Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i2.4367

A COMPREHENSIVE STUDY ON THE SIGNIFICANCE OF POLYMERS IN CREATING SCAFFOLDS FOR TISSUE REGENERATION, DETAILING THEIR PROPERTIES, ADVANTAGES, AND CHALLENGES

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Abstract:
The human skin, the largest and most exposed organ, is prone to various damages, including burns, wounds, and tumours. The complexity of the skin's healing process, especially in cases of deep burns or injuries, has spurred interest in tissue engineering as a potential solution.

Objective: This review explores the advancements and techniques in tissue engineering that facilitate skin regeneration. Emphasis is placed on current strategies such as 3D printing, polymer scaffolds, biodesigned dressings, and other innovative approaches.

Methods: A comprehensive review of recent literature was conducted to compile the latest developments and techniques in skin tissue engineering. Key aspects of tissue regeneration, including biocompatibility, polymers, and various tissue engineering methods, were explored.

Results: Significant strides have been made in tissue engineering, with techniques like 3D bioprinting offering precision in creating skin-like structures. Various methods, such as inkjet and extrusion-based bioprinting, have been detailed, each presenting its advantages and challenges. Polymer

scaffolds have also shown promise in providing mechanical support and facilitating cell growth. Additionally, advancements in laser technology and stereolithography have further enhanced the precision and viability of bio-printed tissues.

Conclusion: Tissue engineering holds immense potential to revolutionize the treatment of skin lesions. As techniques continue to evolve, the future of skin regeneration appears promising, with the potential for personalized, patient-specific treatments that address the unique challenges of various skin conditions.

Keywords: biocompatibility, polymers, tissue engineering, regeneration.

INTRODUCTION:

The largest organ in the human body, the skin, serves as a barrier between an individual's internal and external environments. Burns, severe wounds like venous ulcers, skin excision, tumors, and other dermatological conditions are the leading causes of damage to this. The World Health Organization reports that burns cause 300,000 deaths annually and that 6 million patients worldwide receive burn treatment. Moreover, over 6 million individuals experience chronic skin ulcers; of these, over 3 million patients reside in the United States alone distinct. The injured epidermis can promote self-regeneration because stem cells are present (Dhasmana, Singh, Kadian, & Singh, 2018).

However, the healing process is insufficient in cases of deep burns or injuries, which results in a chronic wound. The process of wound healing and subsequent skin tissue regeneration is intricate and highly regulated. It is contingent upon various factors, including but not limited to the type of wound, burn damage, physical trauma, moisture levels surrounding the wound, inflammation, and secondary infections (Hosseini & Shafiee, 2021).

For the treatment of skin lesions, tissue engineering has emerged as a promising new field. By creating novel biocompatible replacements or reconstructing tissues, the primary objective is to enhance and restore tissue function. One of the main sources of innovation in soft tissue engineering is the intricate hierarchy of wound regeneration techniques. There are many commercially available skin substitutes that are either cellularized or acellular and comprise dermal and/or epidermal components. Research is still being done, though, because burns and severe or extensive wounds are not effectively treated. Numerous articles analyzing current strategies have been published recently. A number of tissue engineering strategies have been considered to address the current shortcomings of skin substitutes (Nourian Dehkordi, Mirahmadi Babaheydari, Chehelgerdi, & Raeisi Dehkordi, 2019).

TISSUE ENGINEERING:

Creating replacement tissues and organs to maintain, repair, or enhance the functions of their damaged or diseased counterparts in vivo is the aim of tissue engineering. In the last ten years, a great deal of products have been found to have potential in clinical settings. Even though a large number of the products that are brought to market are holdovers from earlier times, there haven't been many successful clinical studies for the application of tissue-engineered tissues because of enduring barriers that hinder the biological functions of cellularized constructs from being achieved because of incomplete host compatibility (Yang et al., 2020).

The fact that many of the tissues created through tissue engineering lack certain properties of the functional tissue they are intended to replace is one of the main challenges facing the field. The paucity of comprehensive compatibility is partly ascribed to the scant quantitative information currently available concerning the adaptive response mechanisms that alter the architecture of engineered tissues subsequent to their in vivo transplantation (Tarassoli et al., 2018).

Tissue engineering currently employs an ex vivo approach based on biocompatible expansion, which is then applied to damaged areas. Typically, they are utilized in tissue engineering, different biomaterials. Biomaterials play an important role in controlling the size and shape of the regenerated

tissue, as well as promoting cell adhesion, proliferation, and differentiation by providing mass transport and temporary mechanical support (Shpichka et al., 2019).
Skin substitutes can be categorized according to their coating's duration (permanent, semi-permanent, or temporary), their structural characteristics (epidermal, dermal, or dermo-epidermal), their composition (cellular or acellular), and, in a similar vein, their type of biomaterial (biodegradable, non-biodegradable, or biological) (Sharma, Kumar, Sharma, Bhatt, & Dhot, 2019).

SKIN ANATOMY:

The skin serves as the body's first line of defence against the outside world and regulates body temperature. It is the most vulnerable organ to injury because it is the biggest, most visible organ and acts as a body shell. The skin and endoskeletal fascia are closely integrated with the help of lymphatics, veins, nerves, and reticular ligaments (Weng et al., 2021).
The epidermis, dermis, and hypodermis are the three layers that make up the skin, as seen in figure 1. In addition to being much more permeable to water than the inner layers of the epidermis, the stratum corneum also prevents infections and other foreign materials from entering the body. With cells extending from the basement membrane to the dermis, it has a multilayered structure. Progenitor cells found in the basement membrane give rise to keratinocytes, which then undergo further differentiation and maturation before reaching the skin's surface. The skin's barrier function is provided by the keratinized layer of dead skin cells. Melanin, which is produced by melanocytes found in the epidermis, gives skin its distinctive pigmentation (Goodarzi et al., 2018).
Out of the three layers, the dermis is the thickest. Extracellular matrix, fibroblasts, vascular endothelial cells, hair follicles, sweat glands, sebaceous glands, blood veins, and nerve endings comprise this connective tissue. The hypodermis, a fatty tissue beneath the dermis, acts as a cushion and insulator between the skin and skeletal components like muscles and bones. It also functions as a location for energy storage (Dzobo et al., 2018).

