Review

Progress in Wound Healing Products based on Natural Compounds, Stem Cells and MicroRNA-based Biopolymers in the European, USA, and Asian Markets: Opportunities, Barriers, and Regulatory Issues

Girish Kumar Srivastava , Sofía Martínez Rodríguez , Nur Izzah Md Fadilah , Daniel Looi Qi Hao , Gavin Markey , Priyank Shukla , Mh Busra Fauzi , Fivos Panetsos *

Posted Date: 22 November 2023

doi: 10.20944/preprints202307.2097.v2

Keywords: Skin injuries; Therapy; Caring; Natural Materials; Regulatory Issues; ISO

Review

Progress in Wound Healing Products based on Natural Compounds, Stem Cells and MicroRNA-based Biopolymers in the European, USA, and Asian Markets: Opportunities, Barriers, and Regulatory Issues

Girish K Srivastava [1,2], Sofia Martinez-Rodriguez [2], Nur Izzah Md Fadilah [3], Daniel Looi Qi Hao [3,4], Gavin Markey [5], Priyank Shukla [5], Mh Busra Fauzi [3] and Fivos Panetsos [6,7,8,9]

[1] Departamento de Cirugía, Oftalmología, Otorrinolaringología y Fisioterapia, Facultad de Medicina, Universidad de Universidad, Valladolid, Spain; girishkumar.srivastava@uva.es
[2] Instituto Universitario de Oftalmobiología Aplicada, Facultad de Medicina, Universidad de Valladolid, Valladolid, Spain; sofia.martinez.rodriguez22@estudiantes.uva.es
[3] Centre for Tissue Engineering and Regenerative Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, 56000 Kuala Lumpur, Malaysia; izzahfadilah@ukm.edu.my; dr.daniellooi@cytoholdings.com; fauzibusra@ukm.edu.my
[4] My Cytohealth Sdn. Bhd. 56000 Kuala Lumpur, Malaysia
[5] Personalised Medicine Centre, School of Medicine, Ulster University, C-TRIC Building, Altnagelvin Area Hospital, Glenshane Road, Londonderry, BT47 6SB, UK; markey-g2@ulster.ac.uk; p.shukla@ulster.ac.uk
[6] Neurocomputing and Neurorobotics Research Group, Faculty of Biology and Faculty of Optics, Universidad Complutense de Madrid, 28040 Madrid, Spain
[7] Institute for Health Research San Carlos Clinical Hospital (IdISSC), 28040 Madrid, Spain
[8] Silk Biomed SL, 28260 Madrid, Spain
[9] Bioactive Surfaces SL, 28260 Madrid, Spain
* Correspondence: fivos@ucm.es

Abstract: Wounds are breaks in the continuity of the skin and the underlying tissues, due to external causes, such as cuts, blows and impacts, or even, during surgical interventions. Millions of people suffer minor or serious injuries, sometimes ending in death. Today, there are many commercially available products that promote healing from wounds. The high demand from the healthcare industry has created a huge market that continues to grow, fueling research and development of new wound healing products. In the present article, we review recent advances in wound healing products based on natural biopolymers, stem cells, and microRNAs. We analyze the advances of both, the commercial products and the products that are still in research phase, and we also include an overview of the opportunities, barriers, and regulatory issues for the commercialization of these products in the European, American, and Asian markets.

Keywords: skin injuries; therapy; caring; natural materials; regulatory issues; ISO

1. Introduction

A wound is a break of the anatomical structure of the skin that can extend further to other tissues and structures such as subcutaneous tissue, muscles, tendons, nerves, vessels and even the bones. Skin, the largest organ by surface area in the human body, can be easily injured or burned in daily life. Cuts, scrapes, and scratches, all are examples of wounds that can occur anywhere on the body, and it is essential to provide adequate care to these wounds, to prevent infections and other complications, and to facilitate a prompt and successful recovery [1]. In this context, wound care is an essential part of the wound healing process. The wounded person must follow several steps of

 doi:10.20944/preprints202307.2097.v2

wound care for absolute recovery: (1) wash and sanitize the hands to prevent infection on the wound site, then (2) use clean clothes or bandages to stop the bleeding by applying the pressure at wound site, (3) clean the wound with soap or gauges dipped in saline solution, (4) apply antiseptic solution and wound healing ointment or products, and (5) protect the wound using sterile dressing or pad. Otherwise, a minor wound may ulcerate and create further complications and even pain, and it may require immediate consultation of a medical doctor.

The complete wound healing process is a tissue regeneration and growth progress at a wound spot, and it is carried out in four cascades of processes, called Phases: coagulation and hemostasis, inflammation, proliferation, and remodeling [2]. In the coagulation and hemostasis phase the platelets get activated to form a fibrin clot immediately after the injury. The inflammation stage starts shortly after injury, it is mediated by macrophages and neutrophils to block bacterial invasion, and it is characterized by swelling at the wound site. During the proliferative phase, the wound bed is filled with growing cells; growth factors and cytokines' release support the formation of new tissues and blood vessels at wound site. Finally, remodeling is achieved by synthesizing the components of the extracellular matrix (ECM) and the subsequent transform of granular tissue to scar tissue. Thus, wound healing is the result of interactions among extracellular matrix molecules, mediators, fibroblasts and keratinocytes, infiltrating leukocyte subtypes, cytokines, growth factors and blood [2,3].

Depending on the duration of the healing, skin wounds can be classified into acute and chronic (as healing and non-healing, respectively). Acute wounds progress through the above-described phases, and they exhibit well-defined signs of recovery within four weeks; on the contrary, chronic wounds do not follow the normal healing process, and they don't show obvious recovery signs in the same time interval [1]. Chronic wounds seem to be detained in one or more phases of the wound healing process due to influence of already activated pathophysiological mechanisms, as for example the pathologic processes in the diabetic patients, which make wounds' recovery to need much more time. The antiseptic characteristics and wound healing promoters, with their action potentials, counteract these complications. They regulate hemostasis and inflammation at the wounded site, promote cell proliferation, and facilitate tissue remodeling, ultimately leading to wound healing and recovery.

2. Increased Complexities of Wound Healing and the Burden of Medical Care

A wound is more than a simple tissue injury, and its healing process can be complicated by several factors, including age, health conditions, chronic conditions, and genetic heritage, which can hinder the healing process, and impede overall recovery. Similarly, sick persons will take longer to heal and recover than healthy ones. On the other side, chronic wounds are more difficult to treat and place a significant and often underestimated burden on the individual, on the healthcare systems and on the society as a whole, since individuals with chronic wounds face more challenges than those with acute ones [4,5]. Furthermore, there are wounds that do not heal properly, e.g., those due to accidents or exposure to chemicals. This picture is likely to be made worse by lifestyle, which silently causes diabetic wounds, pressure sores (bedsores), leg and foot ulcers, and ulcers related to venous or arterial disease.

In addition to the above considerations, an especially critical point is that that wound healing is negatively associated with age [4,5], and the age of the world's population is not only high, but it is increasing dramatically every day.

According to the United Nations (UN), in 2019, in the world, there were 703 million people aged ≥65 [6] and this number is projected to double to 1.5 billion by 2050 [6]. In early 2018 there were 101.1 million older people aged ≥65 living in the EU countries, which is almost one fifth (19.7%) of the total population. During the next three decades, this figure is projected to rise up to 149.2 million inhabitants in 2050 (28.5% of the total population [7]. In countries like UK, according to the Office of National Statistics (ONS), in 2018, there were nearly 12 million people aged ≥65, expected to be over 20.6 million in 2048 [8]. In Spain, according to the Spanish National Statistics Office (INE) and the UN, in 2019, there were 9 million people aged ≥65, and their projections suggest that, by 2050, more

 doi:10.20944/preprints202307.2097.v2

than 30% of the Spanish population (almost 13 million people) will be ≥65 years old, making Spain to one of the top 10 world´s oldest country [6]. According to the U.S. Census Bureau, the number of Americans ages ≥65 is projected to nearly double from 52 million in 2018 to 95 million by 2060, and the ≥65 age group's share of the total population will rise from 16.0% to 23.0% [9]. According to the U.S. Census Bureau, in Asia, the number of older people is expected to nearly triple over the next four decades. There were an estimated 414 million Asians aged ≥65 in 2020, projected to grow to more than 1.2 billion in 2060, which implies that one out of every 10 people in the world will be an Asian [10]. Most of the older population in Asia will be residing in the Eastern subregion (491 million) and the Southern subregion (464 million), where China and India are located respectively. Among Asian subregions, 33.7% of Eastern Asia's population is projected to be age ≥65 by 2060. In contrast, Southern Asia (18.6%) and Western Asia (17.9%) are expected to have the lowest proportions of older people of their regional total populations [10]. In Asian countries, Malaysia's ageing population is growing at a faster-than-expected rate where, according to the Department of Statistics of Malaysia, more than 15% of its population will be ≥65 by 2050 [11].

The dramatic increase in the elderly population will pose a major challenge to the healthcare systems due to the expensive nature of wound management. The rising number of surgical cases and the increasing prevalence of chronic diseases worldwide have generated a significant global demand for wound healing products. This demand is further amplified by the ongoing demographic shift towards an ageing population, resulting in a steady increase of the demand for such products, thereby, presenting a challenge for health care systems worldwide.

In Europe and the USA, the healthcare sector already has a significant demand of wound healing products, thus playing a key role in the healthcare market, making them the largest wound healing product markets worldwide. The prevalence and economic burden of wounds are not insignificant, US alone spending over $25 billion annually, to treat chronic wounds in over 6 million patients [12]. In the UK, the annual NHS cost of wound management is £8.3 billion, of which £2.7 billion and £5.6 billion are associated with managing healed and unhealed wounds, respectively [13]. In Europe, 2-4% of the total health annual expenditure is used for wound management [14]. In developing countries like India, approximately 3-4% of all diabetic population have a foot problem and consume 12-15% of the healthcare resources [15], while the Malaysian Ministry of Health's budget for wound care reaches $5 million per year [16] and the other South East Asian countries are in a similar situation.

The global wound care market size was valued at $17.49 billion in 2021 and is projected to grow to $28.23 billion by 2029, and had exhibited a slower growth of 3.1% in 2020 as compared to 2019 due to unprecedented Covid-19 pandemic [17]. The global advanced wound care market targeting surgical wounds and chronic ulcers was valued at $11.38 billion in 2022 and is expected to grow from $11.97 billion in 2023 to $17.48 billion by 2030 [18]. Thus, it is estimated a growth of $11 billion in a period of 2021-2029 in global wound care market and $6 billion in a period of 2022-2030 in global advanced wound care market which is a huge amount for health sector. Thus, the complexities of wound healing are increasingly burdening healthcare systems. The growing demand from the health sector and its vast market are driving research and development efforts to create new wound healing products.

Below we examine recent advances in natural biopolymers-, stem cells- and microRNA-based wound healing products in both the research and the commercial sector, and we provide an overview of the regulatory aspects in the European, American, and Southeast Asian markets, crucial for the commercialization of these products.

3. Wound Healing Biopolymers, based on Natural Compounds

3.1. Wound Healing Biopolymers, based on Natural Compounds in Research

Since the process of wound healing is dynamic and highly complex, effective management of wounds at the initial stages is the best possible prevention strategy. Therefore, the development of therapeutics by using bioactive materials has attracted the interest of both, the scientific wound community, because of the possibilities they offer to interact and modulate the healing biomolecular

 doi:10.20944/preprints202307.2097.v2

processes, and the industry, because of the promising outcomes for fabricating smart wound care dressings. Thanks to the technological advances in bioengineering, nanotechnology, materials sciences, and regenerative medicine, we can create functional biomaterials with improved physical-chemical, and structural characteristics, to meet the highest requirements and quality standards of current wound care, as, for example, to achieve restoration of lost tissue integrity and scarless healing [19].

The incorporation to biopolymers of recent advances in the medical, pharmaceutical, and bioengineering fields helps to develop new strategies for the treatment of wounds, and, in particular, for chronic non-healing ones. Indeed, wound healing products are being fabricated from different polymer biomaterials and incorporating various bioengineering techniques, for example, films, hydrogels, foams, and sponges, some of them incorporating bioactive agents to enhance their healing properties.

Many of todays biopolymers could enhance performance in wound healing and mimicking ECM [20]. They are mainly extracted from their natural origin, including animals (chitosan, collagen, hyaluronic acid), plants (cellulose, starch, rubber), bacteria (exopolysaccharides, bacterial cellulose), fungi (chitin) and algae (alginate). These biopolymers are safe to be used for skin regeneration because of their excellent properties, such as biodegradability, biocompatibility, lower antigenicity, and similarity to macromolecules recognized by the human body [21]. Prior to achieving a key role in the wound healing process, biopolymers offer multiple benefits with their properties including anti-inflammatory, antioxidants, antibacterial or other target actions to enhance the regeneration process (Table 1).

