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Novel therapeutics and treatment regimen in wound healing

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Abstract
Since antiquity, wounds have inflicted enormous pain and suffering to mankind. Amelioration of this pain, faster healing was a daunting task for us from ancient times. The process of wound healing is complex and tightly regulated which mainly affect certain tissues of the bodyprimarily including the skin. It is of paramount importance as it concerns reinstating the integrity of the skin tissues. The cascade of recovery of the wounds may be affected due to a plethora of disease processes, which is further known to induce considerable distress and perturbation to the patients. Medical science has been keen on understanding the mechanism of wound healing and has used many medicaments to help reduce the duration of relapse or recovery. The treatment methods span from the usage of many phytoconstituents to the modern regimen of using novel formulations. The aim of this article is therefore to review the recent biotechnological interventions along with novel treatment regimen that have been devised over the years and pose great potential for the effective treatment of a multitude of wounds.

Keywords: Wound, wound healing, wound dressing

1. Introduction
The human skin is regarded as the single largest organ of the human body and characterizes its first line of defense. It is primarily concerned with the protection of the human body from various mechanical stresses and pressure. It also confines the leverage of variations in physical constants like temperature, atmospheric pressure, and humidity [1]. Thus the skin is such a vital organ, the integrity of the skin has to be restored by a series of physiological processes that have been targeted to repair the impaired tissues. The skin wound is portrayed by an injury made on the skin due to a plethora of conditions including trauma, laceration, abrasion, or contusion [2]. The wound healing and scar formation are highly maintained physiological retort to wound formation in most tissue, oftentimes the cutaneous tissues, in a preponderance of higher organisms, which occurs in a corollary of well-characterized stages. These stages may be categorized into Inflammation, Proliferation, and Remodeling, which are targeted to heal and repair the affected tissues and also to reinstate their routine functions. Seldom owing to a plethora of physiological phenomena, this sequence can also be disturbed, and thus may also come to a standstill before completion, which further results in many undesirable resultants spanning from the formation of a large local scar to organ-circumfusing fibrosis. These processes or outgrowths are generally recognized to cause a lot of cosmetic exasperation and botheration to the individual. These might also pave ways to significantly diminish the loss of function or ability of the tissue and may turn out to chronic non-healing wounds as in the case of ulcers which include venous, arterial, diabetic, pressure, and traumatic ulcers [3].

2. Novel approaches to accelerate wound healing
Faster wound healing is an interplay of plethora of physical, chemical, biological, and microbial factors with an interdisciplinary bridge that help counteract the parameters which delay the healing of wounds.
The most evident factors showing a profound effect on wound healing primarily includes:

2.1 Wound healing by dermal grafts
The usage of Dermal grafting has been a method of choice in a variety of therapies for ages altogether. It has been successfully employed in the treatment and complete cure for both acute and chronic wounds, with the lowest number of morbidities arising as a side-effect and optimum efficacy achieved in the shortest period. This is employed in the treatment of chronic wounds, with an intent to attain complete closure of the wound with the functional regeneration of the injured tissue, contrary to the acute wounds which are done to enhance the aesthetic outcome of a wound using a Full-Thickness wound graft (FTSGs), in the affected

area. The rationale of the regenerative efforts is to diminish the skin defects, these autologous grafts aid as both tissue substitutes and also provide a pharmacological incentive for the recuperation of the wound [4].
The treatments using the grafts are enhanced using the skin flaps which are estimated to bring about more textural durability and contracture, and thereby reducing the complexity of the surgical procedure and the complications arising thereafter, and can be achieved by reducing the duration of hypoxia and consequent ischemia and also increasing the blood supply to the grafted flap and thereby increasing innervation of oxygen permeability to the tissues. This further reduces the ischemic time for the tissues and the skin grafts thus have quality at par with the flaps in precocious points after the transplantation [5].
The efficacy of the flaps can be exponentially increased by the exposure of the patient to a novel technique popularized as the Hyperbaric Oxygen Therapy (HBOT), where the patients daily were made to breathe 100% oxygen through a mask at an absolute pressure of 2-5 atmospheres during four sessions for a total duration of 85 minutes [6].