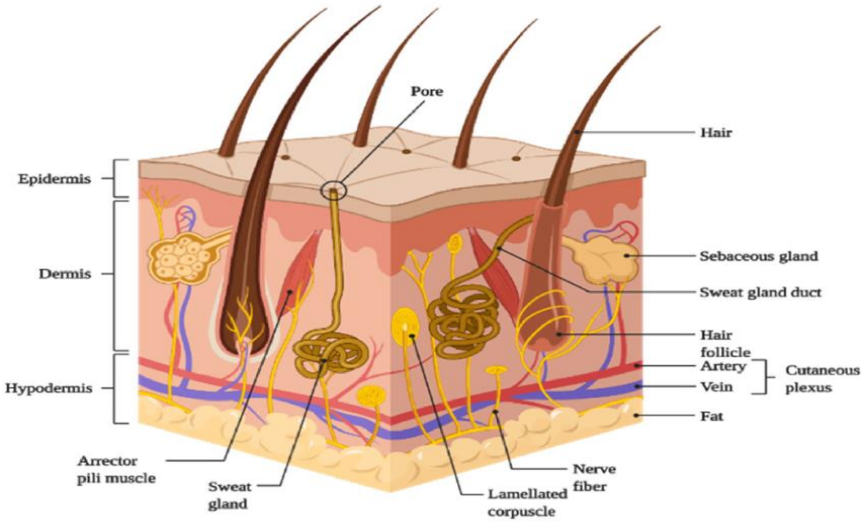

Figure 1. Structure of human skin

WOUNDS AND THEIR HEALING PROCESS:

A wound is characterized as a break or damage to anatomical structure and its functions resulting from an organ's structures breaking down to differing degrees of severity. Damage to the skin can also affect other tissues and structures, including muscles, tendons, nerves, veins, and bones, as well as subcutaneous tissue (Przekora, 2020).
It is challenging for an adult mammal to fully recover its damaged epithelial tissue. Following the healing process, a scar typically forms. While this scar satisfies the basic requirements to avoid infection and dehydration, it can also be viewed as unfavourable because the healing process has removed the sensory and thermoregulatory characteristics. Lack of sebaceous glands and hair

follicles. Moreover, because of its clearly distinct appearance from the surrounding skin, the scar left behind by the healing process can have severe psychological and aesthetic effects that lower the person's quality of life (Lanza, Langer, Vacanti, & Atala, 2020).

The intricate multicellular process of wound healing involves the participation of fibroblasts, keratinocytes, endothelial cells, and inflammatory cells. The inflammatory phase, proliferation phase, and remodelling phase are the three interconnected stages that make up the well designed of events that constitute the healing process. Communication between various molecular groups, such as the extracellular matrix, integrins, trophic factors, and matrix metalloproteinases, controls the phases of the wound-healing process (Abdollahiyan, Oroojalian, & Mokhtarzadeh, 2021).

The goal of the inflammatory phase is to stop bleeding by keeping blood within the walls of injured veins and obstructing it. The intricate process of hemostasis involves the interplay of fibrinolytic proteins, platelets, plasma coagulation cascades, and mediating cytokines. When tissue damage occurs, the hemostatic mechanism isolates the damaged vascular system from surrounding tissues by sealing the damage with blood components and vascular and extravascular receptors. The filtered blood coagulates and the injured veins constrict at the end of the inflammatory phase, help to maintain the integrity of the blood (Aleemardani, Trikić, Green, & Claeyssens, 2021).

The goal of the proliferation phase is to create an essential epithelial barrier to activate keratinocytes by decreasing the area of tissue damaged by contraction and fibroplasia. This stage, which includes fibroplasia, reepithelialization, and angiogenesis, is in charge of the wound's actual closure. This process can continue for up to 14 days following injury and starts in the wound microenvironment within the first 48 hours. Maximizing tensile strength through extracellular matrix reorganization, degradation, and resynthesis is the primary objective of the remodelling process' last stage. During the healing phase, the granular tissue undergoes a gradual remodelling that results in less cellular and vascular scar tissue, as well as a progressive increase in the concentration of collagen fibres. The goal is to restore typical tissue structures (Ude, Miskon, Idrus, & Abu Bakar, 2018).

BIOCOMPATIBLE COMPOUNDS THAT ENCOURAGE TISSUE REGENERATION:

Almost all of the chemicals and materials used in tissue engineering have at least one polymer component. Natural and synthetic polymers are the two main categories into which tissue regeneration-promoting polymers fall (Figure 2). For the formulated polymer, there is a wide range of organic and inorganic types, combinations, and additives available. Owing to the wide range of substances that encourage tissue regeneration, ongoing research is being done to identify new substitutes that are highly compatible with living tissues (Yu et al., 2019).

Because of their advantageous properties, natural polymers like alginate, hyaluronic acid, collagen, and chitosan are utilized often. The three most crucial qualities are its great abundance, biodegradability, and biocompatibility. One of the most crucial qualities of a particular natural material is its biodegradability because it is present in the extracellular matrix, which promotes the cells' growth rate and good compatibility response (Nour, Imani, Chaudhry, & Sharifi, 2021).

This research is one instance of using natural polymers. Quaternized derivatives of β-chitin were created in this study using a chitin-based derivatization reaction in an aqueous medium with KOH/Urea. Because the acetamido groups created positive charges in the structure, the derivatives had antibacterial properties. Moreover, it has been demonstrated that quaternized β-chitin structures encourage collagen fibre regeneration, granular tissue growth, and neovascularization (Farhadihosseinabadi et al., 2018).

