International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Transformative Biomaterials in Burn Care: Utilizing Scaffolds, Hydrogels, And Chitosan for Optimized Healing and Scar Reduction

Vishali[1], Jaspreet Kaur[2], Pratibha Sharma[3], Raveena Jassal[4], Bipin Singh[5], Mohd. Sayam[6], Vishal Kajla[7]

[1]Chandigarh College of pharmacy, Landran, Mohali, Punjab, India. -140307
[2,7]Assistant Professor, College of Pharmacy, RIMT University, Mandi gobindgarh, Punjab, India. -147301
[3]Assistant Professor, JCDM College, Sirsa, Haryana. -125056
[4]Guru Nanak Institute of Pharmacy, Dalewal, Hoshiarpur, Punjab, India. -144208
[5,6]College of Pharmacy, RIMT University, Mandi gobindgarh, Punjab, India. -147301

ABSTRACT
With over a million patients per year in the USA alone, burns are among the most common injuries in the world. In addition to preventing difficulties during burn injuries, the growing impact of scaffolds, hydrogels, cell scaffolds, and cell sheets with healing boosting elements expedite triggers and strengthens re-epithelialization and wound healing, which limits the creation of scars. While superficial partial-thickness and superficial burns typically heal without surgery, severe burns require special care, including topical antimicrobial surgery or bandages. Usually composed of polymeric biomaterials, scaffolds offer the structural support needed for cell adhesion and the subsequent formation of tissue. The term "tissue engineering triad" often refers to cells, scaffolds, and growth-stimulating signals. This may be accomplished in several ways by combining different polymers. Simple (planar) 3D structures may be produced using conventional and rapid prototyping techniques, but complicated structures have been successfully produced by carefully controlling the Molds and processing parameters. For biomedical and tissue engineering applications, chitosan has been widely employed (skin, bone, cartilage, and vascular grafts to substrates for mammalian cell culture). Additionally, it is renewable, biocompatible, biodegradable, nonantigenic, bioactive, and nontoxic.

KEYWORDS: Burns, Scaffolds, Tissue Engineering, Chitosan, Wound Healing

INTRODUCTION

BURN

Burns represent the most common type of injury resulting from damage to the skin caused by radiation, heat, electricity, cold, or friction. These injuries can lead to severe complications, including shock due to hypervolemia and sepsis resulting from bacterial infections [1]. Burn injuries result in both psychological and physical scars, [2] impacting mental health and leading to suffering and an increased risk of premature death [3-5]. Burn injuries are on the decline in high-income countries; however, they continue to be a

significant issue in low- and middle-income nations, where they represent 90% of all burn cases. The World Health Organization reports that burn pose a serious global public health threat, leading to approximately 180,000 deaths annually [3]. The frequency of burn injuries shows considerable variation across different regions [6].

Burns in children younger than five are typically scald injuries, while the incidence of flame-related burns tends to rise as children grow older [7]. The approach to treating burn injuries is influenced by the specific cause of the burn. For instance, frostbite is managed through methods such as moist warming, potential thrombolysis, and careful observation, whereas these same methods are not suitable for treating severe thermal burns [8].

Burns are classified based on their size and depth as follows:

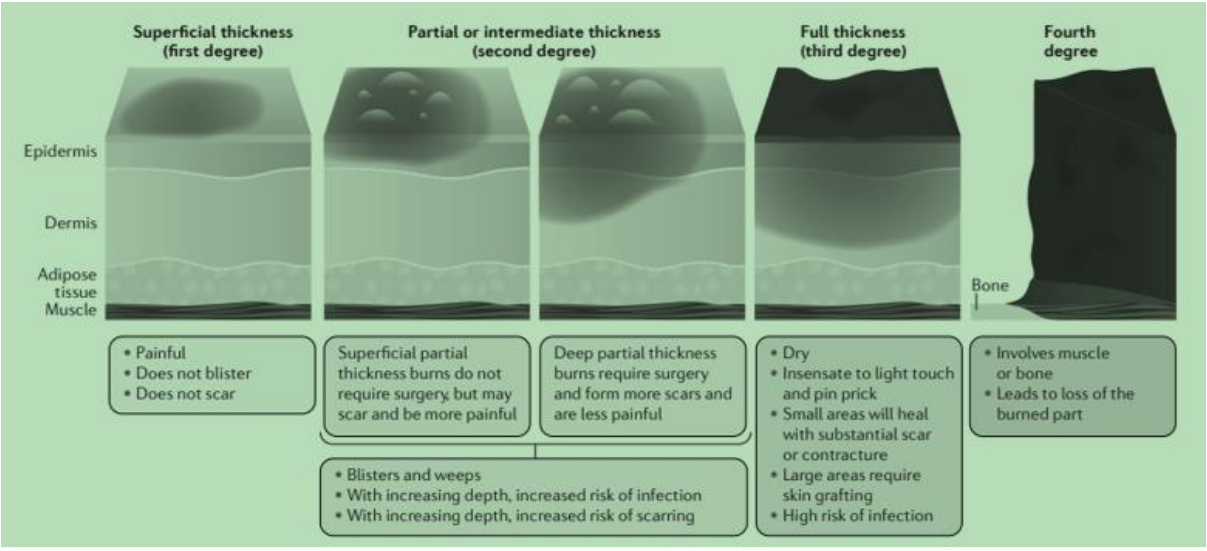
First Degree Burns - Superficial burns affect the epidermis, leading to temporary redness and tenderness of the skin.

Second-degree burns can be classified into two distinct types.

1. Superficial partial thickness burns, classified as 2A burns, are characterized by discomfort and necessitate appropriate wound care and dressing. Surgical intervention is not required; however, there is a possibility of scarring.
2. Deep partial thickness burns, known as 2B burns, tend to be less painful due to the loss of certain pain receptors. Nevertheless, surgical treatment is essential, and there is a likelihood of residual scarring.

Third Degree Burns (full thickness burns) involve damage to nerve endings and extend through the entire dermis, necessitating surgical intervention to avert infection.

Fourth Degree Burns cause harm to deeper tissues, including muscle and bone, leading to the loss of the affected area, which is often discoloured [9].



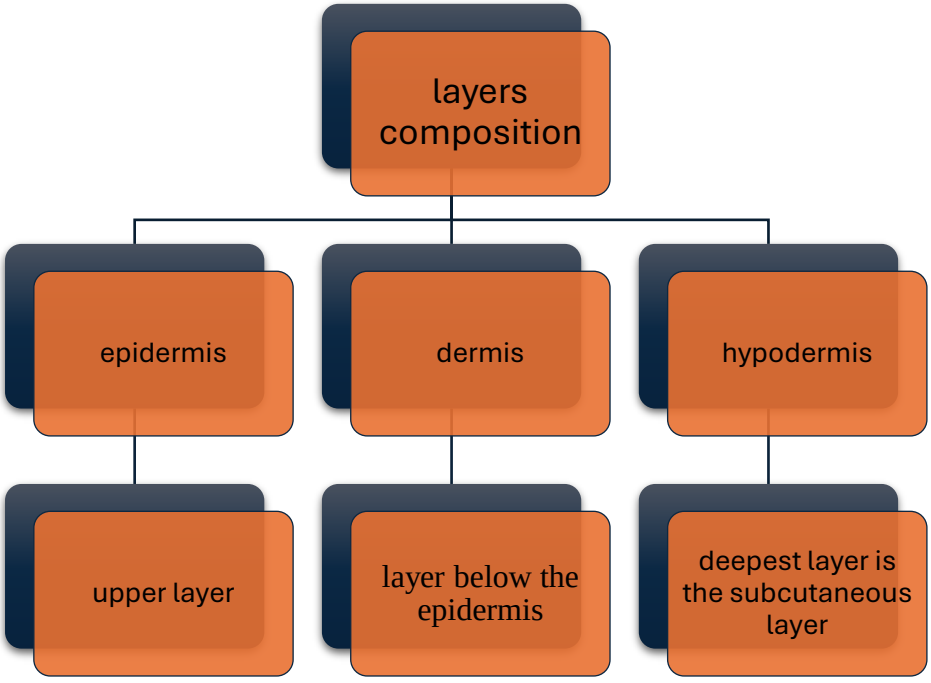
Following a severe burn, a multifaceted array of responses may persist for several years. Typically, an inflammatory response is initiated promptly after the injury to expedite the healing process [9,10].