Table 1: Factors influencing Wound Healing

Local variables	Systemic variables	Medication therapy	Pathological variables
Site of Injury	Age	Non-Steroidal Anti Inflammatory Drugs	Diabetes
Impact of Injury	Gender and Sex Hormones	Chemotherapeutic Agents	Genetic or Hereditary Skin Healing Disorders
Infection	Psychological Stress	Radiation Therapy	Obesity
Vascular Oxygenation	Nutrition	Steroidal Drugs	Immunocompromised Conditions (AIDS, Cancer)
Mechanical Stress	Alcoholism and Smoking Habits	Cholesterol-Lowering Agents	Keloids or Fibrosis
Irritants	Immobility	Glucocorticoid Steroids	Jaundice or Uremia

2.2 Wound healing by hydrogel formulations
Hydrogels are currently regarded as the most efficacious method of wound healing as in cases of both acute and chronic wounds, with little or no side effects and are cogitated to be a potential breakthrough in the very nearer future. These formulations are capable of retaining a damp and moist environment in limits of the injured area, being permeable to gases exchange through the material, and also acting as a skin substitute that resists infection by the pathogens and absorbing the exudate. This can also be removed with great ease and is known to be innocuous to the healing tissues. The injectable hydrogels are known to have an added benefit to encapsulate certain drugs in situ, thereby filling the wounds even at the irregular areas and thereby strongly clinging on to the injured tissues [7].
There is a multitude of hydrogel formulations that are currently employed in the treatment of a plethora of wound injuries, ranging from acute to chronic, and from abrasions to burn injuries. It is therefore of paramount importance that these formulations are having a great anti-bacterial activity to avoid any chances of septicity. Many hydrogels are formulated using Chitosan which is known to possess inherent antibacterial activity alongside certain other advantages including pronounced analgesic effect and haemostatic activity. In addition, the Quaternized chitosan-g-polyaniline copolymer exhibits enhanced water solubility, antibacterial activity, and cytocompatibility, suggesting its stellar performance to prepare an antibacterial injectable hydrogel wound dressing [8].
The novel new-generation hydrogel that has been used for potential applications in the wound dressing possesses self-healing ability and mechanical toughness, with the potential to cure both the skin as well as the muscle damage and thus, has been employed in the treatment of not only primary and secondary but also tertiary degree bruises and wounds. The self-healing ability of the hydrogel is obtained through the hydrogen linking and dynamic Schiff cross-linking between Dopamine Grafted Oxidized Sodium Alginate (OSA-DA) and Poly-Acrylamide (PAM) chains. This covalent cross-linking is calculable for its stable mechanical armature. This unique compilation of both physical and chemical cross-linking contributes to the novel self-healing ability (80% mechanical recuperation in 6 hours), high tensile strength (0.109 MPa), and ultra-stretchability (2550%) which are highly preferred for wound dressing purposes. Owing to the abundance of Catechol groups on the OSA-DA chains, this formulation is known to delineate immense cell affinity and tissue adhesiveness, marking a potential refinement in the wound treatment [9]. The smart-materials, which are thought to instinctively respond to the dynamic inner-state variables of the living tissues are currently the topic of great interest, to develop self-adapting solid materials that can automatically change their orientation, without the influence of any external stimulus, which is conferred by the unique mobility of the solid-gel owing to the self-adapting property of the chitosan-based self-healing hydrogel and the Schiff base network, among the many others that are currently being studied [10].

2.3 Wound healing by employing growth factors
The usage of several growth factors can help trigger some of the most essential agents which are vital in the healing process which includes pivotal roles like neovascularization and cell migration and additionally may eliminate some of the harmful ones like fibrosis, which may have a deleterious effect on the wound and the dermal barrier as a whole. The key players in these include the multitude of growth factors including Transforming Growth Factor-β (TGF-β), Fibroblast Growth Factor (FGF), Epidermal Growth Factor (EGF), Vascular Endothelial Growth Factor (VEGF), Platelet-Derived Growth Factor (PDGF), and Interleukins like Interleukin-1 (IL-1), Interleukin-6 (IL-6) and Interleukin-8 (IL-8), which aid in proper and efficient wound regeneration naturally and synthetically producing advanced skin substitutes [11]. Of the numerous growth factors essential for wound regeneration, we may focus on some really important ones.