Modified natural biomaterials or entirely synthetic materials can be classified as synthetic biomaterials. These materials can either decompose naturally or not. Polyethylene derivatives, polytetrafluoroethylene, polymethylacrylates, polyacrylamides, polyethers, polysiloxanes, polyurethanes, and polyethylene glycol are among the frequently used non-biodegradable materials. Advantages of this kind of material include non-immunogenicity, adequate mechanical properties, good reproducibility, and custom-designed shapes (Amirsadeghi et al., 2020).

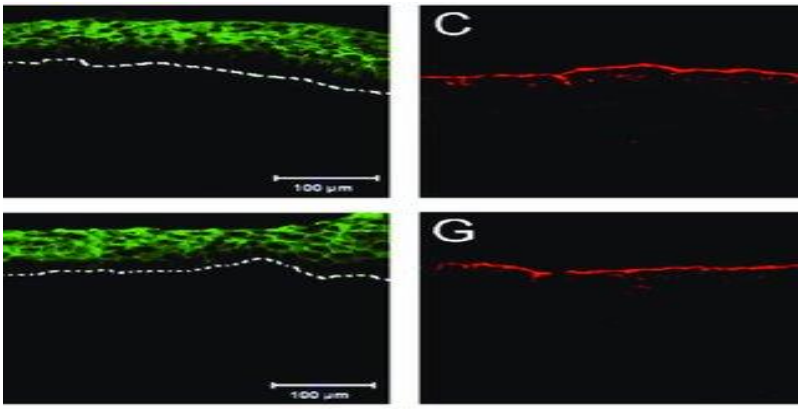

Figure 2: Elastin and collagen fibres in a normal dermis (a, b) and hypertrophic scar tissue (c, d). The elastin fibres are red, and the collagen groups are green in the two-photon excitation microscope images (a, c). Collagen (letter C) is black, and elastin (letter E) is dark red in the transmission electron microscope pictures (b, d). Elastin is distributed as thin fibres among the collagen tufts in the hypertrophic scar, in contrast to the thick and long fibres that are visible among them in the normal dermis [5].

Other synthetic polymers employed are polyethylene glycol, polypropylene glycol, and polyethylene glycol (PPG-PEG-PPG) block polymers. Because of its special qualities in solution, ability to self-assemble, and low toxicity, this polymer is frequently used in biomedicine. Polyesters, poly(α-hydroxy acids), polylactones, polyorthoesters, polycarbonates, polyanhydrides, and polyphosphazenes are frequently used as biodegradable synthetic biomaterials. It is possible to design these biodegradable materials in a way that regulates both the growth factor release rate and the kinetics of degradation (Madni, Kousar, Naeem, & Wahid, 2021).
Dobreikina et al. prepared a series of polyacrylamide (PAM)-based gels with semi-interpenetrating networks for tissue engineering applications in a case involving synthetic biomaterials. In order to create a semi-interpenetrating network, the gels were made by radical polymerization in an aqueous solution using PAM as the primary link chain and a 1:100 ratio between the monomer (gellan gum or xanthan gum) and PAM. The biocompatibility of the gel is enhanced by the addition of polysaccharides at varying concentrations. Additionally, the electrical potential and Young's modulus of the synthetic gel are significantly increased. Soft tissues are characterized by nonlinear behaviour in stress versus strain, which is a feature of the structures developed in this study (Agarwal et al., 2020).

DEVELOPMENTS AND TECHNIQUES IN TISSUE ENGINEERING:

1) 3D PRINTING:

Over the past 25 years, significant advancements have been made in the development of in vitro human skin models, as well as in vitro engineered substitutes that resemble human skin and can be used as skin grafts to replace lost skin. When the properties and uses of biodegradable three-dimensional (3D) scaffolds were described in detail in 1993, the idea of tissue engineering was formally established. Microstructures known as three-dimensional scaffolds are used as a foundation for the placement of cells and other elements required for skin regeneration. These scaffolds should be extremely porous, possess interconnected pore networks, and have a uniform pore size that allows for cell migration and infiltration (Matai, Kaur, Seyedsalehi, McClinton, & Laurencin, 2020).
Afterwards, a number of traditional manufacturing processes, including fibre bonding, phase separation, moulding, and foam forming, were used to create 3D scaffolds between 1993 and 2002. But these approaches have a big flaw: they don't give you enough control over the scaffold architecture, pore network, and pore size, which results in uneven and far from perfect 3D scaffolds. After all, you can't fully replicate the complex cellular matrix interactions found in natural tissues by just seeding cells onto premade polymeric scaffolds. Additionally, using the aforementioned

techniques, certain aspects of the skin substitute's manufacturing process need to be improved. For example, the time needed to produce the surface area required to cover a large wound or extensive burn, as well as the necessity of automating and standardizing these manually performed processes, need to be addressed. In order to solve this issue, it has been suggested to use 3D printing techniques to create customized scaffolds with regulated pore size and structure. This technology has developed into a versatile instrument in regenerative medicine and offers a framework to deal with these issues (Riha, Maarof, & Fauzi, 2021).

The 3D bioprinting systems' technologies enable more accuracy in the spatial relationship between the component parts of the intended tissue. Consequently, the number of studies in the field of 3D printing for tissue engineering has increased dramatically between 2003 and the present, and printing techniques have improved significantly in a static manner, going from 2D to 3D. Bioprinting can be defined as "the use of 3D printing technology that incorporates viable living cells with biomaterials to produce sophisticated tissues or organs". It is also referred to as rapid prototyping, solid free-form manufacturing, or additive manufacturing. Furthermore, this technology not only allows for the simultaneous deposition of various biomaterials and multiple cell types but also offers flexibility in the design and fabrication of customizable patient-specific tissue constructs, demonstrating great potential for the fabrication of complex multicellular tissue constructs. The printers used in this technology can print with high resolution and precision due to the high control of droplet size and deposition speed 3D (Rahmani Del Bakhshayesh et al., 2018).

The three main steps in bioprinting are: first, obtain precise tissue and organ data for pattern identification and material selection; second, convert the data into an electrical signal to operate the printer and print fabrics; and third, build a sturdy structure. Despite the fact that bioprinting has advanced significantly in recent years, the majority of the technologies used in bioprinting are unable to print solid, functional organs. In order to address this issue, research has created models that could be utilized in vivo to aid in the development of vascularized solids like bones (Martín Piedra et al., 2019).