Table no.1 Burn classification according to the cause of injury [11]

Etiology Synopsis	Etiology Synopsis
Scalding	As a result of exposure to heated liquids.
Flame	Due to the heating of contaminated air.
Contact	Arising from interaction with hot or cold materials.

Electricity	Because of the electrical current that flows between the fabrics.
Chemistry	Because of contact with hazardous substances.

A clinical presentation indicative of a specific type of burn [11].
First-degree burns are characterized by pain, a porous texture, and the absence of scarring, with recovery typically occurring within three to six days.
Second-degree burns present with flattening, erythema, and superficial discomfort. The affected area is pressure-sensitive and appears pale; healing generally takes between seven to twenty days.
Deep second-degree burns involve the dermal reticulum and exhibit a speckled white appearance that does not blanch upon pressure. These injuries can result in significant scarring, requiring two to five weeks for healing.
Third-degree burns necessitate skin grafts due to the presence of hard, painless areas on the scalp.
This condition involves a complex tissue structure comprising three distinct layers. [12].



THE PHASES OF SKIN RESTORATION DURING THE RECOVERY PROCESS OF BURN INJURIES.

Severe thermal injury affecting a substantial portion of the skin, estimated at around 20% of the total body surface area (TBSA), along with localized damage at the site of the burn, leads to acute systemic responses typically known as burn shock [13]. Burn shock is characterized by elevated hydrostatic pressure within the microvasculature, heightened capillary permeability, the movement of fluid and proteins into the interstitial space, increased systemic vascular resistance, diminished cardiac output, and hypovolemia, which requires fluid resuscitation [14]. The actual rate of fluid infusion is adjusted on an hourly basis in accordance with the effectiveness of physiological functions, including urine production [15]. Various elements that could influence these requirements encompass the existence or lack of inhalation injuries, the severity of full-thickness burns, and the elapsed time since the incident occurred [16]. Burn damage

can be categorized into three distinct zones, which are determined by the extent of tissue destruction and alterations in blood circulation [16-19].

- Coagulation Zone – This area represents the core of the incision that has sustained the most damage and is most susceptible to heat exposure. When temperatures exceed 41 °C (106 °F), proteins begin to break down and coagulate, leading to significant protein denaturation, degradation, and necrosis at the affected site [16-19].
- Zone of Stasis or Zone of Ischemia- The area exhibits inadequate perfusion and may contain tissue that is potentially salvageable. In the absence of therapeutic intervention, tissue necrosis due to hypoxia and ischemia could occur within 48 hours post-injury. The precise mechanisms that lead to apoptosis and necrosis in the ischemic region are not fully understood; however, they seem to involve a delayed onset of apoptosis occurring between 24 and 48 hours after the injury, alongside rapid autophagy within the initial 24 hours following the event [20].
- Hyperaemia Zone- Inflammatory vasodilation enhances blood circulation to the affected area, which is likely to facilitate the healing of any existing infections or other forms of damage [18].

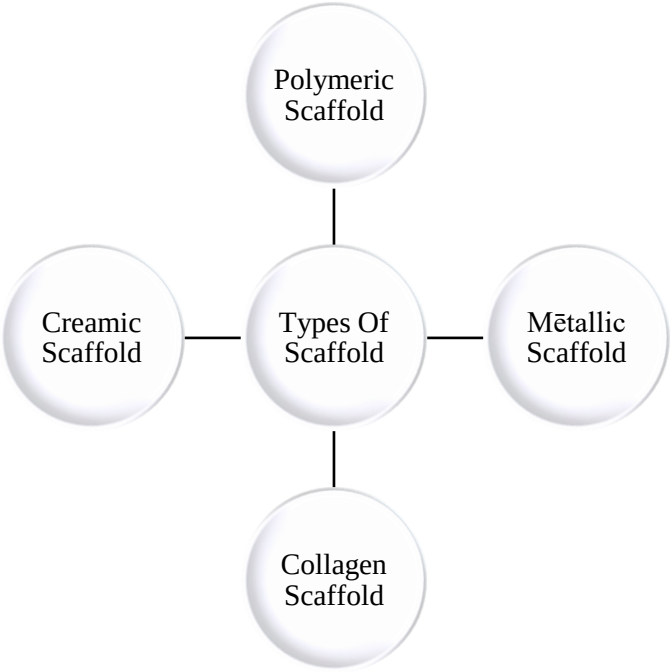
The process of wound healing is inherently dynamic and encompasses multiple stages [21]. Initially, the inflammatory phase involves the recruitment of neutrophils and monocytes to the injury site, facilitated by localized vasodilation and fluid leakage. This phase triggers an immune response that is sustained by the subsequent recruitment of macrophages through chemokine-mediated mechanisms [22]. In addition to preventing infection during the healing process, the inflammatory phase plays a crucial role in the degradation of necrotic tissue and the activation of signals necessary for wound repair [23]. Following and partially overlapping with the inflammatory phase is the proliferative phase, which is marked by the activation of keratinocytes and fibroblasts through the action of cytokines and growth factors. During this phase, keratinocytes migrate across the wound site, which is vital for the healing process as they contribute to wound closure and the formation of a new vascular network [24].

Wound closure and revascularization represent two critical components of the healing process, governed by the intricate communication network among stromal, endothelial, and immune cells. The final phase of healing, which involves the redesigning of the wound, aligns with the proliferative stage [25]. During the remodeling phase, fibroblasts transition into myofibroblasts, leading to the deposition and continuous reconstruction of collagen and elastin, which ultimately forms the scar tissue [26]. Myofibroblasts possess contractile properties that facilitate wound contraction [27]. The transformation of fibroblasts into myofibroblasts is essential for maintaining the delicate balance between contraction and re-epithelialization, a balance that significantly influences the flexibility of the healed wound [28]. Moreover, the conversion of fibroblasts, along with the apoptosis of keratinocytes and inflammatory cells, plays a vital role in the completion of the wound healing process and the overall appearance of the healed area [29].