2.3.1 Transforming Growth Factor-β (TGF-β)
The Transforming Growth Factor-β is a homodimeric protein, of about 25 kilodaltons (kDa) and plays a plentitude of biological functions and has a profound effect on the epithelium-derived and mesenchymal-derived cells [12]. There are mainly three types of TGF-βs which are studied for a significant role in wound healing, namely TGF-β1, TGF-β2,

and lastly TGF-β3. The embryonic wounds that heal without forming any scars are observed to express low levels of TGF-β1 and TGF-β2, but a significantly high level of TGF-β3, in contrast to the adult scarring wounds which express a high level of TGF-β1 and TGF-β2 and a lower amount of TGF-β3 (11). Although, the effect of TGF-β on wound healing and regeneration is quite complicated, but is strongly believed to stimulate collagen production in the dermal fibroblasts by a process of fibroblast-to-myofibroblast transition [13]. The TGF-β is often associated with the inhibition of the epidermal keratinocyte proliferation and growth, although an excess of the latter would increase the cellular rigidity which would result in protrusions and keloid formation [14]. A study including the small compounds that suppressed type-I collagen production in fibroblasts has observed HSc025, which antagonizes the TGF-β/Smad signal, significantly accelerated the healing of the wound in mice models, particularly by the modification of the infiltration, proliferation, and migration of the various cellular and tissue components [15]. Therefore, it shows that TGF-β, possibly functions as a pleiotropic modulator in this process, and its subsequent alterations in adjunct to dermal substitutes may prove as a gold standard to heal wounds with negligible fibrosis, which still is not completely achieved by the current treatment regimens.

2.3.2 Fibroblast Growth Factor (FGF)

The Fibroblast Growth Factor (FGF) is considered to contribute to the wound healing process by primarily improving the angiogenesis, and also by cell migration and proliferation to some extent. The Fibroblast Growth factor-2 (FGF-2), also deemed as the basic FGF (bFGF), is correlated with the neovascularization and subsequent thickening of both the dermis and epidermis [16]. Furthermore, it is attributed to preventing the contraction of the wound through inhibition of the actin filaments of α-smooth muscle, and additional fibrosis reduction by preventing fibroblast differentiating into myofibroblasts [17]. Thus, this factor provides controlled angiogenesis in the wound, therefore breathing life into the newly formed tissue.

2.3.3 Epidermal Growth Factor (EGF)

The Epidermal Growth Factor (EGF) enhances wound healing and regeneration by their pronounced action on enhancing migration and proliferation of the keratinocytes and fibroblasts. Additionally, they prove as an aid in angiogenesis and epithelialization [18]. They indirectly trigger the growth factor secretion produced by the fibroblasts, thus further accelerating the wound healing (19). The Endothelial Growth Factor Receptor (EGFR) and Endothelial Growth Factor (EGF) – like peptides are often over-expressed in human carcinomas and have a profound ability to induce cellular transformations, as suggested by numerous in-vitro and in-vivo studies [20]. Research including the utilization of Epidermal Growth Factor (EGF) and an EGF family member, Neuregulin (NRG-1), whose cellular role is in the promotion of proliferation and migration in fibroblasts and keratinocytes into a wound site during the primordial steps of skin regeneration, induced rapid proliferation of skin cells in an ERK pathway-dependent manner and exhibited efficient wound healing in Sprague-Dawley rat full-thickness excision and grafting model. These results provide the foundation for expanding the growth factor functionalized grafts to clinical applications in cases of severe skin injuries [21].

2.3.4 Vascular Endothelial Growth Factor (VEGF)

The Vascular Endothelial Growth Factor (VEGF) is the major growth factor responsible for angiogenesis, which is defined as the phenomenon involving the growth of new blood vessels from the pre-existing ones [22]. The VEGF protein tyrosine kinase receptors have been proved to show its expression on endothelial cells, including VEGFR1 (alternatively known as Fms-like tyrosine kinase-1) and VEGFR2 (alternatively known as fetal liver kinase-1 or kinase insert domain-containing receptor) [23]. But it is also to be kept in notice that, higher levels of VEGF may be potentially related to numerous cancers, fibrosis, the formation of scars, and microvascular defects in patients diagnosed with diabetes [24].