Variable	Inkjet	Extrusion	Laser-assisted	DLP
Printing Process	Serial (drop by drop)	Serial (line by line)	Serial (dot by dot)	Parallel and continuous
Print speed	Medium (mm/s)	Slow (10-50 µm/s)	Medium (mm/s)	Fast (mm3/s)
Resolution	50 µm	5 µm	<500nm	1µm
Cell viability	>85%	40-80%	>85%	85-95%
Choice of material	Thermo/pH/ photosensitive	Thermo/ photosensitive	Photosensitive	Photosensitive

Table 1: A comparison of the various Bioprinting methods

The key distinctions between these four printing technologies—inkjet-based printing, extrusion-based printing, laser-assisted printing, and DLP-based printing, or dynamic optical projection stereolithography (DOPsL)—are outlined in Table 1. There are numerous forms of bioprinting technologies, but only four are currently in widespread use (Figure 3). Numerous variables, such as the seeding cell species, printing speed, and bioprinting technique, can affect cell viability (Abdo, Sopko, & Milner, 2020).

BIOPRINTING WITH INKJET TECHNOLOGY:

Because the print head cannot produce a continuous flow, the use of inkjet printing has been more restricted than in studies based on extrusion. Using an inkjet printer, biological inks with viscosities less than 10 mPa/s were printed.

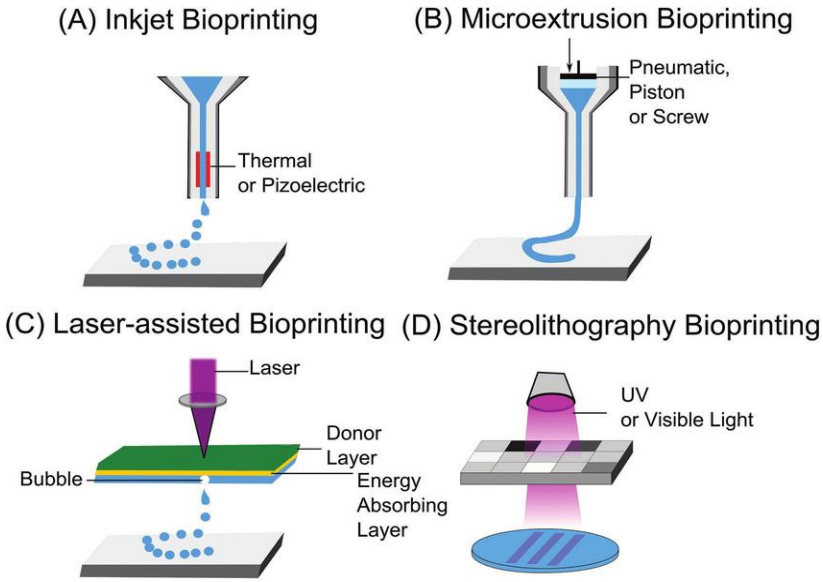

Figure 3. Methods for bioprinting. To create tissues, the inkjet bioprinter progressively ejects tiny droplets of hydrogel and cells. The extrusion bioprinter continuously extrudes a liquid cell hydrogel solution using pneumatic or manual force. c A laser printer's positioning diagram. D Diagram of the dynamic optical projection stereolithography (DOPsL)-based bioprinter.

Inkjet printing has a low cell density but a high production speed when compared to other techniques. Three categories apply to inkjet printing techniques: biological printing via on-demand inkjet, biological printing via electrohydrodynamic injection, and biological printing via continuous inkjet. As illustrated schematically in figure 4, the latter category is the most extensive and prevalent, encompassing thermal, piezoelectric, and electrostatic inkjet Bioprinting (Park, Shin, Kim, & Shin, 2018).

With this kind of printing, Rimann et al. created an all-in-one technique for soft tissue construction. In this work, a commercial 3D bio-inkjet printer under development was used in conjunction with a bio-ink based on polyethylene glycol, and printing was done in a sterile environment. A long-term culture of the printed structures was done to confirm the validity of their work. The findings confirmed that human primary dermal fibroblasts could survive and proliferate for up to seven weeks (Aljohani, Ullah, Zhang, & Yang, 2018).

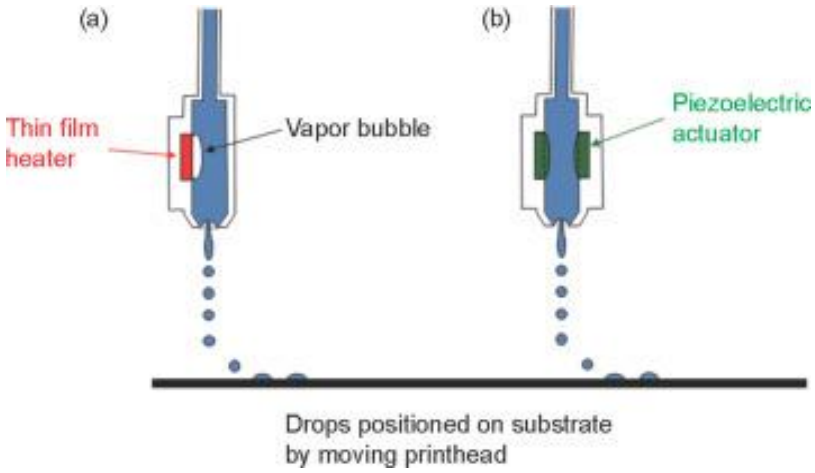

Figure 4: Schematic diagram of the inkjet printing technique that uses piezoelectric and thermal actuators for on-demand printing. Using a heating component to increase the temperature locally and produce a bubble that forces droplets through the nozzle, a thermal print head works. When voltage is applied, a material that changes shape and expels droplets is used with a piezoelectric head.