SCAFFOLDS

Commercial products such as Epicel, Cryoskin, and BioSeed-S incorporate keratinocytes, while Dermagraft, TransCyte, and Hyalograft 3D contain fibroblasts. Additionally, Apligraf, Theraskin, and Or Cell features a combination of both cell types. The inclusion of these cells facilitates the large-scale production of uniform product batches. To promote effective skin regeneration, most of these materials are enriched with growth factors, extracellular matrix components, and cytokines, functioning as non-permanent bioactive dressings [30-32]. Biomaterials are essential in the various tissue-engineered

constructs and dressings utilized in the treatment of burns. The primary aim of employing these materials is to mimic the Extra Cellular Matrix (ECM) of the skin, which consists of proteins such as collagen, elastin, proteoglycans, nidogen, laminin, and perlecan. Proteoglycans contribute to the moisture and viscosity of the skin, elastin ensures elasticity and flexibility, while collagen provides structural strength [33,34]. Skin grafts and substitutes utilize a range of biomaterials, which encompass natural, synthetic, and semi-synthetic options. The choice of these materials during the scaffold fabrication process is crucial, as their properties influence cell behavior and facilitate the development of new tissue, thereby affecting in situ regeneration. Key requirements include permeability, biodegradability, and temporary mechanical support. Scaffolds may be either cell-free or incorporate cells, with the latter further categorized into dermal, epidermal, and epidermal-dermal composites based on the method employed [30]. A scaffold is one of the three fundamental components of the tissue-engineering strategy aimed at reconstructing, regenerating, and modifying living tissues following disease or injury [35]. Tissue engineering has developed numerous processing techniques to fabricate porous scaffolds from one or more biodegradable polymers, selected according to their specific characteristics.



POLYMERIC FRAMEWORKS FOR THE DEVELOPMENT OF BONE TISSUE:

The polymeric material generally enhances the controllability of the scaffold by virtue of its physiochemical characteristics, which include factors such as enzymatic reactions, pore dimensions, biocompatibility, allergic responses, and solubility [36, 37]. Synthetic polymers exhibit outstanding mechanical properties. Their copolymers are employed in the field of bone tissue engineering and generally consist of aliphatic polyesters, including poly(caprolactone) (PCL), poly(lactic acid) (PLA), and poly(glycolic acid) (PGA) [38–42]. These materials can be easily molded into various shapes and possess both biodegradability and biocompatibility [43]. Additionally, other polymers such as polyhydroxybutyrate, polypropylene, polysulfone, poly(methyl methacrylate), polyethylene, poly(ethylene terephthalate), poly(e-caprolactone), and polyether ketone are utilized in the field of bone tissue engineering [44]. Natural scaffolds may arise from cells or tissues [45–48].

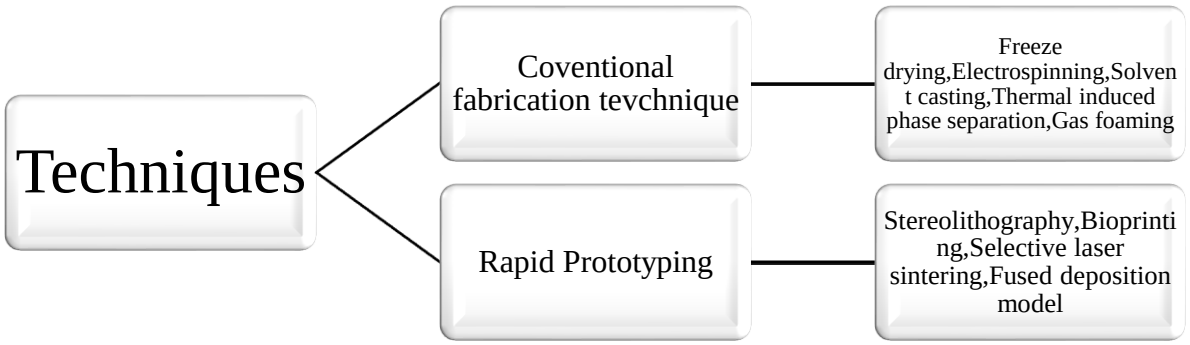
Table No. 2: - A table presenting patents related to scaffolding is displayed below.

S.No.	Patent No.	Assignee	Description	Reference
1	EP2558495B1	Gaithersburg, MD 20878 (USA) Medimmune, Llc	R2-Specific Multimeric Scaffolds for Trails	Manuel et al.(49)
2	US9176129B2	Gaithersburg, Maryland (US) / Medimmune, LLC	Protein Frameworks	Wu et al.(50)
3	US8852621B2	Berkeley, CA-based Nanonerve, Inc. (Us)	Multilayer Fibrous Polymer Frameworks: Production and Utilization Techniques	Patel et al. (51)
4	US10307514B2	Farmington, Connecticut: University of Connecticut (U.S.)	Schistosomial Porous Materials	Nukavarapu et al. (52)
5	US91682312	Berkeley, CA-based Nanonerve, Inc. (Us)	The fibrous Polymer compounds Frameworks with Polymer Fibers Patterned Totally	Patel et al. (53)
6	US9931787B2	Santa Clara, California (USA) is home to Abbott Cardiovascular Systems Inc.	Polymer Scaffolds Being Crimped	Harrington et al. (54)
6	US9931787B2	Santa Clara, California (USA) is home to Abbott Cardiovascular Systems Inc.	Polymer Scaffolds Being Crimped	Harrington et al. (54)
7	US965.5995B2	Huntington, West Virginia: Marshall University Research Corporation (U.S.)	Techniques for Repairing Damaged Cardac Tissue Using Nanofiber Scaffolds	Jingwei Xie (55)
8	US 20180272044A1	Abbott Heart Systems, Inc., Santa Clara, California (USA)	Embroidered Frameworks	Hossainy et al. (56)

A. Fabrication techniques:

The development of a significant quantity of scaffolds employed in three-dimensional cell culture within tissue engineering and drug delivery applications is essential. The characteristics of the scaffold, including

pore size and structure, are determined by various techniques used in its fabrication, such as solvent casting, gas foaming, and thermally induced phase separation [57,58].



Freeze-Drying

Shackell pioneered the technique of freeze-drying various biological components in 1909, marking a significant advancement in the field. It is important to note that Tival did not submit his initial patent application until 1927. Subsequently, in 1934, Flosdorf employed freeze-drying to develop the first stable structures. Furthermore, in 1990, De Groot et al. introduced the first tissue engineering composite [59] by integrating polyurethane and poly(l-lactic acid) (PU/PLLA). The inaugural scaffold utilizing freeze-drying technology was produced five years thereafter [60]. Tissue engineering has increasingly adopted this method in recent times [61,62]. The freeze-drying process, which involves the freezing and sublimation of an aqueous or organic polymeric solution under low pressure and temperature, serves as an effective method for creating highly porous polymeric scaffolds. This technique allows for the incorporation of heat-sensitive components into the scaffold, as it does not require high temperatures. The scaffold's structure can be modified by varying the type of solvent, viscosity, concentration, and molecular weight of the polymer solution. Additionally, the freezing temperature and the rate of cooling are critical processing parameters that significantly affect the structural characteristics of the scaffolds. For example, lowering the freezing temperature results in a reduction of the average pore size, while rapid cooling rates typically yield more uniform pore structures. Another method to enhance the average pore size of scaffolds is through annealing, which involves heating the frozen material to facilitate the growth of ice crystals [63,64]. Freeze-drying is constrained to the creation of fundamental (planar) three-dimensional structures; however, intricate forms have been effectively generated through meticulous management of the molds and processing conditions [65]. Unidirectional porous scaffolds can be created by controlling the growth rate and alignment of ice crystals, which will influence the orientation of the pores [66]. Pore size is influenced by the concentration of the polymer as well as its molecular weight [67]. At present, the primary focus of advancements in scaffold fabrication through freeze-drying technology is to enhance cell adhesion, proliferation, and differentiation by meticulously defining the microstructure of the biomaterial. As previously mentioned, the process has been improved in two distinct pathways to create biomaterials

that mimic sponges (the final product) and hydrogels (the intermediate result). This category of biomaterial presents significant challenges due to its low mechanical strength, which complicates its application in bioreactors where mechanical stimulation is essential for promoting cell growth and proliferation.