2.3.5 Platelet-Derived Growth Factor (PDGF)

The Platelet-Derived Growth Factor (PDGF) is involved in a multitude of growth processes, which during embryogenesis plays a pivotal role in the vascular development by stimulating the proliferation and survival of the vascular mural cells, in contrast to that in adults where it is proven to be a potent mitogen and survival factor for fibroblasts and other mesenchymal cells [25]. The Platelet-Derived Growth Factors (PDGFs) were discovered for more than two decades. The PDGF family consists of five different disulfide-linked dimers built up of four different genes. These isoforms, PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC, and PDGF-DD, act by employing two tyrosine kinase receptors namely PDGF receptors α and β [27]. The potential clinical application of PDGF is a potent agent to improve the tissues deficient in wound repair. Additionally, a thorough understanding of PDGF may also permit the development of specific antagonists to limit its effect in many proliferative diseased conditions [27].

2.4 Wound healing by stem cells

During the proliferative phase of the wound healing procedure, there is a dire need to increase the total epithelial cell count to indemnify for the lost cells, to achieve successful re-epithelialization. Excessive renewal over the differentiation can easily be accomplished by increasing the proportion of the cells that undergo differentiation. The same principle has been exploited in the stem-cell therapy as observed in a multitude of experiments including, when the stem cells from the hair follicle or the infundibulum were engaged upon the injured tissue, they gradually lose their initial identity and get reprogrammed to differentiate to the epithelial wound tissue [28].

This treatment regimen has been tested for more than a decade on various conditions, especially in complex cases of burns and diabetes, where the repair process is not considered sufficient to achieve a concrete remedy, in which the resultant is neither aesthetically nor functionally complete. Although the epidermal stem cells in the basal layer that act as an endogenous source of stem cells are potent enough to regenerate the skin, these are not ample enough to provide an accurate repair after intensive skin damage. Thus, this therapy may be regarded as a novel therapeutic strategy as it employs an exogenous supply of undifferentiated stem cells in such traumatic conditions [29].

The current interest of a multitude of scientists and researchers across the globe, is to find out sources of stem cells that help in the re-epithelialization of the wounds and the injured tissue and which proliferates, differentiate, and is known to survive for a long term and barely targets a committed progenitor population. The stem cells that have been used in an experiment conducted by Mascré *et al*. (2012) included the usage of Keratin 14 which is known to target basal cells of the epidermal tissue also including a progenitor population that proliferates and differentiates and Involculin which only targets a committed progenitor population. Both of these populations were employed at the wounded area, but it was predominantly found that the progenies of Keratin 14 expressing cells survived the long term, in contrast to the progeny of Involculin expressing cells that were lost earlier. This study sheds light on the significance of the relatively undifferentiated cells in the basal layer of the dermal epithelium, and their contribution to wound healing after injury [30].

A lot of research is also being conducted concerning the utilization of Mesenchymal Stem Cells (MSCs), Embryonic Stem Cells (ESCs), and Induced Pluripotent Stem Cells. The harnessing of the adult Mesenchymal Stem Cells (MSCs) avoids the ethical concerns regarding the fetal tissue harvest as in the case with the embryonic-derived tissues. to date have been successfully isolated from a plethora of sources including the Bone Marrow, Umbilical Cord Blood, Wharton's Jelly, and Adipose Tissues, where its origin plays a major determinant of the progenitor characteristics. These have been tested for their efficacy in a multitude of models like the adipose tissue-derived MSCs has proven efficacy to facilitate chondrogenesis possesses substantial osteogenetic potential in rabbit condylar defect model and murine calvarial defect model. Bone-marrow derived MSCs have proven to differentiate into a broad spectrum of non-hematopoietic cells and consequently produce many Growth Factors and Cytokines considered pivotal for tissue repair and remodeling and are currently being evaluated through clinical trials as the remediation of Chronic Obstructive Pulmonary Disorder (COPD), with varying inclusion criteria (varied stages of COPD). Thus, marking this therapy as a novel treatment for wound healing and remodeling [31].