EXTRUSION-BASED BIOPRINTING:

Extrusion-based techniques are very popular because of their defined processing method, which makes them simple, versatile, and predictable. One benefit of extrusion bioprinting is its broad range of printable biomaterials and affordable equipment. Pneumatic, piston, and screw dispensing are the three categories used to group common extrusion-based printing techniques in Figure 5. Whereas vertical and rotational mechanical forces, respectively, start the imprint in piston and screw dispensing, air pressure supplies the necessary driving force in pneumatic dispensing. Printability in extrusion bioprinting is primarily determined by three factors: 1) Material-specific bio fabrication window, 2) bio ink phase before extrusion, and 3) viscosity adjustment. Viscosity needs to be adjusted for various printing techniques because it can be influenced by temperature or shear dilution (Zhou et al., 2020).

In addition, the biological ink needs to be in a liquid phase to prevent nozzle clogging. Lastly, not all biomaterials can be printed on, and those that can might not print across a variety of processing parameters. Employed this technique in this study, wherein two kinds of 3D printed oxidized nanocellulose structures are thought to be wound dressings. The first type was prepared by oxidation mediated by 2,2,6,6-tetramethylpiperidin-1-yl)oxydanyl (TEMPO), while the second type was prepared by oxidation mediated by a combination of periodate and carboxymethylation (Cui, Liang, Liu, Zhang, & Li, 2020).

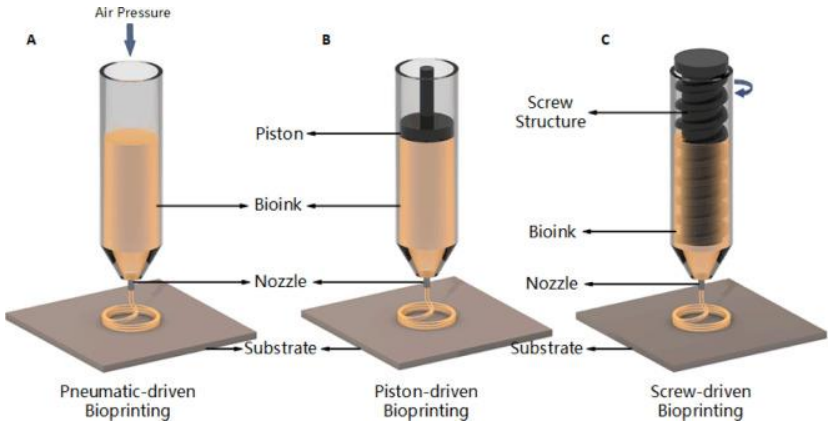

Figure 5: shows a schematic illustration of the three common extrusion-based bioprinting techniques (a pneumatic, b piston, and c screw).

After being created, the nanocellulose bioink was used to print three-dimensional porous structures. It was investigated to see if it supported the growth of bacteria, and it was found that it might transport and release antimicrobial components without supporting the growth of bacteria [30, 32]. In a different study, cell-filled 3D printed tissue constructs were made using a hydrogel based on gelatin, alginate, and collagen. Managing the hydrogel's rate of degradation by adjusting the molar ratio of the hydrogel's sodium alginate to the medium's sodium citrate was a crucial component of this work. The high rate of cell proliferation suggested that the technique employed in this work could be used to improve alginate bioink. A gamma-irritated alginate-based bioink was used to encapsulate stem cells, and its properties were improved by the inclusion of PCL fibres (Im, Kim, Kim, & Jung, 2018).

LASER SUPPORT:

The method known as laser-induced direct transfer (LIFT) makes it possible to deposit materials in liquid or solid phase with high resolution. Figure 3c shows a schematic illustration of one solid-phase material printing version, though there are several variations of this technique. One study printed cells using a variation of the LIFT technique called laser-assisted direct matrix evaporative writing. Calcium chloride was utilized as a cross-linking agent, and sodium alginate that had been loaded with NIH 3T3 mouse fibroblast cells was utilized as a bioink. On cell viability, the effects of gelation and alginate concentration, gelation time, and laser influence were investigated. A longer gelation time

was found to reduce incubation cell viability after 24 hours because of a decrease in nutrition and oxygen transfer through the thick gel wall (Grounds, 2018).

UTILIZING STEREOLITHOGRAPHY FOR BIOPRINTING:

The process of stereolithographic printing involves the use of a precisely controlled light beam reflected from digital micromirrors to polymerize light-sensitive polymers. Stereolithography is a technique with high printing quality, speed, and cell viability when compared to other methods. There have been some documented negative effects of using this strategy, though. For instance, it has been reported that the UV light source, which is used as a common curing method, damages DNA cells and may even be the cause of skin cancer. Visible-light stereolithographic bioprinting systems have garnered interest as a potential solution to this issue. Consider Wang et al. I employed a beam projector and biological ink mixtures based on PEGDA, GelMA, and erosin Y as part of my bioprinting setup (Alderfer, Wei, & Hanjaya-Putra, 2018).

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The outcomes of this NIH 3T3 cell bioprinting study showed that the low-cost system that was suggested could print hydrogels under visible light, polymerize them with a resolution of 50 mm, and maintain relatively high cell viability. The number 3 uses a beam projector to schematically depict stereolithography (Milan et al., 2020).

2) SCAFFOLDS MADE OF POLYMERS:

Polymeric materials that are synthetic or absorbable, natural, biological, degradable, or non-degradable can be used to create scaffolds. These scaffolds need to exhibit specific biological properties, such as the ability to promote keratinocyte adhesion, proliferation, and differentiation. They also possess sufficient mechanical and degradation properties. In order to facilitate natural tissue movements during surgery and to be easily handled, scaffolds need to be sufficiently elastic and strong. In addition, these scaffolds ought to disintegrate solely following sufficient curing, a process that may require over eight weeks (Talikowska, Fu, & Lisak, 2019).