Table: 3 Various scaffolding methods [68]

S.no.	Techniques	Advantages	Disadvantages
1	**Freeze-Drying**	1. It serves a range of functions 2. It can tolerate high temperatures. 3 Another way to regulate the pore size is to alter and regulate the freezing drying procedure.	1 This method needs a lot of energy resources 2 It employs cytotoxic solvents 3 The pore size is irregular.
2	**Particle leaching and solvent casting techniques**	1.Possessing a porosity range of 50% to 90% 2. It is inexpensive. 3. It is compatible with the three-dimensional thin wall's thin membrane.	1 Hazardous solvent application. 2 times as much
2	**Particle leaching and solvent casting techniques**	1.Possessing a porosity range of 50% to 90% 2. It is inexpensive. 3. It is compatible with the three-dimensional thin wall's thin membrane.	1 Hazardous solvent application. 2 times as much
3	**Electrospinning/Electrospraying**	1 practical method for creating non-fibrous scaffolds 2 The homogeneous product is composed of fibers because of its great tensile strength.	1 Toxic solvent use 2 Inability to obtain three-dimensional structures 3 Typically, this procedure is dependent upon the factors.

4	**3D printing using stereolithography (SLA)**	1 High resolution power 2 A homogeneous distribution of pore interconnectivity	1. Photopolymerization is the primary constraint. 2. Requires a lot of monomers
5	**Selective Laser Sintering (SLS)**	1 Power the sinter powder material using a laser. 2 Employ ultrahigh weight molecular polythene	1. The removal of injected powder at a high temperature calls for an additional technique.

The materials employed in the fabrication of scaffolds are polymers:

Scaffold materials exhibit considerable diversity; they can be synthetic, incorporating minimal or no physiological signals or variables, or entirely biological, featuring both inherent and bioactive elements designed to promote tissue development [69–71]. The initial emergence of the issue significantly advanced the field of synthetic biomaterials, drawing extensively from the extensive knowledge gained in chemical synthesis and materials processing. This field has continued to evolve and grow since that time. While classifying these polymers can present difficulties, a common approach is to divide them into two categories: polycondensation and polyaddition polymers. Although this classification system, like others, has its limitations, it effectively organizes systems based on polymer structure and offers a clear representation of the polymer's outcomes [72]. Numerous materials, encompassing both synthetic and biopolymeric types, have been utilized in applications related to tissue engineering [73]. Biopolymers exhibit superior bioactive properties when contrasted with synthetic polymeric scaffolds. Nevertheless, the degradation products of synthetic polymers may generate acids that can adversely affect host tissues and elicit significant immune responses within the body [74, 75]. The similarity in chemical compositions between biopolymers and the host biological system enables them to function as a tissue interface or potentially establish a bond with the host tissue [76,77]. Extracellular matrix (ECM) ligands are sometimes found within biopolymers, which often exhibit precisely regulated structural characteristics and possess the ability to interact with cell receptors. Additionally, biopolymer-based scaffolds can influence cellular growth throughout various stages of development [78,79].

Varieties of polymers	**Polymers**	**Properties**
Natural Polymers	Collagen	1.Main Protein 2. Offers connective tissue support 3. Limited antigenic qualities

		4.Potent direct adhesion properties
	Gelatin	1. Consistent genetic behavior 2. Reaction to amide group that is less invasive 3. A decline in regulations
	Alginate	1. Compatible with biological systems 2. Degradable by nature 3. Non-antigenous
	Chitosan	1. Not harmful 2. Biodegradable 3. Compatible with biological systems 4. Bioactive and non-antigenous
	Hyaluronic acid	1. A rise in angiogensis 2. Encourages scar-free wound healing
	Keratin	1. A large capacity for absorbing water 2. Non-toxic 3. Moistness and pliability
	Keratin	1. A large capacity for absorbing water 2. Non-toxic 3. Moistness and pliability
	Microbial Cellulose	1. Display remarkable wet strength 2. Complying with regulations 3. High degree of flexibility
Synthetic Polymers	Poly(lactide-coglycolide) (PLGA)	1. Degradable by nature 2. Sturdy in body 3. Compatible with biological systems 4. Controls the form of the therapeutic substance 5. FDA authorized
	Polyethylene glycol (PEG)	1. Water-loving 2. Not immune stimulating 3. Compatible with biological systems 4. Adaptable in character
	Poly(vinyl alcohol) (PVA)	1. Take in a substantial amount of water 2. Not cancer-causing 3. Compatible with biological systems 4. Water-loving
	Polyurethane (PU)	1. Protects the wound and surrounding cells 2. A unique porous composition 3. High absorption potential
	Polycaprolactone (PCL)	1. Compatible with biological systems 2. Degradable by nature 3. FDA authorized 4. Non-toxic

Natural polymers:

Natural polymers are frequently utilized in the production of wound dressing materials. Their exceptional biocompatibility and biodegradability have facilitated their use in creating various scaffolds. These polymeric frameworks enable the delivery of cellular tissue structures in three-dimensional configurations while maintaining both chemical and physical integrity.

a. Chitosan

The biopolymer CHN, which is composed of N-acetyl-D-glucosamine and glucosamine, has found widespread use in tissue engineering and various biomedical applications. Its applications include vascular grafts, as well as in the development of skin, bone, and cartilage, in addition to serving as substrates for mammalian cell culture [80-82]. Positive attributes encompass non-toxicity, renewability, biocompatibility, biodegradability, non-antigenicity, and bioactivity. CHN serves as a crucial element in tissue engineering due to its ability to gel at physiological temperatures and its capacity to interact with proteins and growth hormones, thereby facilitating their retention [83,84]. In in vivo conditions, CHN undergoes rapid degradation, limited solely by the quantity of the remaining acetyl component. Due to these beneficial properties, CHN has gained recognition as a preferred material for tissue engineering applications [81]. Porosity, which can be regulated in CHN scaffolds, influences the strength and elasticity of tissue engineering scaffolds [85]. CHN must possess a cationic charge to engage with negatively charged polymers such as HYA, thereby facilitating the formation of a polyelectrolyte complex (PEC). In isolation, HYA and CHN do not create stable scaffolds due to their susceptibility to swelling. However, the development of the PEC results in the generation of both stationary and mobile scaffolds [86]. As a result, the characteristics of the individual polymers, including improved stability, superior cell adhesion, and enhanced mechanical performance, will be augmented by the scaffolds that are developed [83].

b. Hyaluronic acid (HA)

Hyaluronic acid (HA), a linear polysaccharide, is formed through the combination of N-acetyl-D-glucosamine and glucuronic acid. It is frequently utilized in the treatment of severe wounds and burns. The synthetic variants of HA can be produced in various forms, including films, gels, sheaths, or meshes. Research has indicated that this polymer holds significant potential in the engineering of both human and animal skin tissues. HA has been shown to reduce the severity of chronic wounds in comparison to acute wounds and to promote angiogenesis. It facilitates wound healing without scarring. From both a physical and medical perspective, a three-dimensional matrix made of HA and other polymers closely resembles skin. In wound healing applications, HA is often employed in conjunction with silver sulfadiazine within polyurethane foam [87,88].