2.5 Wound Healing by hyperbaric Oxygen Therapy (HBOT)

The HBOT has been successfully proposed in a multitude of ailments ranging from Influenza to carcinomas, since its clinical recognition in 1956. Hyperbaric Oxygen Therapy (HBOT) is a treatment regimen where the patients breathe 100% oxygen gas inside a hyperbaric chamber that is pressurized to more than that of sea level (absolute 1 atmosphere) using a face mask, hood, or an endotracheal tube. For optimum clinical efficacy, the Undersea and Hyperbaric Medical Society (UHMS) standardizes the pressure to more than 1.4 ATA; but in clinical practice, applied pressure ranges from 2 to 3 ATA. In wound healing the protocol invariably adjunct to the standard wound care treatment typically constitutes HBOT Treatments of 1.5-2 hours per treatment and can also go up to 60 treatments. It is most likely for patients to portray better outcomes when treated with HBOT as early as possible following an embolism formation [32]. It is also currently employed as the treatment of choice in atypical wounds comprising Diabetic Foot Ulcers (DFUs) in wounded patients with certain other comorbidities like diabetes. The administration of hyperbaric oxygen increases the systemic oxygen concentration to as high as 2000 mmHg, whereas under normal conditions the tissue oxygen concentration usually ranges from 200 mmHg to 400 mmHg [33]. The HBOT exploits the principle that the Systemic Hyperoxygenation initiates the generation of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS), which in turn stimulates the cascade of increased synthesis of wound growth factor alongside stem cell mobilization which consequently increases the deposition of collagen fibers and fibroblast proliferation. Of all the wound growth factors, the most notable is the Vascular Endothelial Growth Factor (VEGF), which is primarily associated with neovascularization, which increases by about 40% under the hyperbaric conditions. The consequent result is the neovascularization in the injured tissues along with the added benefit of the decreased systemic inflammatory response in the compromised tissue [34]. There also exists another convergent mechanism of action of the HBOT as it is proposed for the treatment of carcinomas and associated wound healing, which departs from the notion of sequential tissue healing stages by activating a cascade of events or waves pertaining to ROS, RNS, Lactate, and Nitric Oxide. Furthermore, it is believed to have effects on several cell signaling events that converge to influence cell recruitment/ chemotaxis and gene regulation/protein synthesis responses which mediate wound healing [35]. This is still believed to be a treatment method for a multitude of disorders especially wound healing as it ensures that the patients obtain safe, effective, and economic treatment in chronic wounds. This currently serves as an arena to be thoroughly explored by the clinicians and researchers as there currently is a lack of clinical trials and advanced studies on the other causes of chronic wounds [36].

2.6 Wound healing using Negative Pressure Wound Therapy (NPWT)

The NPWT is a recent intervention in the field of wound therapy that has proven efficacy to promote healing, and also to reduce the rates of amputation in patients suffering from wounds or in cases of patients with wounds having certain comorbidities like those with Diabetic Foot Ulcers (DFUs). Sometimes, this is unambiguously also addressed as Vacuum-Assisted Wound Closure (VAWC). It is currently accepted as a treatment regimen in wound care and is promoted for use on complex wounds, as an adjunct to the standard care or therapy. It majorly employs the usage of a wound dressing through which a negative pressure or vacuum is applied and the suction created helps in the evacuation of the wound and the tissue fluid from the compromised area, directly into a canister. Although this intervention was developed in the 1990s, it's acceptance and usage has been humongous over the past few years. The US Department of Health and Human Services in 2009 had reported that the Medicare payments from 2001 to 2007 for the NPWT surged from USD 24 million to a phenomenal USD 164 million showing an increase of nearly 600% [37].

