DIANE MUJAWAYEZU

BIOMATERIALS AND THEIR BIOMEDICAL APPLICATIONS FOR ENHANCING SKIN CHRONIC WOUND HEALING

MASTER THESIS 2024

NEAR EAST UNIVERSITY

INSTITUTE OF GRADUATE

DEPARTMENT OF BIOMEDICAL ENGINEERING

BIOMATERIALS AND THEIR BIOMEDICAL APPLICATIONS FOR ENHANCING SKIN CHRONIC WOUND HEALING

M.Sc. THESIS

BY

DIANE MUJAWAYEZU

SUPERVISOR:

PROF. DR. DILBER UZUN OZSAHIN

CO-SUPERVISOR:

ASSOC. PROF. DR. BERNA UZUN

NICOSIA,

JUNE, 2024

NEAR EAST UNIVERSITY

INSTITUTE OF GRADUATE

DEPARTMENT OF BIOMEDICAL ENGINEERING

BIOMATERIALS AND THEIR BIOMEDICAL APPLICATIONS FOR ENHANCING SKIN CHRONIC WOUND HEALING

M.Sc. THESIS

BY

DIANE MUJAWAYEZU

SUPERVISOR:

PROF. DR DILBER UZUN OSZASHIN

CO-SUPERVISOR:

BERNA UZUN

NICOSIA

JUNE, 2024

APPROVAL

We certify that we have read the thesis submitted by **DIANE MUJAWAYEZU** titled "**BIOMATERIALS AND THEIR BIOMEDICAL APPLICATIONS FOR ENHANCING SKIN CHRONIC WOUND HEALING.**" and that in our combined opinion it is fully adequate, in scope, and quality, as a thesis for the degree of Master of Sciences in Biomedical Engineering.

Examining Committee	Name-Surname	Signature
Head of the Committee:	Assoc. Prof. Dr. Süleyman Aşır	
Committee Member*:	Assist. Prof. Dr. Auwalu Saleh Mubarak	
Committee Member*:	Assist. Prof. Dr. Zubaida Said Ameen	
Committee Member*:	Assoc. Prof. Dr. Berna Uzun	
Supervisor:	Prof. Dr. Dilber Uzun Ozsahin	

Approved by the Head of the Department

10/06/2024

Assoc. Prof. Dr. Süleyman Aşır

Head of the Department

Approved by the Institute of Graduate Studies

.../.../20...

Prof. Dr. Kemal Hüsnü Can Başer

Head of the Institute of Graduate Studies

DECLARATION

I hereby declare that all information, documents, analysis, and results in this thesis have been collected and presented according to the academic rules and ethical guidelines of the Institute of Graduate Studies, Near East University. As required by these rules and conduct, I also declare that I have fully cited and referenced information and data that are not original to this study.

Name: **DIANE MUJAYAYEZU**
Signature:
Date:

ACKNOWLEDGMENT

I would like to express my heartfelt gratitude to my esteemed supervisors, Prof. Dr. Dilber Uzun Ozsahin and Assoc. Prof. Dr. Berna Uzun, for their invaluable guidance, mentorship, and support throughout the completion of my master's thesis. Their expertise and dedication have significantly influenced the outcomes of this research, shaped my academic growth and refining the ideas presented in this thesis.

I am grateful to Prof. Dr. Dilber Uzun Ozsahin for her unwavering commitment to teaching and her continuous support. Her insightful feedback, encouragement, and guidance have been instrumental in shaping the direction of this research. Her expertise and thorough understanding of the subject matter have greatly contributed to the quality of this thesis.

I would also like to acknowledge the contributions of Assoc. Prof. Dr. Berna Uzun as my co-supervisor. Her expertise, constructive criticism, and valuable suggestions have played a vital role in the development of this thesis. Her guidance and mentorship have been crucial in expanding my knowledge and improving the overall quality of my work. I would like to express my gratitude to Associate Professor Dr. Süleyman Aşır and Miss Natacha Usanase for their support.

I am deeply grateful to both of my supervisors for their dedication, patience, and commitment to my academic growth. Their guidance and encouragement have pushed me to explore new avenues, challenged me to think critically, and provided the necessary motivation to overcome obstacles.

Lastly, I would like to express my appreciation to my family, friends, and all those who have supported me throughout this journey. Your encouragement, understanding, and belief in my abilities have been a constant source of inspiration and motivation.

To everyone who has played a role in shaping this thesis, I extend my sincerest gratitude. Your support and contribution have been invaluable, and I am honored to have had the opportunity to work under Prof. Dr. Dilber Uzun.

ABSTRACT

BIOMATERIALS AND THEIR BIOMEDICAL APPLICATIONS FOR ENHANCING SKIN CHRONIC WOUND HEALING

MUJAWAYEZU, Diane

M.Sc. Department of Biomedical Engineering

June, 2024, 70 pages

The skin, the largest organ outside the body acts as a protective barrier against pathogens, dangerous substances, and water loss, and it is susceptible to external and internal injuries in the form of wounds. It consists of three layers: epidermis, dermis, and hypodermis. The body's wound-healing process is a continuous and complicated process that can be hindered by several factors such as wound severity or a compromised immune system, making wound care critical under these circumstances. It needs an appropriate environment to accelerate the healing. Because of their persistent nature, length of therapy, and financial challenge, chronic wounds have posed a serious public health risk in recent decades. In response, there has been a notable surge in the biomaterials sector, with a particular emphasis on expediting wound healing and minimizing the treatment period. Alginate, hyaluronic acid, polyglycolic acid, chitosan, cellulose, and collagen are examples of polymers. Presently, films, hydrogels, foams, and sponges are examples of common biomaterial formats. This research used multi-criteria decision-making (MCDM) techniques namely, fuzzy PROMETHEE (fuzzy preference ranking organization method for enrichment evaluation) to assess the effectiveness or efficacy of several biomaterials employed in skin chronic wound healing. Using a linguistic fuzzy scale, the study assesses collagen sponges, chitosan hydrogel, collagen hydrogels, HA hydrogels, PEG hydrogels, alginate hydrogels, PU foam, PU films, and PVA/alginate hydrogels. The results showed that PU foams are the most effective biomaterials suitable for accelerating chronic wound healing (based on selected criteria namely Biocompatibility, Biodegradability, Cytotoxicity, Cost, Availability, Mechanical properties, Antimicrobial Properties, Porosity, Exudate absorption, Flexibility, and Moisture management). This study emphasizes that according to the type of chronic wounds, the location of the wound and the patient’s health or age, the appropriate biomaterials should be used to enhance the healing process. This study also addresses growth factors, wound healing

mechanisms, typologies of wounds, classifications, and the various biomaterials employed in skin chronic wound healing.

***Keywords**:* biomaterials, chronic wounds, wound healing, wound dressings, fuzzy PROMETHEE

ÖZET

CİLDİN KRONİK YARA İYİLEŞMESİNİ ARTTIRMAK İÇİN BİYOMEDİKAL MALZEMELER VE UYGULAMALARI

MUJAWAYEZU, Diane

Yüksek Lisans, Biyomedikal Mühendislik Bölümü

Haziran, 2024, 70 sayfa

Vücudun dışındaki en büyük organ olan deri, patojenlere, tehlikeli maddelere ve su kaybına karşı Vücudun yara iyileştirme süreci, yaranın ciddiyeti veya zayıflamış bağışıklık sistemi gibi çeşitli faktörler tarafından engellenebilen sürekli ve karmaşık bir süreçtir ve bu koşullar altında yara bakımı kritik öneme sahiptir. İyileşmeyi hızlandırmak için uygun bir ortama ihtiyaç vardır. Kalıcı yapıları, tedavi süreleri ve mali zorlukları nedeniyle, kronik yaralar son yıllarda ciddi bir halk sağlığı riski oluşturmuştur. Buna karşılık, yara iyileşmesini hızlandırmaya ve tedavi süresini en aza indirmeye özellikle vurgu yapan biyomalzeme sektöründe kayda değer bir artış olmuştur. Aljinat, hyaluronik asit, poliglikolik asit, kitosan, selüloz, kolajen polimerlere örnek olarak verilebilir. Halihazırda filmler, hidrojeller, köpükler, süngerler yaygın biyomateryal formatlarına örnektir. Bu araştırma, kronik cilt yaralarının iyileşmesinde kullanılan çeşitli biyomateryallerin etkinliğini veya etkisini değerlendirmek için bulanık PROMETHEE (zenginleştirme değerlendirmesi için bulanık tercih sıralama organizasyonu yöntemi) adlı çok kriterli karar verme (ÇKKV) teknikleri kullanmıştır. Çalışmada, dilsel bir bulanık ölçek kullanılarak kolajen süngerleri, kitosan hidrojelleri, kolajen hidrojelleri, HA hidrojelleri, PEG hidrojelleri, aljinat hidrojelleri, PU köpükleri, PU filmleri ve PVA/aljinat hidrojelleri değerlendirmektedir. Sonuçlar, PU köpüklerin kronik yara iyileşmesini hızlandırmak için uygun en etkili biyomateryaller (Biyouyumluluk, Biyobozunurluk, Sitotoksisite, Maliyet, Bulunabilirlik, Mekanik özellikler, Antimikrobiyal Özellikler, Gözeneklilik, Eksüda emilimi, Esneklik ve Nem yönetimi gibi seçilen kriterlere dayanarak) olduğunu göstermiştir. Bu çalışma, kronik yaraların türüne, yaranın konumuna ve hastanın sağlığına veya yaşına göre, iyileşme sürecini geliştirmek için uygun biyomateryallerin kullanılması gerektiğini vurgulamaktadır. Bu çalışmada ayrıca büyüme faktörleri, yara iyileşme mekanizmaları, yara tipolojileri, sınıflandırmalar ve cilt kronik yara iyileşmesinde kullanılan çeşitli biyomateryaller ele alınmaktadır.

Anahtar Kelimeler: biyomateryaller, kronik yaralar, yara iyileşmesi, yara pansumanları, bulanık PROMETHEE

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

NIH: National Institute of Health

MCDM: Multicriteria decision-making

NPWT: Negative pressure wound therapy

ES: Electrical stimulation

HBOT: Hyperbaric oxygen therapy

PU: Polyurethane

PEG: Polyglycol ethylene

HA: Hyaluronic acid

PROMETHEE: Preference ranking organization method for enrichment evaluation

GFs: Growth factors

EGF: Epidermal growth factor

PDGF: Platelet-derived growth factor

GM-CSF: Granulocyte-macrophage colony-stimulating

TGF-β: transforming Growth factor-

FDA: Food and Drug Administration

EMA: European Medicine Agency

bFGF: basic Fibroblast growth factor

PRP: Platelet-rich plasma (PRP

STSG: Split-thickness skin grafts

FTSG: Full-thickness skin grafts

AHP: Analytical Hierarchy Process

VIKOR: ViseKriterijumska Optimizacija Kompromisno Resenje

ELECTRE: Et Choice Translating Reality

DAMP: Damaged associated molecular pattern,

DETC: Dendritic epidermal T cell

MC: Master cell

MMP: Matric metalloproteinase

NET: Neutrophil trap

NO: Nitric oxide

ROS: Reactive oxygen species

T_{reg} cell: Regulatory T cell

CHAPTER I

Introduction

1.1. Introduction

The skin, the largest organ outside the body serves as a protective fence against pathogens, dangerous substances, and water loss. It is made of 3 parts namely the epidermis, dermis, and self-healing layer hypodermis (Naseri & Ahmadi, 2022; Shah et al., 2019). Skin possesses regenerative characteristics, which enable wounds to recover via a complex process (Shah et al., 2019). It goes through several steps to restore its integrity and regular operation. The procedure includes collagen and migration of inflammatory cells, cytokine activity, deposition of ECM, and remodelling of the scar. Scars are usually formed because of wound healing and are not very different from one tissue to another. But occasionally, the skin's natural healing abilities are disrupted, which prevents wounds from healing according to their natural course and places a heavy weight on healthcare systems (Shah et al., 2019). This delayed healing process of the wounds leads to chronic wounds (Ijaola et al., 2022).

Since ancient times, wounds have been a regular occurrence of injury and many strategies have been employed to protect, cure, and prevent infections (Maaz Arif et al., 2021). From 2200 BCE onwards, wound care has had a rich and lengthy history. The "three healing gestures" which are cleaning, plastering, and covering the wound were outlined in the first medical book on a stone tablet. Aside from these, other substances utilized for wound therapy included beer, vinegar, wine, milk, animal grease, leaves, tree resin, and honey (Las Heras et al., 2020). The ancient Greeks utilized fig leaves, cotton, metallic compounds, and poultice-like materials while ancient Egyptians used honey, animal fat, lint, and grease (Maaz Arif et al., 2021).

The statement "I dressed the wound; GOD healed it" by Ambroise Paré (1510 to 1590) contributed to the rise in popularity of wound-covering therapy in the middle and modern times. In the 19th century, the antiseptic technique was developed, and in the 20th century, tissue engineering techniques were established (Las Heras et al., 2020). In 1962 Dr. George Winter introduced wound dressings for wound tissue regeneration which sparked the creation of materials such as hydrogels, hydrocolloids, and clear films (Chandika et al., 2015).

Dr. Winter proved through animal research that wound healing in a wet environment increases the healing rate, decreases wound itching, promotes cell migration and proliferation, and retains bodily fluids. After this idea was presented, Hinman et al. (1975) used human tests to show off its potential. In addition, the migration of new keratinocytes, the healing of pain, and the elimination of damaged tissue and outside elements from the wound are all influenced by moist wound healing. Scientists consequently created wound repair devices based on wet wound repair (Ansari & Darvishi, 2024).

Modern wound dressings have evolved, with a variety of forms accessible for clinical trials based on physical, chemical, and biological characteristics (Maaz Arif et al., 2021). Redefining the paradigm for treating chronic wounds, advances in biomaterials and increased understanding of wound healing have spawned a result of various innovative therapies and approaches (Las Heras et al., 2020). Wounds are injuries that cause tissue damage or loss, which can also harm muscles and organs (Maaz Arif et al., 2021).

There are two (2) categories of wounds, which are acute wounds and chronic wounds (Maaz Arif et al., 2021; Oliveira et al., 2023; Shah et al., 2019). Acute wounds heal quickly due to growth hormones and cytokines, and follow the four phases of the healing process which include hemostasis, inflammation, proliferation, and tissue remodeling; while chronic wounds take longer, (Maaz Arif et al., 2021; Naseri & Ahmadi, 2022; Oliveira et al., 2023; Shah et al., 2019). Normal wound healing takes around 90 days (8-12 weeks) to heal (Agarwal et al., 2020; Shah et al., 2019). Chronic wounds also referred to as ulcers or hard-to-heal wounds, are ones that do not heal adequately over an extended length of time that should be adequate for healing (Olsson et al., 2019).

There are major three types of skin chronic wounds: pressure ulcers, diabetic foot ulcers, and venous leg ulcers (Ijaola et al., 2022; Las Heras et al., 2020; Maaz Arif et al., 2021). Additionally, skin infections, congenital vascular disorders like hemophilia, thrombocytopenia, Willebrand disease, and ischemia are the other types of chronic wounds (Maaz Arif et al., 2021). Each has a distinct etiology. Every group has therapeutic tenets derived from pathophysiology. Compression, unloading, and pressure release are among the treatments. Certain patients may have immunological deficiencies, malnourishment, obesity, drug misuse, alcoholism, smoking, and dysfunctional diabetic fibroblasts, which can all contribute to delayed recovery. It is doubtful that a common solution will be found for

chronic wounds because each may exhibit unique combinations of causes. Chronic wounds are trapped in the inflammatory stage, which is marked by a neutrophil inflow that releases inflammatory mediators and cytotoxic enzymes, resulting in significant collateral damage. Chronic wounds might begin to heal if these mechanisms are adjusted and counterbalanced (Shah et al., 2019).

According to the National Institute of Health (NIH), skin chronic wounds are silent epidemics due to their delayed healing process (Ijaola et al., 2022). Chronic wounds pose a significant global health and economic threat, affecting approximately 1-2% of the global population in developed nations during their lifetime (Maaz Arif et al., 2021). Chronic wounds can be caused by large burns, and chronic disorders such as diabetes, and obesity, and their treatment is hard, costly, and raises the risk of infection (Oliveira et al., 2023; Shah et al., 2019). Moreover, conditions like autoimmune diseases, age, and sensory neuropathies also cause chronic skin wounds (Las Heras et al., 2020; Oliveira et al., 2023). Around 40 million individuals worldwide are suffering from chronic wounds (Las Heras et al., 2020).

Chronic wound healing requires overcoming factors like poor blood supply, necrotic tissue, and underlying infection. The general management procedures for chronic wounds include the use of antiseptics, and analgesics, hyperbaric oxygen therapy, creation of an ideal wound environment, removal of necrotic tissue, and dietary enhancement for the patient. It's important to recognize the classification system of chronic wounds namely pressure ulcers, venous ulcers, and diabetic foot ulcers, to treat them. For diabetic foot ulcers, managing blood flow, treating infection, eliminating callous skin, and controlling diabetes help in their treatment. Osteomyelitis, uncontrolled infection, and significant tissue destruction all call for amputation among diabetic people. Debridement, compression therapy, antibiotics, and calf-muscle exercises are all part of the treatment for venous leg ulcers. The treatment of pressure ulcers includes debridement, routine wound care, infection control, and proper wound dressings (Las Heras et al., 2020; Maaz Arif et al., 2021; Prete et al., 2023).

Traditional wound dressings namely plasters, gauze, lint, bandages, and silver sulfadiazine with pharmaceutical formulations were used to keep the wound site clean minimize pain, and manage microbial infection. However, their strong absorbent capacity, which can quickly dry the wound and encourage bacterial development, limits their effectiveness. Additionally, these dressings are difficult to remove, which damages the skin (Maaz Arif et al., 2021). Moreover, skin replacement is not achieved properly when those methods are used for

chronic wounds since the body is unable to synthesize new skin cells (Las Heras et al., 2020; Miron et al., 2023). To address this, treatment of chronic wounds has gained both medical and research attention. The skin grafts also referred to as skin substitutes, a method introduced by Reverdin (1871), is used for chronic wound healing. This involves skin obtained from the patient's health site of the body (autografts), from animals (xenografts) such as fishes, pigs, etc., or cadavers (allografts) (Miron et al., 2023); or human donors can be administered to help the wound heal (Ijaola et al., 2022).

However, these traditional methods have drawbacks, such as a lack of donor sites (from the same individual or donors), high cost, the spread of infections, discomfort, and proper skin replacement is not achievable (Agarwal et al., 2020; Las Heras et al., 2020; Maaz Arif et al., 2021). Moreover, according to the skin structure, tissue-engineered skin grafts categorized as split-thickness and full-thickness, or artificial skin grafts also demonstrate great outcomes. However, they are limited to the host rejection for the grafts, cost, and availability (Las Heras et al., 2020; Miron et al., 2023).

Considering those reasons, biological materials, also known as biomaterials, have been established and manufactured to minimize limitations for those conventional methods for treating chronic wounds; furthermore, help to facilitate and enhance the chronic wound healing process. Biomaterials are known as non-drug materials that complement or replace body tissues and organs (Ijaola et al., 2022; Shah et al., 2019). First, they act as scaffolds for endogenous cells to encourage growth, and second, as wound closure and temporary bandages for wound healing. The ideal wound dressing biomaterials should protect the wound, retain hydration, and prevent bacterial development (Ijaola et al., 2022; Naseri & Ahmadi, 2022).

They must be biodegradable, biocompatible, and provide excellent oxygen permeability, and mechanical stability and remove exudates (Ijaola et al., 2022; Naseri & Ahmadi, 2022). Furthermore, biomaterials used to treat chronic wounds should encourage tissue regeneration, restore function, and speed up healing. They should degrade at a rate that fits tissue growth, not cause toxicity or immunogenicity, and adhere well to adjacent tissues (Ijaola et al., 2022). Currently, biomaterials used in medicine play a crucial role in both wound healing stimulation and regeneration of tissues to their initial biological activity (Chelu & Musuc, 2023).

The available biomaterials are classified into synthetic biomaterials, natural biomaterials, or hybrids (Downer et al., 2023; Miron et al., 2023; Naseri & Ahmadi, 2022). Synthetic biomaterials include organic and/or inorganic polymers while natural biomaterials are biological products derived from plants, fungi, bacteria, or animals, and hybrids contain both. Hydrogels, films, foams, hydrocolloids, and sponges are some examples of available biomaterials (Miron et al., 2023). Biomaterials can interact with live tissues and carry out certain tasks without having any negative effects. Biomaterials should be biocompatible, bio-functional, biodegradable, and sterilizable because their evaluation is based on safety and performance (Chelu & Musuc, 2023).

Multicriteria decision-making (MCDM) refers to the technique used by the decision-makers to compare, analyze, and carry out complex decisions by criteria, decision-making processes, and alternatives (decision influencers (Balcioglu et al., 2023; Taherdoost & Madanchian, 2023). MCDM consists of different models however fuzzy preference ranking organization method for enrichment evaluation (fuzzy PROMPTHEE) method, the MCDM model (Taherdoost & Madanchian, 2023) is employed in this study, for comparison, and analysis of biomaterials employed in the wound healing process. Biomaterials are the best promising candidates for chronic wound healing due to their ability to mimic the full thickness of functional skin. This study focuses on the most recent biomaterials designed for enhancing the chronic wound healing process, biomaterials properties, and their performance, applications, and how they affect the functional human body.