The review paper by Yang et al. covers polysaccharides as ideal materials for self-healing hydrogels [22]. The authors also discussed the derivatives of cellulose, alginate, hyaluronic acid, and chitosan together with their preparation methods. Following that, collagen is also one of the natural biopolymers commonly used as a biomaterial for tissue engineering applications. It is the human body's most abundant protein and can be easily manufactured in different forms [23]. Another article discussed the ability of collagen to be fabricated into three types of 3D scaffolds, in the form of hydrogel, sponge, and film by using collagen extracted from the ovine tendon. All the collagen scaffolds demonstrated significantly higher attachment and were biocompatible with the human dermal fibroblast cells [24]. In contrast to the other biopolymers mentioned above, silk fibroin has become remarkable as a natural biopolymer often used for biomedical applications, including wound healing [25]. In a research article published in 2021, Dong et al. observed that silk fibroin injectable hydrogel can enhance wound healing efficiency in burn wounds [26]. The authors incorporated ciprofloxacin into graphene oxide/silk fibroin injectable hydrogel as a multifunctional wound dressing to provide effective anti-bacterial, cell compatible, and in vivo wound closure actions. In addition, another notable biopolymer with therapeutics applications is carrageenan. It is extracted from several red seaweed species, mostly from members of the Rhodophyceae class, such as Chondrus crispus, Eucheuma cottonii, Eucheuma spinosum, and Gigartina stellate, having a hydrogalactose and galactose units linked by glycosidic bonds. Neamtu et al. [27] mentioned in their review paper that carrageenan has low cytotoxicity, antimicrobial and antioxidant qualities, thus it does not stick to the wound bed. This biopolymer's versatility in formulations and applications makes them a candidate for developing a novel wound healing product.

Table 1. Characteristics of selected biopolymers extensively used in wound management and their benefits in the healing process.

Biopolymer	Components	Sources	Benefits	Limitations	Study	Reference
Alginate	β-D-mannuronic acid and α-L-guluronic acid linked by α-1,4 glycosidic linkages	Brown algae	Promote wound healing by activating macrophages to produce cytokines. High absorbance	High viscosity, non-homogeneous, and non-transparent formulations	in vitro in vivo	[111]

 doi:10.20944/preprints202307.2097.v2

Carboxymethyl cellulose	β-D-Glucose linked by β-1,4-glycosidic linkage	Modified from wood and cotton	Exudate absorbing capacity Retain the moisture	Weak antibacterial and antimicrobial properties, low mechanical strength	in vitro in vivo	[112]
Chitosan	*N*-acetyl glucosamine linked by β-1,4 glycosidic linkages	Shrimp and crabs	Antimicrobial, antibacterial, analgesic, hemostatic. Promotes neovascularization and dermis regeneration	Limited ability to certain antibacterial	in vitro in vivo	[113]
Collagen	Amino acid linked by amide linkage	Goat and ovine (sheep)	Enrichment of new collagen deposition Hemostatic ability. Control of proteolytic activity	Collagen of porcine and bovine sources. Risk of transmitting diseases, e.g., bovine spongiform encephalopathy (BSE), caused by prions	in vitro in vivo	[114]
Hyaluronic acid	D-glucuronic acid and *N*-acetyl-D-glu-cosamine linked by β-1,4 and β-1,3 glycosidic linkages	Bovine vitreous humor	Exudate absorption capacity. Anti-inflammatory. Induce cell adhesion	Weak mechanical properties, poor adhesion, and rapid degradation	in vitro in vivo ex vivo	[115,116]

3.2. Wound Healing Biopolymers, based on Natural Compounds in Research

A vast number of wound healing products developed using biopolymers have been successfully launched in the market. A list of recently developed and commercially available products is detailed below (Table 2). Key information on each biopolymer including structural components, strengths, limitations, and commercial information is also included. Most of them have shown good market growth due to their beneficial characteristics to patients. Nevertheless, the limitations and deficiencies including the health problems from their use cannot be avoided. The Algisite M Calcium Alginate Dressing is based on Alginate Calcium which allows many benefits to patients for wound healing; however, on its use it is noted that Ca2+ divalent cations can be released and exchange with other monovalent cations in the surrounding media, resulting in the dissolving of the alginate gel [28]. The Collagen based Suprasorb C Collagen Wound Dressing has shown low mechanical strength and low antiseptic properties with several beneficial properties for patients [29]. Any health problem with the product Kito Activator Chitosan Wound Healing Hydrogel Barrier has not been identified till now, nevertheless it is a Chitosan Hydrogel [30]. The Medihoney Honeycolloid Leptospermum Hydrocolloid Dressings contain active leptospermum honey and hydrocolloidal gelling agent, but it may increase the level of exudate upon initial use. It is only suitable to treat the moderately exuding wounds [31]. The Hyperoil that contains Neem (Azadirachtin) and Hypericum (Hyperforin), and the combined overall effect is available in both; gel and oil formulation, however, it showed low antimicrobial properties for wound healing [32]. The Fibracol Plus Collagen Wound Dressing with Alginate is fabricated using 90% collagen and 10% calcium alginate but, in this case, the Ca2+ divalent cations can be released and exchange with other monovalent cations in the surrounding media, resulting in the dissolving of the alginate gel as has been seen in the case of the Algisite M Calcium Alginate Dressing [33]. All these deficiencies support the continuity of investigation for finding and developing better alternatives.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 22 November 2023 doi:10.20944/preprints202307.2097.v2

Table 2. Few commercialized biopolymers based wound healing products in the market.

Products	Components	Benefits	Limitations	Company	Reference
ACTICOAT	Dressings with nanocrystalline silver technology	Sustained silver release into the wound exudate to help promote and retain a moist environment, when used with an appropriate secondary dressing. Bactericide.	Antimicrobial properties but helps the healing/healing process. It only prevents infections.	Smith & Nephew	[117]
Actisorb™	Activated carbon bandage with silver.	Activated carbon traps odor in the dressing and traps bacteria and toxins that impair the healing process. Bactericide.	Limited regenerative effects.	3M	[118]
Algisite M Calcium Alginate Dressing	Alginate Calcium	Fast gelling, high mannuronic acid fibers. Low fiber shed construction; it conforms to wound contours. It moisturizes wound environment, highly absorbent, biodegradable.	Calcium divalent cations can be released and exchange with monovalent cations in the surrounding media and dissolve the alginate gel.	Smith & Nephew	[119]
AmnioExcel®	Human placental amniotic fluid membrane.	Wound protection provided extracellular matrix proteins, growth factors and cytokines, which provides structural tissue and an environment for soft tissue reconstruction and regeneration.	Compositional differences between batches from different donors. Moderate effects, especially in chronic wounds.	Derma Sciences, Inc	[120]
AQUACEL® /Hydrofiber®	Sodium carboxymethyl-cellulose and regenerated cellulose fiber.	Adaptable and highly absorbent. In contact with the exudate, it creates a soft gel, maintaining a moist environment that facilitates progress in the healing process and autolytic debridement. It can be inserted into cavities or place on superficial lesions.	Bacteriostatic only. Healing improvement. Limited to simple and small wounds.	ConvaTec Group Plc	[121]
BIATAIN	Foam dressing with delicate silicone adhesive	Exudate absorption, even under compression. The 3D foam structure absorbs exudate, maintaining a moist environment.	Moderate effects especially on chronic and complex wounds.	Coloplast A/S	[122]
CalciCare™	Alginate, Calcium and Guluronic Acid and Silver Bandage	Absorbent. Hemostatic properties may assist in supporting the control of minor bleeding in superficial wounds. It helps maintaining a moist environment. Aids autolytic debridement.	Moderate effects especially on chronic and complex wounds.	Hollister Incorporated	[123]
Cutimed® Epiona featuring 3D Matrix	Collagen and calcium alginate structure bandage	It can be easily molded to the surface of the wound. It does not contain chemical crosslinkers.	Recreates new extracellular matrix for regeneration: No regenerative cells or factors. Modest results.	Bsn Medical GmbH	[124]
FD3101 (Wound Dressing)	Polyurethane foam and silver	High absorbency. Protection against water and bacteria. Non-adherent to the wound, no pain while removing the dressing.	Bacteriostatic only. Is does not regenerate chronic skin wounds.	Triage Meditech Pvt	[125]
Fibracol Plus Collagen Wound	90% collagen. 10% calcium alginate	Can be cut to fit any size wound. Nonadherent and easily removable. Biodegradable. Low immunogenicity,	Ca2+ divalent cations can be released and exchange with other monovalent cations in	Johnson & Johnson	[126]

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 22 November 2023 doi:10.20944/preprints202307.2097.v2

Dressing with Alginate		noncarcinogenic, collagen synthesis and reepithelization, promotes cell proliferation, provides support for cell attachments. During granulation and at the beginning of the epithelization, it supports collagen fibrils and fibers' formation.	the surrounding media, resulting in the dissolving of the alginate gel		
Granulox®	Purified hemoglobin	Highly purified hemoglobin takes oxygen molecules from the environment. The hemoglobin is distributed by the exudate of the wound and helps its healing.	Indicated for diabetic leg ulcers and venous ulcers. Moderate results.	Mölnlycke Health Care AB	[127]
HyperOil	Neem (Azadirachtin). Hypericum (Hyper forin).	Infection prevention, re-epithelialization, fibrinolytic activity, cleansing activity. Skin regeneration and elasticity promoter. For all kind of wounds (acute, chronic, infected). Biodegradable, nontoxic, non-carcinogenic. Both, gel, and oil formulation	Low antimicrobial properties.	RI.MOS. srl	[128]
KALTOSTAT®	Calcium/sodium and alginate dressings	For ulcers and traumatic wounds. It improves healing. On contact with exudate, it forms a moist, firm, absorbent gel.	Moderate effects especially on deep and complex wounds	ConvaTec Group Plc	[129]
Kito Activator Chitosan Hydrogel Barrier	Chitosan Hydrogel	Synergy effect between kito activator and HR-chitosan depressing. Hemostatic, quick coagulation by strengthening ionic bonds with red blood cell and platelet. Antimicrobial, anti-inflammatory, deodorant. Non-preservative, non-binding, non-antibiotic. Biodegradable, nontoxic, non-carcinogenic.	Nothing found.	Endovision	[130]
Medihoney HoneyColloid Dressing	Active leptospermum honey. Hydrocolloidal gelling agent	Helps reduce overall wound pH. Natural and safe. Effective in all wound healing stages. High osmolarity helps cleansing-debriding. Moisturizing, biodegradable, nontoxic, non-carcinogenic.	May be increase level of exudate upon initial use. Only suitable for moderately exuding wounds.	Derma Sciences	[131]
Mepilex® Ag	Foam bandage containing silver	Antibacterial, antifungal. Improves healing time. Atraumatic during dressing changes. Rapid and sustained activity.	Moderate effects, limited to certain types of wounds (e.g., burns)	Mölnlycke Health Care AB	[132]
NeutroPhase	Hypochlorous acid	Cleaning and debridement, from wounds and neutralization of toxins.	Bacteriostatic only. Not substantial speed up of chronic wounds healing.	Novabay Pharmaceutical, Inc.	[133]
Omnigraft	Bilayer matrix enriched in C6S collagen and silicone	Reduces inflammation, maintains moisture, and promotes cell and vascular growth in the wound.	Limited repairing effects, especially in chronic and complex wounds.	Derma Sciences, Inc	[134]

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 22 November 2023 doi:10.20944/preprints202307.2097.v2

PriMatrix	Acellular dermal matrix enriched in type III collagen	Derived from fetal bovine dermis. It supports cell repopulation and revascularization critical in wound healing. Type III collagen helps tissue development and healing.	Limited repairing effects, especially in chronic and complex wounds.	Derma Sciences, Inc	[135]
Promogran Prisma™	Collagen, oxidized regenerated cellulose (ORC) and silver-ORC bandage	In presence of exudate, it transforms into a soft biodegradable gel. It promotes granulation. It starts wounds that have been stalled in the inflammatory stage. Antimicrobial.	Moderate restorative effects	3M	[136]
REGRANEX	Recombinant platelet-derived growth factor	The only FDA-approved PDGF for diabetic neuropathic ulcers treatment. It increases tissue growth, re-epithelialization and revascularization rate.	Moderate cure rates in diabetic neuropathic ulcers	Smith & Nephew	[137]
Restore™	Hydrocolloid dressing	Occlusive dressing, impermeable to microorganisms, urine, and feces. With a disposable wound measuring guide. Heat-activated, self-adhesive inner layer maintains moist while absorbing wound exudates.	Barrier for bacterial and viral infections. Limited healing effects. Moderate exudate prevention.	Hollister Incorporated	[138]
SILVERCEL ™	Alginate bandage, methylcellulose and silver	Antimicrobial barrier to reduce the risk of infection. Improves healing.	Limited effects on large and complex wounds.	Acelity L.P. Inc	[139]
Suprasorb C Collagen Wound Dressing	Collagen	Porous structure, absorbs fluids, debris and proinflammatory proteases and cytokines. It accelerates granulation tissue formation, induces fibroblasts migration and collagen synthesis. It supports proliferation and migration of epidermal cells. Biodegradable, nontoxic, non-carcinogenic.	Low machinal strength. Low antiseptic properties.	Lohmann & Rauscher	[140]
V.A.C.® Therapy	Programmable device	Negative compression therapy. Accelerates the healing process (reducing edema and promoting blood perfusion).	Very modest results; it prevents further worsening of wound. Very long-term treatments.	Acelity L.P. Inc	[141]
VTG2901	Programmable device for compression therapy (negative pressure).	Negative compression therapy. Accelerates the healing process (reducing edema and promoting blood perfusion). Removes excess fluid and reduces edema. Protects wound from microbes.	Very modest results, although it prevents further worsening of the wound. Very long-lasting treatment.	Triage Meditech Pvt	[142]