The therapy employs the usage of suction pressure, although the amount of pressure used can vary and there is no finite protocol to use, however under the clinical conditions, the applied pressure varies from 75 mmHg to 150 mmHg, with 125 mmHg being the one most commonly used. The NPWT market has certainly grown over the last decade, with the machines becoming more small, compatible, and portable, the most advanced machines also introduced the concept of 'single-use' or 'disposable' negative pressure products (for instance, PICO: Smith & Nephew, UK). Ad hoc, non-commercial, negative pressure devices are also known to be used in resource-deprived settings. These devices are generally known to employ the simple and more primitive wound dressings, such as gauze, or transparent, occlusive (non-permeable) dressings, with a negative pressure being

generated in the hospital by vacuum suction pumps. The NPWT has now been employed by a multitude of health care professionals for use in both primary and secondary community care, especially following the introduction of ambulatory systems [38].
The NPWT therapy aids in wound healing by collecting the high volumes of exudates, thus reducing the frequency to change the dressings especially in cases of anatomically challenging wounds as in cases of wounds pertaining to the patients with comorbidities like diabetes mellitus and accident wounds. Consequently, this also helps keep the wound clean and reduces odour. The therapeutic efficacy of the therapeutic regimen is believed to be because the application of mechanical force onto the wound provides biologically credible processes that promote the wound healing process mainly by the drawing together of the wound edges, enhanced perfusion, and the removal of infectious material and exudate [39]. This is still being a subject of thorough study and much interest of researchers and clinicians as they are still trying to understand the molecular effects of negative pressure on the wound bed [40].

2.7 Wound healing using Bio-Glass therapy
Biomaterials are undoubtedly one of the most critical factors that play a pivotal role in the field of tissue engineering. It has been widely recognized that bioactive materials have a great influence on cellular behaviours during the processes of tissue engineering. Bioglass (BG) is a bioactive silicate material, which is the first man-made inorganic material used in the engineering of bone tissue, because of its pronounced osteostimulatory ability. In the last decade, Bioglass has been employed in the engineering of soft tissues as well. Bioglass constitutes of Silicon Oxide (SiO_2), Sodium Oxide (Na_2O), Calcium Oxide (CaO), and Phosphorous Pentoxide (P_2O_5) in specific proportions, and the reactions that take place on the surface of the Bioglass stimulates the release of soluble ions primarily comprising Si, Ca and P [41].
During some extensive *in vitro* studies, the Bioglass ion extracts prevented the death of the Human Umbilical Vein Endothelial Cells (HUVECs) following a case of hypoxia in a proportional dose-dependent manner, possibly through the connexin hemichannel modulation. BG also proved to show stimulatory effects on the gap junction pertaining between the HUVECs and also upregulated the Connexin 43 (Cx43) expression. Additionally, BG also stimulated the expression of Vascular Endothelial Growth Factor (VEGF) and also the basic Fibroblast Growth Factor (bFGF) as well as their receptors, and Vascular Endothelial Cadherin in HUVECs, all of which are known to play key roles in the vascularization of the granular tissue [42].
The Bioglass formulations are estimated to have room for infinite possibilities due to the varying concentrations of the constituting inorganic components, and slight variation in their concentrations may elicit a spectrum of therapeutic outcomes. They also possess the ability to be formulated into various medicaments having chemical constituents containing proven pharmacophores instilled into the formulation [43]. Several such medicaments are currently being produced, one such is the ones containing gold nanoparticles (AuNPs) as the gold can increase the rate of wound healing including the regeneration of tissue, the formation of connective tissues and, angiogenesis [44]. The Bioglass has also been studied by building an inter-therapeutic regimen that primarily merges the hydrogel therapy and Bioglass formulation, where the Bioglass resembles a hydrogel that encapsulates drug moieties in a Human Serum Albumin (HSA) carrier. This is an ideal carrier for drug delivery being the most abundant plasma protein, its biodegradability, lack of toxicity, and immunogenicity. This has been referred to as a potential biomaterial in recent years. There is a plentitude of studies that show that the free amino side chains of lysine residues on albumin surface can bond with poly (ethylene glycol) disuccinimidyl succinate (PEG-$(SS)_2$) to form amide linkages which consequently result in the formation of hydrogel materials [45]. Certain studies also show that the succinimidyl active esters have the potential to react with the amino groups that are present on the tissue surface, which can result in the adhesion of these hydrogels on tissues [46]. The therapy is also believed to alter the cell therapy and tissue engineering by acting as a reservoir of bioactive silicates which have proven ability to initiate the paracrine effects between the stem cells and the recipient cells, which entirely defines the ability of the regeneration of tissue by the stem cells in the cell therapy. Thus, it is also regarded as a therapy which is believed to have tremendous prospects [47].