Scaffolding Types	Advantages	Disadvantages	Future prospects
Porous	High porosity provides an environment suitable for matrix extracellular (ECM), in addition to providing nutrients to cells. Widely used in acute burns.	The porous nature limits the homogeneous distribution of cells. Different pore sizes are needed for specific types of cells, and therefore, they require a lot of time.	It seeks to improve pore connectivity and Therefore, the structure of the scaffolding.
Fibrous	The highly microporous is favourable for cell adhesion, fibrous proliferation and differentiation.	Functionalization of the surface is required to create the nanofibers from these scaffolds.	Drugs and biological molecules can be included into scaffolding fibrous for liberation applications.
Hydrogel	The biodegradation rate highly biocompatible and controlled.	They have resistance-limited mechanics due to soft structures.	The behavior of degradation of hydrogels and tenacity must be well defined.
Microsphere	It has physical characteristics and controlled areas suitable for slow or fast administration of medications. Has a slow degradation, and of this the reason they are successful when used in transplants.	Sintering methods of microspheres sometimes not are compatible with cells and reduce cell viability.	They can be used as a transporter of medications such as anticancer antibiotics

Compound	They are highly biodegradable and provide resistance mechanics. Greater capacity of absorption.	The acidic byproducts are generating degradation. Low cellular affinity. They require tedious efforts to develop scaffolds compounds.	Currently, they are developing nanobiocer composites amica and polymers with greater degradation.
Acellular	The native ECM is preserved and, therefore, the anatomical characteristics typical. Less response inflammatory and immune with greater mechanical resistance.	Decellularization is required incomplete to avoid immune responses.	Such scaffolds are promising for the development of organs artificial.

Table 2: lists several scaffolding types along with their corresponding benefits, drawbacks, and prospects**.**

Scaffolds must be quickly cross-linked in place for some clinical applications in order to provide the best possible contouring to the wound. As previously mentioned, the majority of natural hydrogels used to promote epidermal regeneration are based on collagen or gelatin and imitate the dermal extracellular matrix naturally. However, these hydrogels frequently have inadequate and unpredictable mechanical and degradation properties. In order to engineer the epidermis for skin tissue engineering applications, substitutes like cross-linked gelatin, or gelatin methacrylamide (GelMA), with adjustable mechanical, degradation, and biological properties, are being explored. With elastic and compressive modules tuned from a few kPa to a few hundred kPa, the results show that the mechanical and degradation properties of the developed hydrogels can be easily modified by varying the hydrogel concentration. and periods of degradation range from a few days to many months. A few days to several months are typical degradation times (Haldar et al., 2019).

In one study, electrospinning was used to create collagen nanofiber-loaded silver nanoparticles. The goal was to establish the ideal conditions for wound healing. Utilizing the natural advantages of collagen nanofiber and broad antimicrobial activity, nanosilver acts as the main structural element of the extracellular matrix, directing cell adhesion, growth, and differentiation in a way that promotes healing (Kwon, Kwon, Lee, Park, & Kim, 2018).

When compared to simple collagen nanofibers, the in vivo study showed that the wound healing rate of nanofiber composite mats was accelerated. Histological examination of the nanofibers made of AgNPs showed enhanced wound contraction, faster reepithelialization, and collagen synthesis. The quality of wound care may be enhanced by electrospun nanofibers, which hold great promise for the creation of nanostructured materials. Because electrospinning is inexpensive and simple to use, it is the most popular method for producing continuous nanofibers. The in vitro scratch test shows that the Curdlan/PVA scaffold has a higher wound closure rate than the PVA scaffold; this is most likely because of the biopolymer's immunomodulatory qualities. According to the findings, the Curdlan/PVA scaffold might be the perfect substance for uses involving wound healing (Ramos & Moroni, 2020).

A hydrogel scaffold made of chitin combined with polybutylsuccinate and chondroitin sulphate nanoparticles is used in skin tissue regeneration research. Because it moistens the wound interface, is oxygen-permeable, acts as a barrier against microorganisms, can remove excess secretions, and has additional qualities like immunological compatibility and flexibility, chitin is a perfect dressing that mimics the natural extracellular matrix. An aliphatic, biodegradable, and biocompatible synthetic polymer with superior mechanical qualities is called polybutylsuccinate, or PBS. Its concentration has an impact on porosity, which is necessary for improved gas and nutrient exchange. Additionally, as seen in the ternary composite (Figure 6C), the addition of chondroitin sulphate nanoparticles (CSnp) increased the scaffold's porosity. A prerequisite for better gas and nutrient exchange is optimal porosity. Additionally, the scaffold's roughness increased (Figure 6D,E). As a result, there would be an increase in scaffold protein adsorption and cell attachment. FTIR (Fourier transform infrared

spectroscopy), SEM (scanning electron microscopy), and swelling ratio analysis were used to characterize this scaffold (Weng et al., 2020).
The in vitro scratch test shows that the Curdlan/PVA scaffold has a higher wound closure rate than the PVA scaffold; this is most likely because of the biopolymer's immunomodulatory qualities. According to the findings, the Curdlan/PVA scaffold might be the perfect substance for uses involving wound healing.The scaffolds ' suitability for dermal tissue engineering applications was assessed with the use of human dermal fibroblasts (HDF), cytotoxicity, cell attachment, and proliferation studies. The scaffold's suitability for skin regeneration is confirmed by cytotoxicity and cell proliferation studies conducted with HDF (Rahmati, Blaker, Lyngstadaas, Mano, & Haugen, 2020).

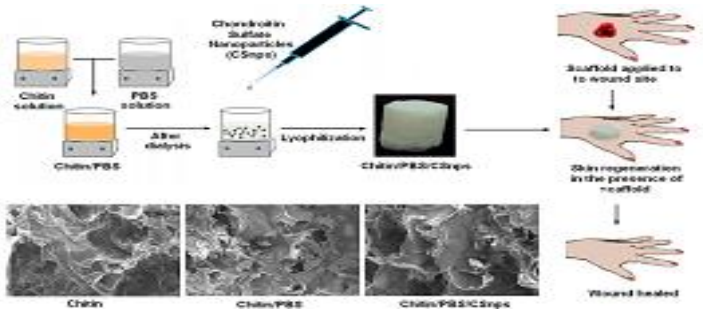

Fig. 6. Chitin, b, d, and c, e Chitin/PBS/CSnps are shown in a SEM image.