4. Stem Cells-Based Wound Healing Biopolymers

4.1. Stem Cells-Based Wound Healing Biopolymers in Research

Stem cells, particularly Mesenchymal stem cells (MSCs), hold enormous potential for accelerating tissue restoration and wound healing through their immune-modulating, regenerative, and paracrine properties. MSCs secrete bioactive molecules like cytokines, growth factors, and

 doi:10.20944/preprints202307.2097.v2

neurotrophic factors that promote tissue regeneration and exhibit anti-inflammatory, angiogenic, and immunomodulatory effects. They can be administered directly or through their secretome, which can be obtained and used as a safer alternative [34–38]. Induced Pluripotent Stem Cells (iPSCs) are the newest class of stem cells with the potential and limitations to achieve wound healing [39]. However, plant stem cells have distinct characteristics compared to human stem cells, but they can still benefit wound healing. Although the growth factors and proteins produced by plant stem cells do not have the same effects in humans as they do in plants, derivatives of plant stem cells can stimulate the production of human skin cells and collagen, while providing beneficial nutrients to the skin. Additionally, extracts from plant stem cells possess antioxidant, antibiotic, and anti-inflammatory properties that support and enhance the wound healing process. While plant stem cells cannot directly repair and regenerate human skin tissue as they would in plants, they offer valuable contributions to wound healing through their unique properties [40]. In the laboratory, researchers are exploring the use of stem cells-based wound healing biopolymers as a potential approach to enhance the healing process of wounds. These biopolymers, which are natural or synthetic materials, are engineered to support the growth, differentiation, and function of stem cells specifically for wound healing applications. Stem cells-based wound healing biopolymers can be designed to provide a three-dimensional structure that mimics the extracellular matrix, creating an environment conducive to stem cell attachment, proliferation, and differentiation. These biopolymers can be modified to have specific physical and chemical properties, such as biodegradability, mechanical strength, and surface characteristics, to optimize their interaction with stem cells and promote wound healing. One approach involves incorporating stem cells directly into the biopolymer matrix. This can be achieved by encapsulating stem cells within hydrogel-based biopolymers or seeding stem cells onto porous scaffolds. The biopolymer matrix provides structural support and acts as a delivery system for bioactive factors secreted by the stem cells. These factors, including growth factors and cytokines, can stimulate various cellular processes involved in wound healing, such as cell proliferation, angiogenesis, and extracellular matrix remodeling. Another approach focuses on utilizing the secretome of stem cells. The secretome refers to the complex mixture of bioactive molecules, including growth factors, exosomes, and other signaling molecules, which are released by stem cells. Biopolymers can be engineered to capture and release these bioactive molecules, either by direct incorporation or through surface modifications. By presenting these signaling factors in a controlled manner, the biopolymer can promote wound healing by modulating cellular activities and promoting tissue regeneration. In this context, researchers are investigating different combinations of stem cells and biopolymers, as well as optimizing their formulation and delivery methods. They are studying the biocompatibility, mechanical properties, degradation kinetics, and release profiles of these biopolymers to ensure their safety and efficacy for wound healing applications. Furthermore, researchers are exploring the use of advanced techniques such as 3D bioprinting and microfabrication to precisely engineer complex biopolymer structures and create customized wound healing platforms [41–44]. Catanzano et al. reviewed the design, characterization, and evaluation of wound healing products integrated with growth factors [45]. Some criteria should be considered when growth factors are loaded into the carrier system (biopolymer), such as their encapsulation efficiency, stability, and controlled release into the wound setting. However, the high cost is one of the limitations when considering growth factor enrichment. Furthermore, Mashiko et al., have found that incorporating adipose-derived stem cells into a recombinant collagen scaffold demonstrated superior wound healing progress compared to the recombinant protein scaffold alone [46]. The structural arrangement of the skin layer is similar to normal skin after treatment with biopolymers and biomaterials [47]. Therefore, good healing potential and results were obtained using these platforms of topical wound healing products, so-called bioactive dressings, which can be considered the best treatment for repairing full-thickness wounds and provide benefits for patients in the future. Thus, stem cells-based wound healing biopolymers in the lab represent a promising area of research, aiming to harness the regenerative potential of stem cells and the supportive properties of biopolymers to improve wound healing outcomes. Further studies and advancements in this field

 doi:10.20944/preprints202307.2097.v2

hold the potential for the development of innovative therapies that could revolutionize the treatment of chronic wounds.

4.2. Stem Cells-Based Wound Healing Biopolymers in the Market

Biopolymers provide a favorable microenvironment for stem cells to proliferate, differentiate, and accelerate wound healing processes. In recent years, there has been noteworthy progress in the development and commercialization of these innovative biopolymers, leading to their availability in the market. As mentioned previously, one of the key advantages of stem cell-based wound healing biopolymers is their ability to enhance tissue regeneration through the release of bioactive factors by the embedded stem cells. These factors promote angiogenesis, collagen synthesis, and recruitment of endogenous cells, which collectively contribute to wound closure and tissue repair. Additionally, these biopolymers offer advantages such as biocompatibility, biodegradability, and ease of application, making them suitable for a wide range of wound types and sizes. Furthermore, the commercial availability of these products allows clinicians to access standardized and quality-controlled formulations, ensuring consistent and reproducible outcomes. There are several components related to wound healing stem cells that are available in the market for clinical use. These components include MSCs, growth factors, extracellular vesicles and exosomes, scaffold materials, and hydrogels and dressings. As described previously, MSCs is the most commonly used type of stem cells for wound healing because they possess the ability to differentiate into different cell types involved in wound healing and secrete bioactive factors that promote tissue regeneration. Various growth factors derived from stem cells are available in the market for wound healing applications. These growth factors include epidermal growth factor (EGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and transforming growth factor-beta (TGF-β) [48]. These factors play a crucial role in stimulating cell proliferation, angiogenesis, and collagen synthesis, leading to accelerated wound healing. Stem cells release extracellular vesicles, including exosomes, which contain a variety of bioactive molecules such as proteins, lipids, and nucleic acids. These extracellular vesicles have shown promising therapeutic effects in wound healing by promoting cell migration, angiogenesis, and tissue regeneration [49]. Commercially available exosome-based products are emerging as potential treatments for wound healing. Stem cell-based wound healing often involves the use of biocompatible scaffold materials that provide a three-dimensional structure for stem cell attachment, proliferation, and differentiation. These scaffolds can be made from natural or synthetic materials and are designed to mimic the extracellular matrix. They provide a supportive environment for stem cells to enhance wound healing processes. Stem cell-based wound healing hydrogels and dressings are also available in the market. These products are designed to provide a moist environment for wound healing and can be loaded with stem cells or stem cell-derived factors. Hydrogels and dressings help maintain optimal conditions for stem cell activity, protect the wound from infection, and facilitate the healing process. Thus, these components represent the diverse range of products available in the market that harness the potential of stem cells for wound healing. They offer a variety of approaches to promote tissue regeneration, angiogenesis, and accelerated wound healing, providing clinicians with valuable tools in the treatment of chronic wounds.

Table 3 presents a compilation of novel stem cell-based wound healing products developed in recent years. Among them, allo-APZ2 comprises ABCB5-MSCs, TruStem incorporates hematopoietic and MSCs, and XSTEM utilizes human stem cells along with Integrin $\alpha 10\beta 1$ [50–53] The first and last products mentioned are currently undergoing clinical trials. TruStem demonstrates an extended response time, taking weeks to months to observe therapeutic effects. Additionally, there are many other cell-based, growth factor-based, and natural ECM-based wound healing products available in the market. A few to mention are: ReGenerCell™, DermaPure®, Grafix®, NuCel®, Myskin®, Cryoskin, ReCell®, BioDfentor, BioDfence®, Appligraf®. ReGenerCell™ utilizes a patient's own skin cells, which are processed and sprayed onto wounds using the ReCell® device. The product aims to promote wound healing and reduce scarring by delivering a population of cells, including keratinocytes, to the wound site [54]. DermaPure® is an autologous (patient-derived) cell therapy that utilizes a patient's own cells to create a bioactive wound dressing. The product is designed to enhance wound

 doi:10.20944/preprints202307.2097.v2

healing by providing a cellular and growth factor-rich environment [55]. Grafix® is a cryopreserved placental membrane-based product that contains various components, including MSCs, growth factors, and extracellular matrix proteins. The product aims to facilitate wound healing by providing a regenerative environment [56]. Therefore, technically sound approaches that facilitate wound healing are found at the core of all these wound healing products. It is also noted that many of them have been using the amniotic membrane as an ECM to support and retain the cells and growth factors. The amniotic membrane's natural ECM properties, including its protective barrier function, abundance of bioactive factors, anti-inflammatory effects, and support for tissue regeneration, make it a highly favorable choice for promoting effective wound healing and achieving optimal clinical outcomes [57]. However, several of these products share common limitations, including possibility of contaminations, compatibility issues with allogeneic cell source, and relatively modest wound healing outcomes. Moreover, wound healing products need to undergo rigorous regulatory scrutiny to ensure the safe and ethical use of stem cells derived from both human and animal sources in clinical settings.

Table 3. Wound healing products based on animal origin stem cells under clinical trials.

Product	Components	Problem, Deficiencies, Limitation	Company	Reference
allo-APZ2	ABCB5-mesenchymal stem cells	Limitations inherent to the use of stem cells (contamination, allogeneic transplantation, modest healing)	Rheacell	[143]
TruStem	Hematopoietic and mesenchymal stem cells	Limitations inherent to the use of stem cells (contamination, allogeneic transplantation, modest healing). Indefinite response time (weeks-months to notice therapeutic effects)	TruStem Cell Therapy	[144]
XSTEM	Human Stem Cells. Integrin $\alpha 10\beta 1$	Inherent limitations of stem cell use (cell line contamination, allogeneic transplant compatibility, modest healing)	Xintela	[145]

5. MicroRNA-Based Wound Healing Biopolymers

5.1. MicroRNA-Based Wound Healing Biopolymers in Research

MicroRNAs (miRs) are small non-coding RNAs that average 22 nucleotides in length. Primarily transcribed from DNA sequences they are known to play a key role in the regulation of gene expression. Mature miRs predominantly interact with the 3′ untranslated region (3′UTR) of messenger RNA (mRNA) resulting in the degradation and translational repression of mRNA transcripts. However, they are also known to interact with other regions including the 5′ UTR, gene promoter regions and coding sequences [58]. There are currently over 2,500 known miRs in humans, some of which target mRNAs involved in a wide range of biological and pathophysiological processes [59]. Due to this it is vital to consider not only how the presence of an individual miR will benefit in wound healing, but also how it may impact gene expression in surrounding tissue [60].

As previously stated, wound healing is a multi-step process involving coagulation and hemostasis, inflammation, proliferation, and remodeling of tissue. Following tissue damage miRs are transiently expressed to suppress excessive inflammatory responses, promote proliferation and migration of keratinocytes, and improve collagen expression and the ECM remodeling [59]. In recent years many miRs have been discovered that contribute to wound healing during the inflammation (21, 125b, 132, 146a, 155, 223), proliferation (21, 31, 99, 132, 210) and remodeling (29a, 29b, 29c, 192) phases, detailed in Table 4 [59]. In order to exploit these miRs to enhance wound healing using biopolymers several criteria must be met; (1) the biopolymer must be positively charged to facilitate adhesion as all miRs are negatively charged, (2) cellular uptake of miRs at the site of the wound must be stable, avoid lysosomal degradation and positively contribute to the wound healing process, (3) the biopolymer/miR complex must be non-toxic and biocompatible with the surrounding tissue and microenvironment [61,62]. Biopolymers can also overcome limitations of traditional viral vector-

 doi:10.20944/preprints202307.2097.v2

based delivery systems such as, limited capacity for genetic cargo resulting in poor immunogenicity, possibility of viral mutagenesis leading to malignant transformation of cells, and other unwanted cytotoxic effects [63].