1.2. Problem statement

Chronic skin wounds are epidemics due to their delayed healing process that kills patients silently and their treatment tends to be difficult. Several complications associated with chronic skin wounds include microbial infections, pain, amputation, death, and necrosis of tissue which is detrimental to the patient's health and is fatal. In the past, different techniques were used to promote the healing process of chronic wounds, however, skin replacement was not achieved properly since the body is unable to synthesize new skin cells. This led to the development of new methods to accelerate the chronic wound healing process. Many people suffering from chronic wounds tend to start their treatment process late when they are in the last stage where their wounds are beyond treatment. This study discusses the most recent biomaterials designed for the healing of chronic wounds, including several properties of biomaterials, their performance, applications, and how they affect the functional human body. Biomaterials are the best promising candidates for chronic wound healing due to their ability

to mimic the full thickness of functional skin. Therefore, with the help of the fuzzy PROMPTHEE technique, an MCDM model, in this research, we will be able to compare and analyze several biomaterials employed in the wound healing process and select the safe ones.

1.3. Study purpose

The aims of this study include the following:

- The main aim is to analyze, compare, and rank the most recent biomaterials used in chronic wound healing by using multicriteria decision-making (MCDM) models.
- To classify biomaterials-based wound dressings based on the biological polymeric constituents.
- To analyze biomaterials' physical forms used in chronic wound healing.

1.4. Significance of the Study

This study has various significance to doctors, patients, and researchers. This includes the following:

- To aid or help or support doctors (dermatologists) and patients in choosing or selecting the appropriate wound dressings based on the category, and wound location.
- To understand the physiology of the wound, its types, and its healing process.
- To select appropriate wound treatments based on the stage of the wound healing process and type.
- The analytical results of this research are considered a reference for doctors and students so that they can test the best biomaterials-based wound dressings, and understand their components.

1.5. Limitations

The study has several drawbacks which include the following:

- The used data is collected from the literature.
- If there is an addition or removal of any alternative or criteria, the results of the study are likely to change.
- The adjustment of the selected importance weights for the criteria can also be modified by the decision maker, potentially leading to changes in the ranking results of the alternatives.
- The selection of biomaterials employed in chronic wound healing can be different for each type of chronic wound, the location of the wound, and the patient.

1.6. Definition of Terms

Wound: is an injury to the body that leads to a loss or damage of tissues that affects the physiological function of organs and muscles.

Wound dressing: is a protective covering that helps to protect and heal wounds. It acts as a barrier, lowering contamination risk.

Biomaterial: is a medically created substance that interacts with biological systems for therapeutic or diagnostic purposes. It can be obtained from nature or synthesized in laboratories using several methods with different components such as polymers, etc.

CHAPTER II

Literature review

2.1.1. Physiology of native Human skin structure

The human skin acts as a protective barrier against pathogens, dangerous substances, water loss (Naseri & Ahmadi, 2022; Shah et al., 2019), and other external influences like cold, heat, electricity, and radiation (Prete et al., 2023); and it also possesses regenerative characteristics (self-repairability and extensibility features), which enable wounds to recover via a complex process (Shah et al., 2019). It encompasses the exterior surface and makes up 8% of the body's mass. It carries out tasks like sensory detection, self-repair, fluid homeostasis, prevention of microbes invasion, self-renewal, selective permeability, defence against outside influences, and so on (Ijaola et al., 2022; Oliveira et al., 2023). It also participates in thermoregulation, preventing the loss of liquids and regulating blood flow (Prete et al., 2023).

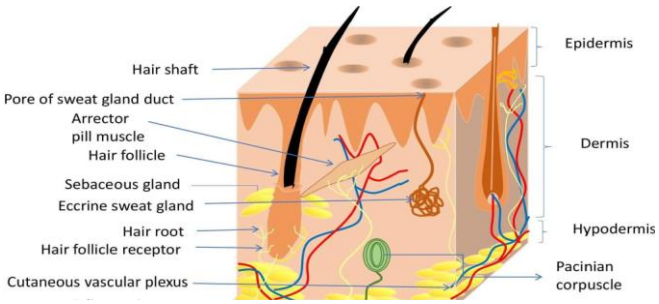
It consists of layers namely the epidermis, dermis, and self-healing layer hypodermis (also known as the subcutaneous layer) (Gruppuso et al., 2021; Naseri & Ahmadi, 2022; Shah et al., 2019). The superficial layer known as the epidermis consists of a highly cellular thin structure which helps it retain moisture and shield it from outside stimulants. Along with non-cellular elements, the mature epidermis consists of keratinocytes, melanocytes, and Langerhans cells. Collagen, laminin granules, desmosomes, hemidesmosomes, keratin, tonofibrils, and vitamin D3 are examples of non-cellular components that interact with cellular components to maintain structural integrity, stop water loss, and control the production of the immune system (Gruppuso et al., 2021; Ijaola et al., 2022; Oliveira et al., 2023).

Beneath the skin's outer layer is the dermis. It is made up of collagen-rich extracellular matrix fibroblasts, elastin, and glucosaminoglycans (GAG). It performs several functions, such as supporting the nerve bundles and the lymphatic system, providing physical strength to the skin, providing vascular flow, and regulating immune and inflammatory responses. Underneath it, the vascularized adipose tissue that makes up the hypodermis affects the mechanical and thermoregulatory characteristics of the skin (Ijaola et al., 2022; Oliveira et al., 2023). The hypodermis, the deepest layer, detains significant lipid reserves, leading to improved heat retention. The skin has metabolic characteristics, including vitamin D synthesis. Moreover, it contains a crucial sensory function, registering and transmitting

pressure, pain, and thermal stimuli (Prete et al., 2023). Figure 1 shows the anatomy of the skin.

Figure 1**.**

Skin Anatomy, Layers, and Composition (Sharma et al., 2022)



2.1.2. Wounds and wound healing physiology

A wound is created when the skin is punctured, cut, or torn. Generally, a wound refers to a loss or damage of tissues that affects the physiological function of organs and muscles (Maaz Arif et al., 2021).

The human skin is prone to various diseases, injuries, and burns. Skin damage is a serious problem that needs to be treated, especially in cases of superficial and localized wounds. Wounds are intricate and dynamic biological processes that can be caused by pathological diseases, endogenous causes, physical trauma, and burns. Dust and bacterial infections can have an impact on wound healing. As a result, treating wounds to prevent these infections (infections caused by Staphylococcus aureus, Escherichia coli, etc.) is crucial to the healing process since they can jeopardize human health (Ansari & Darvishi, 2024).

2.1.2.1. Types of skin wounds

There are two (2) categories of wounds, which are chronic wounds and acute wounds based on the healing period (Firlar et al., 2022; Maaz Arif et al., 2021; Oliveira et al., 2023; Shah et al., 2019). Also, wounds can be categorized based on the source (Ansari & Darvishi, 2024).

2.1.2.1.1. Acute wounds

Acute wounds are wounds that heal quickly due to growth hormones and cytokines, and follow the normal four phases of the healing process namely, hemostasias, inflammation, proliferation, and tissue remodelling (Naseri & Ahmadi, 2022; Oliveira et al., 2023) and heal within 8 to 12 weeks (M. Zhang & Zhao, 2020). These wounds are also referred to as non-chronic wounds (Firlar et al., 2022). Acute wounds can be caused by burns and/or cuts (M.

Zhang & Zhao, 2020). Acute wounds can be classified into abrasions, cuts, surgical injuries, trauma, and skin burns (Agarwal et al., 2020; Gruppuso et al., 2021). Table 1 shows the difference between acute and chronic wounds, while Table 1 and Figure 2 illustrate the visual representation of these wound types and Figure 3 shows the schematic structure of the wound classification.

Table 1.

The Difference Between Acute and Chronic Wounds (Ijaola et al., 2022)

Characteristics	**Acute wounds**	**Chronic wounds**
Level of Bacteria	⇩	⇧
Levels of reactive protease species	⇩	⇧
Inflammatory cytokines	⇩	⇧
Mitogenic activity	⇧	⇧
Functional matrix	Intact	Degraded
Types of the Cell	Mitotically competent cells	Senescent cells

Keywords: high (⇧), low (⇩)

Figure 2.

Illustration of types of wounds based on healing time (Agarwal et al., 2020)

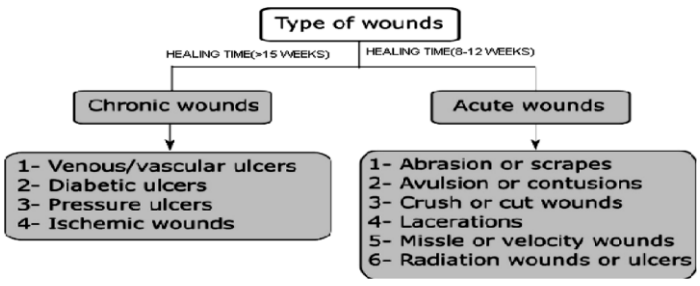
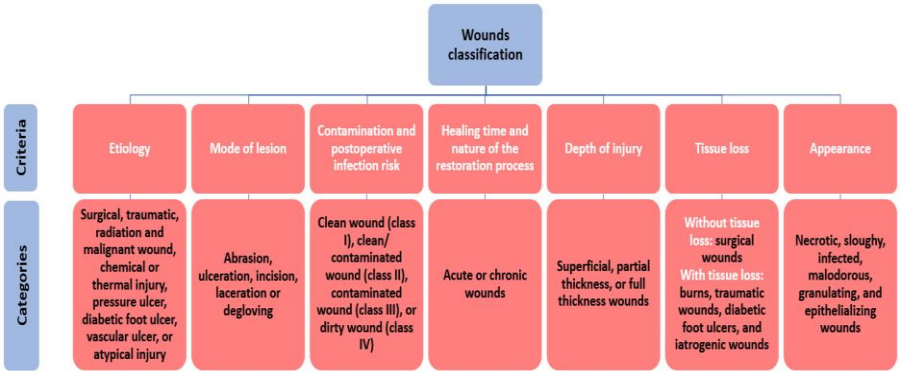


Figure 3.

Schematic structure of wound classification (Niculescu & Grumezescu, 2022)



2.1.2.1.2. Chronic wounds

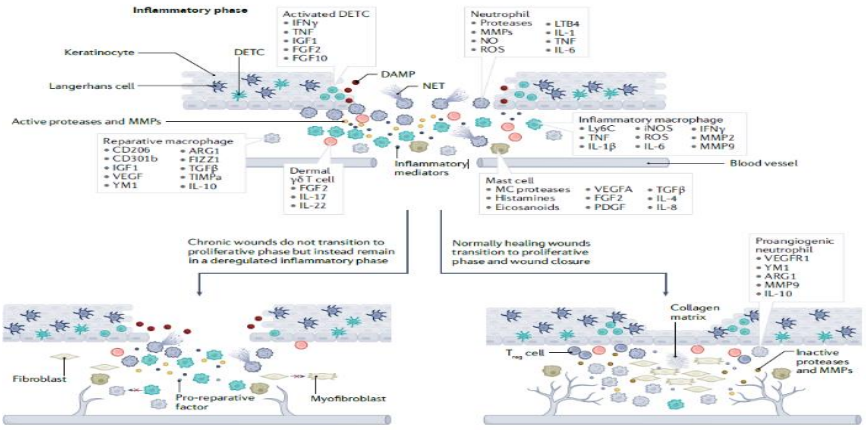
Chronic wounds mostly damage the skin's inner layer (M. Zhang & Zhao, 2020) and are characterized by delayed healing (Las Heras et al., 2020; Naseri & Ahmadi, 2022; Oliveira et al., 2023). Chronic wounds persist in the inflammatory phase (Las Heras et al., 2020) and stop proceeding to the next phase. The progress requires considering elements such as necrotic tissue, bacterial load, and wound moisture homeostasis. Wound healing is also impacted by the health factors of the patient, immunosuppression, immunodeficiency, peripheral vascular disease, radiation therapy, medicines, and metabolic illnesses for instance diabetes (Naseri & Ahmadi, 2022).

2.1.2.1.2.1. Chronic wounds pathophysiology

Chronic wounds heal slowly and are not fully re-epithelialized in the proper order for tissue restoration. They exhibit high levels of inflammatory cytokines, proteases, senescent cells, and a modest mitogenic response. Barriers to wound healing: inadequate blood flow, necrotic tissue, underlying infections, chronic trauma, and levels of elevated matrix metalloproteinase, frequently exacerbate chronic wounds. Chronic wound healing is also influenced by variables such as diet inadequacies, low body temperature, zinc and vitamin C insufficiency, and hormone deficiencies (Maaz Arif et al., 2021). Figure 4 shows the components of inflammatory phase for chronic and normal wound healing.

Figure 4.

Components of inflammatory phase for chronic and normal wound healing (Falanga et al., 2022)



Normal wound healing progresses to the proliferative phase, in which immune cells switch to anti-inflammatory and/or proliferative responses to help in tissue repair. Chronic wounds fail to suppress local inflammatory responses, resulting in an inactive and unregulated inflammatory phase. This leads to tissue healing failure. Key terms include damaged associated molecular pattern (DAMP), dendritic epidermal T cell (DETC), master cell (MC), matric metalloproteinase (MMP), neutrophil trap (NET), nitric oxide (NO), reactive oxygen species (ROS), and regulatory T cell (T_{reg} cell) (Falanga et al., 2022).

Due to the recruitment of neutrophils and macrophages and the continuous eosinophil cationic protein (ECP) degradation, these variables prolong the wound healing inflammatory stage and impede its progression (Maaz Arif et al., 2021). Reduced mitogenic activity, growth factor suppression, angiogenesis suppression, increased proteases and cytokines, excessive MMP synthesis, and ROS are all characteristics of chronic wounds that lead to a protracted healing time. Infections are more common in chronic wounds (Gruppuso et al., 2021).

2.1.2.1.2.2. Types of chronic wounds

Chronic wounds are divided into primary types: venous or arterial ulcers, diabetic ulcers, and pressure ulcers (Ijaola et al., 2022; Las Heras et al., 2020; Maaz Arif et al., 2021; Naseri & Ahmadi, 2022; Oliveira et al., 2023; Shah et al., 2019; M. Zhang & Zhao, 2020).

2.1.2.1.2.2.1. Diabetic ulcers

The most common type of chronic diabetic ulcers are wounds, which impact around 15 percent (%) of the world's society. These ulcers usually take a place in the feet and legs and may require hospitalization, leading to limb amputation (Maaz Arif et al., 2021). Diabetic ulcers are common in patients with peripheral neuropathy (Firlar et al., 2022). Prolonged diabetes can cause tissue oxygen rate reduction, leading to damage to blood vessels and resulting in chronic non-healing ulcers. Most of this prevalent kinds of diabetes ulcers can lead to consequences such as foot infections, neuropathy, ischemia, hyperglycemia, and microangiopathy (Maaz Arif et al., 2021; Niculescu & Grumezescu, 2022; Shi et al., 2020).

Additionally, elevated glucose causes, increased ROS, elevated protein kinase C, modification of DNA, and inflammation surrounding the wound are their causes. The severity of the condition varies among patients, affecting wound healing times due to factors namely synthesis of growth factors, cell migration, collagen deposition, protease ECM modification, etc., (Firlar et al., 2022).

2.1.2.1.2.2.2. Pressure ulcers

Pressure ulcers, often found in older, frail, paralyzed, or spinal cord-injured patients, take a place in places like heels, shoulder blades, and sacrum due to continuous, furthermore, shear forces to the skin and underlying tissues, resulting in decreased oxygen diffusion and chronic ulcers.(Maaz Arif et al., 2021). They are also caused by prolonged pressure, leading to injury-related hypoxia and ischemia. This inflammatory response is triggered by adipocytes as a result. Therefore, higher neutrophil concentrations and necrotic tissue are observed in patients with Pressure ulcers. Pressure ulcers may become more severe in patients with vascular insufficiencies (Firlar et al., 2022).

2.1.2.1.2.2.3. Vascular ulcers (Venous or arterial ulcers)

Vascular ulcers are divided into arterial insufficiency (ischemic) ulcers, and blood vessel (venous) ulcers classes. Ischemic ulcers result from atherosclerosis, causing necrosis of tissues and ischemia. Venous ulcers are identified by venous insufficiencies, hyper-pigmented zones, varicose veins, and hemosiderin accumulation, leading to stiffness in the legs. Venous ulcers may be preceded by stiffness and discomfort in the legs and limbs (Firlar et al., 2022).

Venous ulcers, often affecting older patients, occur in the lower limbs and are caused by a destroyed system of superficial and deep venous, leading to venous hypertension and decreased venous return. This results in reduced blood flow, ischemia, and failure of wound treatment. Increased blood pressure in the vessels alters vessel wall permeability, causing fibrin and other components to leakage into the perivascular space (Maaz Arif et al., 2021; Niculescu & Grumezescu, 2022; Shi et al., 2020). The study of wound healing stages for various chronic wound types is crucial for understanding mechanisms and developing effective treatments.

Figure 5.

Presentation of clinical chronic wounds (Falanga et al., 2022)

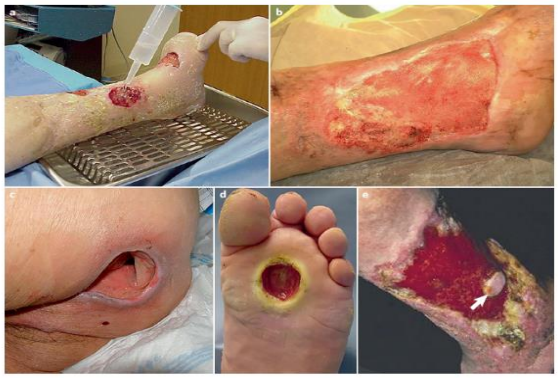


Figure 5 depicts clinical pictures of chronic skin wounds, including **(a)** diabetic ulceration, **(b)** a venous ulcer with lipodermatosclerosis, **(c)** a deep pressure ulcer in the sacral area, **(d)** a nephroopathic diabetic ulcer on the diabetic patient's sole with Charcot foot, **(e)** extensive ulceration of the lower leg caused by mixed venous and lymphatic illness. The deep red granulation tissue is atypical and could indicate bacterial invasion. Wound borders and island of the skin at a wound center are not able to migrate onto the surrounding red tissue (Falanga et al., 2022). Table 2 shows the main causes and symptoms of the chronic wounds in detail.

Table 2.

Types of Chronic wounds.

Type	The main causes	Symptoms	Reference
Diabetic ulcers	Chronic hyperglycemia Neuropathy	Common symptoms include endothelial dysfunction, mild leg discomfort, and changes to the smooth muscle. Other symptoms include elevated ROS and hyperglycemia, NO blockade, modification of DNA, elevated protein kinase C, ischemia, reduced size of capillary, arteriolar hyalinosis, and thickening of the basement membrane. Synthesis of GF, deposition of collagen, and modification of ECM by proteases. Skin tissue necrosis	(Falanga et al., 2022; Firlar et al., 2022; Maaz Arif et al., 2021; Shi et al., 2020)
Pressure ulcers	Prolonged pressure, and shear forces	Ischemia of tissue, mechanical stress, high levels of neutrophil, reoxygenation, skin splits, and skin tissue necrosis are all symptoms of this condition.	(Falanga et al., 2022; Firlar et al., 2022; Maaz Arif et al., 2021; Shi et al., 2020)
Venous ulcers	Venous insufficiency	Discomfort and stiffness in legs and limbs, varicose veins, hyperpigmented zones, edema, and high hemosiderin levels are common symptoms.	(Falanga et al., 2022; Firlar et al., 2022; Maaz Arif et al., 2021)

Table 2 (Continued)

Arterial insufficiency (ischemic) ulcers	Atherosclerosis	Ischemia of Tissue Skin tissue necrosis	(Falanga et al., 2022; Firlar et al., 2022; Maaz Arif et al., 2021)

2.1.2.2. Requirements for wound healing

Two factors affect wound repair and healing: systemic and intrinsic and/or local factors. Systemic factors include a patient's health and age, while intrinsic and/or local factors consist of infections, foreign bodies, low levels of blood supply, and topical steroids. Infection is the primary key in wound healing and occurs when the surface layer of the skin is destroyed, exposing underlying tissue. It causes swelling, pain, discomfort, secretions, wound fluid, unpleasant smell, and increased wound site temperature (Ansari & Darvishi, 2024).

Improper care can slow wound healing, potentially leading to limb loss, amputation, or even death. Factors like of patients' number suffering from numerous wounds annually, costs of adequate care for wound healing are crucial. Therefore, it is essential to consider these factors to ensure effective wound healing (Ansari & Darvishi, 2024). Additionally, several GF play a crucial function in wound healing. Table 3 presents the roles and biological properties of GF that facilitate wound healing.

Table 3.

Major Growth Factors that Participate in Wound Healing (Fadilah et al., 2022)

Growth factor	**Biological activities**	**Functions**
PDGF	Regulate synthesis of matrix components and increase fibroblast proliferation.	Formation of matrix and remodeling, formation of granulation tissue, and re-epithelization
EGF	Ascends the endometrial cells and keratinocytes proliferation, IGF production.	Re-epithelization

Table 3 (Continued)

IGF	Offers induction of keratinocyte proliferation and descend catabolism of proteins (fibroblasts)	Re-epithelization
TGF	Ascends the keratin expression and fibroblast proliferation, and provides regulation of cell proliferation and matrix components synthesis	Formation of matrix and remodeling, formation of granulation tissue, and re-epithelization
PGF	Facilitate synthesis and component of EMC deposition; and during re-epithelization, it ascends the mobility of keratinocytes.	Formation of matrix and remodeling, formation of granulation tissue, and re-epithelization

Healing of the wound is influenced by wound moist environment, which encourages bacterial growth. If the immune system fails to eliminate bacteria, wounds become infected and inflamed, causing pain. Wound dressings with antibacterial properties can lead to wound repair and lower patient pain (Zhao et al., 2023).

2.1.2.3. The process of wound healing

The healing of a wound is a natural process that is classified into 4 phases: hemostasis, inflammation, proliferation, and tissue remodeling (Fadilah et al., 2023; Gruppuso et al., 2021; Las Heras et al., 2020; Naseri & Ahmadi, 2022; Oliveira et al., 2023). To heal properly, these stages must occur in the proper order in a specific time frame. Adult wound healing includes angiogenesis, re-epithelialization, differentiation, multiplication, homeostasis, inflammatory response, and collagen production for tissue solidarity (Firlar et al., 2022). As revealed in Figure 4. different biopolymers, cells, and mediators play a crucial function in wound healing.