3) DRESSINGS FOR WOUNDS:
Traditionally, burn patients would undergo daily wound cleanings, excision of dead tissue, application of an antibiotic dressing until granulation tissue forms, and finally, grafting. To improve and lessen wound symptoms, various donor site care and dressing techniques have been employed, which suggests the potential for a donor site from the same location in the future [40]. Suturing is a time-consuming, highly skilled procedure that can result in inflammatory reactions, secondary infections, scarring, and wound oedema. Sufficient closure and stabilization of the wound margins in the intended position are crucial steps that determine how well a surgical procedure goes. Anaesthetics are necessary for suturing, but they can be costly and lead to an incorrect estimation of the wound. Thus, it is critical to create tissue adhesives that allow surgeons to substitute quick, safe, and operator-independent methods for laborious traditional suturing or stapling procedures (Beheshtizadeh, Lotfibakhshaiesh, Pazhouhnia, Hoseinpour, & Nafari, 2020).

So far, numerous kinds of wound dressings have been created, such as hydrogels, rubber, foam, membranes, and electrospun nanofibers. Hydrogel dressing is one of these dressings that can help patients feel better by keeping the wound moist, absorbing tissue exudates, allowing oxygen to enter the wound, and cooling the wound surface. Generally speaking, the best hydrogels for dressing wounds should possess a number of unique qualities. Initially, they need adhesives that are easily released from the delicate surface and have a sufficient adhesive strength that is compatible with the delicate skin tissue of the patients(Conese et al., 2020).

The majority of conventional adhesive products, like bandages, adhesive, and medical dressings, typically have an excessive adhesive strength, which can cause localized trauma or pain to the patient, particularly in elderly, paediatric, and fragile skin patients. They also need to be robust enough to adjust to the mechanical properties of skin tissues. Thirdly, there ought to be little localized skin trauma to the patient during their removal. Fourthly, they ought to possess the ability to readhesion for patients who need adhesive dressings to be applied to the same area of the body on a regular basis for a prolonged amount of time. Lastly, they need to be non-toxic, biocompatible, and non-irritating to human skin. Hydrogels are highly hydrophilic macromolecular networks that are created through the cross-linking of soluble polymers, either chemically or physically. They exhibit particular

environmental parameters like temperature, pH, and ionic strength, and they can both absorb and desorb water reversibly (Sahana & Rekha, 2018).

Consequently, hydrogels' intelligent physiological response to variations in physiological variables points to various biomedical applications for them. Finding an injectable wound hydrogel that is self-healing and has conductive, antioxidant, and anti-infective qualities to aid in wound healing is desired. However, the design of such a gel is still difficult. Specifically, the electroactive hydrogel dressing that is both antibacterial and antioxidant that was presented by Zhao and colleagues. It demonstrates special qualities like adhering to wounds, filling wound sites (even in irregular spaces), and encapsulating drugs in situ. Most injectable hydrogels without strong elasticity may deform or be damaged by external mechanical forces after being applied to the wound site, even though the injectable hydrogel dressing fills the wound and sticks to the wound to shield it from the outside environment (Golberg et al., 2018).

Based on quaternized chitosan-g-polyaniline (QCSP) and polyethylene glycol-co-poly (glycerolsebacate), which serves as a benzaldehyde group as an electroactive antibacterial dressing and antioxidant for healing, Zhao creates a range of injectable conductive hydrogels for self-healing. Wounds on the skin. Excellent self-healing, electroactivity, capacity to scavenge free radicals, antibacterial activity, adhesiveness, conductivity, swelling index, and biocompatibility were all displayed by these hydrogels. It's interesting to note that the hydrogel PEGS-FA with an ideal cross-linker concentration of 1.5% m/m demonstrated remarkable blood clotting ability in vivo and produced noticeably better outcomes in the wound healing process on living, full-thickness skin (Borrelli, Hu, Longaker, & Lorenz, 2020).

Defect model, in contrast to commercial wound dressings (Tegaderm TM film) and quaternized chitosan hydrogel/PEGS-FA, controlling the expression of growth factors, such as VEGF, EGF and TGF-b, and encouraging the deposition of collagen and granulation tissue thickness. In conclusion, because of their multifunctional qualities, hydrogel injectable electroactive antibacterial dressings significantly accelerated the in vivo wound healing process and prolonged the dressing life based on self-healing ability. This makes them excellent options for the healing of all kinds of skin wounds thicknesses (Wang et al., 2019).

4) METHODS THAT RELY ON THE APPLICATION OF STEM CELLS:

Selecting the right kind of stem cells to aid in full skin regeneration is crucial. To further optimize cell repair and regeneration, additional research is required on the following topics: the identification and isolation of pure populations of adult stem cells, protocol optimization for seeding cells in matrices, and scaffold structure design textiles (Mantha et al., 2019).

Due to their sensitivity to the microenvironment, stem cells' characteristics can be affected by a wide range of chemical and physical stimuli, which frequently leads to low viability, restricted proliferation, and unintended differentiation. Combining stem cells with smart matrices that contain nanoparticles that can imitate the stem cell niche and guide, instruct, and enable stem cell survival is one possible tactic (Zheng et al., 2018).

Mesenchymal stem cells (MSCs) are derived from bone marrow, adipose tissue, and the umbilical cord, among other tissues. They have been shown to enhance cutaneous wound healing, have the capacity to self-renew, and differ from several lineages. In addition to promoting quick wound closure, MSCs also boost angiogenesis, reduce inflammation in wounds, control extracellular matrix remodelling, and advance skin regeneration and wound healing. In addition, they offer many benefits over clinical applications in terms of mending or renewing injured tissues, particularly since they do not involve the moral dilemmas surrounding the use of embryonic stem cells (Kim et al., 2018).