Wound treatment strategies using miRs predominantly focus on either upregulating miRs that have a positive effect on wound healing or downregulating those which have a negative effect. This task is complicated by changes in miR expression throughout the wound healing process, alongside differences in miR expression profiles in different tissue types and in those with chronic wounds such as venous ulcers (VUs) and diabetic foot ulcers (DFUs) [64]. Due to this many natural biopolymer-based products incorporating miRs often focus on treating acute cutaneous wounds (burns, bacterial infection) or chronic wounds (VUs, DFUs) that are associated with unique miR profiles. This approach has been successful in recent in vivo studies in mice for both acute and chronic wounds. Using a Chitosan, Puerarin hydrogel (C@P) Zeng et al. [65] successfully inhibited miR-29ab1, resulting in the downregulation of IL-1β and TNF-α secreted by M1 macrophages, significantly accelerating the wound healing process in diabetic mice. Similarly, Zhang et al. [66]. used a Jiang Tang Xiao Ke (JTXK) based hydrogel to inhibit miR-139-5p to promote accelerate healing process in S.aureus infected wounds.

Another recent study comparing miR expression in chronic venous insufficiency patients against a healthy population of similar age resulted in the identification of seventeen pathologically relevant miRs that contributed to persistent inflammation and proliferation phase inhibition. The study found that three miRs (34a, 424, 516) were consistently upregulated in patients with VUs, the most common chronic nonhealing wound type [67]. Similarly, patients suffering from diabetes mellitus complicated by chronic non-healing wounds such as DFUs exhibit an overexpression of miR-29ab1 from M1 macrophages. All this research confirms sufficient progress of microRNA-based wound healing biopolymers in recent years.

Table 4. miRNAs associated with the wound healing process. Wound healing phase and associated wound type have been listed alongside a brief synopsis of the miRNA function that promotes wound healing.

Phase	miRNA	Function	Associated Wound Type	Reference
Inflammation	miR-23b	Reduces pro-inflammatory cytokines	Acute	[146]
Inflammation	miR-27b	Downregulation of miR-27b promotes fibroblast proliferation	Acute (burn)	[147]
Inflammation	miR-34a/b	Promotes production of chemokines and cytokines prolonging inflammation	Chronic (venous ulcers)	[148]
Inflammation	miR-146a	miR-146a deficiency is associated with enhanced inflammatory response in diabetic wounds	Diabetic foot ulcers	[149]
Inflammation	miR-203	Inhibits proliferation and migration of keratinocytes	Diabetic foot ulcers	[150]
Inflammation	miR-223	Enhances clearance of *S.aureus* through neutrophil activation	Acute (Bacterial infection)	[151]
Inflammation/Proliferation	miR-21	Down-regulates PTEN/RECK & activates MAPK/ERK cascade, inhibiting inflammation	Acute	[152]
Inflammation/Proliferation	miR-31	Enhances keratinocyte proliferation and migration	Acute	[153]
Inflammation/Proliferation	miR-125b	Interacts with TP53INP1 promoting cell migration and proliferation	Acute	[154]
Inflammation/Proliferation	miR-132	Promotes endothelial cell proliferation, migration, and angiogenesis	Acute (burn)	[155]

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 22 November 2023 doi:10.20944/preprints202307.2097.v2

Inflammation/Proliferation	miR-139-5p	Suppresses miR-139-5p expression enhancing neutrophil migration and proliferation in *S.aureus* wounds	Acute (Bacterial infection)	[66]
Inflammation/Proliferation	miR-155	Promotes keratinocyte migration and cellular proliferation	Acute	[156]
Proliferation	miR-99a/b	Suppresses keratinocyte migration and cellular proliferation	Acute (slow healing)	[157]
Remodeling	miR-29a/b/c	Represses extracellular matrix expression and fibroplasia, preventing fibrotic scars	Acute (scar prevention)	[158]
Remodeling	miR-192	Enhances collagen expression targeting SMAD-interacting protein 1 (SIP1)	Acute	[159]

5.2. MicroRNA-Based Wound Healing Biopolymers in the Market

Research into small RNA based therapeutics containing miRs or small interfering RNAs (siRs) is currently in a state of relative infancy, and although there are no commercially available miR-based therapeutics today, over 2,000 patents have been filed relating to their use, with several studies having reached the latter stages, i.e., Stages III and IV, of clinical trials [68]. There are however numerous obstacles that hinder progress through clinical trials, such as wound healing being a species-specific process, meaning no animal model can fully predict clinical outcomes in humans. There is also the potential for unwanted off-target effects as many miRs can upregulate/repress numerous genes. This coupled with a limited availability of positively charged, affordable biopolymers, capable of carrying sufficient genetic cargo that can survive rapid degradation of miRs is another key factor. These obstacles, coupled with the robust regulations surrounding gene-based therapeutics, are pivotal to understanding why miR based biopolymers have yet to become commercially available despite several products having had recent success in clinical trials [69,70].

Currently treatment strategies for chronic and slow healing wounds (severe burns, VUs, DFUs) often requires lengthy hospitalization, constant reapplication of surgical dressings at the site of the wound, courses of nonsteroidal anti-inflammatory drugs (NSAIDs) and topical antimicrobial ointments. Cellular/tissue-based products capable of accelerating the wound healing process are often costly and usually only administered after 4 weeks of standard care [71]. With the global financial burden of wound treatment estimated between $28.1-$96.8 billion, of which chronic wounds represent a huge portion, identification of wound specific miRs is vital to developing biopolymer based miR treatment strategies. Chronic wounds are also more common in the elderly and as global life expectancy and healthcare costs continue to rise so too will this financial burden [18].

6. Market Growth of Wound Healing Products

6.1. USA, Europe, and Asia's Potential to Meet the Growing Demand for Biomaterials

The demand for biomaterials is expected to grow in the coming decade. Based on a recent survey, the global market value for biomaterials was estimated at $60 - $100 billion in 2020, despite the economic downfall introduced by the SARS-CoV-2 (COVID-19) pandemic. The latest market survey and analysis (2020 to 2030) predicts that the market value of biomaterials will triple at a Compound annual growth rate (CAGR) of ≥12% to reach ≥$200 billion (USD) by the end of the decade (Table 5) [72–76]. Market surveys were segmented according to commonly referenced biomaterials products such as medical implants, diagnostic tools, tissue engineering and regenerative medicine or drug delivery tools.

Evidently, the USA has played a leading role in driving innovations, applications, and information technology in the introduction of biomaterials into the wound care market. As global pioneers, the strength bore by USA is in the presence of large market players [77]. The availability of investors for research and development, and the healthcare infrastructures to support such efforts are never scarce. Some of the dominant conglomerates, not confined by geographical factors, were

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 22 November 2023 doi:10.20944/preprints202307.2097.v2

incidentally based in the USA. These include 3M Healthcare, Stryker, Johnson & Johnson, and more [72–77]. Another prominent factor from the USA belongs to their impactful lab-to-market transitions. Solely having investment power is not definitive enough to determine success but conducting thorough market analysis is within their specialty. This process is crucial in securing credibility, resourcefulness and predicting the future of any product or service. It compartmentalizes all the necessary information including supply and demand, client preferences, competitors, and other market-related variables. Given the presence of major regulatory bodies originating from the USA like the Food and Drug Administration (FDA), quickens decision-making process for researchers and scientists to channel their products into the market.

Europe, similar to the USA, stands at the forefront of pioneering innovative biomaterials for wound healing applications, driven by its robust scientific research capabilities and extensive network of universities, research institutions, and industry collaborations. What sets Europe apart is its strong emphasis on translational research, enabling a seamless transition from laboratory discoveries to practical clinical applications. This is achieved through close partnerships between academic researchers, industry stakeholders, and healthcare professionals, facilitating the integration of scientific advancements into real-world patient care. To ensure the safety and effectiveness of these wound healing products, the European Medicines Agency (EMA) and national regulatory bodies uphold rigorous testing and evaluation procedures, assessing parameters such as biocompatibility, stability, and performance [78]. Compliance with these stringent regulatory requirements guarantees that biomaterial-based wound healing products meet elevated standards of quality, safety, and efficacy prior to their approval for clinical use [78]. By fostering ongoing research, encouraging innovation, and promoting collaboration, Europe is poised to effectively meet the growing demand for advanced biomaterials, making significant contributions towards enhancing wound healing outcomes [79].

Asia possesses immense potential to meet the escalating demand for biomaterials in wound healing [80]. The rich biodiversity, advanced scientific research, and thriving healthcare industries of India, China, Japan, Korea, Singapore, Malaysia, Indonesia, Thailand and many other Asian countries make this continent an ideal hub for the development and production of innovative biomaterials [81]. With a diverse array of natural resources and traditional medicine practices, Asia offers a vast pool of materials and knowledge that can be harnessed to create effective wound healing solutions [82]. Furthermore, Asia's rapidly growing economies and increasing investments in research and development provide a conducive environment for collaboration between academia, industry, and healthcare sectors, fostering the translation of cutting-edge research into practical applications [83]. As Asia continues to harness its unique strengths and capabilities, it is poised to play a pivotal role in meeting the growing global demand for biomaterials in wound healing, benefiting countless individuals worldwide.

Recent progress in healthcare management has extended worldwide life expectancy from 67.1 to 73.2 years, from 2000 to 2020 [84]. Furthermore, three of the top five countries ranked in life expectancy are of Asian demographic, namely Japan (2nd, 85.03 years); Macao (3rd, 84.68 years) and Singapore (5th, 84.07 years). According to WHO, by 2030, 1 in 6 people in the world will be aged ≥60 years. At this time the share of the population aged ≥60 will increase from 1 billion in 2020 to 1.4 billion. By 2050, the world's population of people ≥60 will double (2.1 billion). The number of persons aged ≥80 is expected to triple between 2020 and 2050 to reach 426 million. By 2050, two-thirds of the world's population ≥60 will live in low- and middle-income countries [85]. Consequently, geriatric care associated to wounds will be a major industrial driver in Asia.

Table 5. Global market forecasts for biomaterials, 2020 to 2030 period.

Forecasting Period (Years)	CAGR (%)	Reference Value (USD Billions)	Forecasted Value (USD Billions)	Reference
2020-2027	12.2	110.0	245.6	[73]
2020-2027	15.2	109.4	390.9	[76]
2021-2030	12.7	165.0	212.4	[74]

 doi:10.20944/preprints202307.2097.v2

2022-2030	15.4	135.4	488.7	[72]
2022-2030	12.2	121.4	343.7	[75]

6.2. Barriers in the Process to Meet the Growing Demand for Biomaterials

Unfortunately, the same barriers that have existed before, still remain today [86,87]. Diminishing sources or depletion of raw materials are always a competitive issue in most industries. Hence, it often leads to more drastic acts or regulations, which ultimately serve to limit or prohibit new players to access the market, and this is in turn translated into higher efforts and costs for the new industries and, possibly, and impediment for the smaller ones to partake. As is the case of all markets that are in similar conditions, as smaller companies merge or are acquired by larger entities, the market becomes less diverse and discouraged from changing. This, in turn, creates a monopolizing effect between pre-existing or established conglomerates. Downstream, consumers are constantly threatened by price escalation, regardless of life-threatening situations.

In contrast to the strengths of the USA and Europe mentioned in "Section 6a," there are several countries with an unexplored potential for the biomaterial industry. This lack of knowledge is primarily due to insufficient financial, labor, and raw material resources, as well as inadequate technology infrastructure and customer/market relations, among other factors. Additionally, a considerable number of countries lack the necessary governing bodies or guidelines to facilitate the development of this industry. Recognizing the significant benefits that the biomaterial industry has contributed to the medical, economic, and educational sectors, Asian countries have started exploring the production of biomaterial products. By adopting regulatory bodies or guidelines similar to those in the Western countries, it is possible to prevent any false or malicious entities from exploiting the market [88,89]. As a result, Asia was recently cited as the fastest growing region [72–76]. Most of these countries include financial powerhouses such as India, China, Japan, Korea, Singapore, and specific countries in the Middle East, while others that follow closely include Malaysia, Indonesia, Thailand, etc. This is important because Asia remains an untapped potential and their willingness to explore further into this industry is a good sign. It is possible that a minimally biased and diversified market could exists with greater emphasis on Research and Development of new or improved versions of existing products. This model could also test more resource-efficient and cost-saving methods, relative to the challenges plaguing the West.

The success of biomaterial products is also due to the prevalence of various health problems. While the US has led the way in impairments associated with metabolism such as obesity and diabetes for years, an increase in new cases has now been reported in Asia [90–93]. These diseases impair the innate recovery or the natural homeostasis of those affected. Therefore, a reliance on extrinsic methods through surgical interventions, drugs or medical devices is necessary. However, the treatability of these conditions should not be exploited for benefit purposes but used only when necessary and to raise medical awareness.

7. Global Regulatory Issues for Wound Healing Products

Adherence to quality standards is crucial for the safe use of a medical device; otherwise, it can result in several clinical cases, such as the one we have observed with a medical device causing visual impairment in multiple countries [94,95].

