cellulose- based wound dressing hydrogel: effect of electron beam irradiation doses and concentration of acrylic acid. *Journal of Biomedical Materials Research Part B: Applied Biomaterials*, *105*(8), 2553-2564.
[31] Yu, R., Zhang, H., & Guo, B. (2022). Conductive biomaterials as bioactive wound dressing for wound healing and skin tissue engineering. *Nano-micro letters, 14*, 1-46.
[32] Zhong, Y., Xiao, H., Seidi, F., & Jin, Y. (2020). Natural polymer-based antimicrobial hydrogels without synthetic antibiotics as wound dressings. *Biomacromolecules*, *21*(8), 2983-3006.
[33] Abrigo, M., McArthur, S. L., & Kingshott, P. (2014). Electrospun nanofibers as dressings for chronic wound care: advances, challenges, and future prospects. *Macromolecular bioscience*, *14*(6), 772-792.
[34] Saghazadeh, S., Rinoldi, C., Schot, M., Kashaf, S. S., Sharifi, F., Jalilian, E., ... & Khademhosseini, A. (2018). Drug delivery systems and materials for wound healing applications. *Advanced drug delivery reviews*, *127*, 138-166.
[35] Lan, Z., Kar, R., Chwatko, M., Shoga, E., & Cosgriff- Hernandez, E. (2023). High porosity PEG- based hydrogel foams with self- tuning moisture balance as chronic wound dressings. *Journal of Biomedical Materials Research Part A*, *111*(4), 465-477.
[36] Amiri, N., Golin, A. P., Jalili, R. B., & Ghahary, A. (2022). Roles of cutaneous cell- cell communication in wound healing outcome: an emphasis on keratinocyte- fibroblast crosstalk. *Experimental Dermatology*, *31*(4), 475-484.
[37] Wright, J. B., Lam, K., Hansen, D., & Burrell, R. E. (1999). Efficacy of topical silver against fungal burn wound pathogens. *American journal of infection control*, *27*(4), 344-350.

[38] Ren, Y., Zhang, D., He, Y., Chang, R., Guo, S., Ma, S., ... & Guan, F. (2021). Injectable and antioxidative HT/QGA hydrogel for potential application in wound healing. *Gels*, *7*(4), 204.
[39] Dong, R., & Guo, B. (2021). Smart wound dressings for wound healing. *Nano Today*, *41*, 101290.
[40] Simões, D., Miguel, S. P., Ribeiro, M. P., Coutinho, P., Mendonça, A. G., & Correia, I. J. (2018). Recent advances on antimicrobial wound dressing: A review. *European journal of pharmaceutics and biopharmaceutics*, *127*, 130-141.
[41] Xue, H., Hu, L., Xiong, Y., Zhu, X., Wei, C., Cao, F., ... & Liu, G. (2019). Quaternized chitosan-Matrigel-polyacrylamide hydrogels as wound dressing for wound repair and regeneration. *Carbohydrate polymers*, *226*, 115302.
[42] Abdollahiyan, P., Oroojalian, F., Mokhtarzadeh, A., & de la Guardia, M. (2020). Hydrogel-based 3D bioprinting for bone and cartilage tissue engineering. *Biotechnology journal*, *15*(12), 2000095.