2.1.2.3.1. Phase 1: Hemostasis

Homeostasis is the initial step in wound healing, where blood arteries contract to reduce blood loss (Firlar et al., 2022). Hemostasis, which has four stages: platelet aggregation, coagulation system activation, fibrinolytic enzymes, and vasoconstriction, is a process involved in wound healing (Zhao et al., 2023). As the first phase of the body's reaction to a

wound injury, inflammatory cells, and platelets gather at the wound site, adhere to the exposed collagen, and release clotting factors such as fibronectin. (Eriksson et al., 2022; Fadilah et al., 2023; Firlar et al., 2022; Gruppuso et al., 2021; Las Heras et al., 2020; Naseri & Ahmadi, 2022; Oliveira et al., 2023; M. Zhang & Zhao, 2020).

2.1.2.3.2. Phase 2: Inflammation

The inflammatory phase is triggered by platelet-secreted cytokines transforming growth factors – β (TGFs-β), and platelet-derived growth factors (PDGTs) allowing neutrophils to enter, which opens the door for neutrophil infiltration. Then the neutrophils go to the damaged site, this happens concurrently with hemostasis (Gruppuso et al., 2021) with vasodilation of local capillaries facilitating the transfer of exudates and leucocytes near the wound site (Firlar et al., 2022). Neutrophils lie on the wound site for 24 hours before undergoing apoptosis, playing an antimicrobial role and triggering wound healing (Gruppuso et al., 2021).

After differentiating into tissue macrophages; blood monocytes and lymphocytes attract fibroblasts, endothelial cells, and keratinocytes to repair damaged blood vessels through the release of growth factors known as vascular endothelial growth factor (VEGF) and cytokines (for example interleukin-17 (IL-17)) (Eriksson et al., 2022; Fadilah et al., 2023; Gruppuso et al., 2021; Las Heras et al., 2020; Oliveira et al., 2023; M. Zhang & Zhao, 2020). Neutrophils clear cellular debris and destroy foreign microbes by generating ROS and releasing toxic proteases. Macrophages are critical for skin tissue regeneration, producing cytokines to accelerate immune response and induce apoptosis. Pain and redness around the wound are mostly observed during this phase (Firlar et al., 2022).

2.1.2.3.3. Phase 3: Proliferation

This phase begins thereafter in 2-3 days. It is identified by the formation of granulation tissue from procollagen, fibroblasts, proteoglycans, elastin, and hyaluronic acid (Gruppuso et al., 2021). Granulated tissue with an extracellular matrix (ECM) forms during proliferation when there is moisture and oxygen present (Firlar et al., 2022). Proliferating fibroblasts and deposition of collagen are the main activities during the proliferation phase, which starts two to three days after damage and lasts until wound closure (Eriksson et al., 2022; Gruppuso et al., 2021; Las Heras et al., 2020; Oliveira et al., 2023; M. Zhang & Zhao, 2020).

While cytokines released by neutrophils attract monocytes and help them develop into macrophages during death, keratinocyte proliferation provides defense against the external

environment. To guarantee wound resolution, macrophages undergo phenotypic changes, turning from pro- to anti-inflammatory and secreting chemokines to trigger the T cell response, which promotes angiogenesis, extracellular matrix deposition, and wound healing (Gruppuso et al., 2021). Differentiation of endothelial cells to new capillaries, and fibroblasts become myofibroblasts, which close the wound and engulf the surface to build a new layer of tissue (Eriksson et al., 2022; Fadilah et al., 2023; Firlar et al., 2022; Gruppuso et al., 2021; Las Heras et al., 2020; Oliveira et al., 2023; M. Zhang & Zhao, 2020).

2.1.2.3.4. Phase 4: Remodeling

Restoring normal tissue structure through elemental maturation and extracellular matrix modifications is the last remodeling phase for wound healing. It is the reconstitution of the extracellular matrix (ECM) to resemble normal tissue (Firlar et al., 2022).

As a result of this process' collagen the primary extracellular matrix (ECM) component is synthesized proteoglycans are deposited, and granulation tissue fibroblasts become myofibroblasts, which can contract accumulated granulation tissues can replenish elasticity and tensile strength. The balance between healing events is reflected in the phenotypic intensity seen in scars, which is the outcome of this remodeling of the extracellular matrix (ECM) from provisional to final. But difficulties can occur, which could cause tissue restoration to be delayed or take an indeterminate amount of time (Eriksson et al., 2022; Fadilah et al., 2023; Gruppuso et al., 2021; Moreira et al., 2024). Overall, several biomolecules and Cell types have a crucial role during wound healing phases, while the most efficient treatment approach depends on the specific wound's healing stage. An Overview of the Healing Process is presented in Figure 6. The timelines of wound healing phases are provided in Figure 7. The mediators and cells found in the healing process of wound is illustrated in Figure 8.

Figure 6.

An Overview of the Healing Process (Firlar et al., 2022; M. Zhang & Zhao, 2020)

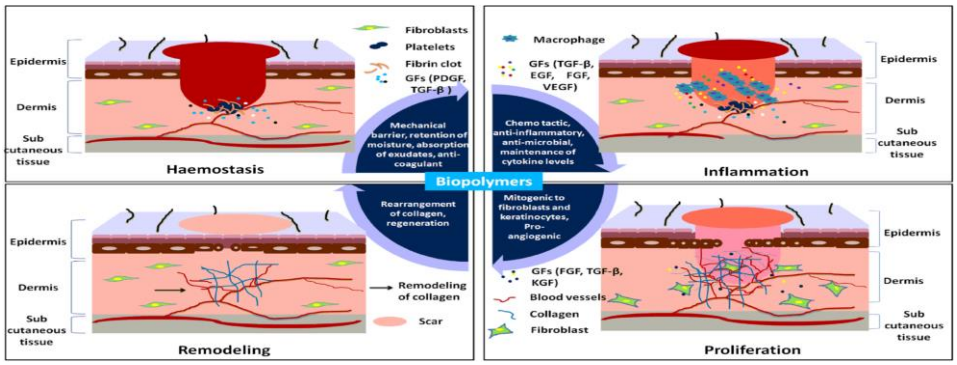


Figure 7.

The timelines of wound healing phases (Gruppuso et al., 2021)

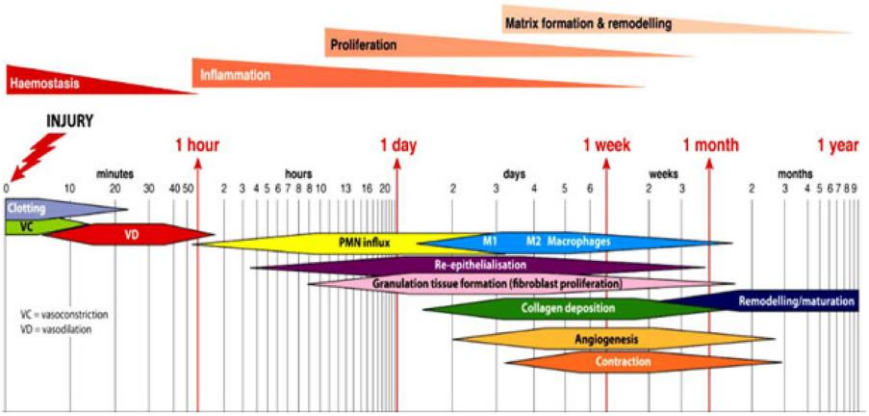


Figure 8.

Illustration of Mediators and Cells Found in the Healing Process of Wound (Ijaola et al., 2022)

2.1.3. Wounds care treatments

The goal of managing wounds is to reduce pain and scarring while promoting quick wound healing. In the past, traditional dressings did not actively encourage the healing of wounds (Prete et al., 2023). The goals of modern dressings, which are separated into traditional and advanced dressings, are to reduce trauma, remove exudates and necrotic debris, keep the microenvironment moist, and prevent infection. Although the skin has an amazing capacity to heal small wounds on its own, the use of suitable devices or dressings is essential when the damage is substantial or widespread. Traditional dry dressings provide physical protection but have limited benefits in preventing infection. Modern dressings, such as foam, hydrogel, film, and scaffold, offer comfort and many advantages (Prete et al., 2023).

2.1.3.1. Current chronic wound treatment

Chronic wound healing requires overcoming factors like necrotic tissue, insufficient blood supply, and underlying infection. Management protocols include analgesics, antiseptics, debridement, optimal wound environment, hyperbaric oxygen therapy, and patient nutritional refinement. Understanding chronic non-healing ulcers is crucial for effective management (Maaz Arif et al., 2021). The following section describes several methods used in chronic wound care management.

2.1.3.1.1. Physical treatments

2.1.3.1.1.1. Debridement

It is the routine process a part of traditional wound care that involves the removal of dead tissues and invading materials from the wound site. It can be mechanical, surgical, bio-surgical using larvae, autolytic, enzymatic, or chemical (Firlar et al., 2022; Las Heras et al., 2020). Moreover, hydrogels, conventional dressings, and polysaccharide beads can be used. Clinical specialists are the ones who must carry out the procedure. The procedure may need to be repeated if inadequate non-viable tissue is removed since it could harm nearby tissues. On the other hand, excessive removal may result in the loss of tissue and increase the healing period. Skin tissue reconstitution and wound vitality are best preserved by a single procedure that causes the least amount of cell loss possible. Both during and after the procedure, pain is possible, and different patients respond differently to it (Eriksson et al., 2022; Firlar et al., 2022).

2.1.3.1.1.2. Compression therapy

It is employed in venous leg ulcer treatments and involves applying external pressure gradually with specific bandages or multilayer compression bandage systems to overthrow pathological abnormalities in the venous system (Firlar et al., 2022; Las Heras et al., 2020).

2.1.3.1.1.3. Negative pressure wound therapy (NPWT)

It is also referred to as VAC (vacuum-assisted closure) therapy which involves using an airtight dressing to remove fluid and air from a wound. This method increases blood flow in the tissues surrounding the wound, increases moisture and oxygen levels, and enhances healing in large chronic wounds. VAC therapy is commonly employed in healthcare facilities, but it may limit patient mobility and cause discomfort due to noise. It can also be employed as a primary and secondary treatment technique (Eriksson et al., 2022; Firlar et al., 2022). NPWT, introduced in the 1990s, involves eliminating exudates from the wound by vacuum devices. It has been proven to lessen edema, lower the number of bacteria present, assist angiogenesis, ascend local perfusion, and accelerate granulation tissue formation. However, some studies claim that results remain unclear and more detailed investigations are required to justify its widespread usage (Las Heras et al., 2020).

2.1.3.1.1.4. Electrical stimulation (ES)

ES uses electromagnetic energy to stimulate fibroblasts, enhancing collagen, α-smooth muscle, TGF-β, and VEGF production (Las Heras et al., 2020).

2.1.3.1.1.5. Hyperbaric oxygen therapy (HBOT)

Hyperbaric oxygen therapy refers to a method that uses a special oxygen chamber to increase blood oxygen concentration in wounds, particularly diabetic ulcers. It improves and shortens wound healing in cases where revascularization is not feasible. However, it requires expensive specialized equipment and is typically limited to diabetic wounds and pressure ulcers. Despite its benefits, hyperbaric oxygen therapy remains a costly treatment option (Eriksson et al., 2022; Firlar et al., 2022; Gounden & Singh, 2024).

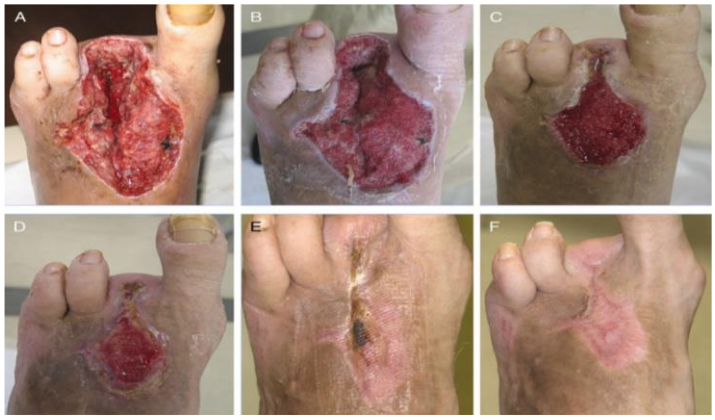
HBOT has shown satisfactory outcomes in treating chronic wounds, with increased neovascularization, reduced proinflammatory enzyme presence, and increased collagen and growth factor production. Nevertheless, HBOT dramatically accelerated wound healing in the

initial stages but did not sustain the improvement over time, according to a 2015 Cochrane review, highlighting the need for additional studies to assess HBOT's efficacy in treating chronic wounds (Firlar et al., 2022; Las Heras et al., 2020).

Additionally, research on chronic wound management has explored shockwaves, photobiomodulation, and ultrasounds. Although no randomized controlled trials have been done, shockwave therapy may aid in the healing of venous leg ulcers. With the use of LEDs and lasers, photobiomodulation raises blood perfusion, lowers neutrophil infiltration, and promotes fibroblast growth. There are differences (disagreement on dosage, wavelength, and therapeutic outcomes) of opinion on the value of high-frequency versus low-frequency ultrasounds as well as standardized techniques (Las Heras et al., 2020). Figure 9 shows the NPWT and HOBT, and the ORC/collagen dressings effects in diabetic foot ulcer.

Figure 9.

Illustration of NPWT and HOBT, and the ORC/collagen Dressings in Diabetic Foot Ulcer (Maaz Arif et al., 2021)



(A) Wound following amputation and debridement, (B) following two weeks with therapy from HBOT and NPWT treatments, (C) following 5 weeks of wound treatment with HBOT and NPWT, (D) following three weeks of with ORC/collagen (oxidized regenerated cellulose/collagen) dressings, (E) almost completely healed after seven weeks of treatment with ORC/collagen dressing, and (F) following three months follow up visit after full healing (Maaz Arif et al., 2021).

2.1.3.1.2. Systemic administration

Systemic drugs like antibiotics are commonly used to treat skin disorders like severe burns or chronic wounds aiming to manage symptoms and lessen deterioration and infections. These drugs barely penetrate wound biofilms, making antisepsis a suitable method for treating or preventing bacteria in wounds. Other systemic approaches include administering antibodies and peptides, such as infliximab (anti-TNF-α) for recalcitrant ulcerating necrobiosis lipoidica and the neuropeptide α-melanocyte-stimulating hormone for regenerative healing. Exenatide hormone promotes positive responses in fibroblast functions and has been demonstrated to be more beneficial than local administration for wound healing (Las Heras et al., 2020).

2.1.3.1.3. Pharmacological treatment

Antiseptics and antimicrobials are commonly used topically in wound care due to their effectiveness in preventing bacteria from colonizing or infecting chronic wounds. Antibiotics used systemically seldom break through wound biofilms, although they can work wonders topically. Natural substances like berberine, rosemary oil, Aloe Vera, curcumin, and thyme extract honey have also been used in wound healing treatment for their antibacterial, angiogenic, and regenerative effects. Growth factors (GFs) are physiologically active peptides that are used topically in wounds in the form of gels, creams, and intralesional injections. They control cell migration, differentiation, growth, and communication throughout the healing process (Las Heras et al., 2020).

Furthermore, Growth factors (GFs) have been shown to significantly improve skin healing with no secondary effects. Different GFs, such as EGF, PDGF, bFGF, GM-CSF, and TGF-β, are used topically. The only GF approved for wound healing is Regranex® (Johnson&Johnson), a gel-based GF approved by the FDA (1997) and EMA (2003) (Las Heras et al., 2020. Since 2001 in Japan, bFGF fabricated as a spray been used for pressure ulcers, with a brand name “Fiblast”. Autologous platelet-rich plasma (PRP) is a rich source of abundant GFs, which has shown excellent outcomes in wound healing. However, sustained release of GFs is crucial for wound tissue repair due to their short half-life (Las Heras et al., 2020).

2.1.3.1.4. Skin grafting

The most common method for rebuilding skin defects is skin grafting, which is also the gold standard for treating thermal injuries. It speeds up wound healing, offers sufficient coverage

for wounds, and guards against infections. Split-thickness skin grafts (STSG) and full-thickness skin grafts (FTSG) are the two forms of skin grafts. During recovery, graft contracture occurs in STSGs, which are employed for broad damage coverage and survive in grafted sites with less vascular. FTSGs are appropriate for exposed locations such as the face or neck because they require superior vasculature in the grafted zone however contract low during the healing process. Keratinocytes are essential to the therapeutic outcome of epidermal skin grafts, which are only made of the epidermis layer (Las Heras et al., 2020).

Skin grafts are obtained as autografts (from the patient her/himself), allografts (from deceased or living patients), or xenografts (from animals). Clinical trials for diabetic foot ulcers have demonstrated encouraging results using autologous grafts; nevertheless, these grafts are unpleasant and have limited availability and expense. Allografts (living donors or cadaver grafts) are commonly employed but are constrained by cost and availability. These problems are resolved by xenografts, which are primarily made from pig skin, but they often cause a host immunogenic response in less than a week. Genetically modified pig xenografts can live just as long as allografts, according to recent research (Firlar et al., 2022; Las Heras et al., 2020). Table 4 shows the detailed information of the current chronic wound treatment types and their advantages and disadvantages.

Table 4.

Current Chronic Wound Care Management

Current chronic wound treatment	**Advantages**	**Disadvantages**	**Application**	**Reference**
Debridement	Aim to keep the viable tissue area stable while halting the growth of the non-viable tissue area.	The operation is costly, requires a specialist, may cause discomfort for the patient, and may not always produce the desired outcomes.	All types of chronic wounds	(Falanga et al., 2022; Firlar et al., 2022; Las Heras et al., 2020; Shi et al., 2020; X. Zhang et al., 2020)

Table 4 (Continued)

Hyperbaric oxygen therapy	The healing process can be considerably accelerated by an increase in the concentration of oxygen in the blood in the wound area.	Require a professional to apply. It is expensive	Diabetic ulcers	(Firlar et al., 2022; Gounden & Singh, 2024; Las Heras et al., 2020; Shi et al., 2020; X. Zhang et al., 2020)
Negative pressure wound therapy (NPWT)	Boost the amount of moisture and blood flowing to the wound.	Need a suitable medical facility and a medicine expert. Limit the patient's range of motion. Cause the sufferer discomfort.	Specific kinds of pressure and vein ulcers	(Firlar et al., 2022; Gounden & Singh, 2024; Las Heras et al., 2020)
Skin grafting	Widely employed simple to use	Used only on large wounds Need an expert to apply it and an appropriate medical facility. Expensive Less available in some countries	Large chronic wounds (e.g. pressure and venous ulcers)	(Falanga et al., 2022; Firlar et al., 2022; Las Heras et al., 2020)

II.1.3.1.5. Wound dressings

These dressings are essential for wound care, giving protection, isolation, moisture, and promoting healing by boosting the synthesis of collagen, re-epithelialization, and pH of the wound bed. In the past, natural materials like leaves, gauze, honey, cobwebs, and cotton bandages were used as dressings. Foams, hydrocolloids, and hydrogels are examples of modern dressings. They can be bioactive, interactive, or passive based on the nature of the action. While interactive dressings give transparency, permeability, and biodegradability, passive dressings just offer minimal covering. Active ingredients are delivered to the wound site by bioactive dressings (Prete et al., 2023). Passive dressings like gauze may cause pain and lack antibacterial activity. Multifunctional dressings can improve healing by controlling infection and cell proliferation. The dressing selection depends on the type of wound, location, extent, and depth (M. Zhang & Zhao, 2020). Gauze dressings, once the standard treatment for wounds, are now outdated due to their detrimental effects on the healing process and increased discomfort for patients (Firlar et al., 2022; Prete et al., 2023).

George Winter's concept of moist healing revolutionized wound management by promoting granulation tissue growth and wound healing. Ideal wound dressings should stop bleeding, relieve pain, absorb excess exudate, be easy to adhere to healthy skin, have great gas and water vapor permeability, lessen the risk of infection, enhance healing and granulation tissue formation, and be biocompatible and nontoxic. A range of synthetic and/or natural polymeric wound dressings have been created, including hydrogels, foams, etc. Alginate hydrogel has been widely studied as a wound dressing material due to its biocompatibility and nontoxic nature (M. Zhang & Zhao, 2020).

Requirements for assessing the optimal wound dressing have been developed through research in tissue engineering and wound care. Closed wounds heal faster than open wounds and occlusive dressings help restore tissue by exposing wounds to growth factors, chemotaxis, cytokines, and platelets. Healing is best done in a moist environment, which is maintained by dressings that have the best water vapor or gas exchange transmission rate. Hydrocolloids and foams are examples of absorbent dressings that are frequently used; films and hydrogels are examples of non-absorbent dressings (Maaz Arif et al., 2021; M. Zhang & Zhao, 2020).

2.1.3.1.5. 1. Classification of Wound dressings

There are 2 main classes: traditional dressings and advanced dressings (also known as modern dressings) (Jones et al., 2006). Wound dressings are either biological, polymeric, conductive, or hydroconductive types. Traditional dressings, such as gauze, cotton wool, etc., have been used since 1970 for wound care due to their cost-effectiveness and ease of application. However, they have limited effects due to their high absorbent capacity, which can dry the wound rapidly and promote bacterial growth. They don't come off easily, causing skin damage. Recent research suggests that blending these dressings with polymeric materials (alginate, chitosan, etc.) can improve moisture and reduce contagion risk. Biological wound dressings, also known as autografting, are efficient for wound healing but are limited to acute surgical wounds and dermatological surgery (Maaz Arif et al., 2021). The classification of wound dressings is shown in Table 5.

Table 5.