7.1. USA Regulatory Issues

The Food and Drug Administration (FDA) oversees the regulatory framework for wound healing products in the United States [96], as the regulatory issues are an integral aspect of the healthcare business, especially for wound healing treatments. The FDA plays a crucial role in ensuring that wound healing products are safe, effective, and in accordance with applicable rules. In the USA, the regulation procedure for wound healing products can be difficult and time-consuming. Wound healing products are classified as medical devices and are subject to the FDA's Center for Devices and Radiological Health's regulatory standards (CDRH) [97]. Generally speaking, the

 doi:10.20944/preprints202307.2097.v2

regulatory procedure for wound healing devices consists of two phases: premarket review and postmarked monitoring [98]. Prior to allowing a wound healing product to be commercialized in the United States, the FDA assesses it through the premarket review procedure. The premarket review procedure consists in several steps, including product categorization, device testing, and the filing of a premarket notice or premarket approval application.

Classification of a product is a crucial stage in the premarket evaluation process [99,100]. Class I devices are deemed low-risk and are only subject to general regulations, such as labelling requirements and good manufacturing procedures. Class II medical devices are moderately risky and are subject to stringent regulations, including performance criteria and post-market surveillance. Class III devices are regarded as high-risk and require clearance prior to commercial release. Testing of the device is another crucial phase in the premarket evaluation procedure. The FDA demands testing of wound healing products to guarantee their safety and effectiveness. The testing standards differ, depending on the classification of the device. Class I medical devices are normally exempt from testing, but Class II and Class III medical devices may require bench testing, animal testing, or clinical trials [101]. After classifying and testing a wound healing product, the company must file an FDA premarket notice or premarket approval application. Class I and Class II devices must submit a premarket notification, whereas Class III ones must submit an application for premarket clearance [100]. The premarket notice or premarket approval application must contain information on the product, its intended use, its performance characteristics, and any testing or clinical studies completed.

Post-market monitoring is the method through which the FDA monitors wound healing products after they have been introduced to the marketplace [97,98]. Post-market surveillance is to detect and address any safety or efficacy concerns that may develop after a medical device has been licensed for sale. Manufacturers must report adverse occurrences related with their devices to the FDA, and the FDA may conduct inspections or investigations to ensure that devices continue to comply with regulatory standards. In addition to the FDA, additional regulatory organizations may be engaged in wound healing product regulation. For instance, the Federal Trade Commission (FTC) controls wound healing product makers' advertising and marketing claims. The Occupational Safety and Health Administration (OSHA) may regulate the workplace usage of wound healing products [102].

Thus, regulatory issues are an integral part of the United States wound healing product sector. The regulatory procedure consists of many processes, including product categorization, device testing, and premarket evaluation. The FDA plays a crucial role in ensuring that wound healing products are safe, effective, and in accordance with applicable rules. Also, manufacturers must be aware of various regulatory agencies that may be engaged in wound healing product regulation. Overall, the regulatory process can be difficult and time-consuming, but it is vital to guarantee that patients receive high-quality, safe, and effective wound healing treatments.

7.2. European Regulatory Issues

The European Pharmacopoeia (Ph. Eur.) serves as the primary source of official quality standards for medicines and their ingredients within Europe. However, medical devices, which include products or equipment intended for medical purposes, are not categorized as medicines and, in accordance with the ‘classification rules’ set out in Annex VIII of Regulation (EU) 2017/745 on medical devices (MDR), a wound healing product is classified according to Rule 4 as "Device that meet injured skin or mucous membrane". These products are labelled as class I if they are used as simple wound dressings for skin or mucous membranes, as class IIa if used as dressings for wounds or injuries (such as non-medicated, hydrogel dressings), and as class IIb if used for severe wounds on the skin or mucous membranes (e.g., ulcers, burns, severe decubitus wounds) or as a temporary skin substitute [103]. However, any wound healing product incorporating, as an integral part, a substance which, if used separately, can be a medicinal product, as defined in point 2 of Article 1 of Directive 2001/83/EC, and that has an action ancillary to that of the device, are labelled as class III, in accordance with Rule 14. Therefore, a wound healing dressing incorporating, for example, an

 doi:10.20944/preprints202307.2097.v2

antimicrobial agent which has an ancillary action on the wound, will be labelled as class III product. This classification necessitates the requirement of clinical studies to obtain a CE mark. Regardless of the classification of a wound healing product, it is essential for all products to comply with the relevant obligations outlined in the MDR. However, the specific requirements vary based on the classification of the wound healing product. A real case is represented by silk fibroin, a 100% biocompatible natural protein, totally free of any dangerous particle/molecule, with intrinsic antioxidant and reparative properties [104,105]. A clear candidate for natural polymer-based class I wound care products. Silk fibroin could be a suitable natural polymer to produce high-performance wound caring product, if combined with antioxidant treatments, inflammation suppressors, and promotors of skin cells regeneration, e.g., silk protein hydrogels incorporating extracts of stem cells, medicinal plants, or stem cell secretome [106]. Nevertheless, since this silk fibroin incorporates substances with medicinal properties, when used independently, to enhance its therapeutic properties, its classification would pass from class I to class III.

A wound healing product must adhere to the general safety and performance requirements, which include providing the necessary information, as specified in Annex I of the MDR, by the manufacturer. Additionally, the product should comply with reporting requirements outlined in the medical device vigilance system, obtain CE marking (with exceptions for custom-made devices and devices intended for clinical investigation, which must comply with the provisions of Art. 52.8 and Annex XIII or Articles 62-80, 82 and Annex XV respectively), be assigned a Unique Device Identifier (UDI) number, and be registered in the electronic system in accordance with Article 29 of the MDR.

7.3. Asian Regulatory Issues

The collective contributions of China, India, Japan, and South Korea demonstrate their crucial role in the wound healing product market. The regulatory issues in these countries also play a vital role in ensuring the safety, efficacy, and quality of these products within their respective markets. Of particular interest because of its diversity and large population is Southeast Asia: Indonesia, Malaysia, the Philippines, Singapore, Thailand, Vietnam, Brunei, Cambodia, Laos, Burma, and Timor-Leste. To market the goods across this area, makers of wound healing treatments must traverse several regulatory systems, as each nation has its own regulatory framework. In Asia also, wound healing items are often classified as medical devices and are subject to special regulatory regimes [107]. Each nation in the area has its own regulatory authority responsible for assessing and approving medical devices, such as wound healing treatments, prior to their commercialization and distribution inside its boundaries [108]. These regulatory authorities include the National Medical Products Administration (NMPA) in China, the Central Drugs Standard Control Organization (CDSCO) in India, the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, the Ministry of Food and Drug Safety (MFDS) in South Korea, the National Pharmaceutical Regulatory Agency (NPRA) in Malaysia, the National Agency for Drug and Food Control (NADFC) in Indonesia, the Health Sciences Authority (HSA) in Singapore and the Food and Drug Administration (FDA) in both Thailand and Philippines [109].

In Asia, the regulatory standards for wound healing products differ by nation. However, product classification, clinical data, quality control, labeling, and packaging are examples of common needs [110]. The regulatory framework for wound healing products is based on the norms and regulations established by each country's regulatory organizations. The regulatory structure is intended to guarantee that all medical goods, including wound healing treatments, are safe, effective, and of high quality. The essential components of the regulatory framework for wound healing goods in Asia are as follows [45]:

- Product Classification: Medical products are categorized according to their intended purpose, level of risk, and mechanism of action. Depending on its mechanism of action and intended usage, wound healing products are often classed as Class III or IV medical devices. However, the classification system ranges from Class I (low-risk) to Class IV (high-risk). Each class has specific regulatory requirements and evaluation processes.

 doi:10.20944/preprints202307.2097.v2

- Pre-Market Approval: Before a wound healing product may be sold in Asia, it must be authorized by each country's regulatory agency. The approval procedure requires the submission of a dossier covering all pertinent information regarding the product, such as its safety, effectiveness, and quality.
    - Clinical Trials and Evaluation: Depending on the risk classification, wound healing products may be subject to clinical trials and evaluation to assess their safety and efficacy. Clinical data and evidence are required to demonstrate the product's performance and benefits in promoting wound healing.
    - Quality Management System: Compliance with quality management system requirements, such as Good Manufacturing Practice (GMP) and ISO certification, is necessary for wound healing product manufacturers. These standards ensure consistent product quality and safety throughout the manufacturing process. Harmonization with international regulations and standards with global guidelines is necessary to facilitate international trade and ensure product quality and safety.
- Post-Market Surveillance: Once a wound healing product has been approved and sold, the regulatory authority performs post-market monitoring to ensure that the product continues to fulfill safety, effectiveness, and quality criteria. Adverse event reporting, post-market studies, and periodic safety updates are required to identify and address any potential safety concerns.
- Labeling and Advertising: The labeling and advertising of wound healing products must adhere to the norms and guidelines established by each country's regulatory agency. The labeling and advertising must be precise, honest, and not deceptive.

Thus, Asia's regulatory environment for wound healing products is complicated and demanding. Manufacturers must traverse different regulatory systems, show the safety and efficacy of their goods, and adhere to each country's unique standards. Inadequate regulatory agencies' coordination and inadequate resources can also result in manufacturing delays and cost increases. Notwithstanding these obstacles, Asia remains a very attractive market for wound healing products, and firms that can effectively negotiate the regulatory framework will benefit from the expanding demand of this region.

8. Conclusions

Wound, especially chronic wound is like an epidemic, silently, affecting large populations worldwide but with stronger effects in the developing countries since in advanced countries this is diagnosed earlier due to health facilities.

Wound healing is a complex process that requires the use of specific care products. Due to the increase in the world's aging population and the increase in cases of diabetes and obesity among the younger generations, there is a very large increase in people susceptible to injuries and an increase in the need for effective products for their care; and this increasing demand for wound healing products translates into a large additional financial burden. However, this demand also creates opportunities for growth in the global market for wound care products. These products mainly consist of natural polymeric materials, stem cells and microRNA. Despite these advances, achieving complete healing of chronic wounds continues to pose significant challenges and, at the same time, great market opportunities.

Author Contributions: Conceptualization, coordination, writing & draft preparation, G.K.S.; writing, editing and table preparation of biopolymers for wound healing, N.I.M.F. and M.B.F; writing, editing and table preparation of market growth, D. L.Q.H.; writing, editing and table preparation of microRNAs for wound healing, G.M. and P.S.; table preparation of wound healing products in market, references editing, S.M.R.; supervision, writing, and revision, F.P.

Funding: G.K.S. receives funding from the Universidad de Valladolid-Spain for a distinguished senior investigator. S.M.R. receives funding from the Universidad de Valladolid-Spain for a pre-doctoral contract. F.P was funded by the General Direction of Technologic Innovation, Community of Madrid-Spain, grant numbers 82017/BMD-3760 (NEUROCENTRO-CM) and P2022/BMD-7236 (MINA-CM).

Conflicts of Interest: Authors declare no conflicts of interest.