Synthetic Polymers

Synthetic polymers are dependable and cost-effective materials that can be customized to produce various shapes and configurations, such as fibres, mats, meshes, films, sheaths, and scaffolds, aimed at addressing skin imperfections and wounds. They are frequently utilized as cross-linking or blending agents, enhancing the mechanical stability of natural polymers. The combination of natural and synthetic polymers serves as temporary scaffolds, facilitating the transfer of dermal and epidermal cells essential for the healing of full-thickness wounds.

a. Poly(lactide-co-glycolide) (PLGA)

PLGA, a biodegradable copolymer composed of polyglycolic acid and polylactic acid, has received FDA approval for applications in skin tissue engineering. Its ability to degrade in a controlled manner and its

customizable mechanical properties render it a favored option for skin substitutes. The PLGA/PLA mesh is effective in treating diabetic foot ulcers and promoting wound healing. Nonetheless, its hydrophobic nature poses challenges for cell adhesion. To enhance cell distribution, PLGA can be knitted, and it can also be combined with collagen60 to achieve a more uniform cell distribution [89,90].

APPLICATIONS:

Assessment for infectious diseases:

Infectious diseases pose a considerable challenge to global health. The World Health Organization (WHO) reports that 17 million individuals are at risk of contracting different infectious diseases [91]. In 2008, the World Health Organization (WHO) indicated that there have been shifts in health concerns related to infectious diseases when compared to non-communicable diseases. A significant challenge to global health is the ongoing transmission of the coronavirus 2 (commonly referred to as COVID-19 or SARS-CoV-2), which has marked a resurgence of infectious diseases [92]. These viruses spread rapidly and can lead to fatalities before mass immunization efforts can eliminate them. Additionally, among the infectious diseases with the highest mortality rates are tuberculosis and HIV/AIDS. The World Health Organization classified the latest outbreak of SARS-CoV-2 as a global pandemic due to its swift proliferation across the globe. Statistics indicate that 135 million people have been infected with SARS-CoV-2, resulting in 2.9 million deaths attributed to the virus [93]. Numerous initiatives were undertaken to develop a sensor capable of facilitating the rapid detection of COVID-19. For example, Jiao et al. [94] A DNA nano-scaffold platform has been developed for the monitoring and detection of COVID-19. This sensor is founded on the hybrid chain reaction (HCR) method, which can identify the RNA of SARS-CoV-2. The underlying mechanism, which relies on fluorescence, has been illustrated. Setyawati et al. [95] Rapidly detect pathogens such as Escherichia coli (E. coli) and Staphylococcus aureus (S. aureus) through the attachment of gold nanoclusters (AuNCs) to a DNA scaffold nanostructure. Liu et al. employed graphene-functionalized scaffolds along with DNAzyme in their research. [96] A fluorescence-based sensor has been developed for the detection of E. coli, as reported by Xu et al. [97] A method for bacterial detection utilizing barcode technology was established through the use of hydrogel scaffolds composed of poly(ethylene glycol) (PEG), as reported by Zhang et al. [98], Silver nano clusters (AgNCs) can be altered through the use of a DNA hairpin template, which serves as a framework for detecting Salmonella typhimurium (S. typhimurium). The interaction between S. typhimurium and the scaffold material resulted in an enhancement of fluorescence intensity. Additionally, Mobed et al. presented an electrochemical biosensor designed for the detection of Legionella pneumophila (L. pneumophila) [99]. Chitosan/AuNPs scaffolds were electrodeposited to modify the surface of the gold electrode. An electrochemical biosensor can detect the low concentration of L. pneumophila at the zeptomolar level. The DNA sensor developed by Mobed et al. employs electrochemical methods [99]. The sensor, which is based on DNA hairpin technology, demonstrates the highest efficacy in bacterial detection [98] The constructed sensor exhibits commendable performance characterized by both sensitivity and simplicity.

Cancer Diagnosis

Cancer represents a significant global cause of death and distress among individuals. A vital element in managing the cancer epidemic is the early detection of the disease, supported by extensive coverage and effective results. The assessment and recognition of biomarkers linked to the occurrence and progression of cancer enable timely diagnosis at an early stage [100]. Biomarkers are biological indicators present in bodily fluids, and their levels can influence the progression of a disease. One significant application of

biomarkers is in the early detection of malignant tumors. They play an essential role in assessing treatment efficacy and in the identification of rare diseases [101]. Consequently, numerous biomarkers have been discovered in tumors and cancerous cells; protein-based biosensors have been utilized to detect these cancer biomarkers [102,103]. Various assay-based techniques, such as polymerase chain reaction (PCR), immunohistochemistry, and flow cytometry, have been utilized to measure multiple biomarkers [104–108]. Biosensors have gained attention for their rapidity and ease of use in the early detection of cancer [109]. The advantages of scaffold-based materials, including their non-toxic nature, porosity, mechanical strength, and extensive surface area, have resulted in their extensive use as instruments for cancer detection.

Protein marker

Numerous protein biomarkers, including carcinoembryonic antigen (CEA), human epidermal growth factor receptor 2 (HER2), telomerase, alkaline phosphatase (ALP), prostate-specific antigen (PSA), and protein tyrosine kinase-7 (PTK7), have been employed in various techniques for cancer detection [110–115]. Protein markers have been assessed through various analytical methods, as they serve as crucial biomarkers for identifying the presence and progression of prostate cancer [116]. DNA scaffolds serve as valuable biomaterials that possess remarkable properties, including the capacity to identify various biomolecules and minimize non-specific adsorption [117]. To identify PSA, Chen et al. [118] developed an immunological sensor by linking gold nanoparticles (AuNPs) to a deoxyribonucleic acid (DNA) scaffold. The sensitivity of PSA detection is influenced by the distance between the immobilized antibodies, which function as both signal reporters and amplification agents, and the AuNPs. The use of scaffold DNA, grounded in nanotechnology, enhances the interaction between antibodies and PSA molecules, resulting in heightened sensitivity with a limit of detection (LOD) of 1.0 pg/ml. Specific mobile receptors that participate in signaling pathways are in the cell membranes of both cancerous and healthy cells. These receptors serve various roles in cancer, including sensing [121–124], drug delivery [119], and treatment [120]. The human epidermal growth factor receptor 2 (HER2) protein belongs to the family of epidermal growth factor receptors. This receptor plays a crucial role in the development and advancement of epithelial cancers, affecting various sites such as the prostate, ovary, pancreas, lung, bladder, oral cavity, and breast. To facilitate the immobilization of specific HER2 proteins, Gu et al. have conducted relevant research [125] A composite material was synthesized that incorporates carbon dots (CDs) within ZrHf-metal organic frameworks (MOFs) by immersing a bimetallic ZrHf MOF in amino-functionalized CDs. This process led to the development of a scaffold-based biosensor utilizing MOFs for the calibration of carcinoembryonic antigen (CEA), a glycoprotein associated with various cancers. The biosensor was designed by Guo et al. for potential application in clinical cancer diagnostics [126] The foundation of this work lies in AgNCs@Apt@UiO-66. The sensor, constructed on a scaffold, utilizes a zirconium metal-organic framework (Zr-MOF, UiO-66), gold nanoclusters (AuNCs), and an aptamer specifically targeting CEA. Bimetallic metal-organic frameworks (MOFs) exhibit a synergistic effect and demonstrate superior physicochemical properties compared to their monometallic equivalents. A bimetallic MOF integrated into a nanocomposite of MOF was developed by Zhou et al. [127] The objective was to identify the tyrosine-protein kinase-like protein, specifically the cell membrane protein PTK7. Furthermore, the researchers developed an apt sensor utilizing bimetallic composites of Zr-MOF-on-Zn-MOF and Zn-MOF-on-Zr-MOF. A near-infrared (NIR) fluorescence method was established by Park et al. [128] The objective is to identify the cancer biomarker known as alkaline phosphatase (ALP). To detect protein-based biomarkers, methods utilizing electrochemical and optical techniques have been employed. These