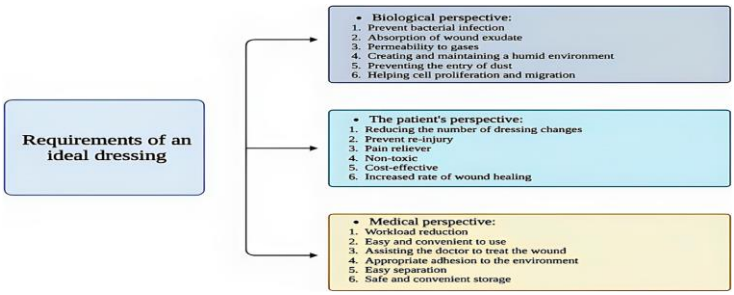
Classification of Wound dressings

Wound dressings	**Examples**	**Reference**
Traditional dressings	gauze, cotton wool	(Maaz Arif et al., 2021; Miron et al., 2023)
Biological dressings	Skin grafts: autografts, allografts and xenografts	(Maaz Arif et al., 2021; Miron et al., 2023)
Polymeric dressings	Alginate, chitosan, etc	(Maaz Arif et al., 2021; Miron et al., 2023)
Modern dressings	foams, hydrocolloids, and hydrogels	(Miron et al., 2023; Prete et al., 2023)

There are various qualities of an ideal wound dressing, namely, accessible for removal; transparent, offers a good barrier against bacterial invasion to prevent infection, great biocompatibility, widely available, low cost, etc., (Barbu et al., 2021; X. Zhang et al., 2020). Figure 10. demonstrate several key requirements for ideal dressings for wound healing from different perspectives.

Figure 10.

Key Requirements for Ideal Dressings for Wound Healing (Ansari & Darvishi, 2024)



2.1.4. Biomaterials for chronic wound healing

The demand for biomaterials has increased in recent years due to their broad range of uses in healthcare and medical sectors (regenerative medicine, healing of wounds, tissue engineering, orthopedic disorders, plastic surgeries, drug delivery systems, and implantable devices). Biomaterials should possess non-toxicity, non-allergenicity, biocompatibility, and biodegradability. Generally, they are classified into metallic (employed in orthopedics and dentistry), ceramic, glass (for bone repair and dental restoration), polymeric, and composite classes (Samadian et al., 2020).

The most important issues to address include molecular structures, physicochemical and biological features, interfacial interactions, controlled conversion, engineering for specific cellular responses, and tuning bioadhesive properties. Recent advances in materials science and nanotechnology can address these issues. Polymeric biomaterials, divided into synthetic, semi-synthetic, and natural polymers, offer advantages such as biocompatibility, serializability, and excellent processability. However, their applications in biomedical fields have been limited by their cytotoxicity issues and specific protein binding sites (Samadian et al., 2020)**.**

Biomaterials refer to the materials that are used for healing and repair, and they are designed to be biologically compatible with living things. Their eco-friendliness and biodegradability make them commonly used in therapeutic and diagnostic applications. Because of the way biomaterials interact with bodily organs, how resilient their cellular activity is, how well their immune systems coordinate, and because of their biomimetic properties, which may one day lead to the cure of human body problems, biomaterials have a bright future in both medicine and technology advancement (Agarwal et al., 2020).

2.1.4.1. Properties of biomaterials for chronic wound healing

Extensive study on biomaterials as therapeutic agents, particularly in wound healing applications, has been prompted by the growth of tissue engineering and regenerative medicine. With wound treatment emerging as a major concern, biomaterials like dermal templates and wound dressings have a bright future in the health sector. To contain cells, promote cellular proliferation, and aid in tissue regeneration, biomaterials must be immunogenicity-free, biocompatible, and have the right microstructural characteristics. Inducing an inadequate inflammatory response is one way that biomaterials can improve wound healing (Fadilah et al., 2023).

Biomaterials that give physical support, encourage cell migration and growth, and aid in the production of new tissue is used to enhance wound healing. Biomaterials must have certain mechanical characteristics, such as the right amount of mechanical strength, flexibility, porosity, structure, biodegradability, and biocompatibility, to support these processes (Downer et al., 2023). Table 6 illustrates the most important properties of biomaterials for wound healing. In addition to offering excellent gas permeability, improved mechanical stability effective control of moisture while eliminating exudates, the perfect biomaterial-based wound dressing should be both biodegradable as well as biocompatible (Naseri & Ahmadi, 2022).

Table 6.

Properties of Biomaterials for Wound Healing

Properties	**Descriptions**	**Reference**
Biocompatibility	• Biomaterials must be able to interact with biological systems in a way that doesn't damage them. • Biomaterials should not cause unfavorable reactions in biological systems.	(Downer et al., 2023)

Table 6. (Continued)

Biodegradability	• Biomaterials should degrade at a rate that fits skin tissue growth, not cause toxicity or immunogenicity, and adhere well to adjacent tissues. • Biodegradability promotes the material to break down naturally into harmless components.	(Downer et al., 2023; Ijaola et al., 2022)
Porosity	• The important considerations when creating biomaterials for wound healing applications are pore size, volume, distribution, and interconnectivity. • Biomaterials with around 60-95 percent (%) porosity are more favorable for wound healing uses. • Porosity is essential for oxygenation, nutrition, removal of waste products, and other cellular activities in wound healing.	(Downer et al., 2023; Ijaola et al., 2022)
Moisture content	• It is essential for the transmission of bioactive substances and the healing of wounds. Scaffolds used in skin tissue engineering must have an ideal water vapor transfer rate (WVTR). • Low WVTR inhibits gaseous exchange, which increases the risk of infection, bacterial penetration, and CO2 accumulation and exudate deposition in the wound media while High WVTR causes wound surfaces to dry out too quickly and lose water quickly, which makes dressings stick to the wound. • Prompt wound epithelialization and wound healing are facilitated by adequate gaseous exchange, especially oxygen, to the wound, which is enhanced by effective wound-healing dressings.	(Ijaola et al., 2022)

Table 6. (Continued)

Mechanical strength	• Biomaterial scaffolds should possess certain properties, such as mechanical strength and stiffness, to facilitate tissue regeneration and allow for manipulation during implantation. • The biomaterial's strength is defined by the bonds between its atoms. When evaluating its mechanical strength for tissue regeneration, elongation-to-break failure elastic modulus, and yield strength are critical factors. • It provides structural support and maintains the scaffold's porous architecture for cell infiltration, migration, adhesion, and proliferation. • It facilitates nutrient, oxygen, and waste transportation during tissue regeneration. Therefore, the selection of good mechanical properties without compromising other qualities is essential during manufacturing and implantation. • Biomaterials should mimic the Mechanical properties of native tissue	(Downer et al., 2023; Ijaola et al., 2022)
Flexibility	It allows the biomaterial to fit into the shape of the wound.	(Downer et al., 2023)
Scaffold structure	The hydrophobicity and hydrophilicity of the biomaterial are important keys to determining tissue regeneration, cell growth, absorption of fluids (exudates), and maintaining a moist environment for the wound.	(Downer et al., 2023; Ijaola et al., 2022)

2.1.4.2. Classification of biomaterials employed in wound healing

Available biomaterials are classified into synthetic and/or natural biomaterials or hybrids (Downer et al., 2023; Miron et al., 2023; Naseri & Ahmadi, 2022; Shi et al., 2020) and hybrids contain both (Miron et al., 2023). In this section, we discuss some of the common natural/synthetic biomaterial-based wound dressing used in the healing process of chronic wounds.

2.1.4.2.1. Natural biomaterials

Natural biomaterials are biological products derived from plants, fungi, bacteria, or animals. For instance collagen, alginate, chitosan, cellulose, etc., (Miron et al., 2023). The use of natural biomaterials in wound healing is growing. Their advantages include excellent biodegradability and biocompatibility, ease of manufacturing, good adhesion, high absorption, and permeability, and the ability to regenerate and repair damaged tissue. Due to their natural state and the fact that they are extracted from biomasses in the food, textile, and other industries, they are more readily available and hence a better option for environmental protection. The potential of these biomaterials, for use in wound treatment materials is being investigated (Ansari & Darvishi, 2024; Shi et al., 2020).

2.1.4.2.2. Synthetic biomaterials

These are artificially engineered materials designed for various applications in both the biomedical and medical health industries. Synthetic biomaterials include both organic and inorganic polymers (Miron et al., 2023). For instance, polyethylene glycol, polyurethane, etc. Since synthetic biomaterials are bioabsorbable, biocompatible, low toxicity, have controlled synthesis, and biodegradability, and are compatible with their intended use, they are employed in numerous applications such as tissue engineering, wound healing, and drug delivery (Ansari & Darvishi, 2024; Oliveira et al., 2023; Shi et al., 2020).

2.1.4.3. Polymers-based biomaterials for wound healing

2.1.4.3.1. Natural polymers

As the name suggests, natural polymers are obtained from natural sources such as animals, plants, and microbial biomass. Natural-derived polymers are characterized by high biocompatibility, biodegradability (Oliveira et al., 2023; Prete et al., 2023), high regeneration capacity (renewability) (Ansari & Darvishi, 2024; Prete et al., 2023), and biological activity which oblige them to be a perfect match for health-related applications. Their versatility in tissue engineering applications stems from their ability to replace the skin's cellular backdrop and natural extracellular matrix (ECM) structural components (i.e. They are perfect replacements for the natural skin environment and extracellular matrix). However, they have limitations in controlling the rate of degradation. Natural polymers can enhance wound healing, serve as drug delivery vehicles, and form scaffolds with 3D networks (Oliveira et al., 2023; Prete et al., 2023).

2.1.4.3.1.1. Alginate

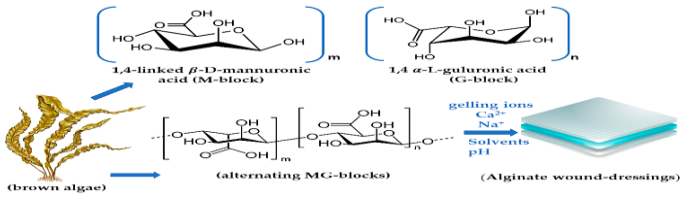
Alginate, obtained from seaweeds (cell walls of brown algae) (Naseri & Ahmadi, 2022), bacteria strains like Pseudomonas or Azobacter, are employed within the pharmaceutical sector for healing wounds due to their ability to reduce pain, cool the wound bed, and non-adhesive properties (Prete et al., 2023). It is a linear anionic polymer made of G blocks (guluronic acid) and M blocks (mannuronic acid) used for skin regeneration. It is a polysaccharide extracted from seaweed (Agarwal et al., 2020; Da Silva et al., 2023; Ko & Liao, 2023). It can be categorized into sodium or calcium alginates (Miron et al., 2023).

It is adaptable and easily modified by varying the kind and concentration of the cross-linker, generating hydrogels. Excellent biocompatibility, biodegradability, minimal immunogenicity, ease of gelation, control over degradation, and affordability are some of the benefits of alginate. Its reduced immunogenicity and easier processing are due to its greater G block ratio. Alginate is suited for use as wound dressings because of its antibacterial qualities, low toxicity, conformability, good water absorption, and ideal water vapor transmission rate. It is versatile, forming hydrogels, and can be easily adapted by cross-linker type and concentration (Naseri & Ahmadi, 2022; Oliveira et al., 2023; Samadian et al., 2020).

Alginate has advantages like excellent biocompatibility, biodegradability, low immunogenicity, simple gelation, control of degradation, and low cost. Its higher G block ratio makes it easier to process and lowers immunogenicity. Alginate also has antiseptic properties, low toxicity, conformability, good water absorption, and optimal water vapor transmission rate, making it suitable for wound dressings (Naseri & Ahmadi, 2022; Oliveira et al., 2023; Samadian et al., 2020). Because of its advantageous qualities, alginate, which has been approved by the US FDA, is frequently utilized in the biomedical and engineering industries (Prete et al., 2023; M. Zhang & Zhao, 2020). Figure 11 shows the schematic structure of alginate in the polymeric chain.

Figure 11.

Schematic Structure of Alginate in the Polymeric Chain (Barbu et al., 2021)

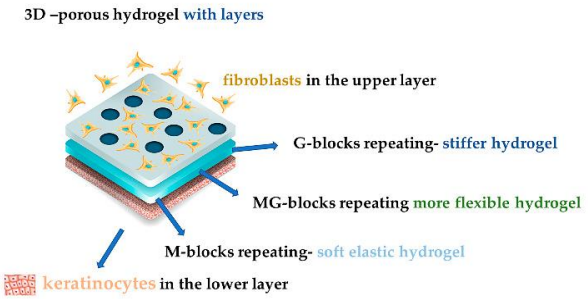


The mentioned properties make it a promising biomaterial in numerous biomedical sectors. Biomaterials based on alginate, such as hydrogels, film, etc., (Samadian et al., 2020; M. Zhang & Zhao, 2020) have been created and used in biomedical settings. Alginate hydrogels show promise for wound healing, cell therapy, drug administration, and tissue engineering because of their swelling characteristics and structural resemblance to real tissue endothelial cells (ECM). A variety of crosslinking techniques, such as chemical techniques, have been developed to enhance the mechanical characteristics of physically crosslinked hydrogels based on alginate (Samadian et al., 2020).

When it is combined with sodium, it forms sodium alginate hydrogel, which has excellent chelating activity. Hydrogels are 3D networks of hydrophilic high-water content polymers, which cause cells to swell when incorporated, removing cellular waste and supplying basic nutrients. The alginate hydrogel exhibits thermos-reversibility and can transform into a gel-like structure when temperature and pH are changed simultaneously. This makes it an abundant natural biomaterial (Oliveira et al., 2023). Figure 12 shows the structure of alginate hydrogel used in wound healing.

Figure 12.

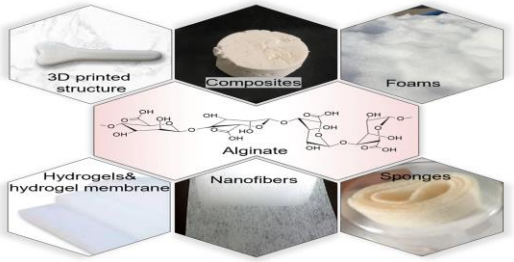
Structure of Alginate Hydrogel Used in Wound Healing (Barbu et al., 2021)



Alginate dressings exhibit good hemostatic qualities and are appropriate for ulcers with significant secretion. After administration, alginate is biocompatible and does not result in systemic responses. 3D calcium alginate scaffolds that are highly porous demonstrate remarkable swelling properties inside wounds, so enabling a progressive release of medication (Prete et al., 2023). Figure 13 shows the alginate and alginate-based biomaterials used in wound healing.

Figure 13.

Illustration of Alginate and Alginate-Based Biomaterials Used in Wound Healing (M. Zhang & Zhao, 2020)

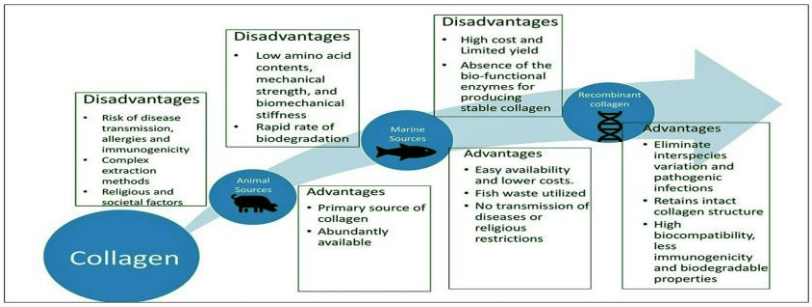


2.1.4.3.1.2. Collagen

The most abundant protein in the human body is collagen. It is a component of ECM (extracellular matrix) and plays a crucial role in wound healing (Da Silva et al., 2023; Samadian et al., 2020). It inhibits bleeding by initiating the blood clotting mechanism and creates a fibrin clot. Collagen type I and IV collagens attract neutrophils, leading to increased immune response and phagocytosis, known as inflammatory mediators. Collagen, particularly type I, is effective in inhibiting or stimulating angiogenesis, recruiting endothelial cells, and ultimately regenerating the ECM within the wound (Ansari & Darvishi, 2024; Ren et al., 2022; Ribeiro et al., 2024; Sharma et al., 2022). Collagen can be extracted from animals for example bovines, rodents, marine animals such as fishes, etc., or by using recombinant technologies (Davison-Kotler et al., 2019). Figure 14 illustrates the source of collagen along with its advantages and disadvantages.

Figure 14.

The Source of Collagen (Gajbhiye & Wairkar, 2022)

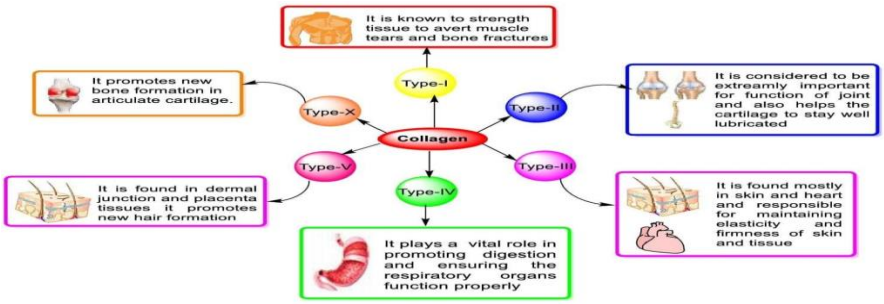


Collagen type I is the most widely used kind because it is plentiful in natural dermal tissue and is used to create skin scaffolds (Chattopadhyay & Raines, 2014; Naseri & Ahmadi, 2022;

Oliveira et al., 2023; Prete et al., 2023). The 16 members of the collagen family make up 80–90% of the body, with kinds I, II, and III making up the majority. Collagen has limited clinical applicability due to its low mechanical strength and low structural stability upon hydration, despite its biocompatibility, degradability, and low immunogenicity. Intermolecular crosslinking has the potential to improve stability and mechanical strength. (Downer et al., 2023; Mathew-steiner et al., 1969; Samadian et al., 2020; Sharma et al., 2022). Figure 15 shows the types of collagen and their function in the human body.

Figure 15.

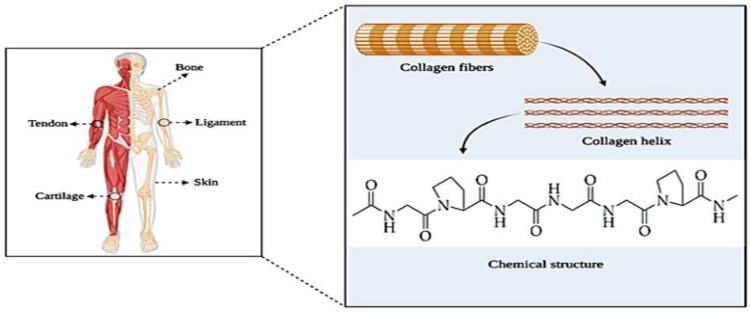
Types of Collagen and Their Function in The Human Body (Sharma et al., 2022)



Collagen is perfect for wound healing applications because of its strong mechanical strength, low antigenicity, and biocompatibility (Sharma et al., 2022). Combining it with other polymers such as chondroitin sulfate, hyaluronic acid, and chitosan can enhance its characteristics (Chattopadhyay & Raines, 2014; Naseri & Ahmadi, 2022; Oliveira et al., 2023; Prete et al., 2023). Figure 16 shows the chemical structure of collagen.

Figure 16.

The Chemical Structure of Collagen (Ansari & Darvishi, 2024)



In 1881, Joseph Lister, a founder of modern surgery, and William Macewen employed collagen, a collagen-rich biomaterial, for the first time in modern surgery (Chattopadhyay & Raines, 2014; Mathew-steiner et al., 1969; Sharma et al., 2022). Collagen is elastic and dynamic and is primarily responsible for preserving the biological and structural integrity of the extracellular matrix. It has more biocompatibility than other natural polymers and can pass through lipid-free interfaces because it has surface activity. Nontoxic and mildly antigenic, exogenous collagen has no known side effects (Chattopadhyay & Raines, 2014).

According to recent research, collagen may release medications, including antibiotics like ciprofloxacin, which can be used to treat diabetic foot ulcers (Prete et al., 2023). There are different commercialized products of collagen used the chronic wound healing (Table 7). These include collagen sponges, collagen powder, collage hydrogels, collagen fibers, etc. (Mathew-Steiner et al., 1969; Sharma et al., 2022). Among them, Collagen-based hydrogels have drawn the most interest in biomedical applications because of their ability to replicate the structure of ECM (extracellular matrix), high swelling ratio, and high water retention capacity (Samadian et al., 2020). Commercialized collagen-based wound dressings forms are shown in Table 7.

Table 7.

Commercialized Collagen-Based Wound Dressings (Mathew-steiner et al., 1969; Sharma et al., 2022).

Forms	**Name of the brand**
Collagen (Col) fiber	Avitene, Helitene, InstatFibrillar
Collagen powder	Biocore
Collagen sponge	Instat, SkinTemp, Helistat, ActiFoam
Collagen composite	Biobrane, Fibracol
Hydrolyzed Collagen	Chronicure
Partially purified skin	Gelfoam

2.1.4.3.1.3. Chitosan

A polymer obtained from the deacetylation of chitin, chitosan is advantageous due to its high degree of homeostasis, biocompatibility, microbial activity, hydrophilicity, and lack of

toxicity. It is a desirable contender for tissue engineering applications because it resembles the extracellular matrix structure, which promotes cell adhesion and proliferation. According to studies, chitosan can increase the hydrophilicity and biocompatibility of different biomaterials as well as the activity of inflammatory cells during wound healing (Chattopadhyay & Raines, 2014; Da Silva et al., 2023; Naseri & Ahmadi, 2022; Oliveira et al., 2023; Prete et al., 2023; Samadian et al., 2020; Zhao et al., 2023).