Additionally, mesenchymal stem cells derived from human induced pluripotent stem cells, or hiPSC-MSCs, offer a promising substitute for stem cell transplantation therapy. Exosomes derived from mesenchymal stem cells, or MSC-Exos, have significant potential applications in the restoration of injured tissue. Nevertheless, there are currently no reports that show how hiPSC-MSC-Exos can be used to heal skin wounds, and little is known about the underlying mechanisms of this technique for tissue repair. The current study reports that the transplantation of hiPSC-MSC-Exos into wound sites led to decreased scar width, faster reepithelialization, and encouraged collagen development. Furthermore, he expedited the maturation of newly created ships at wound sites and encouraged the creation of new ones. The findings suggest that by encouraging collagen synthesis and angiogenesis, hiPSC-MSC-Exos can aid in the healing of wounds. These findings offer the first proof of hiPSC-MSC-Exos' potential for treating skin wounds (Pina et al., 2019).

Conversely, Tg Lewis-luciferase was discovered to be intravenously transplanted into a rat tissue expansion model in a study on rat MSCs in order to determine its localization and transduction. Genes differentially expressed between human MSCs and mechanically stretched controls were found using a methodical approach. Bioinformatic techniques were employed to analyze the biological significance of these modifications. By controlling MSC expression of genes linked to hypoxia, vascularization, cell proliferation, and enhancement of MSCs transplanted into the expanded skin, mechanical stretching is thought to aid in skin regeneration (Bacakova et al., 2019).

Based on conducted studies, silk fibroin (SF) seeded with MSC has demonstrated improved outcomes in skin wound healing experimental models. Using an excision wound splint model, Rivero investigated the effects of electrospun SF scaffolds cellularized with Wharton's jelly MSCs (Wj-MSCs-SF) on wound healing. After transplantation, they also carried out an immunohistopathological analysis, which verified the existence of CD90-positive human fibroblast-like cells infiltrated into the dermis of the group treated with Wj-MSCs-SF and resulted in neoangiogenesis, a reduction in the inflammatory infiltrate. and myofibroblast growth, decreased collagen matrix synthesis, and full epidermal regeneration. These results focused on the potential therapeutic benefits of the wound by demonstrating how Wj-MSCs transplanted into the wound using a silk fibroin scaffold enhance the formation of well-organized and vascularized tissue, improve wound reepithelialization, and decrease the formation of fibrotic scar tissue (Nosrati, Khodaei, Alizadeh, & Banitalebi-Dehkordi, 2021).

Tissue engineering techniques based on Wj-MSCs for non-healing wounds. The data show that, when combined with cellularized scaffolds covering the wound area and Wj-MSC treatment injected into the wound, greater wound healing was achieved than when using just one of the treatments alone or the cellularized SF scaffold (Selvan, Shanmugarajan, & Uppuluri, 2020).

One study looked into alternatives to polyvinyl alcohol (PVA) hydrogel and suggested stem cell therapy as a complement. This is because stem cell therapy is safe and has a limited application due to PVA's lack of bioactivity. A technique for making a dressing was discovered of PVA (ADSC/PVA) derived from stem cells derived from adipose tissue (ADSC) for wound healing. One aspect of photoreactive gelatin (Az-Gel) was added to the PVA dressing to change it (Monavarian, Kader, Moeinzadeh, & Jabbari, 2019).

ADSCs could, therefore, adhere and multiply on PVA dressings by ultraviolet (UV) irradiation (Az-Gel/PVA), keeping the other side of the dressing non-adherent to the wound. Equipment for materials testing and scanning electron microscopy (SEM) were used to characterize the mechanics and structure of Az-Gel/PVA. Afterwards, cell counting and live staining allowed for the observation of ADSC adhesion and proliferation. Ultimately, studies conducted both in vivo and in vitro were utilized to validate the impact of ADSC/PVA dressing on wound healing. The outcomes demonstrated that Az-Gel was immobilized in PVA hydrogels and had minimal impact on their mechanical

characteristics. Surface modification of this might promote ADSC adhesion and proliferation (Keirouz, Chung, Kwon, Fortunato, & Radacsi, 2020).

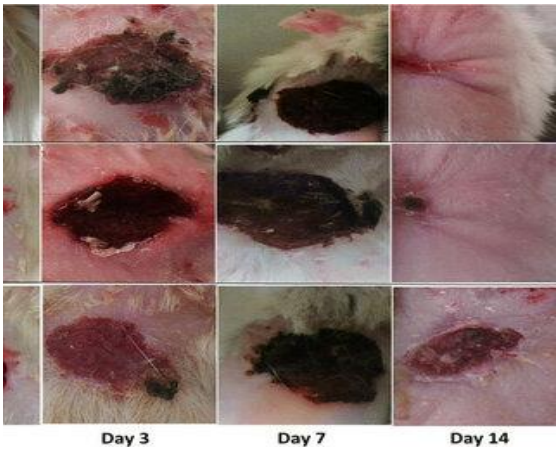

Fig 7. Pictures of rats' wounds healing over varying time periods.

The proteins suggested that the wound could be penetrated by bioactive substances secreted by ADSCs. Lastly, studies conducted in vitro and in vivo revealed that ADSC/PVA may facilitate wound healing by secreting bioactive substances from ADSCs. In addition to encouraging wound healing, the ADSC/PVA dressing offers a novel approach to the safe application of stem cells, which holds significant promise for skin tissue engineering (Yahya et al., 2021).

CONCLUSION:

Depending on the kind of injury, stem cells are directly in charge of self-generation. Serious or extensive burns cannot be healed by the human body on its own. The inherent complexity of the skin organ and the wide range of individual differences place limitations on tissue engineering. Human-manipulated stem cells require some form of assistance. Through the use of sophisticated, biocompatible polymers that collaborate with the skin's natural repair cells, all of the techniques examined in this article seek to enhance the skin's natural healing process. Bioprinting is superior to other technologies because it allows for the customization and configuration of the scaffolds' properties, along with significant structural and physicochemical benefits. As a result, it may be the way that tissue engineering is done in the future.

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