sensors offer numerous advantages, such as user-friendliness, superior bioanalytical performance, rapid production processes, cost-effectiveness, and the possibility of miniaturization.

Nucleic acid-derived biomarker:

MicroRNAs, commonly referred to as miRNAs, are naturally occurring non-coding small RNAs that play a crucial role in various biological functions. The irregular expression of miRNAs within tissues and living cells serves as a diagnostic tool for numerous biological processes and related diseases. To facilitate the imaging and identification of miRNAs in live cells, a Y-shaped backbone-rigidified triangular DNA scaffold (YTDS) was developed, incorporating novel aptamers. This innovative method employs fluorescence and is characterized by its high sensitivity and biocompatibility, making it a promising tool for future biological research. Additionally, it encompasses the application of miRNAs in disease detection [129]. DNA walkers are utilized in an electrochemical sensor developed by Wang and colleagues [130].

Cell Delivery

Scaffolds function as a means for the delivery of cells, contributing to the improvement of conditions such as osteoarthritis and myocardial infarction [131–134]. Cell delivery often results in low retention rates and inadequate integration at the site of administration [135]. Establish a setting in which cells are introduced, allowing for the scaffold developed through tissue engineering to be directly administered to the defect site. Surgical techniques, including matrix-assisted chondrocyte implantation (MACI), have demonstrated greater efficacy compared to direct delivery methods [136]. Cells are introduced onto scaffolds through either a dynamic or static method [137]. The static method of seeding involves placing a cell suspension directly onto the surface of the scaffold, whereas the dynamic approach utilizes different mechanical stimuli, including shaking or stirring, to enhance the uniformity and density of the cells.

Drug and Biomolecule delivery

Systemic delivery challenges, including inadequate localization of biomolecules to the intended target and suboptimal delivery efficiency, can be addressed through the utilization of scaffolds designed to transport bioactive molecules and pharmaceuticals [138]. Drugs and biomolecules can become immobilized on the surface of a scaffold through either covalent bonding or physical adsorption [139].

FUTURE PROSPECTIVE

Future advancements in scaffold-based biomaterials offer promising applications across wound care, regenerative medicine, cancer diagnostics, and pharmaceuticals. Next-generation wound dressings will be customizable and bioactive, adjusting to healing processes with real-time delivery of growth factors and antimicrobials. Smart, hybrid scaffolds with controlled release capabilities can significantly improve tissue engineering by mimicking natural tissue properties, while biosensing scaffolds show potential for early cancer detection and targeted therapy. Research into biodegradable polymers and natural proteins aims to enhance biocompatibility and support cell function, expanding scaffold applications for drug delivery, organ support, and sustained, patient-specific regenerative treatments.

CONCLUSION

By increasing and decreasing the synthesis of proteins and growth factors, scaffolds serve as locations for cell attachment, proliferation, differentiation, and migration. They transfer inductive chemicals or cells to the healing site and offer mechanical support. Additionally, scaffolds offer cues to regulate the composition and functionality of freshly produced tissue. By increasing and decreasing the synthesis of proteins and growth factors, scaffolds serve as locations for cell attachment, proliferation, differentiation,

and migration. They transfer inductive chemicals or cells to the healing site and offer mechanical support. Additionally, scaffolds offer cues to regulate the composition and functionality of freshly produced tissue. Natural and synthetic polymers that are biocompatible and biodegradable will significantly advance the creation of innovative forms of wound dressings and have remarkable uses in the biomedical field, particularly for regenerative medicine. In this regard, natural polymers including alginates, chitin, chitosan, heparin, and chondroitin, as well as proteins (collagen, gelatin, fibrin, keratin, silk fibroin, eggshell membrane) and proteoglycans, continue to be the basis for the most promising materials for wound and burn dressing. It can be applied in various fields like cancer diagnosis, protein marker, burn wound dressings.

REFRENCES:

1. American Burn Association. National Burn Repository 2019 Update. Report of data from. 2009;2018:2019.
2. Sasor SE, Chung KC. Upper extremity burns in the developing world: a neglected epidemic. Hand clinics. 2019 Nov 1;35(4):457-66.
3. Logsetty S, Shamlou A, Gawaziuk JP, March J, Doupe M, Chateau D, Hoppensack M, Khan S, Medved M, Leslie WD, Enns MW. Mental health outcomes of burn: a longitudinal population-based study of adults hospitalized for burns. Burns. 2016 Jun 1;42(4):738-44.
4. Mason SA, Nathens AB, Byrne JP, Diong C, Fowler RA, Karanicolas PJ, Moineddin R, Jeschke MG. Increased rate of long-term mortality among burn survivors: a population-based matched cohort study. Annals of surgery. 2019 Jun 1;269(6):1192-9.
5. Stone J, Gawaziuk JP, Khan S, Chateau D, Bolton JM, Sareen J, Enns J, Doupe M, Brownell M, Logsetty S. Outcomes in adult survivors of childhood burn injuries as compared with matched controls. Journal of Burn Care & Research. 2016 Mar 1;37(2):e166-73.
6. Smolle C, Cambiaso-Daniel J, Forbes AA, Wurzer P, Hundeshagen G, Branski LK, Huss F, Kamolz LP. Recent trends in burn epidemiology worldwide: a systematic review. Burns. 2017 Mar 1;43(2):249-57.
7. Tegtmeyer LC, Herrnstadt GR, Maier SL, Thamm OC, Klinke M, Reinshagen K, Koenigs I. Retrospective analysis on thermal injuries in children—demographic, etiological and clinical data of German and Austrian pediatric hospitals 2006–2015—approaching the new German burn registry. Burns. 2018 Feb 1;44(1):150-7.
8. Jeschke MG, van Baar ME, Choudhry MA, Chung KK, Gibran NS, Logsetty S. Burn injury. Nature reviews Disease primers. 2020 Feb 13;6(1):11.
9. Jeschke MG, Chinkes DL, Finnerty CC, Kulp G, Suman OE, Norbury WB, Branski LK, Gauglitz GG, Mlcak RP, Herndon DN. Pathophysiologic response to severe burn injury. Annals of surgery. 2008 Sep 1;248(3):387-401.
10. Stanojcic M, Abdullahi A, Rehou S, Parousis A, Jeschke MG. Pathophysiological response to burn injury in adults. Annals of surgery. 2018 Mar 1;267(3):576-84.
11. Garcia-Espinoza JA, Aguilar-Aragon VB, Ortiz-Villalobos EH, Garcia-Manzano RA, Antonio BA, Aron J. Burns: definition, classification, pathophysiology and initial approach. Gen Med. 2017;5(5):1-5.
12. Mathes SH, Ruffner H, Graf-Hausner U. The use of skin models in drug development. Advanced drug delivery reviews. 2014 Apr 20;69:81-102.