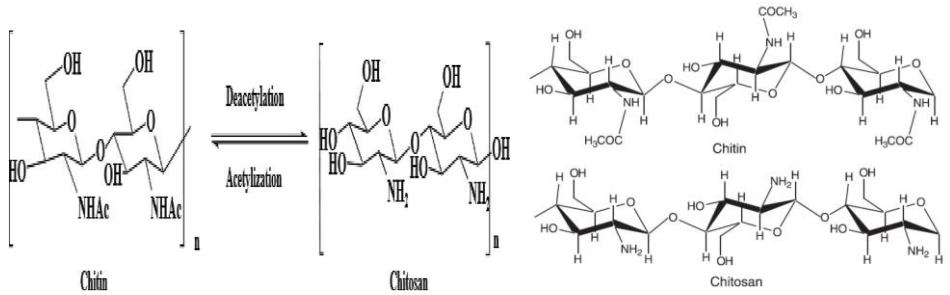
By incorporating collagen fibers into the extracellular matrix, chitosan—an amino group devoid of chitosan—promotes wound healing and evens out the production of scars. For skin burns and ulcers, chitosan hydrogel wound dressings show promise due to its low pH interaction with polymers. It is difficult to alter chitosan hydrogel at various phases of wound healing, though. Consequently, chitosan hydrogels with various functional needs could be made in response to modifications in the wound environment (Zhao et al., 2023).

Natural anti-inflammatory chitosan promotes platelet and red blood cell aggregation, prevents blood vessel blockage, and promotes blood vessel repair, all of which have hemostatic effects. Because of its exceptional antibacterial qualities, it is frequently used to treat wounds. Its mode of action and inhibitory impact, however, differ for Gram-positive and Gram-negative bacteria. Despite this, chitosan uses electrostatic interaction to break down the cell walls and membranes of bacteria (Ren et al., 2022; Zhao et al., 2023).

Plants high in deacetylation and low in molecular weight, such as chitosan, have a major effect on fibroblast proliferation. Studies reveal that the degree of deacetylation affects cell adhesion and growth. More adhesion and proliferation are supported by higher deacetylated chitosan scaffolds (>85%) than by lesser ones (75-85%). To demonstrate the relationship between molecular weight and fibroblast cell growth, human skin fibroblast (HSF) cells are utilized. Additionally, chitosan stimulates the release of growth factors for cells, including PDGF, IL-1, and TGF-β. Collagen secretion, fibroblast proliferation, and macrophage migration are all stimulated by TGF-β, whereas PDGF promotes fibroblast migration and proliferation. Through encouraging angiogenesis, fibroblast proliferation, and collagen production, IL-1 facilitates wound healing (Zhao et al., 2023). Figure 17 illustrates the chitin and chitosan and chitosan production by chitin through deacetylation.

Figure 17.

The illustration of Chitin and Chitosan and Chitosan production by Chitin Through Deacetylation (Jayakumar et al., 2011; Zhao et al., 2023).



2.1.4.3.1.4. Hyaluronic acid (HA)

HA is an essential part of the extracellular matrix (ECM) and stimulates cell motility by binding water (Prete et al., 2023). It is also known as hyaluronan (Samadian et al., 2020)**.** All living things contain HA, a non-sulfated glycosaminoglycan polymer that is especially abundant in the dermis of the skin (Oliveira et al., 2023), joints, umbilical cord, connective tissue, etc (Ansari & Darvishi, 2024). It is synthesized in fibroblasts and extruded into ECM(Samadian et al., 2020). It is a glycans sub-class known as GAGs (glycosaminoglycans), a subgroup of heteropolysaccharides (Ansari & Darvishi, 2024; Graça et al., 2020; Ren et al., 2022).

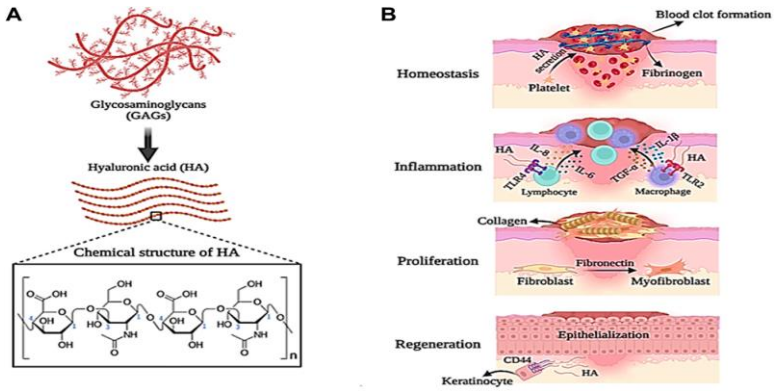
It consists of repetitive linear disaccharide polymers of N-acetyl-D-glucosamine and D-glucuronic acid linked together by glucuronidic β (1-3) bonds (Ansari & Darvishi, 2024; Oliveira et al., 2023). Additionally, it can be created through a microbial fermentation process (Ansari & Darvishi, 2024). HA is essential for cell division and proliferation, promoting early inflammation in the healing of wounds. However, its primary drawback in physiological media is that it degrades quickly due to enzymatic action. Despite this, HA is frequently utilized in the creation of tissue scaffolds and cosmetic products because of its qualities, which include its non-adhesiveness, hydrophilicity, biodegradability, and ease of production. Whether in hydrogel or solution form, its physical and biological properties enhance bodily restoration (Naseri & Ahmadi, 2022; Oliveira et al., 2023; Prete et al., 2023; Samadian et al., 2020)**.**

The healing process of a wound is greatly aided by HA during its inflammatory phase. HA is secreted by platelets during the hemostasis phase, which causes fibrinogen to deposit and a

primary blood clot to form. Additionally, it controls the recruitment of neutrophils and the release of α-TNF, IL-1β, and IL-8 interleukins. When macrophages and lymphocytes migrate to the wound site during the latter stage of the inflammatory process, HA ((low molecular weight (LMW-HA) binds to their Toll-like receptors and triggers the production of these interleukins. In addition, LMW-HA promotes fibroblast cell migration, proliferation, and differentiation into myofibroblasts, which are essential for collagen deposition and wound healing. HA interacts with CD44 receptors on the surface of keratinocyte cells during the tissue regeneration phase, activating and regulating (Ansari & Darvishi, 2024; Prete et al., 2023). Figure 18 represents the structure of HA and its role in the healing of wound.

Figure 18.

The Representation of Structure of HA (A) and Its Role In The Healing of Wound (B) (Ansari & Darvishi, 2024)



Because of its high hydrophilicity, distinct rheological behavior, biodegradability, biocompatibility, non-toxicity, non-immunogenicity, and non-inflammatory qualities, HA is a hydrophilic substance with a wide range of biomedical uses. Using a bi-functional reagent or highly reactive derivatives, it can be crosslinked physically, chemically, or enzymatically to overcome its poor mechanical qualities and quick in vivo disintegration (Samadian et al., 2020).

2.1.4.3.1.5. Cellulose

Cellulose is a polymer which is found in the cell walls of plants and bacteria such as Acetobacter, Sarcina ventriculi, and Agrobacterium. Bacterial cellulose, with its high purity, holds promise as a biopolymer for wound healing and managing wound exudate. However,

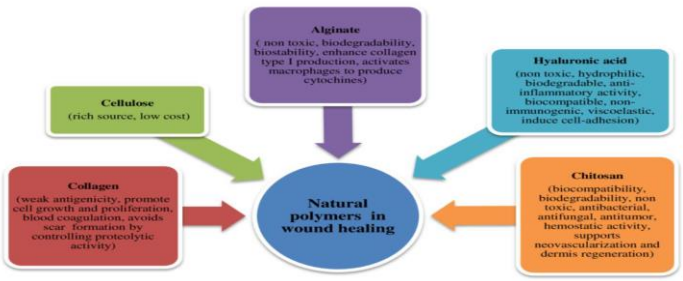
its antibacterial activity is lacking. Cellulose nanostructure offers advantageous properties, biocompatibility, and biodegradability (Prete et al., 2023). Due to its similarity to skin in terms of porous structure, it is highly hydrophilic and perfect for wound dressings (Da Silva et al., 2023; Oliveira et al., 2023; Prete et al., 2023).

To treat diabetic wounds, Diaz-Gomez et al. (2022) developed a 3D-printed carboxymethyl cellulose scaffold supplied with platelet-rich plasma. For active dressings, the scaffold showed prolonged release of growth factors and improved granulation, re-epithelialization, and angiogenesis in the skin (Da Silva et al., 2023; Oliveira et al., 2023; Prete et al., 2023). With a 3D structure that resembles the extracellular matrix of skin, it encourages tissue regeneration. Potential uses for bacterial cellulose include medicine delivery, implants, and artificial organs (Prete et al., 2023; Samadian et al., 2020).

Carboxymethyl cellulose (CMC) is a multipurpose polymer that can be used as a dermal filler, pressure sore treatment, diabetic foot ulcer treatment, surgical wound care, and wound dressings of both partial and full thickness. It is physiologically safe and available at low cost, making it suitable for use in various wound conditions. It has been discovered that CMC scaffolds, whose molecular weight strongly influences the regulation of transepidermal water loss, accelerate wound healing in rats by preventing moisture loss without excessively retaining water (Shah et al., 2019). Figure 19 illustrates the natural polymers employed in wound healing and their main characteristics.

Figure 19.

Illustration of Natural Polymers Employed in Wound Healing and Their Main Characteristics (Prete et al., 2023)



2.1.4.3.2. Synthetic polymers

Chemical synthesis is used to create synthetic polymers, which enables precise property modification. They are stable, have regulated deterioration, and have consistent physicochemical properties. They possess mechanical properties that can be adjusted and biological properties like biocompatibility. While some, like polyesters, have the potential to biodegrade, they also have toxicity hazards and offer no therapeutic benefits (Prete et al., 2023).They also have poor cellular interaction, requiring surface treatment or blending with natural polymers to enhance compatibility and biological activity, and proximity to ECM tissues. (Oliveira et al., 2023). Examples include PVA, PEO, PEG, PCL, PU, PLA, PVP, and PGA. These materials can be adapted to specific applications, but have high costs and different structures from the extracellular matrix (Da Silva et al., 2023; Prete et al., 2023).

They are approved by the FDA for biomedical applications due to their biocompatibility, biodegradability, and non-toxic properties. PLGA is commercially available, inexpensive, biocompatible, and biodegradable, making it ideal for drug delivery and wound healing. PEG, on the other hand, exhibits excellent biocompatibility, biodegradability, hydrophilicity, and wettability, making it widely used in biomedical applications. It also has anti-fouling properties, enhancing drug release and maintaining nanofiber surface properties (Xiao Liu & Jia, 2018).

2.1.4.3.2.1. Polyurethane (PU)

PU is a multipurpose material possessing a range of attributes such as resilience, longevity, biocompatibility, and rate of degradation. It can be used with propolis for antibacterial activity and mechanical strength, or with olive oil for antioxidant qualities and photoprotection. Dextran fiber electrospinning has strong anti-inflammatory and good angiogenesis activity, which speeds up the healing of cutaneous wounds. (Oliveira et al., 2023) It has been widely used in wound healing due to its flexibility, biocompatibility, and gas permeability, and also provides a cheaper resource compared to other natural polymers (Da Silva et al., 2023; Naseri & Ahmadi, 2022; Prete et al., 2023).

2.1.4.3.2.2. Polyethylene glycol (PEG)

PEG is a hydrophilic, bioinert, biocompatible, and non-biodegradable substance with superior biological and physicochemical qualities, and it consists of ethylene oxide monomers.

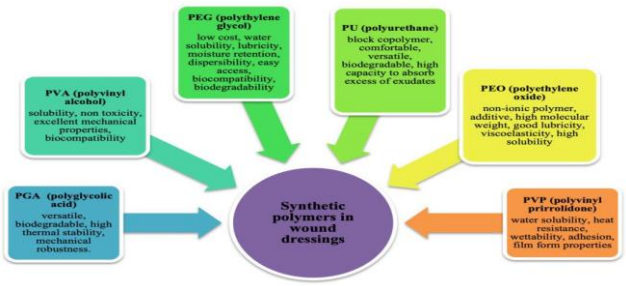
Because of its simple construction and chemical composition control, it's a desirable scaffold material for tissue engineering applications, wound healing, and drug delivery. PEG smart hydrogels were found to improve cellular functioning and increase wound healing in diabetics (Ansari & Darvishi, 2024; Chattopadhyay & Raines, 2014; Da Silva et al., 2023; Oliveira et al., 2023; Prete et al., 2023).

2.1.4.3.2.3. Polyvinyl alcohol (PVA)

With its repeating hydroxyl group, PVA is a water-soluble, biodegradable, biocompatible polymer that is non-toxic. It can be conjugated with other polymers, such as chitosan and polyhydroxy butyrate, to form nanofibers for tissue engineering applications, such as wound healing, indicating its potential in a range of biomedical fields (Ansari & Darvishi, 2024; Chattopadhyay & Raines, 2014; Da Silva et al., 2023; Oliveira et al., 2023; Prete et al., 2023). Figure 20 shows the properties of synthetic polymers used in wound healing.

Figure 20.

Illustration of Properties of Synthetic Polymers Used in Wound Healing (Prete et al., 2023)



For use as wound dressings, hybrid biomaterials like chitosan/collagen/alginate, alginate/PVA, PVA/starch/chitosan, and PCL/chitosan, have been researched. These biopolymers have the potential to enhance wound healing, biodegradation, and medication release. A standalone biocompatible polymer with a broad spectrum of biodegradation and release rates is polylactic-co-glycolic acid (PLGA) (Naseri & Ahmadi, 2022).

2.1.4.4. Biomaterials platforms for choric wound healing

2.1.4.4.1. Hydrogels

Because of the hydrophilic moieties in their polymeric backbone, hydrogels are 3D crosslinked networks that can absorb significant volumes of biological fluids while retaining their 3D architecture. Fluid absorption causes them to become stretchy and squishy, which lowers mechanical friction between them (Samadian et al., 2020; Shi et al., 2020; M. Zhang & Zhao, 2020). Hydrogels consist of over 90% water content, providing a hydrophilic porous structure for water absorption (M. Zhang & Zhao, 2020).

Hydrogels enhance wound healing by producing an ideal microclimate between the wound bed and the dressing, resulting in a cooling, calming effect and minimizing the pain associated with dressing changes. Their reduced adhesion enables for simple removal without giving additional stress to the healing tissue, and their transparency allows for clinical evaluation without removing the dressing (Gupta et al., 2019). However, they can cause fluid accumulation in high exudate wounds, leading to skin maceration and bacterial proliferation. (Las Heras et al., 2020; Liang et al., 2022; Xiao Liu & Jia, 2018).

Their thickness ranges from nanometers to centimeters and their mobility makes them suitable for confined spaces. Hydrogels have been widely used as wound dressings in the biomedical field due to their biodegradability, biocompatibility, and bioactivity (Zhao et al., 2023). Because they are pliable, non-adhesive, and have qualities akin to live tissue, hydrogels are the perfect dressing because they promote faster wound healing by supplying water to the wound site (Gajbhiye & Wairkar, 2022; M. Zhang & Zhao, 2020).

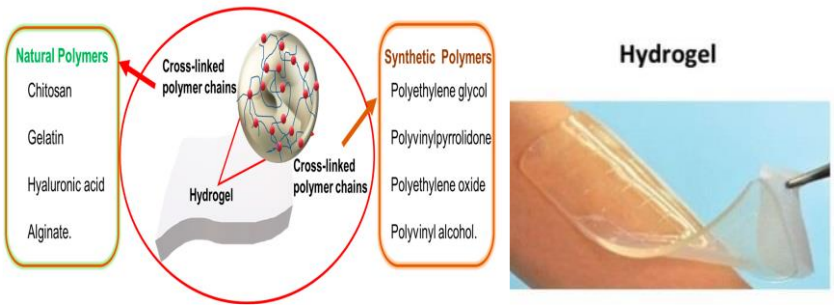
The matrix of hydrogels constitutes either insoluble natural or synthetic polymers such as collagen, chitosan, HA or PEG, PU, etc. respectively (Sharma et al., 2022). According to the U.S. FDA hydrogels can hydrate, retain moisture, cool wounds, reduce pain, and minimize drug toxicity or side effects. These characteristics make hydrogels the best choice for wound dressings (M. Zhang & Zhao, 2020). For debridement of wounds, hydrogels are reversible, non-toxic, biocompatible, and therapeutically beneficial materials. Natural autolysis is promoted by the rehydration of non-viable tissue. Necrotic wounds are OK, but gangrenous or high-exudate wounds should not be treated with them. Adding bioactive agents is made possible by their tri-dimensional structure (Prete et al., 2023).

They can be classified based on the source (natural, synthetic or hybrid hydrogels), polymeric composition (homopolymeric, co-polymeric or multipolymeric hydrogels), crosslinking approach (physical, chemical or enzymatic approach), configuration (amorphous, crystalline, or semi-crystalline), physical appearance (film, microsphere, matrix), and network electric charge (neutral, zwitterionic, ionic, or amphoteric electrolyte). The hydrogel's physicochemical and biological properties depend on various factors, including its stiffness, intermolecular forces, polymer chain molecular weight, functional group type, and technique of production. Hydrogels can be used for in vivo purposes due to their elastomeric consistency (Samadian et al., 2020).

Compared to synthetic hydrogels, natural hydrogels have better physicochemical and biological properties, including variable/controllable solubility, 3D geometry, excellent biocompatibility, biodegradability, low immunogenicity, cellular and/or tissue response, antigenicity, and sufficient stability. However, because of their natural origin, poor processability, low mechanical properties, limited sources, high production costs, high rates of biodegradation and catabolization, and microbial spoilage, they are challenging to control consistently. Large-scale production of synthetic hydrogels is affordable, more repeatable, and flexible in terms of their mechanical and chemical composition. Their biological characteristics, such as biodegradability and biocompatibility, are a major worry, though, as foreign substances that lack the right biological components may be thrombogenic in vivo by nature (Samadian et al., 2020). Figure 21 shows the polymers used in hydrogels and hydrogel wound dressing.

Figure 21.

Illustration of Polymers Used in Hydrogels and Hydrogel Wound Dressing (Gounden & Singh, 2024; Trucillo & Di Maio, 2021)



Hydrogels are beneficial due to their biological aspects, such as biocompatibility and biodegradability, as they prevent thrombogenesis in vivo due to protein denaturation, thrombi propagation, coagulation factor activation, inflammatory response provocation, and debris accumulation. They are used in food additives, hygienic products, agriculture, sensing, and biomedical applications (tissue engineering), drug delivery systems, wound healing, cell therapies, etc.) (Samadian et al., 2020).

2.1.4.4.2. Films

Films are biopolymer sheets that are thin, elastic, transparent, and sticky. They shield wounds from outside bacteria and water loss. Benefits include versatility as primary or secondary dressings, drug loading possibility, and observation of wound progression. Polyurethane, silicon, chitosan, collagen, and HA are examples of common polymers that are employed. Since the early 20th century, films have been used to treat wounds; today, they are sold commercially under names including Bioclusive, Tegaderm, Transeal, and Simpurity. Since the early 20th century, these films have been in use (Fadilah et al., 2023; Gajbhiye & Wairkar, 2022; Las Heras et al., 2020; Liang et al., 2022; Rani Raju et al., 2022; Shi et al., 2020; Xiao Liu & Jia, 2018). Figure 22 illustrates the films wound dressing form.

Figure 22.

Films Wound Dressing (Nguyen et al., 2023)

Because of their permeability to vapors and oxygen, film dressings are frequently used to treat wounds because they create a moist environment that promotes speedier healing. Their tiny pores facilitate the passage of tiny molecules like oxygen, preventing the infiltration of microorganisms. They are thin, transparent, flexible, inexpensive, and simple to make, doctors can keep an eye on wound healing without taking them off the dressing. However, they cannot be used for severe wounds with significant exudates due to their low swelling capabilities. Antioxidant chemicals have the potential to stabilize and improve the functionality of films (Fadilah et al., 2023).

To produce a moist environment for wound healing, film polymers such as co-polymers, homopolymers, and plasticized polymers are utilized. They are permeable to air and water vapor but impervious to liquids and microorganisms. Contemporary dressing films are flexible, semi-permeable, and appropriate for light-exudate wounds with superficial exudate (Liang et al., 2022; Prete et al., 2023).

2.1.4.4.3. Hydrocolloids

Hydrocolloid dressings are impenetrable to microorganisms, offer a moist environment, and absorb moderate amounts of exudates. Because of their gel-like qualities, they aid in the growth and repair of granulation tissue and are utilized in the treatment of pressure sores. These dressings are made up of an outer layer that is flexible and water-resistant and a thin dressing that contains gelling chemicals. They work well under venous compression products and are self-adherent and simple to apply. For wounds that produce little exudate, DUODERM CGF is an excellent option (Liang et al., 2022; Prete et al., 2023; Shi et al., 2020). Figure 23 shows the hydrocolloid wound dressing form.

Figure 23.

Hydrocolloid Wound Dressing (Trucillo & Di Maio, 2021)

Because hydrocolloids are easy to use, inexpensive, and painless to remove—especially in cases involving children—they are frequently used to treat venous, pressure, abdominal, and neurosurgical wounds (Gruppuso et al., 2021).

2.1.4.4.4. Foams

Usually composed of silicone or PU, foam dressings are polymer solutions with open cells that hold fluids. They distribute exudate efficiently, provide thermal insulation, aid in the exchange of oxygen and water vapor, and stop it from escaping into the surrounding environment. Made from silicone elastomer, silicone foam dressings provide a soft, open-cell

dressing by molding to the shape of the wound. They provide wound care and effective fluid control as well (Liang et al., 2022; Prete et al., 2023; Shi et al., 2020). Figure 24 shows the foams wound dressing form.

Figure 24.

Foams Wound Dressings (Nguyen et al., 2023)

2.1.4.4.5. Sponges

Sponges are well-known for their ability to retain moisture and provide heat insulation due to their interconnected porous nature. The hydrophilicity and cell contact of these substances makes them popular choices for use as materials and hemostatic agents for healing burn wounds. However, issues with wound maceration, inadequate antibacterial activity, and poor mechanical strength pose practical application hurdles. Additionally, they shouldn't be used on wounds with dry eschar or severe burns. Many microbial agents, including antibiotics and cationic polymers, have been loaded into the networks of sponge dressings to enhance their antimicrobial characteristics; these compounds exhibit interesting applications in wound healing (Fadilah et al., 2023; Liang et al., 2022; Sharma et al., 2022).