References

1. Rodrigues: M.; Kosaric, N.; Bonham, C.A.; Gurtner, G.C. Wound Healing: A Cellular Perspective. *Physiol. Rev.* **2019**, *99*, 665–706. https://doi.org/10.1152/physrev.00067.2017.
2. Dhivya, S.; Padma, V.V.; Santhini, E. Wound Dressings – a Review. *BioMedicine* **2015**, *5*, 22. https://doi.org/10.7603/s40681-015-0022-9.
3. Rezvani Ghomi, E.; Khalili, S.; Nouri Khorasani, S.; Esmaeely Neisiany, R.; Ramakrishna, S. Wound Dressings: Current Advances and Future Directions. *J. Appl. Polym. Sci.* **2019**, *136*, 47738. https://doi.org/10.1002/app.47738.
4. Heyer, K.; Augustin, M.; Protz, K.; Herberger, K.; Spehr, C.; Rustenbach, S.J. Effectiveness of Advanced versus Conventional Wound Dressings on Healing of Chronic Wounds: Systematic Review and Meta-Analysis. *Dermatology* **2013**, *226*, 172–184. https://doi.org/10.1159/000348331.
5. Denny, K.; Lawand, C.; Perry, S. Compromised Wounds in Canada. *Healthc. Q.* **2014**, *17*, 7–10. https://doi.org/10.12927/hcq.2014.23787.
6. World Population Ageing 2019: Highlights. **2019**.
7. Ageing Europe - Looking at the Lives of Older People in the EU - Eurostat 2019 Report Available online: https://www.age-platform.eu/publications/ageing-europe-looking-lives-older-people-eu-eurostat-2019-report (accessed on 23 June 2023).
8. Overview of the UK Population - Office for National Statistics 2023.
9. Mark, M.; Paola, S.; Lillian, K. Fact Sheet: Aging in the United States Available online: https://www.prb.org/resources/fact-sheet-aging-in-the-united-states/ (accessed on 6 June 2023).
10. He, W.; Gookind, D.; Kowal, P.; Almasarweh, W.I.S.; Giang, T.L.; Islam, M.M.; Lee, S.; Teerawichitchainan, B.; Tey, N.P. Asia Aging: Demographic, Economic, and Health Transitions. **2022**.
11. Malaysia Attained Ageing Nation Status. Department of Statistics Malaysia Official Portal 2023.
12. Cross, K.; Harding, K. Risk Profiling in the Prevention and Treatment of Chronic Wounds Using Artificial Intelligence. *Int. Wound J.* **2022**, *19*, 1283–1285. https://doi.org/10.1111/iwj.13952.
13. Guest, J.F.; Fuller, G.W.; Vowden, P. Cohort Study Evaluating the Burden of Wounds to the UK's National Health Service in 2017/2018: Update from 2012/2013. *BMJ Open* **2020**, *10*, e045253. https://doi.org/10.1136/bmjopen-2020-045253.
14. Pokorná, A.; Leaper, D. Assessment and Documentation of Non-healing, Chronic Wounds in Inpatient Health Care Facilities in the Czech Republic: An Evaluation Study. *Int. Wound J.* **2014**, *12*, 224–231. https://doi.org/10.1111/iwj.12372.
15. M, P.; P, S. lingam; Balan, Y.; Pyati, A.K.; M, P.; P, S. lingam; Balan, Y.; Pyati, A.K. A Comparative Study Between Vacuum Dressing and Normal Saline Dressing for Chronic Non-Healing Ulcers. *Cureus* **2022**, *14*. https://doi.org/10.7759/cureus.23870.
16. Is Malaysian Market Ripe for Advanced Wound Care Products? | LinkedIn Available online: https://www.linkedin.com/pulse/malaysian-market-ripe-advanced-wound-care-products-ariyanchira/.
17. Advanced Wound Care Market Share, Growth | Forecast [2030] Available online: https://www.fortunebusinessinsights.com/industry-reports/advanced-wound-care-market-100060.
18. Sen, C.K. Human Wounds and Its Burden: An Updated Compendium of Estimates. *Adv. Wound Care* **2019**, *8*, 39–48. https://doi.org/10.1089/wound.2019.0946.
19. Sahana, T.G.; Rekha, P.D. Biopolymers: Applications in Wound Healing and Skin Tissue Engineering. *Mol. Biol. Rep.* **2018**, *45*, 2857–2867. https://doi.org/10.1007/s11033-018-4296-3.
20. Neha, R.; Radha, R.; Rakesh, P.; Madhu, G. Biopolymers and Treatment Strategies for Wound Healing: An Insight View. *Int. J. Polym. Mater. Polym. Biomater.* **2022**, *71*, 359–375. https://doi.org/10.1080/00914037.2020.1838518.
21. Gardikiotis, I.; Cojocaru, F.-D.; Mihai, C.-T.; Balan, V.; Dodi, G. Borrowing the Features of Biopolymers for Emerging Wound Healing Dressings: A Review. *Int. J. Mol. Sci.* **2022**, *23*, 8778. https://doi.org/10.3390/ijms23158778.
22. Yang, Y.; Xu, L.; Wang, J.; Meng, Q.; Zhong, S.; Gao, Y.; Cui, X. Recent Advances in Polysaccharide-Based Self-Healing Hydrogels for Biomedical Applications. *Carbohydr. Polym.* **2022**, *283*, 119161. https://doi.org/10.1016/j.carbpol.2022.119161.
23. Böhm, S.; Strauß, C.; Stoiber, S.; Kasper, C.; Charwat, V. Impact of Source and Manufacturing of Collagen Matrices on Fibroblast Cell Growth and Platelet Aggregation. *Mater. (Basel, Switzerland)* **2017**, *10*, 1086. https://doi.org/10.3390/ma10091086.
24. Busra, F.M.; Lokanathan, Y.; Nadzir, M.M.; Saim, A.; Idrus, R.B.H.; Chowdhury, S.R. Attachment, Proliferation, and Morphological Properties of Human Dermal Fibroblasts on Ovine Tendon Collagen Scaffolds: A Comparative Study. *Malaysian J. Med. Sci. MJMS* **2017**, *24*, 33–43. https://doi.org/10.21315/mjms2017.24.2.5.

25. Sultan, M.T.; Lee, O.J.; Kim, S.H.; Ju, H.W.; Park, C.H. Silk Fibroin in Wound Healing Process. *Adv. Exp. Med. Biol.* **2018**, *1077*, 115–126. https://doi.org/10.1007/978-981-13-0947-2_7.
26. Dong, M.; Mao, Y.; Zhao, Z.; Zhang, J.; Zhu, L.; Chen, L.; Cao, L. Novel Fabrication of Antibiotic Containing Multifunctional Silk Fibroin Injectable Hydrogel Dressing to Enhance Bactericidal Action and Wound Healing Efficiency on Burn Wound: In Vitro and in Vivo Evaluations. *Int. Wound J.* **2022**, *19*, 679–691. https://doi.org/10.1111/iwj.13665.
27. Neamtu, B.; Barbu, A.; Negrea, M.O.; Berghea-Neamțu, C. Ștefan; Popescu, D.; Zăhan, M.; Mireșan, V. Carrageenan-Based Compounds as Wound Healing Materials. *Int. J. Mol. Sci.* **2022**, *23*, 9117. https://doi.org/10.3390/ijms23169117.
28. Algisite M Calcium Alginate Dressing. *MedicalDressings* 2023.
29. Suprasorb C Collagen Wound Dressing, 12 x 8 Cm by SUPRASORB - Shop Online for Health in Australia 2023.
30. KITO ACTIVATOR CHITOSAN WOUND HEALING HYDROGEL BARRIER | Tradekorea 2023.
31. Medihoney HoneyColloid Leptospermum Hydrocolloid Dressings 2023.
32. Hyperoil - For Any Wound, Any Time. *Hyperoil* 2023.
33. Fibracol Plus Collagen Wound Dressing with Alginate 2023.
34. Ayavoo, T.; Murugesan, K.; Gnanasekaran, A. Roles and Mechanisms of Stem Cell in Wound Healing. *Stem Cell Investig.* **2021**, *8*, 4. https://doi.org/10.21037/sci-2020-027.
35. Srivastava, G.K.; Rodriguez-Crespo, D.; Fernandez-Bueno, I.; Pastor, J.C. Factors Influencing Mesenchymal Stromal Cells in in Vitro Cellular Models to Study Retinal Pigment Epithelial Cell Rescue. *Hum. Cell* **2022**, *35*, 1005–1015. https://doi.org/10.1007/s13577-022-00705-5.
36. Di Lauro, S.; Garcia-Gutierrez, M.T.; Fernandez-Bueno, I. Quantification of Pigment Epithelium-Derived Factor (PEDF) in an Ex Vivo Coculture of Retinal Pigment Epithelium Cells and Neuroretina. *2020* **2020**, *2*, 81.
37. Maria L., A.-A.; Girish K., S.; Ricardo, U.-M.; Maria T., G.-G.; José Carlos, P.; Ivan, F.-B. Mesenchymal Stem Cell Secretome Enhancement by Nicotinamide and Vasoactive Intestinal Peptide: A New Therapeutic Approach for Retinal Degenerative Diseases. *Stem Cells Int.* **2020**, *2020*, 1–14. https://doi.org/10.1155/2020/9463548.
38. Trzyna, A.; Banaś-Ząbczyk, A. Adipose-Derived Stem Cells Secretome and Its Potential Application in "Stem Cell-Free Therapy." *Biomolecules* **2021**, *11*, 878. https://doi.org/10.3390/biom11060878.
39. Gorecka, J.; Kostiuk, V.; Fereydooni, A.; Gonzalez, L.; Luo, J.; Dash, B.; Isaji, T.; Ono, S.; Liu, S.; Lee, S.R.; et al. The Potential and Limitations of Induced Pluripotent Stem Cells to Achieve Wound Healing. *Stem Cell Res. Ther.* **2019**, *10*, 1–10. https://doi.org/10.1186/s13287-019-1185-1.
40. Paik, D.T.; Chandy, M.; Wu, J.C. Patient and Disease–Specific Induced Pluripotent Stem Cells for Discovery of Personalized Cardiovascular Drugs and Therapeutics. *Pharmacol. Rev.* **2020**, *72*, 320–342. https://doi.org/10.1124/pr.116.013003.
41. Nourian Dehkordi, A.; Mirahmadi Babaheydari, F.; Chehelgerdi, M.; Raeisi Dehkordi, S. Skin Tissue Engineering: Wound Healing Based on Stem-Cell-Based Therapeutic Strategies. *Stem Cell Res. Ther.* **2019**, *10*, 1–20. https://doi.org/10.1186/s13287-019-1212-2.
42. Maarof, M.; Mohd Nadzir, M.; Sin Mun, L.; Fauzi, M.B.; Chowdhury, S.R.; Idrus, R.B.H.; Lokanathan, Y. Hybrid Collagen Hydrogel/Chondroitin-4-Sulphate Fortified with Dermal Fibroblast Conditioned Medium for Skin Therapeutic Application. *Polymers (Basel).* **2021**, *13*, 508. https://doi.org/10.3390/polym13040508.
43. Ling-Chun, C.; Shyr-Yi, L.; Ming-Thau, S.; Ching-Hua, S.; Hong-Liang, L.; Chien-Ming, H. Fabrication and Characterization of Rhizochitosan and Its Incorporation with Platelet Concentrates to Promote Wound Healing. *Carbohydr. Polym.* **2021**, *268*, 118239. https://doi.org/10.1016/j.carbpol.2021.118239.
44. Md Fadilah, N.I.; Mohd Abdul Kader Jailani, M.S.; Badrul Hisham, M.A.I.; Sunthar Raj, N.; Shamsuddin, S.A.; Ng, M.H.; Fauzi, M.B.; Maarof, M. Cell Secretomes for Wound Healing and Tissue Regeneration: Next Generation Acellular Based Tissue Engineered Products. *J. Tissue Eng.* **2022**, *13*. https://doi.org/10.1177/20417314221114273.
45. Catanzano, O.; Quaglia, F.; Boateng, J.S. Wound Dressings as Growth Factor Delivery Platforms for Chronic Wound Healing. *Expert Opin. Drug Deliv.* **2021**, *18*, 737–759. https://doi.org/10.1080/17425247.2021.1867096.
46. Mashiko, T.; Takada, H.; Wu, S.-H.; Kanayama, K.; Feng, J.; Tashiro, K.; Asahi, R.; Sunaga, A.; Hoshi, K.; Kurisaki, A.; et al. Therapeutic Effects of a Recombinant Human Collagen Peptide Bioscaffold with Human Adipose-Derived Stem Cells on Impaired Wound Healing after Radiotherapy. *J. Tissue Eng. Regen. Med.* **2018**, *12*, 1186–1194. https://doi.org/10.1002/term.2647.
47. Sezer, A.D.; Cevher, E.; Sezer, A.D.; Cevher, E. *Biopolymers as Wound Healing Materials: Challenges and New Strategies*; IntechOpen, 2011; ISBN 978-953-307-661-4.
48. Growth Factors in Wound Healing – A Review Available online: https://biomedpharmajournal.org/vol14no3/growth-factors-in-wound-healing-a-review/.