13. Robins EV. Burn shock. Critical Care Nursing Clinics of North America. 1990 Jun 1;2(2):299-307.
14. Pham TN, Cancio LC, Gibran NS. American Burn Association practice guidelines burn shock resuscitation. Journal of burn care & research. 2008 Jan 1;29(1):257-66.
15. Dries DJ. Management of burn injuries–recent developments in resuscitation, infection control and outcomes research. Scandinavian journal of trauma, resuscitation and emergency medicine. 2009 Dec;17:1-3.
16. Nisanci M, Eski M, Sahin I, Ilgan S, Isik S. Saving the zone of stasis in burns with activated protein C: an experimental study in rats. Burns. 2010 May 1;36(3):397-402.
17. Jackson DM. The diagnosis of the depth of burning. Journal of British Surgery. 1953 May;40(164):588-96.
18. Hettiaratchy S, Dziewulski P. Pathophysiology and types of burns. Bmj. 2004 Jun 10;328(7453):1427-9.
19. Rowan MP, Cancio LC, Elster EA, Burmeister DM, Rose LF, Natesan S, Chan RK, Christy RJ, Chung KK. Burn wound healing and treatment: review and advancements. Critical care. 2015 Dec;19:1-2.
20. Tan JQ, Zhang HH, Lei ZJ, Ren P, Deng C, Li XY, Chen SZ. The roles of autophagy and apoptosis in burn wound progression in rats. Burns. 2013 Dec 1;39(8):1551-6.
21. Gurtner GC, Werner S, Barrandon Y, Longaker MT. Wound repair and regeneration. Nature. 2008 May;453(7193):314-21.
22. Tiwari VK. Burn wound: How it differs from other wounds?. Indian journal of plastic surgery. 2012 May;45(02):364-73.
23. Reinke JM, Sorg H. Wound repair and regeneration. European surgical research. 2012 Jul 11;49(1):35-43.
24. Pastar I, Stojadinovic O, Yin NC, Ramirez H, Nusbaum AG, Sawaya A, Patel SB, Khalid L, Isseroff RR, Tomic-Canic M. Epithelialization in wound healing: a comprehensive review. Advances in wound care. 2014 Jul 1;3(7):445-64.
25. Widgerow AD. Cellular/extracellular matrix cross-talk in scar evolution and control. Wound repair and regeneration. 2011 Mar;19(2):117-33.
26. Singer AJ, Clark RA. Cutaneous wound healing. New England journal of medicine. 1999 Sep 2;341(10):738-46.
27. Hinz B. Formation and function of the myofibroblast during tissue repair. Journal of Investigative Dermatology. 2007 Mar 1;127(3):526-37.
28. Snowden JM. Wound closure: an analysis of the relative contributions of contraction and epithelialization. Journal of Surgical Research. 1984 Dec 1;37(6):453-63.
29. Shih B, Garside E, McGrouther DA, Bayat A. Molecular dissection of abnormal wound healing processes resulting in keloid disease. Wound repair and regeneration. 2010 Mar;18(2):139-53.
30. Shevchenko RV, James SL, James SE. A review of tissue-engineered skin bioconstructs available for skin reconstruction. Journal of the royal Society Interface. 2010 Feb 6;7(43):229-58.
31. Boateng JS, Matthews KH, Stevens HN, Eccleston GM. Wound healing dressings and drug delivery systems: a review. Journal of pharmaceutical sciences. 2008 Aug 1;97(8):2892-923.
32. Boateng J, Catanzano O. Advanced therapeutic dressings for effective wound healing—a review. Journal of pharmaceutical sciences. 2015 Nov 1;104(11):3653-80.

33. Lu C, Fuchs E. Sweat gland progenitors in development, homeostasis, and wound repair. Cold Spring Harbor perspectives in medicine. 2014 Feb 1;4(2):a015222.
34. Mikkola ML, Millar SE. The mammary bud as a skin appendage: unique and shared aspects of development. Journal of mammary gland biology and neoplasia. 2006 Oct;11:187-203.
35. Stanojcic M, Abdullahi A, Rehou S, Parousis A, Jeschke MG. Pathophysiological response to burn injury in adults. Annals of surgery. 2018 Mar 1;267(3):576-84.
36. Fuchs JR, Nasseri BA, Vacanti JP. Tissue engineering: a 21st century solution to surgical reconstruction. The Annals of thoracic surgery. 2001 Aug 1;72(2):577-91.
37. Meyer U, Wiesmann HP. Bone and cartilage. Springer Berlin Heidelberg; 2006.
38. Ma PX. Scaffolds for tissue fabrication. Materials today. 2004 May 1;7(5):30-40.
39. Kretlow JD, Mikos AG. Mineralization of synthetic polymer scaffolds for bone tissue engineering. Tissue engineering. 2007 May 1;13(5):927-38.
40. Moradi A, Dalilottojari A, Pingguan-Murphy B, Djordjevic I. Fabrication and characterization of elastomeric scaffolds comprised of a citric acid-based polyester/hydroxyapatite microcomposite. Materials & Design. 2013 Sep 1;50:446-50.
41. Ali Akbari Ghavimi S, Ebrahimzadeh MH, Solati-Hashjin M, Abu Osman NA. Polycaprolactone/starch composite: Fabrication, structure, properties, and applications. Journal of biomedical materials research Part A. 2015 Jul;103(7):2482-98.
42. Ghavimi SA, Ebrahimzadeh MH, Shokrgozar MA, Solati-Hashjin M, Osman NA. Effect of starch content on the biodegradation of polycaprolactone/starch composite for fabricating in situ pore-forming scaffolds. Polymer Testing. 2015 May 1;43:94-102.
43. Ishaug SL, Yaszemski MJ, Bizios R, Mikos AG. Osteoblast function on synthetic biodegradable polymers. Journal of biomedical materials research. 1994 Dec;28(12):1445-53.
44. Wang M. Developing bioactive composite materials for tissue replacement. Biomaterials. 2003 Jun 1;24(13):2133-51.
45. Pei M, Li JT, Shoukry M, Zhang Y. A review of decellularized stem cell matrix: a novel cell expansion system for cartilage tissue engineering. Eur Cell Mater. 2011 Nov 24;22(333):43.
46. Qiang YA, Jiang PE, Lu SB, Guo QY, Bin ZH, Zhang L, Wang AY, Xu WJ, Qun XI, HU YC, XU BS. Evaluation of an extracellular matrix-derived acellular biphasic scaffold/cell construct in the repair of a large articular high-load-bearing osteochondral defect in a canine model. Chinese medical journal. 2011 Dec 1;124(23):3930-8.
47. Koob S, Torio-Padron N, Stark GB, Hannig C, Stankovic Z, Finkenzeller G. Bone formation and neovascularization mediated by mesenchymal stem cells and endothelial cells in critical-sized calvarial defects. Tissue Engineering Part A. 2011 Feb 1;17(3-4):311-21.
48. Biltz RM, Pellegrino ED. The chemical anatomy of bone: I. A comparative study of bone composition in sixteen vertebrates. JBJS. 1969 Apr 1;51(3):456-66.
49. BACA M, THISTED T, SWERS J, TICE D, Medimmune, LLC. TRAIL R2-SPECIFIC MULTIMERIC SCAFFOLDS. EUROPEAN PATENT SPECIFICATION. 2019.
50. PROTEIN SCAFFOLDS. United States Patent. 2015.
51. Patel S, Kurpinski K, Wong YC, Nanonerve, Inc. MULTILAYER FIBROUS POLYMER SCAFFOLDS, METHODS OF PRODUCTION AND METHODS OF USE. United States Patent. 2014.