Several polymers such as collagen have been used to formulate sponges as wound dressers in chronic wound healing processes. Figure 25 shows the structure of collagen forms employed in chronic wound healing processes.

Figure 25.

Collagen Forms Used in Wound Healing (Sklenářová et al., 2022)

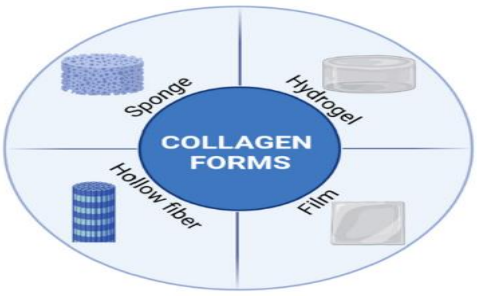


Table 8.

Commercially Available Biomaterials-Based Wound Dressings in Clinical Usage

Biopolymer	**Forms**	**Examples (Brand names)**	**Application**	**References**
Collagen	Hydrogels, sponges	Integra, Alloderm, Apligraf, Biobrane	Diabetic foot ulcers, venous ulcers, pressure ulcers	(Das & Baker, 2016; Gruppuso et al., 2021; Maaz Arif et al., 2021; Ren et al., 2022)
Alginate	Hydrogels	Calcicare, Nuderm, Seasorb, Sorbsan, Algisite, Kaltostat	Diabetic foot ulcers, heavily exudating ulcers, surgical wounds, Hemorrhagic wounds, burns	(Das & Baker, 2016; Fadilah et al., 2022; Gounden & Singh, 2024; Gruppuso et al., 2021; Gupta et al., 2019; Maaz Arif et al., 2021; Ren et al., 2022)
Chitosan	Hydrogels, sponges	Aaaaxiosta, Chitoflex, Chitopoly, Tegasorb	Diabetic foot ulcers, venous ulcers, pressure ulcers, Hemorrhagic wounds, burns, abrasions, lacerations, surgical wounds	(Das & Baker, 2016; Gruppuso et al., 2021; Maaz Arif et al., 2021; Ren et al., 2022)
Hyaluronic acid	Hydrogels, Films, sponges	Bionect, Dermaplex, Integra, Hyalofill, Hylomatrix, Regeneracare, Hyasponge	Diabetic foot ulcers, pressure ulcers, venous ulcers, traumatic wounds	(Das & Baker, 2016; Gounden & Singh, 2024; Graça et al., 2020; Maaz Arif et al., 2021; Ren et al., 2022)

Table 8 (Continued)

Polyurethane	Films	Tegaderm, Clrearsite, Opsite, Dermaview, Suresite,	Diabetic foot ulcers, pressure ulcers, venous ulcers, Hemorrhagic wounds, burns, heavily exudating ulcers, abrasions	(Das & Baker, 2016; Fadilah et al., 2022; Gruppuso et al., 2021; Gupta et al., 2019; Maaz Arif et al., 2021; Ren et al., 2022; Shah et al., 2019)
	Foams	Euroderm, Polymem, Lyofoam, Optifoam, COPA, Gentleheal,		Foams
PEG	Hydrogels	Iodosorb, Duoderm	PEG	Hydrogels
Cellulose	Films	Dermafil, Aquacel, Exu-dry cellulose, Curity, Promogran	Cellulose	Films
PVA/ Alginate	Hydrogels	Calcicare, Nuderm, Seasorb, Sorbsan, Algisite, Kaltostat	PVA/ Alginate	Hydrogels

2.1.4.5. Techniques for manufacturing biomaterials employed in wound healing

A variety of methods, such as solvent casting, electrospinning, electrospraying, and 3D printing, are used to create biomaterial-based wound dressings. High porosity is required for oxygen gas permeability and wound respiration, and these needs must be met by the manufacturing process (Naseri & Ahmadi, 2022; Prete et al., 2023).

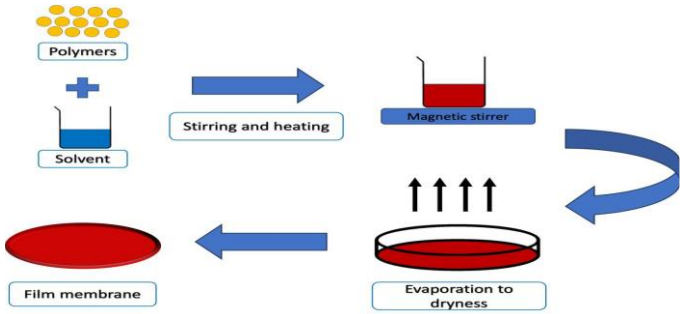
2.1.4.5.1. Solvent casting

The most popular technique for creating wound dressing films is solvent casting, which offers improved gas permeability, flexibility, and ease of application. Nevertheless, making porous films is challenging and necessitates leaching with pebbles or salt to extract integrated

medications (Ko & Liao, 2023; Naseri & Ahmadi, 2022; Negut et al., 2020; Prete et al., 2023). Figure 26 shows the process of the solvent casting method.

Figure 26.

Solvent Casting Method (Prete et al., 2023)

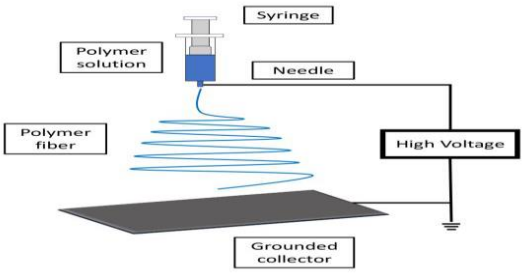


2.1.4.5.2. Electrospinning

Electrospinning is a popular technique for biomaterials such as PCL, PVA, and alginate because it has a high surface-to-volume ratio, variable porosity, and adaptability. The ability of polymer electrospinning to encapsulate drugs is superior (Naseri & Ahmadi, 2022; Negut et al., 2020; Prete et al., 2023; Riha et al., 2021). Figure 27 shows the process of the electrospinning system.

Figure 27.

Electrospinning System (Prete et al., 2023)



2.1.4.5.3. Electrospraying

Similar to electrospinning, electrospraying involves the ejection of charged droplets from the nozzle. The use of nanofiber wound dressings in early wound healing and film wound dressings in the proliferation phase is recommended (Naseri & Ahmadi, 2022; Riha et al., 2021).

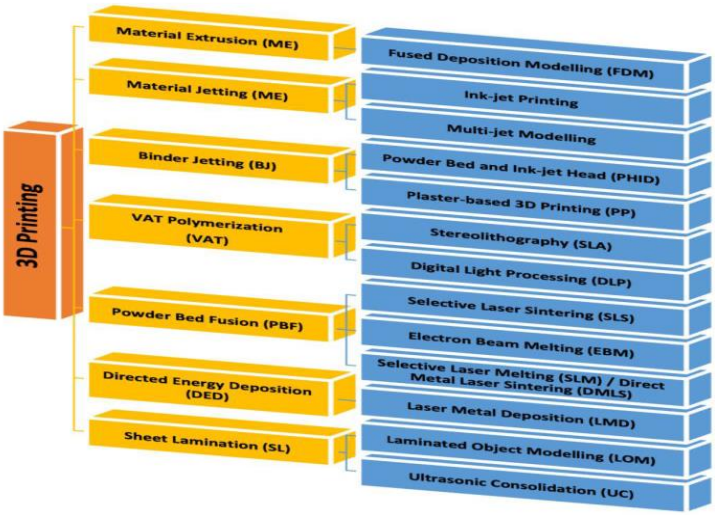
2.1.4.5.4. Three-dimensional (3D) bioprinting

3D printing is a revolutionary technique for wound dressing fabrication, ensuring porosity and enabling arbitrary geometries. It is revolutionizing drug delivery by providing excellent control over the porosity and geometry of wound healing, enhancing the healing process. 3D printing allows for the stacking of layers of biomaterials with different compositions to fabricate arbitrary geometries (Naseri & Ahmadi, 2022; Prete et al., 2023; Riha et al., 2021).

At the moment, wound dressings are not customized to meet the demands of patients or certain wound situations. There are four types of bioprinting methods used: dynamic optical projection stereolithography (DOPsL), extrusion-based, laser-assisted, and inkjet-based. Soft material fabrication is done using processes like extrusion, inkjet, and vat photopolymerization printing. Unfortunately, the usage of specific polymers limits the application of vat photopolymerization processes in drug-eluting wound dressings (Naseri & Ahmadi, 2022; Prete et al., 2023; Riha et al., 2021). Figure 28 shows the different categories of 3d printing processes.

Figure 28.

Different Categories of 3D Printing Processes (Prete et al., 2023)



Despite its potential to coat microneedles with drug-containing polymers, inkjet printing is limited in its application to wound dressings because of the high-stress levels involved in the jetting and deposition processes. The process of extrusion Biomaterials are extruded from a micronozzle in 3D printing using solvents or high-temperature melt extrusion (FDM), however, to prevent high temperatures, therapeutic drugs must be added after printing. To

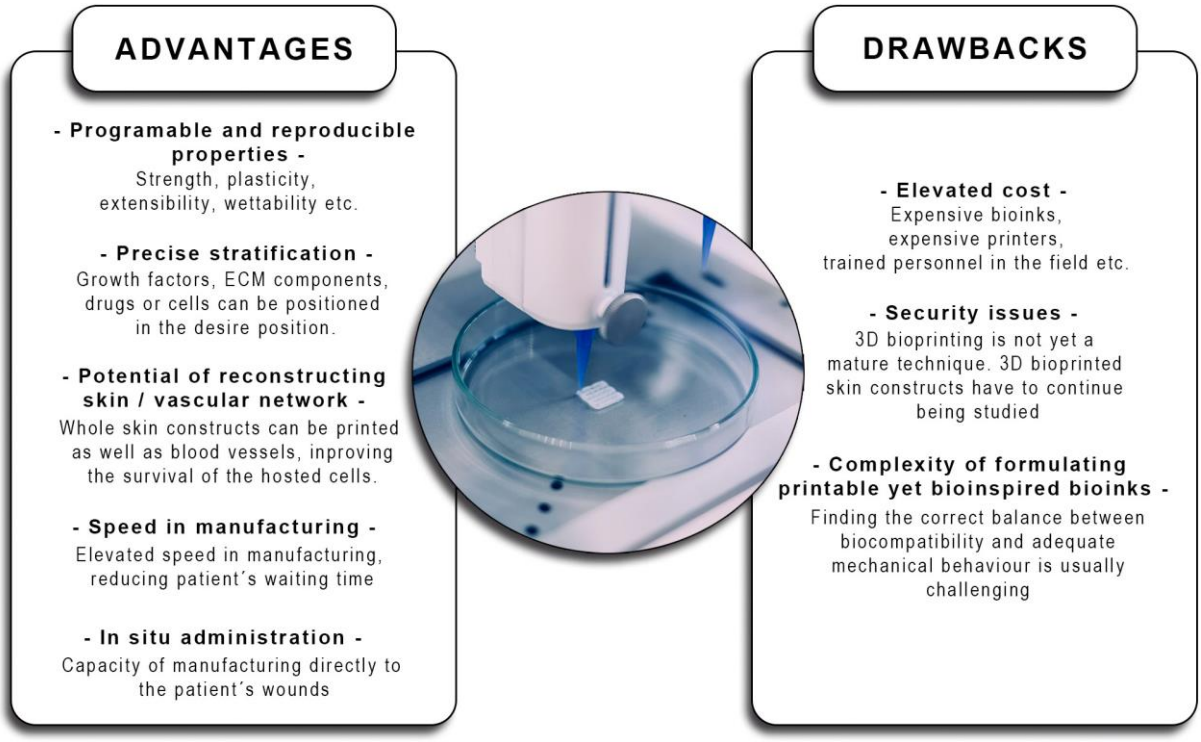
avoid excessive temperatures, low-temperature solvent-based extrusion, also known as past extrusion, is employed. Before 3D printing, biomaterial inks need to be described, and removing organic solvents is essential to preserving medication integrity. With the help of 3D printing, wound dressing geometry and physical attributes can be customized to achieve the desired drug release rate, diffusion, and degradation characteristics (Naseri & Ahmadi, 2022; Negut et al., 2020; Prete et al., 2023).

2.1.4.5.4.1. Advantages and disadvantages of 3D bioprinting

3D bioprinting has several benefits and drawbacks such as time management, high cost, etc. respectively. Figure 29 illustrates some of the advantages and disadvantages of 3D bioprinting.

Figure 29.

Illustration Advantages and Disadvantages of 3D Bioprinting (Negut et al., 2020)



CHAPTER III

Methodology

This section focuses on specific biomaterials used in wound healing as wound dressings selected for the assessment, and methods used in analysis, comparing and ranking them.

3.1. Data collection procedures

Data were collected by performing a search on 5 databases (PubMed, SCOPUS, Web of Science, Google Scholar, and Research Gate) using the keywords chronic wounds, wounds, wound healing, wound dressings, biomaterials, and biomaterial-based wound dressings. The results were retrieved in the last five years until 2024, and the search revealed millions of results, including articles, scientific research, and doctoral theses.

3.2. Criteria for Research Inclusions

The criteria on which the research relied were the comparisons between the biomaterial-based wound dressings, polymeric constituents, advantages and drawbacks of each biomaterial in all aspects. The reliance was placed on trials that were conducted in laboratories and clinics to study specific types of biomaterials. Article information was obtained from some medical research and practical experiments conducted on some patients. Many studies met the wanted criteria, but in the end, only a few studies were highly relied upon these studies included trials, systematic reviews, and scientific studies.

3.3. Materials

- **Chitosan hydrogels**

Chitosan hydrogels are a promising biomaterial for wound healing due to their three-dimensional structure, biocompatibility, and water retention capabilities. They are extensively employed in tissue engineering and drug delivery systems. These hydrogels have excellent bioactivities, water retention, antimicrobial properties, drug embedding ability, high biocompatibility and biodegradability, antimicrobial activity**,** low cytotoxicity, mechanical properties, moisture retention, and low cost. However, their mechanical strength can be improved through crosslinking techniques or combining with other materials. Chitosan hydrogels also encourage the clotting process of blood, accelerate tissue regeneration, and prevent microbial growth; this makes them suitable for various wound types (Alven & Aderibigbe, 2020; Ansari & Darvishi, 2024; Gupta et al., 2019; Peers et al., 2020; Shah et al., 2019; Zhao et al., 2023, 2023)

- **Alginate hydrogels**

Alginate hydrogel is a non-toxic, biodegradable, and high-water absorptive medical dressing that maintains a moist environment on wound surfaces. Its hydrogel network prevents secondary wound injuries and collects exudate from healthy skin tissue surrounding the wound which is known as "lateral wicking." High mannuronic acid content can prevent lateral wicking of the dressing. Alginate hydrogel offers several benefits over traditional medical dressings, including biodegradability, high moisture permeability, and exudate absorption. It also exhibits low cytotoxicity, making it safe and effective for chronic wound healing (Miron et al., 2023; M. Zhang & Zhao, 2020).

Hydrogels are a promising alginate form for wound healing due to their ability to retain moisture, absorb excess exudate, reduce local pain, and hold active compounds like drugs or stem cells. However, they have disadvantages such as high cost and mechanical instability. The structure of the gel influences its properties, with repeating M-blocks resulting in a softer, more elastic gel, and repeating G-blocks providing good mechanical resistance but stiffness. High G content ALG has interesting gel formation properties, particularly for ocular drug delivery. Despite its potential benefits, mechanical instability and cost are drawbacks. The structure of ALG affects the gel's characteristics, with repeating M-blocks making it softer and more elastic, and G-blocks providing strong mechanical resistance but rigidity. High G-content gels work better for ocular medication (Barbu et al., 2021; Negut et al., 2020; Ren et al., 2022).

- **HA hydrogels**

HA hydrogels are promising for chronic wound healing due to their unique properties such as hydrophilicity, viscoelasticity, and biocompatibility. They have low cytotoxicity, flexibility, excellent water absorption, and non-immunogenicity, making them ideal for chronic wound dressings. To enhance healing, biomolecules or medications are often added to HA hydrogels. These hydrogels have multifunctional properties, including adhesion, antibacterial, anti-inflammatory, and pre-angiogenic bioactivities. Techniques like enzymatic crosslinking and radical polymerization can increase their (Samadian et al., 2020; Xu et al., 2021).

HA contains numerous free active sites, allowing for functionalization strategies for creating cross-linkable hydrogels. However, uncross linked soluble HA has poor mechanical strength and fast in vivo degradation. It can be physically, chemically, and enzymatically crosslinked. Tailoring HA hydrogels through chemical modifications and various forms, such as nano gels

and injectable hydrogels, has shown potential in wound healing and regenerative medicine (Ko & Liao, 2023; Samadian et al., 2020; Xu et al., 2021).

- **Collagen hydrogels**

Collagen Hydrogels are used in wound healing for both chronic and acute wounds due to their high biocompatibility, high water retention capacity, high swelling ratio, fast degradation rate, no toxicity, good gas permeability, high porosity, excellent fluids absorbance, and good mechanical properties. They are abundant in the extracellular matrix and can be adjusted for different wound types. Collagen hydrogels function as scaffolds for cell attachment and proliferation due to their integrin-binding sites. They are biodegradable and contain bioactive chemicals that control cellular activity, aiding in the healing process. Their moisture retention aids cell migration, reduces dehydration, and enhances autolytic debridement, making them crucial for wound healing (Lee et al., 2019; Murray et al., 2019; Y. Zhang et al., 2023).

- **PEG hydrogels**

PEG hydrogels are crucial in chronic wound healing due to their tissue repair, infection prevention, and therapeutic release regulation. They are biocompatible, low toxic, widely available, cost-effective, and have excellent water-retaining properties. They help maintain a moist wound bed, a critical factor in wound healing. PEG hydrogels can absorb wound exudates and can be tailored to match native tissues by adjusting their molecular weight and cross-linking density. Overall, PEG hydrogels are an invaluable tool in wound management and treatment (Ansari & Darvishi, 2024; Ko & Liao, 2023).

- **PVA/Alginate hydrogel**

PVA/alginate hydrogels are effective in the care management of chronic wounds because of their biocompatibility, moisture retention, exudate management, mechanical strength, barrier protection, biodegradability, pain reduction, hemostatic properties, ease of application, compatibility with other treatments, and odor control. These properties collectively contribute to a more effective and patient-friendly approach to chronic wound care, promoting faster and more comfortable healing (Ko & Liao, 2023; Kodous et al., 2024; Murray et al., 2019; Negut et al., 2020; Ren et al., 2022).

- **PU Foams**

Polyurethane absorptive foam dressings are effective in wound healing due to their hydrophilic and hydrophobic surfaces, biocompatibility, and non-toxic nature. They are suitable for, small burns, donor sites, venous insufficiency ulcers, diabetic ulcers, and light to severe exudates, slough covered or granulating wounds. They have good mechanical strength, moderate moisture vapor transmission rate, and excellent fluid absorption and retention capabilities. Porous structures promote cell adhesion, which is beneficial for tissue regeneration during wound healing (Peng et al., 2022; Trucillo & Di Maio, 2021).

- **PU Films**

Polyurethane films are crucial for managing chronic wounds due to their biocompatibility, breathability, moisture management, barrier protection against viruses and bacteria, flexibility, and compatibility with various therapies. Their semi-permeable nature allows oxygen and water vapor to pass while inhibiting liquids and bacteria, promoting a moist wound environment for better healing and infection prevention. Their strong mechanical properties and durability ensure the dressing remains intact and functional for the necessary amount of time, making them an effective approach to chronic wound care (Abazari et al., 2021; Das & Baker, 2016; Hodge et al., 2022; Kanikireddy et al., 2020; Nguyen et al., 2023; Peng et al., 2022)

- **Collagen Sponges**

Collagen sponges are a popular treatment for chronic wound healing due to their unique properties, including mechanical strength, biocompatibility, low toxicity, biodegradability, bioactivity, high moisture retention, hemostatic qualities, porous structure, low immunogenicity, ease of application, reduced cost, and high mechanical strength. They support cell growth and are commonly used in wound dressings due to their high porosity and water adsorption. However, their fast degradation limits their in-vivo application. To optimize wound healing, the degradation rate of collagen sponges must be tailored to match the wound's healing requirements. Fast degrading sponges are suitable for acute wounds, while moderate degrading sponges are used for chronic wounds (Prete et al., 2023; Valenzuela-Rojo et al., 2020).

3.4. The Fuzzy based MCDM models

Multicriteria decision-making (MCDM) is a study that helps decision-makers compare, analyze, and carry out complex decisions by criteria, decision-making processes, and alternatives (decision influencers). It is also known as multiple-criteria decision analysis (MCDA), a field that analyzes available choices in a situation field in scientific research, engineering, medicine, and other areas (Balcioglu et al., 2023; Hansen & Devlin, 2023; Taherdoost & Madanchian, 2023). Since it can evaluate several options according to different criteria for making decisions, it is especially helpful in resolving complicated real-life issues (Emovon & Oghenenyerovwho, 2020; Taherdoost & Madanchian, 2023).

3.4.1. The classification of MCDM methods

Most widely used MCDM methods include preference ranking organization method for enrichment evaluation (PROMETHEE), the technique for order preference by similarity to ideal solution (TOPSIS), ViseKriterijumska Optimizacija Kompromisno Resenje (VIKOR), Et Choice Translating Reality (ELECTRE), and the analytical hierarchy process (AHP) (Eltarabishi et al., 2020; Emovon & Oghenenyerovwho, 2020; Taherdoost & Madanchian, 2023). The MCDM techniques exist in three groups: the first group utilizes the utility functions to rate performance related to criteria, for example, AHP, the second group works based on the relationships of preference between alternatives, such as ELECTRE and PROMETHEE, and the third group use the same principle with different paradigms, to identify the maximum and minimum value ranges as well as Positive Ideal Solution (PIS) and Negative Ideal Solution (NIS). For instance TOPSIS, VIKOR (Abdelli et al., 2020; Taherdoost & Madanchian, 2023).