49. Aguiar Koga, B.A.; Fernandes, L.A.; Fratini, P.; Sogayar, M.C.; Carreira, A.C.O. Role of MSC-derived Small Extracellular Vesicles in Tissue Repair and Regeneration. *Front. Cell Dev. Biol.* **2023**, *10*, 1047094. https://doi.org/10.3389/fcell.2022.1047094.
50. RHEACELL >< Technology 2023.
51. Allo-APZ2 Available online: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3192160.
52. Home of TruStem Cell Therapy - Top U.S. Stem Cell Therapy & Treatment Center TruStem Cell Therapy™ 2023.
53. Xintela XSTEM Available online: https://www.xintela.se/en/press-release?slug=xintela-starts-clinical-study-of-xstem-r-in-knee-osteoarthritis.
54. Avita Medical A Feasibility Study of the ReGenerCellTM Autologous Cell Harvesting Device for Diabetic Foot Ulcer Available online: Clinicaltrials.gov.
55. Kimmel, H.; Gittleman, H. Retrospective Observational Analysis of the Use of an Architecturally Unique Dermal Regeneration Template (Derma Pure®) for the Treatment of Hard-to-Heal Wounds. *Int. Wound J.* **2017**, *14*, 666–672. https://doi.org/10.1111/iwj.12667.
56. Lavery, L.A.; Fulmer, J.; Shebetka, K.A.; Regulski, M.; Vayser, D.; Fried, D.; Kashefsky, H.; Owings, T.M.; Nadarajah, J.; Group, T.G.D.F.U.S. The Efficacy and Safety of Grafix® for the Treatment of Chronic Diabetic Foot Ulcers: Results of a Multi-Centre, Controlled, Randomised, Blinded, Clinical Trial. *Int. Wound J.* **2014**, *11*, 554–560. https://doi.org/10.1111/iwj.12329.
57. Ruiz-Cañada, C.; Bernabé-García, Á.; Liarte, S.; Rodríguez-Valiente, M.; Nicolás, F.J. Chronic Wound Healing by Amniotic Membrane: TGF-β and EGF Signaling Modulation in Re-Epithelialization. *Front. Bioeng. Biotechnol.* **2021**, *9*.
58. O'Brien, J.; Hayder, H.; Zayed, Y.; Peng, C. Overview of MicroRNA Biogenesis, Mechanisms of Actions, and Circulation. *Front. Endocrinol. (Lausanne).* **2018**, *9*, 402. https://doi.org/10.3389/fendo.2018.00402.
59. Meng, Z.; Zhou, D.; Gao, Y.; Zeng, M.; Wang, W. MiRNA Delivery for Skin Wound Healing. *Adv. Drug Deliv. Rev.* **2018**, *129*, 308–318. https://doi.org/10.1016/j.addr.2017.12.011.
60. Weiss, C.N.; Ito, K. A Macro View of MicroRNAs: The Discovery of MicroRNAs and Their Role in Hematopoiesis and Hematologic Disease. *Int. Rev. Cell Mol. Biol.* **2017**, *334*, 99–175. https://doi.org/10.1016/bs.ircmb.2017.03.007.
61. Banerjee, J.; Sen, C.K. MicroRNA and Wound Healing. *Adv. Exp. Med. Biol.* **2015**, *888*, 291–305. https://doi.org/10.1007/978-3-319-22671-2_15.
62. Singh, R.; Shitiz, K.; Singh, A. Chitin and Chitosan: Biopolymers for Wound Management. *Int. Wound J.* **2017**, *14*, 1276–1289. https://doi.org/10.1111/iwj.12797.
63. Ramamoorth, M.; Narvekar, A. Non Viral Vectors in Gene Therapy- An Overview. *J. Clin. Diagn. Res.* **2015**, *9*, GE01–GE06. https://doi.org/10.7860/JCDR/2015/10443.5394.
64. Kolimi, P.; Narala, S.; Nyavanandi, D.; Youssef, A.A.A.; Dudhipala, N. Innovative Treatment Strategies to Accelerate Wound Healing: Trajectory and Recent Advancements. *Cells* **2022**, *11*, 2439. https://doi.org/10.3390/cells11152439.
65. Zeng, X.; Chen, B.; Wang, L.; Sun, Y.; Jin, Z.; Liu, X.; Ouyang, L.; Liao, Y. Chitosan@Puerarin Hydrogel for Accelerated Wound Healing in Diabetic Subjects by MiR-29ab1 Mediated Inflammatory Axis Suppression. *Bioact. Mater.* **2023**, *19*, 653–665. https://doi.org/10.1016/j.bioactmat.2022.04.032.
66. Zhang, W.; Qu, X.; Zhu, Z.; Wang, L.; Qi, Q.; Zhou, P.; Wang, X.; Li, W. Inhibition of MiR-139-5p by Topical JTXK Gel Promotes Healing of Staphylococcus Aureus-Infected Skin Wounds. *Cells Dev.* **2021**, *166*, 203658. https://doi.org/10.1016/j.cdev.2021.203658.
67. Liu, Z.; Zhang, L.; Toma, M.A.; Li, D.; Bian, X.; Pastar, I.; Tomic-Canic, M.; Sommar, P.; Xu Landén, N. Integrative Small and Long RNA Omics Analysis of Human Healing and Nonhealing Wounds Discovers Cooperating MicroRNAs as Therapeutic Targets. *Elife* **2022**, *11*, e80322. https://doi.org/10.7554/eLife.80322.
68. Hanna, J.; Hossain, G.S.; Kocerha, J. The Potential for MicroRNA Therapeutics and Clinical Research. *Front. Genet.* **2019**, *10*, 478. https://doi.org/10.3389/fgene.2019.00478.
69. Zomer, H.D.; Trentin, A.G. Skin Wound Healing in Humans and Mice: Challenges in Translational Research. *J. Dermatol. Sci.* **2018**, *90*, 3–12. https://doi.org/10.1016/j.jdermsci.2017.12.009.
70. Chakraborty, C.; Sharma, A.R.; Sharma, G.; Lee, S.-S. Therapeutic Advances of MiRNAs: A Preclinical and Clinical Update. *J. Adv. Res.* **2021**, *28*, 127–138. https://doi.org/10.1016/j.jare.2020.08.012.
71. Hoversten, K.P.; Kiemele, L.J.; Stolp, A.M.; Takahashi, P.Y.; Verdoorn, B.P. Prevention, Diagnosis, and Management of Chronic Wounds in Older Adults. *Mayo Clin. Proc.* **2020**, *95*, 2021–2034. https://doi.org/10.1016/j.mayocp.2019.10.014.
72. Global Biomaterials Market Size & Share Report, 2022 - 2030 2023.
73. Biomaterials Market Size, Growth | Global Industry Analysis, 2027 2023.
74. Biomaterials Market Size | Key Analysis | Forecast - 2030. *Allied Mark. Res.* 2023.
75. Biomaterials Market 2023.
76. Biomaterials Market Size to Hit US$ 390.92 Billion by 2027 2023.

77. Ltd, M.D.F. North America Biomaterials Market Analysis | 2022 to 2027. *Mark. Data Forecast* 2023.
78. EMA Medical Devices. *Eur. Med. Agency* 2018.
79. Fergal, D. European Perspectives on Biomaterials for Health. *Eur. Wound Manag. Assoc. J.* **2015**, *15*, 54–58.
80. APAC Biomaterials Market Available online: http://www.marketdataforecast.com/.
81. Rômulo RN, A.; Ierecê ML, R. Biodiversity, Traditional Medicine and Public Health: Where Do They Meet? *J. Ethnobiol. Ethnomed.* **2007**, *3*, 14. https://doi.org/10.1186/1746-4269-3-14.
82. Shedoeva, A.; Leavesley, D.; Upton, Z.; Fan, C. Wound Healing and the Use of Medicinal Plants. *Evidence-Based Complement. Altern. Med.* **2019**. https://doi.org/10.1155/2019/2684108.
83. ASEAN Investment Report 2020–2021.
84. Life Expectancy by Country and in the World (2023) - Worldometer 2023.
85. Ageing and Health 2023.
86. Uludağ, H. Grand Challenges in Biomaterials. *Front. Bioeng. Biotechnol.* **2014**, *2*.
87. Williams, D.F. Challenges With the Development of Biomaterials for Sustainable Tissue Engineering. *Front. Bioeng. Biotechnol.* **2019**, *7*.
88. Ebrahimi, M. Chapter 12 - Standardization and Regulation of Biomaterials. In *Handbook of Biomaterials Biocompatibility*; Mozafari, M., Ed.; Woodhead Publishing Series in Biomaterials; Woodhead Publishing, 2020; pp. 251–265 ISBN 978-0-08-102967-1.
89. Biomaterial-Based Metabolic Regulation in Regenerative Engineering - Ma - 2019 - Advanced Science - Wiley Online Library 2023.
90. Overweight & Obesity.
91. Diabetes Fast Facts.
92. Zainuddin, L.R.M.; Isa, N.; Muda, W.M.W.; Mohamed, H.J. The Prevalence of Metabolic Syndrome According to Various Definitions and Hypertriglyceridemic-Waist in Malaysian Adults. *Int. J. Prev. Med.* **2011**, *2*, 229–237.
93. Ranasinghe, P.; Mathangasinghe, Y.; Jayawardena, R.; Hills, A.P.; Misra, A. Prevalence and Trends of Metabolic Syndrome among Adults in the Asia-Pacific Region: A Systematic Review. *BMC Public Health* **2017**, *17*, 101. https://doi.org/10.1186/s12889-017-4041-1.
94. Januschowski, K.; Irigoyen, C.; Pastor, J.C.; Srivastava, G.K.; Romano, M.R.; Heimann, H.; Stalmans, P.; Van Keer, K.; Boden, K.; Szurman, P.; et al. Retinal Toxicity of Medical Devices Used during Vitreoretinal Surgery: A Critical Overview. *Ophthalmologica.* **2018**, 1–8. https://doi.org/10.1159/000488504.
95. Kalaiselvan, V.; Shubhang, A.; Rajeev Singh, R. A Systematic Review on Research Documentation of Ocular Medical Device Focused on Perfluorocarbon Liquid (PFCL). *J. Allbiosolution* **2023**, *5*, 221.
96. Iglesias-Lopez, C.; Agustí, A.; Obach, M.; Vallano, A. Regulatory Framework for Advanced Therapy Medicinal Products in Europe and United States. *Front. Pharmacol.* **2019**, *10*.
97. Jarow, J.P.; Baxley, J.H. Medical Devices: US Medical Device Regulation. *Urol. Oncol.* **2015**, *33*, 128–132. https://doi.org/10.1016/j.urolonc.2014.10.004.
98. Sweet, B. V.; Schwemm, A.K.; Parsons, D.M. Review of the Processes for FDA Oversight of Drugs, Medical Devices, and Combination Products. *J. Manag. care Pharm. JMCP* **2011**, *17*, 40–50. https://doi.org/10.18553/jmcp.2011.17.1.40.
99. Bliznakov, Z.; Mitalas, G.; Pallikarakis, N. Analysis and Classification of Medical Device Recalls. In Proceedings of the World Congress on Medical Physics and Biomedical Engineering 2006; Magjarevic, R., Nagel, J.H., Eds.; Springer: Berlin, Heidelberg, 2007; pp. 3782–3785.
100. Oberweis, C.V.; Marchal, J.A.; López-Ruiz, E.; Gálvez-Martín, P. A Worldwide Overview of Regulatory Frameworks for Tissue-Based Products. *Tissue Eng. Part B. Rev.* **2020**, *26*, 181–196. https://doi.org/10.1089/ten.TEB.2019.0315.
101. Kramer, D.B.; Xu, S.; Kesselheim, A.S. Regulation of Medical Devices in the United States and European Union. *N. Engl. J. Med.* **2012**, *366*, 848–855. https://doi.org/10.1056/NEJMhle1113918.
102. Lisa M., S.; Steven, W. Medical Marketing in the United States, 1997-2016. *JAMA* **2019**, *321*, 80–96. https://doi.org/10.1001/jama.2018.19320.
103. *Fundamental Texts On European Private Law*; Hart Publishing, 2016; ISBN 978-1-78225-864-3 978-1-78225-865-0 978-1-78225-866-7 978-1-78225-867-4.
104. Yonesi, M.; Garcia-Nieto, M.; Guinea, G. V.; Panetsos, F.; Pérez-Rigueiro, J.; González-Nieto, D. *Silk Fibroin: An Ancient Material for Repairing the Injured Nervous System*; 2021; Vol. 13; ISBN 3491067928.
105. Yonesi, M.; Ramos, M.; Ramirez-Castillejo, C.; Fernández-Serra, R.; Panetsos, F.; Belarra, A.; Chevalier, M.; Rojo, F.J.; Pérez-Rigueiro, J.; Guinea, G. V; et al. Resistance to Degradation of Silk Fibroin Hydrogels Exposed to Neuroinflammatory Environments. *Polymers (Basel).* **2023**, *15*. https://doi.org/10.3390/polym15112491.
106. Martín-Martín, Y.; Fernández-García, L.; Sanchez-Rebato, M.H.; Marí-Buyé, N.; Rojo, F.J.; Pérez-Rigueiro, J.; Ramos, M.; Guinea, G. V.; Panetsos, F.; González-Nieto, D. Evaluation of Neurosecretome from Mesenchymal Stem Cells Encapsulated in Silk Fibroin Hydrogels. *Sci. Rep.* **2019**, *9*, 1–15. https://doi.org/10.1038/s41598-019-45238-4.