3. Recent advancements and clinical trials in wound healing
The list of all the active clinical trials on the novel therapies of wound healing is appended as follows with a reference to and was compiled as “Wound healing” on the official website “clinicaltrials.gov” and “PubMed”.

Table 2: Recent clinical trials in wound healing

Sr. No.	Name	Condition	Intervention	Status	Reference
1.	Cold Plasma Therapy for Acceleration of Wound Healing in Diabetic Foot	▪ Diabetic Foot	▪ Device: Argon Plasma Jet ▪ Device: Placebo	Active	NCT04205942
2.	Safety and Efficacy of SLI-F06 in Wound Healing and Scar Appearance	▪ Scars	▪ Drug: SLI-F06 ▪ Drug: Formulation Buffer	Active	NCT03880058
3.	Allograft Reconstruction of Massive Rotator Cuff Tears vs Partial Repair Alone	▪ Rotator Cuff Syndrome ▪ Rotator Cuff Injury ▪ Disorder of Rotator Cuff	▪ Procedure: Partial Rotator Cuff Repair ▪ Procedure: Partial Rotator Cuff Repair with Allograft Augmentation	Active	NCT01987973
4.	ACell MatriStem Pelvic Floor Matrix vs Native Tissue Repair (Comparative Study)	▪ Pelvic Organ Prolapse	▪ Device: MatriStem Pelvic Floor Matrix ▪ Procedure: native tissue repair	Active	NCT02021279
5.	G-Wound (VZ for Wound treatment)	▪ Wounds ▪ Wound Heal	▪ Device: VZ powder (purified clinoptilolite) ▪ Procedure: Standard of care (SoC)	Active	NCT04417647
6.	Prospective Randomized Clinical Trial comparing outcomes of secondary	▪ Wound Surgical ▪ Wounds Heal	▪ Procedure: Debridement	Active	NCT03880331

	Intention Wound care Methods				
7.	Investigation of a Novel Wound gel to improve wound healing in chronic wounds	▪ Wound Infection	▪ Drug: Benzalkonium Gel ▪ Other: standard of care topical gel ▪ Procedure: Debridement	Active	NCT03686904
8.	Efficacy of Continuous Sciatic Nerve block in Diabetic Foot Patients	▪ Diabetic Foot ▪ Wound Heal	▪ Procedure: Group C (Continuous sciatic nerve block) ▪ Procedure: Group S (sciatic nerve block)	Active	NCT04212325
9.	Healing Chronic venous stasis wounds with autologous cell therapy	▪ Wound, Nonpenetrating	▪ Device: Transpose ® RT System ▪ Other: debridement/dressing of the wound	Active	NCT02961699

4. Conclusions

Wounds have created significant emotional, functional trauma to patient and at the same time heavy burden on healthcare professionals. Still, wound healing is one of the underrated research area which need more emphasis. Over the course, nature and cause of wounds have changed but it problem continues to scare the mankind. Last two decades have witnessed a sea of changes resulting metamorphosis in our understanding, knowledge, techniques and technologies. It is a very unfortunate to have wounded lesions, especially in cases including chronic wounds, however the normal physiological mechanisms are always working round the clock to reinstate the normal anatomical and physiological barrier, particularly because of the pivotal role it plays in the body. However, the time it takes for reinstating depends upon numerous factors and can be delayed by various pathological states, and thus there are numerous effective approaches employed by the cosmetic surgeons and physicians to accelerate the process and enhance the patient compliance to the regimen. The most recent advances in the same included the aforementioned therapies, which can be used to treat the cases involving wounds which would naturally take a prolonged duration to heal and often end up with scars. In coming years, the acceptance of these and another newer biotechnological modalities will create room for better and compliant treatment across the globe.

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