One well-liked technique for deciding on weight criteria, ranking possibilities, or doing both at once is the analytical hierarchy process (AHP). It has been used for workforce selection issues, mobile health apps, and maintenance strategy selection (Eltarabishi et al., 2020), (Taherdoost & Madanchian, 2023). AHP provides the optimum solution according to the criteria and degree of importance. However, as the criteria and alternatives increase, the method gets more complicated (Emovon & Oghenenyerovwho, 2020).

PROMETHEE is an outranking technique that determines how strong one alternative is in comparison to another. The PROMETHEE the outranking method calculates the relative strength of each alternative (comparison of alternatives) based on the criteria. An outranking

technique called ELECTRE employs pair-wise comparison to favor an alternative. It is appropriate for choice problems with limited criteria and a large number of alternatives since it eliminates the least preferable option. Compared to other approaches, it has a lengthy computational procedure (Eltarabishi et al., 2020; Taherdoost & Madanchian, 2023).

3.4.2. Fuzzy PROMETHEE Approach

The PROMETHEE technique is a favored MCDM model. It is effective and unique by handling multiple criteria. It is rational, applicable to real life, possesses high-ranking competitiveness, and accommodates both quantitative and qualitative data. In 1985 Brans and Vince established this method. It compares available alternatives according to the selected criteria. (Balcioglu et al., 2023; Feng et al., 2020; Gul et al., 2018). The PROMETHEE method finds the best response based on the given situation by utilizing an outrank relationship between option pairings. It provides a preference function that describes the distinction in selecting alternatives on each parameter by comparing pairs of possibilities for each attribute (Molla et al., 2021).

Fuzzy PROMETHEE allows decision makers to analyze and rank available alternatives based on selected criteria of each alternative. It handles quantitative and qualitative criteria simultaneously and deals with uncertainties, fuzzy relations, and vagueness (Yildirim et al., 2021). The importance weight given to the chosen criterion and the preference function preferred by the decision-maker are the two pieces of information needed by the PROMETHEE approach. By using this method, the decision-makers decide the best response according to their objectives and situational awareness (Molla et al., 2021; Ozsahin et al., 2023).

Fuzzy-based MCDM models analyze qualitative cases where numerical data are unavailable and aid decision-makers in vague or linguistic data (Balcioglu et al., 2023; Feng et al., 2020) Fuzzy logic refers to a technique that studies reasoning systems where consideration of the notions of truth and falsehood exist in a graded fashion. It analyzes and tolerates the vagueness, in natural language and produces the best solutions (Feng et al., 2020; Ozsahin et al., 2020). It was originally introduced by Dr. Lotfi A. Zadeh in his paper called “Fuzzy Sets”. According to fuzzy set theory, elements have a degree of membership in a set, which may be stated as a number between 0 and 1. Degrees between 0 and 1 imply unclear membership. When applying fuzzy set theory to MCDA, decision-makers must identify uncertain items and design membership functions to capture the ambiguities. The purpose of

the fuzzy PROMETHEE model is to compare two fuzzy sets by evaluating the fuzzy numbers (Balcioglu et al., 2023; Feng et al., 2020; Ozsahin et al., 2023).

It works as “To account for the data's inherent ambiguity, the fuzzy PROMETHEE treats the input data as fuzzy numbers. In light of the lack of data, the fuzzy-PROMETHEE ranking provides a more accurate failure mode rating”. The fuzzy-PROMETHEE method entails the steps below (Balcioglu et al., 2023).

i. Problem identification,
ii. Option selection,
iii. Criteria establishment,
iv. Preference function selection,
v. Weight determination, outranking relationships,
vi. Outranking flows, selection of a partial pre-order, and
vii. Computation of the net flow for each option, followed by ranking.

3.4.3. Applications Fuzzy PROMETHEE in the selection of biomaterials employed in skin chronic wounds treatment.

This study adopts the fuzzy PROMETHEE method to rank, evaluate, and compare biomaterials employed in skin chronic wound healing. The triangle linguistic fuzzy scale was used to assess the linguistic values in the study and define the selection criteria weights as demonstrated in Table 6.

Table 9.

Linguistic Fuzzy Scale.

Linguistic scale	**Triangular fuzzy scale**	**Criteria**
Very high	(0.75,1,1)	Biocompatibility, cost
High	(0.50,0.75,1)	Biodegradability, cytotoxicity, antimicrobial properties
Moderate	(0.25,0.50,0.75)	Availability, Exudate absorption
Low	(0.00,0.25,0.50)	Moisture management, porosity
Very low	(0.00,0.00,0.25)	Mechanical property, flexibility

In this study, the triangular linguistic fuzzy scale represents the linguistic terms namely, very high (VH), high (H), moderate (M), low (L), and very low (VL), with their accompanying scaling of fuzzy numbers/sets. The biomaterials employed in skin chronic wound healing were explained and determined using the triangular linguistic fuzzy scale. The factors considered for skin chronic wound healing include biocompatibility, biodegradability, cytotoxicity, cost, availability, mechanical properties, antimicrobial properties, porosity, exudate absorption, flexibility, and moisture management.

The selected criteria and their weights are evaluated using fuzzy set with a triangular fuzzy linguistic scale and the Yager index applied for defuzzification process. Options were evaluated using the Gaussian preference function, and fuzzy data was analyzed using the PROMETHEE tool. Table 10 shows the dataset of this study and the Table 11 shows the aim and the selected weights for each criteria.

Table 10.

Biomaterials Employed in Skin Chronic Wounds Treatment.

Alternative / Criteria	Biocompatibility	Biodegradability	Cost	Availability	Cytotoxicity	Mechanical strength	Antimicrobial properties	Porosity	Exudate absorption	Flexibility	Moisture management
Alginate hydrogels	Very high (Moreira et al., 2024; Shah et al., 2019; M. Zhang & Zhao, 2020)	High (Moreira et al., 2024; Shah et al., 2019; M. Zhang & Zhao, 2020)	High (Oliveira et al., 2023)	High (Oliveira et al., 2023; M. Zhang & Zhao, 2020)	Very Low (Oliveira et al., 2023)	Moderate (Ijaola et al., 2022; Oliveira et al., 2023)	Moderate (Niculescu & Grumezescu, 2022)	High (Ijaola et al., 2022)	Very high (Miron et al., 2023; M. Zhang & Zhao, 2020)	High (Ijaola et al., 2022) (Prete et al., 2023)	Very high (Liang et al., 2022; Niculescu & Grumezescu, 2022; M. Zhang & Zhao, 2020)

Table 10 (Continued)

Chitosan hydrogels	High (Ijaola et al., 2022; Shah et al., 2019)	High (Ijaola et al., 2022; Shah et al., 2019)	Low (Zhao et al., 2023)	Very High (Ijaola et al., 2022; Shah et al., 2019)	0 % (Ijaola et al., 2022; Jayakumar et al., 2011; Shah et al., 2019)	Low (Ijaola et al., 2022)	High (Shah et al., 2019) (Ijaola et al., 2022)	High (50% - 90%) (Zhao et al., 2023)	High (Moreira et al., 2024)	High (Ijaola et al., 2022; Jayakumar et al., 2011)	High (Moreira et al., 2024)
Hyaluronic acid hydrogels	High (Graça et al., 2020; Moreira et al., 2024)	High (Moreira et al., 2024)	Low (Moreira et al., 2024)	High (Moreira et al., 2024)	Low (Ijaola et al., 2022; Moreira et al., 2024)	Low (Shah et al., 2019)	Moderate (Moreira et al., 2024)	High (Ijaola et al., 2022)	Very High (Hargis et al., 2024)	High (Nguyen et al., 2023)	Very High (Moreira et al., 2024)
Collagen hydrogels	Very High (Ijaola et al., 2022; Y. Zhang et al., 2023)	Very High (Ijaola et al., 2022)	Low (Agarwal et al., 2020; Oliveira et al., 2023)	High (Agarwal et al., 2020; Oliveira et al., 2023)	0 % (Ijaola et al., 2022; Moreira et al., 2024; Y. Zhang et al., 2023)	Low (Ijaola et al., 2022)	Moderate (Ijaola et al., 2022; Moreira et al., 2024)	Very High (Ijaola et al., 2022)	High (Hargis et al., 2024)	High (Nguyen et al., 2023)	High (Moreira et al., 2024)
Polyethylene glycol hydrogels	Very High (Ansari & Darvishi, 2024b; Ko & Liao, 2023)	High (Ansari & Darvishi, 2024)	Low (Ansari & Darvishi, 2024)	Very High (Ansari & Darvishi, 2024)	Low (Ansari & Darvishi, 2024)	Very low (Ansari & Darvishi, 2024)	Moderate (Ijaola et al., 2022)(Moreira et al., 2024)	High (Ijaola et al., 2022)	High (Hargis et al., 2024)	Moderate (Hargis et al., 2024)	Very High (Ansari & Darvishi, 2024b)
PVA/ Alginate hydrogel	High (Ijaola et al., 2022) (Negut et al., 2020)(Ren et al., 2022)	High (Negut et al., 2020) (Shah et al., 2019) (Ijaola et al., 2022)	Moderate (Ren et al., 2022)	High (Ren et al., 2022)	0% (Shah et al., 2019) (Ijaola et al., 2022) (Negut et al., 2020)	Moderate (Negut et al., 2020; Ren et al., 2022)	High (Ijaola et al., 2022; Negut et al., 2020; Shah et al., 2019)	High (Negut et al., 2020; Ren et al., 2022)	Very High (Ijaola et al., 2022; Shah et al., 2019)	Moderate (Ren et al., 2022)	High (Ijaola et al., 2022; Negut et al., 2020; Shah et al., 2019)

Table 10 (Continued)

Polyurethane Foams	Very High (Niculescu & Grumezescu, 2022)	High (Hargis et al., 2024)	Low (Niculescu & Grumezescu, 2022)	Very High (Hargis et al., 2024)	Low (Niculescu & Grumezescu, 2022)	High (Niculescu & Grumezescu, 2022)	High (Hargis et al., 2024)	High (Ijaola et al., 2022)	Very high (Miron et al., 2023; Niculescu & Grumezescu, 2022)	High (Niculescu & Grumezescu, 2022)	High (Hargis et al., 2024)
Polyurethane Films	High (Las Heras et al., 2020; Niculescu & Grumezescu, 2022)	High (Las Heras et al., 2020; Niculescu & Grumezescu, 2022)	Low (Las Heras et al., 2020)	High (Las Heras et al., 2020)	Low (Hodge et al., 2022; Las Heras et al., 2020; Niculescu & Grumezescu, 2022)	High (Prete et al., 2023)	High (Miron et al., 2023; Prete et al., 2023)	High (Las Heras et al., 2020; Liang et al., 2022)	High (Miron et al., 2023; Prete et al., 2023)	High (Nguyen et al., 2023)	High (Miron et al., 2023)
Collagen Sponges	High (Ijaola et al., 2022; Liang et al., 2022)	High (Ijaola et al., 2022)	Moderate (Ijaola et al., 2022; Liang et al., 2022)	High (Ijaola et al., 2022; Liang et al., 2022)	Low (Ijaola et al., 2022)	High (Ijaola et al., 2022; Liang et al., 2022; Prete et al., 2023)	High (Liang et al., 2022)	High (≥70%) (Ijaola et al., 2022; Liang et al., 2022)	High (Prete et al., 2023; Rezvani Ghomi et al., 2019)	High (Ijaola et al., 2022; Liang et al., 2022)	High (Ijaola et al., 2022; Liang et al., 2022)

Table 11.

The selected weights of criteria for biomaterials employed in chronic wound treatment.

	Biocompatibility	Biodegradability	Cost	Availability	cytotoxicity	Mechanical properties	Antimicrobial strength	Porosity	Exudate absorption	Gas/water permeability	Flexibility	Moisture management
Aim	Maximum	Maximum	Minimum	Maximum	Minimum	Maximum	Maximum	Minimum	Maximum	Maximum	Maximum	Maximum
Weight of importance	0.92	0.75	0.92	0.92	0.75	0.75	0.92	0,75	0.92	0.92	0.75	0.92

CHAPTER IV

Results

Table 12 illustrates the obtained ranking results for biomaterials employed in chronic wound healing using fuzzy PROMETHEE approach. Each alternative's strength is shown by the positive outranking flow while its weakness is shown by the negative outranking flow. The findings of the net flow indicate the net ranking, with the choice with the highest net flow being the most effective. Polyurethane Foams and Polyurethane Films outrank other biomaterials employed in chronic wound healing with a net flow of 0.00140 and 0.00090 respectively. The last option of biomaterial for enhancing chronic wound healing is Polyethylene glycol hydrogels as shown in Table 12.

These results were obtained from the fuzzy PROMETHEE technique using Gaussian preference function and could give the decision-makers facts about the effectiveness of biomaterials for enhancing chronic wound healing. Figure 30 shows the strengths and weaknesses of biomaterials employed in chronic wound healing. Based on their effect on alternatives, the biomaterials criteria are ranked above or below the zero-threshold level. The most extremely used and preferred biomaterials employed in chronic wound healing are Polyurethane (PU) foams with the majority of criteria above the threshold level. These results are essential to patients, doctors, the government, and hospitals during decision-making on biomaterials employed in chronic wound healing.

Table 12.

Complete Ranking of Biomaterials Employed in Chronic Wound Healing

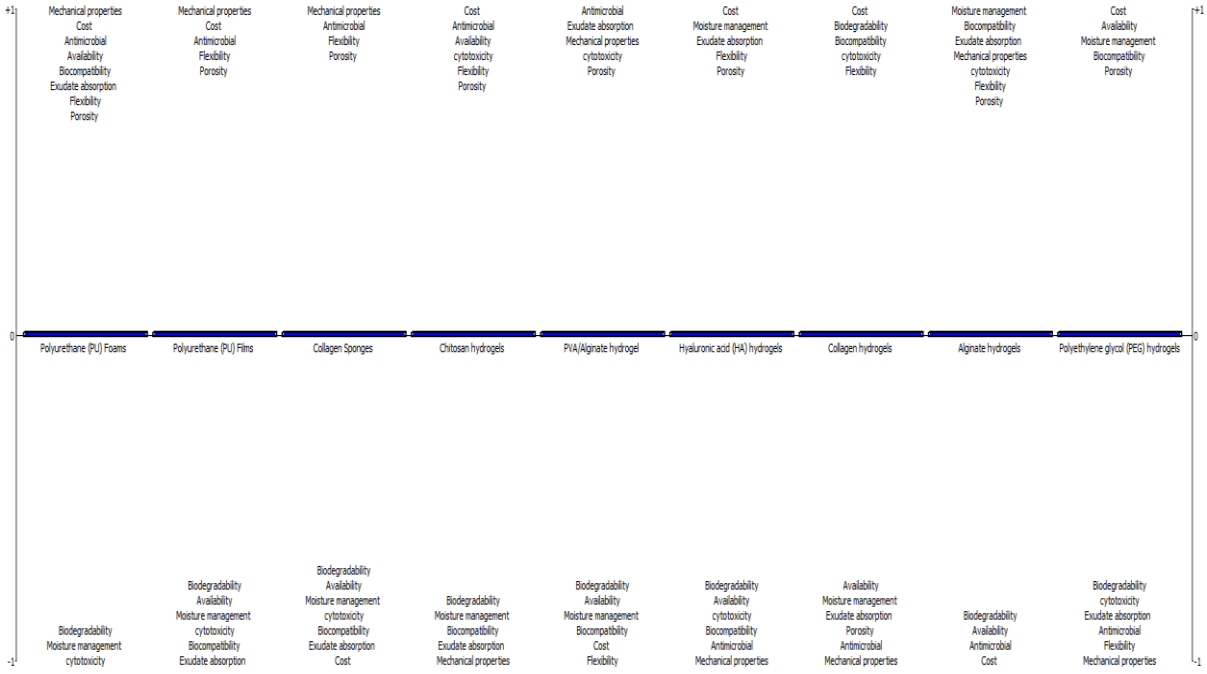
Rank	**Alternatives**	**Net flow (Φ)**	**Positive flow (Φ +)**	**Negative flow (Φ -)**
1	Polyurethane Foams	0.00140	0.00160	0.00010
2	Polyurethane Films	0.00090	0.00130	0.00040
3	Collagen Sponges	0.00040	0.00100	0.00060
4	Chitosan hydrogels	0.00000	0.00070	0.00070
5	PVA/Alginate hydrogel	-0.00020	0.00060	0.00080
6	Hyaluronic acid hydrogels	-0.00030	0.00060	0.00090
7	Collagen hydrogels	-0.00040	0.00070	0.00100
8	Alginate hydrogels	-0.00080	0.00070	0.00150

Table 12 (Continued)

9	Polyethylene glycol hydrogels	-0.00100	0.00060	0.00160

Figure 30.

Positive and Negative Aspects of Each Biomaterial Employed in Chronic Wound Healing



CHAPTER V

Discussion

In this study, we compared biomaterial employed in chronic wound healing between 2019 and May 2024 with MCDM methods. Various research and clinical studies, and trials for biomaterials employed in chronic wound healing are still ongoing. In our study, the most preferred biomaterials in chronic wound healing are obtained as PU foams based on selected parameters and the weights of the parameteres. PU forms are used as wound dressers to enhance the healing process of the chronic wound. They are effective in wound healing due to their hydrophilic and hydrophobic surfaces, biocompatibility, and non-toxic nature. Moreover, they are suitable for light to severe exudates, granulating or slough-covered wounds, donor sites, small burns, diabetic ulcers, and venous insufficiency ulcers. Their porous structures promote cell adhesion, which is beneficial for tissue regeneration during wound healing (Peng et al., 2022; Trucillo & Di Maio, 2021).

Following PU foams, PU films were found to be the second-best biomaterials for enhancing the healing process of chronic wounds. They are effective for managing chronic wounds due to their biocompatibility, breathability, moisture management, barrier protection against viruses and bacteria, flexibility, and compatibility with various therapies. Their semi-permeable nature allows oxygen and water vapor to pass while inhibiting liquids and bacteria, promoting a moist wound environment for better healing and infection prevention. Their strong mechanical properties and durability ensure the dressing remains intact and functional for the necessary amount of time, making them an effective approach to chronic wound care (Abazari et al., 2021; Das & Baker, 2016; Kanikireddy et al., 2020; Peng et al., 2022)

In the third place was Collagen sponges. They are also popular treatments for chronic wound healing due to their unique properties, including mechanical strength, biocompatibility, low toxicity, biodegradability, high moisture retention, porous structure, reduced cost, etc. They support cell growth and are commonly used in wound dressings due to their high porosity and water adsorption. However, their fast degradation limits their in-vivo application. To optimize wound healing, the degradation rate of collagen sponges must be tailored to match the wound's healing requirements (Prete et al., 2023; Valenzuela-Rojo et al., 2020). The other biomaterials employed in chronic wound healing include Chitosan hydrogels, PVA/Alginate hydrogel, HA hydrogels, Collagen hydrogels, and Alginate hydrogels.

Skin chronic wounds are global problems in the healthcare sector due to their delayed healing process. They are known as silent killers. It is important to discover new treatments or technologies to manage and enhance their healing process. The evaluated other biomaterials employed in chronic wound healing using MCDM methods will be beneficial to healthcare professionals and patients when managing the healing process of chronic wounds. In this study, the average type of chronic wound was considered to show the effectiveness of the biomaterials using MCDM, so the gender or age of the patient was not included. Several factors can be included in the analysis since fuzzy PROMETHEE can handle a large number of inputs to extend the study.

The selection of biomaterials employed in chronic wound healing can be different for each type of chronic wound, the location of the wound, and the patient. When evaluating options for the selection problem with both quantitative and qualitative input, fuzzy PROMETHE works well. It enables decision-makers to identify the issue in the face of ambiguity. It does not, however, include a mechanism for weighing criteria, therefore expert judgment is necessary to ensure accurate findings in real-world applications.

CHAPTER VI

Conclusion and Recommendations

In this study, we analyzed different biomaterials employed in chronic wound healing using the fuzzy PROMETHE method. Overall, several wound dressings and treatments are available for chronic wound healing. Those include traditional wound dressings (for example, gauze, etc.) and hyperbaric oxygen therapy (HBOT), etc. All chronic wound treatments are different depending on their categories. The key factors to skin chronic wound treatment are to manage the infections, stages of wound healing, improve the patient's diet, etc. Biomaterials employed in chronic wound healing come in different platforms such as hydrogels, foams, etc., and different polymers are used to fabricate them.

The above biomaterials help to accelerate the skin's healing process for chronic wounds; however, their efficacy and effectiveness need further confirmation. In the future, new alternatives and criteria could be considered once available and their weights could be assigned based on the decision-makers' opinions. We showed the application of the fuzzy PROMETHEE method, the MCDM technique, informing the decision-makers in terms of selecting the best biomaterials for enhancing the healing process of skin chronic wounds.

Recommendations for further research include the following:

- To analyze new alternatives and criteria for biomaterials employed in chronic wound healing.
- To apply other MCDM techniques in the selection of the right biomaterials used in chronic wound healing.
- To study and evaluate biomaterials using MCDM techniques considering patients conditions.