107. akovljevic, M.; Wu, W.; Merrick, J.; Cerda, A.; Varjacic, M.; Sugahara, T. Asian Innovation in Pharmaceutical and Medical Device Industry - beyond Tomorrow. *J. Med. Econ.* **2021**, *24*, 42–50. https://doi.org/10.1080/13696998.2021.2013675.
108. George, B. Registration of Medical Devices. *Perspect. Clin. Res.* **2010**, *1*, 90–93.
109. Mohit; Deep, A.; Khurana, G.; Kumar, J.; Monga, A. Comparison of Regulatory Requirements for Registration of Pharmaceutical Drugs in Asean and GCC Regions. *Appl. Clin. Res. Clin. Trials Regul. Aff.* **2019**, *6*, 62–70.
110. Aprile, P.; Letourneur, D.; Simon-Yarza, T. Membranes for Guided Bone Regeneration: A Road from Bench to Bedside. *Adv. Healthc. Mater.* **2020**, *9*. https://doi.org/10.1002/adhm.202000707.
111. Postolović, K.; Ljujić, B.; Kovačević, M.M.; Đorđević, S.; Nikolić, S.; Živanović, S.; Stanić, Z. Optimization, Characterization, and Evaluation of Carrageenan/Alginate/Poloxamer/Curcumin Hydrogel Film as a Functional Wound Dressing Material. *Mater. Today Commun.* **2022**, *31*, 103528. https://doi.org/10.1016/j.mtcomm.2022.103528.
112. Diaz-Gomez, L.; Gonzalez-Prada, I.; Millan, R.; Da Silva-Candal, A.; Bugallo-Casal, A.; Campos, F.; Concheiro, A.; Alvarez-Lorenzo, C. 3D Printed Carboxymethyl Cellulose Scaffolds for Autologous Growth Factors Delivery in Wound Healing. *Carbohydr. Polym.* **2022**, *278*, 118924. https://doi.org/10.1016/j.carbpol.2021.118924.
113. Hou, L.; Wang, W.; Wang, M.-K.; Song, X.-S. Acceleration of Healing in Full-Thickness Wound by Chitosan-Binding BFGF and Antimicrobial Peptide Modification Chitosan Membrane. *Front. Bioeng. Biotechnol.* **2022**, *10*.
114. Mh Busra, F.; Rajab, N.F.; Tabata, Y.; Saim, A.B.; B H Idrus, R.; Chowdhury, S.R. Rapid Treatment of Full-Thickness Skin Loss Using Ovine Tendon Collagen Type I Scaffold with Skin Cells. *J. Tissue Eng. Regen. Med.* **2019**, *13*, 874–891. https://doi.org/10.1002/term.2842.
115. Hussain, Z.; Pandey, M.; Thu, H.E.; Kaur, T.; Jia, G.W.; Ying, P.C.; Xian, T.M.; Abourehab, M.A.S. Hyaluronic Acid Functionalization Improves Dermal Targeting of Polymeric Nanoparticles for Management of Burn Wounds: In Vitro, Ex Vivo and in Vivo Evaluations. *Biomed. Pharmacother.* **2022**, *150*, 112992. https://doi.org/10.1016/j.biopha.2022.112992.
116. Zhang, Y.; Zheng, Y.; Shu, F.; Zhou, R.; Bao, B.; Xiao, S.; Li, K.; Lin, Q.; Zhu, L.; Xia, Z. In Situ-Formed Adhesive Hyaluronic Acid Hydrogel with Prolonged Amnion-Derived Conditioned Medium Release for Diabetic Wound Repair. *Carbohydr. Polym.* **2022**, *276*, 118752. https://doi.org/10.1016/j.carbpol.2021.118752.
117. ACTICOAT Available online: https://www.smith-nephew.com/es-es/health-care-professionals/products/advanced-wound-management/acticoat-global#overview.
118. 3M™ Actisorb™ Silver 220 Activated Charcoal Dressing with Silver Available online: https://www.3m.co.za/3M/en_ZA/p/d/b5005265071/.
119. ALGISITE M Calcium Alginate Dressing Available online: https://www.smith-nephew.com/es-es/health-care-professionals/products/advanced-wound-management/algisite-ppl.
120. AmnioExcel® Available online: https://www.integralife.com/es/amnioexcel-amniotic-allograft-membrane/product/wound-reconstruction-care-outpatient-clinic-private-office-treat-amnioexcel-amniotic-allograft-membrane.
121. AQUACEL® /Hydrofiber® Available online: https://www.convatec.com/es-es/productos/cuidado-avanzados-de-heridas/tipo-de-herida/pc-wound-burns/aquacel-extra/.
122. Biatain® Silicone Available online: https://productos.coloplast.com.ar/coloplast/heridas/biatain-silicone/biatain-silicone/.
123. CalciCare™ Calcium Alginate Dressing | Calcium Alginate Dressings | Hollister US Available online: https://www.hollister.com/en/products/wound-care-products/wound-dressings/calcium-alginate-dressings/calcicare-calcium-alginate-dressing#.
124. Cutimed Available online: https://medical.essity.de/marken/cutimed.html.
125. Advanced Wound Dressings | Triage Meditech Available online: https://www.triagemeditech.com/advance-wound-dressings.
126. Fibracol Plus Collagen Wound Dressing with Alginate Available online: https://www.vitalitymedical.com/johnson-and-johnson-fibracol-plus-collagen-wound-dressing-with-alginate.html.
127. Granulox® Available online: https://www.molnlycke.es/productos-soluciones/granulox/.
128. Hyperoil - For Any Wound, Any Time Available online: https://hyperoil.com/.
129. Kaltostat® Available online: https://www.convatec.com/es-es/productos/cuidado-avanzados-de-heridas/tipo-de-herida/pc-wound-diabetic-foot-ulcers/b68c3a76-bd08-404d-a982-efeb45b1879d/.
130. KITO ACTIVATOR CHITOSAN WOUND HEALING HYDROGEL BARRIER | Tradekorea Available online: https://www.tradekorea.com/product/detail/P766932/KITO-ACTIVATOR-CHITOSAN-WOUND-HEALING-HYDROGEL-BARRIER.html.

131. Medihoney HoneyColloid Leptospermum Hydrocolloid Dressings Available online: https://www.vitalitymedical.com/derma-sciences-medihoney-honeycolloid-dressing-leptospermum-hydrocolloid.html.
132. Mepilex® Ag Available online: https://www.molnlycke.es/productos-soluciones/mepilex-ag/.
133. NeutroPhase Available online: https://novabay.com/products/neutrophase/.
134. Omnigraft Available online: https://www.integralife.com/es/omnigraft-dermal-regeneration-matrix/product/wound-reconstruction-care-outpatient-clinic-private-office-treat-omnigraft-dermal-regeneration-matrix.
135. PriMatrix® Dermal Repair Scaffold Available online: https://www.integralife.com/primatrix-dermal-repair-scaffold/product/wound-reconstruction-care-inpatient-acute-or-primatrix-dermal-repair-scaffold.
136. 3M™ Promogran Prisma™ Collagen Matrix with ORC and Silver Available online: https://www.3m.com/3M/en_US/p/d/b5005265080/.
137. REGRANEX Available online: https://www.smith-nephew.com/en-us/health-care-professionals/products/advanced-wound-management/regranex#productfeatures.
138. Restore™ Hydrocolloid Dressing with Foam Backing | Wound Dressings | Hollister US Available online: https://www.hollister.com/en/products/wound-care-products/wound-dressings/hydrocolloid-dressings/restore-hydrocolloid-dressing-with-foam-backing.
139. SILVERCEL™ Available online: https://www.acelity.com/healthcare-professionals/global-product-catalog/catalog/silvercel-dressing.
140. Suprasorb C Collagen Wound Dressing, 12 x 8 Cm by SUPRASORB - Shop Online for Health in Australia Available online: https://www.fishpond.com.au/Health/Suprasorb-C-Collagen-Wound-Dressing-12-x-8-cm/9999131799251?utm_source=googleps&utm_medium=ps&utm_campaign=AU.
141. V.A.C.® Therapy Available online: https://www.acelity.com/healthcare-professionals/global-product-catalog/catalog/vac-freedom.
142. Insticare VTG2901 Manufacturer & Supplier | Triage Meditech Available online: https://www.triagemeditech.com/vtg-2901-new-advanced-solution.
143. RHEACELL >< Technology Available online: https://www.rheacell.com/en/technology/.
144. Home of TruStem Cell Therapy - Top U.S. Stem Cell Therapy & Treatment Center TruStem Cell Therapy™ Available online: https://trustemcell.com/.
145. XSTEM Available online: https://www.xintela.se/en/press-release?slug=xintela-starts-clinical-study-of-xstem-r-in-knee-osteoarthritis.
146. Li, H.; Han, X.; Zuo, K.; Li, L.; Liu, J.; Yuan, X.; Shen, Y.; Shao, M.; Pang, D.; Chu, Y.; et al. MiR-23b Promotes Cutaneous Wound Healing through Inhibition of the Inflammatory Responses by Targeting ASK1. *Acta Biochim. Biophys. Sin. (Shanghai).* **2018**, *50*, 1104–1113. https://doi.org/10.1093/abbs/gmy109.
147. Bi, Q.; Liu, J.; Wang, X.; Sun, F. Downregulation of MiR-27b Promotes Skin Wound Healing in a Rat Model of Scald Burn by Promoting Fibroblast Proliferation. *Exp. Ther. Med.* **2020**, *20*, 63. https://doi.org/10.3892/etm.2020.9191.
148. Wu, J.; Li, X.; Li, D.; Ren, X.; Li, Y.; Herter, E.K.; Qian, M.; Toma, M.-A.; Wintler, A.-M.; Sérézal, I.G.; et al. MicroRNA-34 Family Enhances Wound Inflammation by Targeting LGR4. *J. Invest. Dermatol.* **2020**, *140*, 465-476.e11. https://doi.org/10.1016/j.jid.2019.07.694.
149. Bi, X.; Zhou, L.; Liu, Y.; Gu, J.; Mi, Q.-S. MicroRNA-146a Deficiency Delays Wound Healing in Normal and Diabetic Mice. *Adv. Wound Care* **2022**, *11*, 19–27. https://doi.org/10.1089/wound.2020.1165.
150. Liu, L.; Chen, R.; Jia, Z.; Li, X.; Tang, Y.; Zhao, X.; Zhang, S.; Luo, L.; Fang, Z.; Zhang, Y.; et al. Downregulation of Hsa-MiR-203 in Peripheral Blood and Wound Margin Tissue by Negative Pressure Wound Therapy Contributes to Wound Healing of Diabetic Foot Ulcers. *Microvasc. Res.* **2022**, *139*, 104275. https://doi.org/10.1016/j.mvr.2021.104275.
151. de Kerckhove, M.; Tanaka, K.; Umehara, T.; Okamoto, M.; Kanematsu, S.; Hayashi, H.; Yano, H.; Nishiura, S.; Tooyama, S.; Matsubayashi, Y.; et al. Targeting MiR-223 in Neutrophils Enhances the Clearance of Staphylococcus Aureus in Infected Wounds. *EMBO Mol. Med.* **2018**, *10*, e9024. https://doi.org/10.15252/emmm.201809024.
152. Xie, J.; Wu, W.; Zheng, L.; Lin, X.; Tai, Y.; Wang, Y.; Wang, L. Roles of MicroRNA-21 in Skin Wound Healing: A Comprehensive Review. *Front. Pharmacol.* **2022**, *13*, 828627. https://doi.org/10.3389/fphar.2022.828627.
153. Li, D.; Li, X.I.; Wang, A.; Meisgen, F.; Pivarcsi, A.; Sonkoly, E.; Ståhle, M.; Landén, N.X. MicroRNA-31 Promotes Skin Wound Healing by Enhancing Keratinocyte Proliferation and Migration. *J. Invest. Dermatol.* **2015**, *135*, 1676–1685. https://doi.org/10.1038/jid.2015.48.
154. Zhang, X.-F.; Wang, T.; Wang, Z.-X.; Huang, K.-P.; Zhang, Y.-W.; Wang, G.-L.; Zhang, H.-J.; Chen, Z.-H.; Wang, C.-Y.; Zhang, J.-X.; et al. Hypoxic UcMSC-Secreted Exosomal MiR-125b Promotes Endothelial Cell Survival and Migration during Wound Healing by Targeting TP53INP1. *Mol. Ther. - Nucleic Acids* **2021**, *26*, 347–359. https://doi.org/10.1016/j.omtn.2021.07.014.

155. Jiang, B.; Tang, Y.; Wang, H.; Chen, C.; Yu, W.; Sun, H.; Duan, M.; Lin, X.; Liang, P. Down-Regulation of Long Non-Coding RNA HOTAIR Promotes Angiogenesis via Regulating MiR-126/SCEL Pathways in Burn Wound Healing. *Cell Death Dis.* **2020**, *11*, 1–15. https://doi.org/10.1038/s41419-020-2247-0.
156. Yang, L.; Zheng, Z.; Zhou, Q.; Bai, X.; Fan, L.; Yang, C.; Su, L.; Hu, D. MiR-155 Promotes Cutaneous Wound Healing through Enhanced Keratinocytes Migration by MMP-2. *J. Mol. Histol.* **2017**, *48*, 147–155. https://doi.org/10.1007/s10735-017-9713-8.
157. Jin, Y.; Tymen, S.D.; Chen, D.; Fang, Z.J.; Zhao, Y.; Dragas, D.; Dai, Y.; Marucha, P.T.; Zhou, X. MicroRNA-99 Family Targets AKT/MTOR Signaling Pathway in Dermal Wound Healing. *PLoS ONE* **2013**, *8*, e64434. https://doi.org/10.1371/journal.pone.0064434.
158. Gallant-Behm, C.L.; Piper, J.; Lynch, J.M.; Seto, A.G.; Hong, S.J.; Mustoe, T.A.; Maari, C.; Pestano, L.A.; Dalby, C.M.; Jackson, A.L.; et al. A MicroRNA-29 Mimic (Remlarsen) Represses Extracellular Matrix Expression and Fibroplasia in the Skin. *J. Invest. Dermatol.* **2019**, *139*, 1073–1081. https://doi.org/10.1016/j.jid.2018.11.007.
159. Mulholland, E.J.; Dunne, N.; McCarthy, H.O. MicroRNA as Therapeutic Targets for Chronic Wound Healing. *Mol. Ther. Nucleic Acids* **2017**, *8*, 46–55. https://doi.org/10.1016/j.omtn.2017.06.003.