REFERENCES

Abazari, M. F., Gholizadeh, S., Karizi, S. Z., Birgani, N. H., Abazari, D., Paknia, S., Derakhshankhah, H., Allahyari, Z., Amini, S. M., Hamidi, M., & Delattre, C. (2021). Recent advances in cellulose-based structures as the wound-healing biomaterials: A clinically oriented review. *Applied Sciences (Switzerland)*, *11*(17). https://doi.org/10.3390/app11177769

Abdelli, A., Mokdad, L., & Hammal, Y. (2020). Dealing with value constraints in decision making using MCDM methods. *Journal of Computational Science*, *44*, 101154. https://doi.org/10.1016/j.jocs.2020.101154

Agarwal, K. M., Singh, P., Mohan, U., Mandal, S., & Bhatia, D. (2020). Comprehensive study related to advancement in biomaterials for medical applications. *Sensors International*, *1*(September), 1–11. https://doi.org/10.1016/j.sintl.2020.100055

Alven, S., & Aderibigbe, B. A. (2020). Chitosan and cellulose-based hydrogels for wound management. *International Journal of Molecular Sciences*, *21*(24), 1–30. https://doi.org/10.3390/ijms21249656

Ansari, M., & Darvishi, A. (2024). A review of the current state of natural biomaterials in wound healing applications. *Frontiers in Bioengineering and Biotechnology*, *12*(March), 1–26. https://doi.org/10.3389/fbioe.2024.1309541

Balcioglu, O., Usanase, N., Uzun, B., & Ozsahin, I. (2023). *A comparative analysis of DOACs vs warfarin for venous thromboembolism treatment in renal insufficiency*. *32*(1), 42–50. https://doi.org/10.9739/tjvs.2022.09.018

Barbu, A., Neamtu, B., Zăhan, M., Iancu, G. M., Bacila, C., & Mireșan, V. (2021). Current trends in advanced alginate-based wound dressings for chronic wounds. *Journal of Personalized Medicine*, *11*(9). https://doi.org/10.3390/jpm11090890

Chandika, P., Ko, S. C., & Jung, W. K. (2015). Marine-derived biological macromolecule-based biomaterials for wound healing and skin tissue regeneration. *International Journal of Biological Macromolecules*, *77*, 24–35. https://doi.org/10.1016/j.ijbiomac.2015.02.050

Chattopadhyay, S., & Raines, R. T. (2014). Review collagen-based biomaterials for wound healing. *Biopolymers*, *101*(8), 821–833. https://doi.org/10.1002/bip.22486

Chelu, M., & Musuc, A. M. (2023). Advanced Biomedical Applications of Multifunctional Natural and Synthetic Biomaterials. *Processes*, *11*(9). https://doi.org/10.3390/pr11092696

Da Silva, J., Leal, E. C., Carvalho, E., & Silva, E. A. (2023). Innovative Functional Biomaterials as Therapeutic Wound Dressings for Chronic Diabetic Foot Ulcers. *International Journal of Molecular Sciences*, *24*(12). https://doi.org/10.3390/ijms24129900

Das, S., & Baker, A. B. (2016). Biomaterials and nanotherapeutics for enhancing skin wound healing. *Frontiers in Bioengineering and Biotechnology*, *4*(OCT), 1–20. https://doi.org/10.3389/fbioe.2016.00082

Davison-Kotler, E., Marshall, W. S., & García-Gareta, E. (2019). Sources of collagen for biomaterials in skin wound healing. *Bioengineering*, *6*(3), 1–15. https://doi.org/10.3390/bioengineering6030056

Downer, M., Berry, C. E., Parker, J. B., Kameni, L., & Griffin, M. (2023). Current Biomaterials for Wound Healing. *Bioengineering*, *10*(12). https://doi.org/10.3390/bioengineering10121378

Eltarabishi, F., Omar, O. H., Alsyouf, I., & Bettayeb, M. (2020). Multi-criteria decision making methods and their applications-A literature review. *Proceedings of the International Conference on Industrial Engineering and Operations Management*, *0*(March), 2654–2663.

Emovon, I., & Oghenenyerovwho, O. S. (2020). Application of MCDM method in material selection for optimal design: A review. *Results in Materials*, *7*(June), 100115. https://doi.org/10.1016/j.rinma.2020.100115

Eriksson, E., Liu, P. Y., Schultz, G. S., Martins-Green, M. M., Tanaka, R., Weir, D., Gould, L. J., Armstrong, D. G., Gibbons, G. W., Wolcott, R., Olutoye, O. O., Kirsner, R. S., & Gurtner, G. C. (2022). Chronic wounds: Treatment consensus. *Wound Repair and Regeneration*, *30*(2), 156–171. https://doi.org/10.1111/wrr.12994

Fadilah, N. I. M., Maarof, M., Motta, A., Tabata, Y., & Fauzi, M. B. (2022). The Discovery and Development of Natural-Based Biomaterials with Demonstrated Wound Healing Properties: A Reliable Approach in Clinical Trials. *Biomedicines*, *10*(9).

https://doi.org/10.3390/biomedicines10092226

Fadilah, N. I. M., Phang, S. J., Kamaruzaman, N., Salleh, A., Zawani, M., Sanyal, A., Maarof, M., & Fauzi, M. B. (2023). Antioxidant Biomaterials in Cutaneous Wound Healing and Tissue Regeneration: A Critical Review. *Antioxidants*, *12*(4). https://doi.org/10.3390/antiox12040787

Falanga, V., Isseroff, R. R., Soulika, A. M., Romanelli, M., Margolis, D., Kapp, S., Granick, M., & Harding, K. (2022). Chronic wounds. *Nature Reviews Disease Primers*, *8*(1), 1–21. https://doi.org/10.1038/s41572-022-00377-3

Feng, F., Xu, Z., Fujita, H., & Liang, M. (2020). Enhancing PROMETHEE method with intuitionistic fuzzy soft sets. *International Journal of Intelligent Systems*, *35*(7), 1071–1104. https://doi.org/10.1002/int.22235

Firlar, I., Altunbek, M., McCarthy, C., Ramalingam, M., & Camci-Unal, G. (2022). Functional Hydrogels for Treatment of Chronic Wounds. *Gels*, *8*(2), 1–23. https://doi.org/10.3390/gels8020127

Gajbhiye, S., & Wairkar, S. (2022). Collagen fabricated delivery systems for wound healing: A new roadmap. *Biomaterials Advances*, *142*(October), 213152. https://doi.org/10.1016/j.bioadv.2022.213152

Gounden, V., & Singh, M. (2024). Hydrogels and Wound Healing: Current and Future Prospects. *Gels*, *10*(1). https://doi.org/10.3390/gels10010043

Graça, M. F. P., Miguel, S. P., Cabral, C. S. D., & Correia, I. J. (2020). Hyaluronic acid—Based wound dressings: A review. *Carbohydrate Polymers*, *241*(February), 116364. https://doi.org/10.1016/j.carbpol.2020.116364

Gruppuso, M., Turco, G., Marsich, E., & Porrelli, D. (2021). Polymeric wound dressings, an insight into polysaccharide-based electrospun membranes. *Applied Materials Today*, *24*. https://doi.org/10.1016/j.apmt.2021.101148

Gul, M., Celik, E., Gumus, A. T., & Guneri, A. F. (2018). A fuzzy logic based PROMETHEE method for material selection problems. *Beni-Suef University Journal of Basic and Applied Sciences*, *7*(1), 68–79. https://doi.org/10.1016/j.bjbas.2017.07.002

Gupta, A., Kowalczuk, M., Heaselgrave, W., Britland, S. T., Martin, C., & Radecka, I. (2019). The production and application of hydrogels for wound management: A review.

European Polymer Journal, *111*(November 2018), 134–151. https://doi.org/10.1016/j.eurpolymj.2018.12.019

Hansen, P., & Devlin, N. (2023). *Multi-Criteria Decision Analysis (MCDA) in Healthcare Decision- Healthcare Decision-Making and Multi-Criteria Decision Analysis*. *March*, 1–26.

Hargis, A., Yaghi, M., Bermudez, N. M., & Gefen, A. (2024). Foam Dressings for Wound Healing. *Current Dermatology Reports*, *13*(1), 28–35. https://doi.org/10.1007/s13671-024-00422-2

Hodge, J. G., Zamierowski, D. S., Robinson, J. L., & Mellott, A. J. (2022). Evaluating polymeric biomaterials to improve next generation wound dressing design. In *Biomaterials Research* (Vol. 26, Issue 1). BioMed Central. https://doi.org/10.1186/s40824-022-00291-5

Ijaola, A. O., Akamo, D. O., Damiri, F., Akisin, C. J., Bamidele, E. A., Ajiboye, E. G., Berrada, M., Onyenokwe, V. O., Yang, S. Y., & Asmatulu, E. (2022). Polymeric biomaterials for wound healing applications: a comprehensive review. *Journal of Biomaterials Science, Polymer Edition*, *33*(15), 1998–2050. https://doi.org/10.1080/09205063.2022.2088528

Jayakumar, R., Prabaharan, M., Sudheesh Kumar, P. T., Nair, S. V., & Tamura, H. (2011). Biomaterials based on chitin and chitosan in wound dressing applications. *Biotechnology Advances*, *29*(3), 322–337. https://doi.org/10.1016/j.biotechadv.2011.01.005

Jones, V., Grey, J. E., & Harding, K. G. (2006). Wound dressings. *BMJ (Clinical Research Ed.)*, *332*(7544), 777–780. https://doi.org/10.1136/bmj.332.7544.777

Kanikireddy, V., Varaprasad, K., Jayaramudu, T., Karthikeyan, C., & Sadiku, R. (2020). Carboxymethyl cellulose-based materials for infection control and wound healing: A review. *International Journal of Biological Macromolecules*, *164*, 963–975. https://doi.org/10.1016/j.ijbiomac.2020.07.160

Ko, A., & Liao, C. (2023). Hydrogel wound dressings for diabetic foot ulcer treatment: Status-quo, challenges, and future perspectives. *BMEMat*, *1*(3). https://doi.org/10.1002/bmm2.12037

Kodous, A. S., Abdel-Maksoud, M. A., El-Tayeb, M. A., Al-Sherif, D. A., Mohamed, S. S. A., Ghobashy, M. M., Emad, A. M., Abd El-Halim, S. M., Hagras, S. A. A., Mani, S., Rao, A. K. D. M., Hussein, A. M., & Saada, H. N. (2024). Hesperidin - loaded PVA/alginate hydrogel: targeting NFκB/iNOS/COX-2/TNF-α inflammatory signaling pathway. *Frontiers in Immunology*, *15*(April), 1–16. https://doi.org/10.3389/fimmu.2024.1347420

Las Heras, K., Igartua, M., Santos-Vizcaino, E., & Hernandez, R. M. (2020). Chronic wounds: Current status, available strategies and emerging therapeutic solutions. *Journal of Controlled Release*, *328*(September), 532–550. https://doi.org/10.1016/j.jconrel.2020.09.039

Lee, J., Song, B., Subbiah, R., Chung, J. J., Choi, U. H., Park, K., Kim, S. H., & Oh, S. J. (2019). Effect of chain flexibility on cell adhesion: Semi-flexible model-based analysis of cell adhesion to hydrogels. *Scientific Reports*, *9*(1), 1–9. https://doi.org/10.1038/s41598-019-38951-7

Liang, Y., Liang, Y., Zhang, H., & Guo, B. (2022). Antibacterial biomaterials for skin wound dressing. *Asian Journal of Pharmaceutical Sciences*, *17*(3), 353–384. https://doi.org/10.1016/j.ajps.2022.01.001

Maaz Arif, M., Khan, S. M., Gull, N., Tabish, T. A., Zia, S., Ullah Khan, R., Awais, S. M., & Arif Butt, M. (2021). Polymer-based biomaterials for chronic wound management: Promises and challenges. *International Journal of Pharmaceutics*, *598*(August 2020), 120270. https://doi.org/10.1016/j.ijpharm.2021.120270

Mathew-steiner, S. S., Roy, S., & Sen, C. K. (1969). Collagen in wound healing. *Injury*, *1*(1), 76. https://doi.org/10.1016/s0020-1383(69)80037-9

Miron, A., Giurcaneanu, C., Mihai, M. M., Beiu, C., Voiculescu, V. M., Popescu, M. N., Soare, E., & Popa, L. G. (2023). Antimicrobial Biomaterials for Chronic Wound Care. *Pharmaceutics*, *15*(6), 1–19. https://doi.org/10.3390/pharmaceutics15061606

Molla, M. U., Giri, B. C., & Biswas, P. (2021). Extended PROMETHEE method with Pythagorean fuzzy sets for medical diagnosis problems. *Soft Computing*, *25*(6), 4503–4512. https://doi.org/10.1007/s00500-020-05458-7

Moreira, T. D., Martins, V. B., da Silva Júnior, A. H., Sayer, C., de Araújo, P. H. H., &

Immich, A. P. S. (2024). New insights into biomaterials for wound dressings and care: Challenges and trends. *Progress in Organic Coatings*, *187*(October 2023). https://doi.org/10.1016/j.porgcoat.2023.108118

Murray, R. Z., West, Z. E., Cowin, A. J., & Farrugia, B. L. (2019). Development and use of biomaterials as wound healing therapies. *Burns & Trauma*, *7*, 1–9. https://doi.org/10.1186/s41038-018-0139-7

Naseri, E., & Ahmadi, A. (2022). A review on wound dressings: Antimicrobial agents, biomaterials, fabrication techniques, and stimuli-responsive drug release. *European Polymer Journal*, *173*(January). https://doi.org/10.1016/j.eurpolymj.2022.111293

Negut, I., Dorcioman, G., & Grumezescu, V. (2020). *Sca ff olds for Wound Healing Applications*.

Nguyen, H. M., Ngoc Le, T. T., Nguyen, A. T., Thien Le, H. N., & Pham, T. T. (2023). Biomedical materials for wound dressing: recent advances and applications. *RSC Advances*, *13*(8), 5509–5528. https://doi.org/10.1039/d2ra07673j

Niculescu, A. G., & Grumezescu, A. M. (2022). An Up-to-Date Review of Biomaterials Application in Wound Management. *Polymers*, *14*(3), 1–24. https://doi.org/10.3390/polym14030421

Oliveira, C., Sousa, D., Teixeira, J. A., Ferreira-Santos, P., & Botelho, C. M. (2023). Polymeric biomaterials for wound healing. *Frontiers in Bioengineering and Biotechnology*, *11*(July), 1–19. https://doi.org/10.3389/fbioe.2023.1136077

Olsson, M., Järbrink, K., Divakar, U., Bajpai, R., Upton, Z., Schmidtchen, A., & Car, J. (2019). The humanistic and economic burden of chronic wounds: A systematic review. *Wound Repair and Regeneration*, *27*(1), 114–125. https://doi.org/10.1111/wrr.12683

Ozsahin, D. U., Usanase, N., Uzun, B., Ozsahin, I., & Balcioglu, O. (2023). The Efficacy and Safety of Direct Oral Anticoagulants for The Treatment of Venous Thrombosis in Cancer Using Fuzzy PROMETHEE. *2023 Advances in Science and Engineering Technology International Conferences, ASET 2023*, 1–5. https://doi.org/10.1109/ASET56582.2023.10180505

Ozsahin, D. U., Uzun, B., Ozsahin, I., & Mustapha, M. T. (2020). *Fuzzy logic in medicine* (Issue January). https://doi.org/10.1016/B978-0-12-818946-7.00006-8

Peers, S., Montembault, A., & Ladavière, C. (2020). Chitosan hydrogels for sustained drug delivery. *Journal of Controlled Release*, *326*(June), 150–163. https://doi.org/10.1016/j.jconrel.2020.06.012

Peng, W., Li, D., Dai, K., Wang, Y., Song, P., Li, H., Tang, P., Zhang, Z., Li, Z., Zhou, Y., & Zhou, C. (2022). Recent progress of collagen, chitosan, alginate and other hydrogels in skin repair and wound dressing applications. *International Journal of Biological Macromolecules*, *208*(December 2021), 400–408. https://doi.org/10.1016/j.ijbiomac.2022.03.002

Prete, S., Dattilo, M., Patitucci, F., Pezzi, G., Parisi, O. I., & Puoci, F. (2023). Natural and Synthetic Polymeric Biomaterials for Application in Wound Management. *Journal of Functional Biomaterials*, *14*(9). https://doi.org/10.3390/jfb14090455

Rani Raju, N., Silina, E., Stupin, V., Manturova, N., Chidambaram, S. B., & Achar, R. R. (2022). Multifunctional and Smart Wound Dressings—A Review on Recent Research Advancements in Skin Regenerative Medicine. *Pharmaceutics*, *14*(8), 1–22. https://doi.org/10.3390/pharmaceutics14081574

Ren, S., Guo, S., Yang, L., & Wang, C. (2022). Effect of composite biodegradable biomaterials on wound healing in diabetes. *Frontiers in Bioengineering and Biotechnology*, *10*(November), 1–28. https://doi.org/10.3389/fbioe.2022.1060026

Rezvani Ghomi, E., Khalili, S., Nouri Khorasani, S., Esmaeely Neisiany, R., & Ramakrishna, S. (2019). Wound dressings: Current advances and future directions. *Journal of Applied Polymer Science*, *136*(27), 1–12. https://doi.org/10.1002/app.47738

Ribeiro, M., Simões, M., Vitorino, C., & Mascarenhas-Melo, F. (2024). Hydrogels in Cutaneous Wound Healing: Insights into Characterization, Properties, Formulation and Therapeutic Potential. In *Gels* (Vol. 10, Issue 3). https://doi.org/10.3390/gels10030188

Riha, S. M., Maarof, M., & Fauzi, M. B. (2021). Synergistic effect of biomaterial and stem cell for skin tissue engineering in cutaneous wound healing: A concise review. *Polymers*, *13*(10). https://doi.org/10.3390/polym13101546

Samadian, H., Maleki, H., Allahyari, Z., & Jaymand, M. (2020). Natural polymers-based light-induced hydrogels: Promising biomaterials for biomedical applications. *Coordination Chemistry Reviews*, *420*. https://doi.org/10.1016/j.ccr.2020.213432

Shah, S. A., Sohail, M., Khan, S., Minhas, M. U., de Matas, M., Sikstone, V., Hussain, Z., Abbasi, M., & Kousar, M. (2019). Biopolymer-based biomaterials for accelerated diabetic wound healing: A critical review. *International Journal of Biological Macromolecules*, *139*, 975–993. https://doi.org/10.1016/j.ijbiomac.2019.08.007

Sharma, S., Rai, V. K., Narang, R. K., & Markandeywar, T. S. (2022). Collagen-based formulations for wound healing: A literature review. *Life Sciences*, *290*(October 2021), 120096. https://doi.org/10.1016/j.lfs.2021.120096

Shi, C., Wang, C., Liu, H., Li, Q., Li, R., Zhang, Y., Liu, Y., Shao, Y., & Wang, J. (2020). Selection of Appropriate Wound Dressing for Various Wounds. *Frontiers in Bioengineering and Biotechnology*, *8*(March), 1–17. https://doi.org/10.3389/fbioe.2020.00182

Sklenářová, R., Akla, N., Latorre, M. J., Ulrichová, J., & Franková, J. (2022). Collagen as a Biomaterial for Skin and Corneal Wound Healing. *Journal of Functional Biomaterials*, *13*(4). https://doi.org/10.3390/jfb13040249

Taherdoost, H., & Madanchian, M. (2023). Multi-Criteria Decision Making (MCDM) Methods and Concepts. *Encyclopedia*, *3*(1), 77–87. https://doi.org/10.3390/encyclopedia3010006

Trucillo, P., & Di Maio, E. (2021). Classification and production of polymeric foams among the systems for wound treatment. *Polymers*, *13*(10). https://doi.org/10.3390/polym13101608

Valenzuela-Rojo, R. D., López-Cervantes, J., Sánchez-Machado, D. I., Escárcega-Galaz, A. A., & Martínez-Macias, M. del R. (2020). Antibacterial, mechanical and physical properties of collagen - chitosan sponges from aquatic source. *Sustainable Chemistry and Pharmacy*, *15*(November 2019). https://doi.org/10.1016/j.scp.2020.100218

Xiao Liu, M., & Jia, G. (2018). Modern Wound Dressing Using Polymers/Biopolymers. *Journal of Material Science & Engineering*, *07*(03), 7–10. https://doi.org/10.4172/2169-0022.1000454

Xu, Q., Torres, J. E., Hakim, M., Babiak, P. M., Pal, P., Battistoni, C. M., Nguyen, M., Panitch, A., Solorio, L., & Liu, J. C. (2021). Collagen- and hyaluronic acid-based hydrogels and their biomedical applications. *Materials Science and Engineering R:*

Reports, *146*(April), 100641. https://doi.org/10.1016/j.mser.2021.100641

Yildirim, F. S., Sayan, M., Sanlidag, T., Uzun, B., Ozsahin, D. U., & Ozsahin, I. (2021). Comparative Evaluation of the Treatment of COVID-19 with Multicriteria Decision-Making Techniques. *Journal of Healthcare Engineering*, *2021*. https://doi.org/10.1155/2021/8864522

Zhang, M., & Zhao, X. (2020). Alginate hydrogel dressings for advanced wound management. *International Journal of Biological Macromolecules*, *162*, 1414–1428. https://doi.org/10.1016/j.ijbiomac.2020.07.311

Zhang, X., Shu, W., Yu, Q., Qu, W., Wang, Y., & Li, R. (2020). Functional Biomaterials for Treatment of Chronic Wound. *Frontiers in Bioengineering and Biotechnology*, *8*(June), 1–15. https://doi.org/10.3389/fbioe.2020.00516

Zhang, Y., Wang, Y., Li, Y., Yang, Y., Jin, M., Lin, X., Zhuang, Z., Guo, K., Zhang, T., & Tan, W. (2023). Application of Collagen-Based Hydrogel in Skin Wound Healing. *Gels*, *9*(3). https://doi.org/10.3390/gels9030185

Zhao, J., Qiu, P., Wang, Y., Wang, Y., Zhou, J., Zhang, B., Zhang, L., & Gou, D. (2023). Chitosan-based hydrogel wound dressing: From mechanism to applications, a review. *International Journal of Biological Macromolecules*, *244*(May). https://doi.org/10.1016/j.ijbiomac.2023.125250

APPENDICES

Appendix A

Turnitin Similarity Report