52. Nukavarapu SP Et Al, University Of Connecticut. GRADIENT POROUS SCAFFOLDS. United States Patent. US 10,307,514 B2, 2019.
53. Patel S Et Al, Kurpinski K. FIBROUS POLYMER SCAFFOLDS HAVING DIAMETRICALLY PATTERNED POLYMER FIBERS. US Patent. 2015.
54. Harrington J, Mccoy J, Abbott Cardiovascular Systems Inc. CRIMPING POLYMER SCAFFOLDS. United States Patent. US 9,931,787 B2, 2018.
55. NANOFIBER SCAFFOLDS AND METHODS FOR REPAIRING DAMAGED CARDAC TSSUE. United States Patent. 2017. P. 2.
56. Hossainy SFA Et Al. BRAIDED SCAFFOLDS. US 2018/0272044 A1. 2018.
57. Dutta RC, Dey M, Dutta AK, Basu B. Competent processing techniques for scaffolds in tissue engineering. Biotechnology advances. 2017 Mar 1;35(2):240-50.
58. Tsang VL, Bhatia SN. Fabrication of Three-Dimensional Tissues: Tissue Engineering II. InAdvances In Biochemical Engineering/Biotechnology, V103 2005 (pp. 189-205). Springer Berlin, Heidelberg.
59. De Groot JH, Nijenhuis AJ, Bruin P, Pennings AJ, Veth RP, Klompmaker J, Jansen HW. Use of porous biodegradable polymer implants in meniscus reconstruction. 1) Preparation of porous biodegradable polyurethanes for the reconstruction of meniscus lesions. Colloid and Polymer Science. 1990 Dec;268:1073-81.
60. Whang K, Thomas CH, Healy KE, Nuber G. A novel method to fabricate bioabsorbable scaffolds. Polymer. 1995 Jan 1;36(4):837-42.
61. Szymczyk-Ziółkowska P, Łabowska MB, Detyna J, Michalak I, Gruber P. A review of fabrication polymer scaffolds for biomedical applications using additive manufacturing techniques. Biocybernetics and Biomedical Engineering. 2020 Apr 1;40(2):624-38.
62. Brougham CM, Levingstone TJ, Shen N, Cooney GM, Jockenhoevel S, Flanagan TC, O'Brien FJ. Freeze-drying as a novel biofabrication method for achieving a controlled microarchitecture within large, complex natural biomaterial scaffolds. Advanced healthcare materials. 2017 Nov;6(21):1700598.
63. Pawelec KM, Husmann A, Best SM, Cameron RE. A design protocol for tailoring ice-templated scaffold structure. Journal of the Royal Society Interface. 2014 Mar 6;11(92):20130958.
64. Raeisdasteh Hokmabad V, Davaran S, Ramazani A, Salehi R. Design and fabrication of porous biodegradable scaffolds: a strategy for tissue engineering. Journal of biomaterials science, polymer edition. 2017 Nov 2;28(16):1797-825.
65. Brougham CM, Levingstone TJ, Shen N, Cooney GM, Jockenhoevel S, Flanagan TC, O'Brien FJ. Freeze-drying as a novel biofabrication method for achieving a controlled microarchitecture within large, complex natural biomaterial scaffolds. Advanced healthcare materials. 2017 Nov;6(21):1700598.
66. Deville S. Freeze-casting of porous biomaterials: structure, properties and opportunities. Materials. 2010 Mar 17;3(3):1913-27.
67. Qian L, Zhang H. Controlled freezing and freeze drying: a versatile route for porous and micro-/nano-structured materials. Journal of Chemical Technology & Biotechnology. 2011 Feb;86(2):172-84.
68. Eltom A, Zhong G, Muhammad A. Scaffold techniques and designs in tissue engineering functions and purposes: a review. Advances in materials science and engineering. 2019;2019(1):3429527.

69. DeForest CA, Polizzotti BD, Anseth KS. Sequential click reactions for synthesizing and patterning three-dimensional cell microenvironments. Nature materials. 2009 Aug;8(8):659-64.
70. Hubbell JA. Biomaterials in tissue engineering. Bio/technology. 1995 Jun 1;13(6):565-76.
71. Lutolf MP, Hubbell JA. Synthetic biomaterials as instructive extracellular microenvironments for morphogenesis in tissue engineering. Nature biotechnology. 2005 Jan 1;23(1):47-55.
72. Izdebska-Podsiadły J, Thomas S, editors. Printing on polymers: fundamentals and applications. William Andrew; 2015 Sep 24.
73. Liao J, Qu Y, Chu B, Zhang X, Qian Z. Biodegradable CSMA/PECA/graphene porous hybrid scaffold for cartilage tissue engineering. Scientific reports. 2015 May 11;5(1):9879.
74. Chen G, Ushida T, Tateishi T. A biodegradable hybrid sponge nested with collagen microsponges. Journal of Biomedical Materials Research: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials. 2000 Aug;51(2):273-9.
75. Lahiji A, Sohrabi A, Hungerford DS, Frondoza CG. Chitosan supports the expression of extracellular matrix proteins in human osteoblasts and chondrocytes. Journal of biomedical materials research. 2000 Sep 15;51(4):586-95.
76. Jaikumar D, Sajesh KM, Soumya S, Nimal TR, Chennazhi KP, Nair SV, Jayakumar R. Injectable alginate-O-carboxymethyl chitosan/nano fibrin composite hydrogels for adipose tissue engineering. International journal of biological macromolecules. 2015 Mar 1;74:318-26.
77. Unnithan AR, Sasikala AR, Murugesan P, Gurusamy M, Wu D, Park CH, Kim CS. Electrospun polyurethane-dextran nanofiber mats loaded with Estradiol for post-menopausal wound dressing. International Journal of Biological Macromolecules. 2015 Jun 1;77:1-8.
78. Kavya KC, Jayakumar R, Nair S, Chennazhi KP. Fabrication and characterization of chitosan/gelatin/nSiO2 composite scaffold for bone tissue engineering. International journal of biological macromolecules. 2013 Aug 1;59:255-63.
79. Kim J. Bone regeneration using hyaluronic acid-based hydrogel with bone morphogenic protein-2 and human mesenchymal stem cells. Biomaterials. 2007.
80. Nettles DL, Elder SH, Gilbert JA. Potential use of chitosan as a cell scaffold material for cartilage tissue engineering. Tissue engineering. 2002 Dec 1;8(6):1009-16.
81. De Azevedo EP. Chitosan hydrogels for drug delivery and tissue engineering applications. International Journal of Pharmacy and Pharmaceutical Sciences. 2015;7:8-14.
82. Nikpour MR, Rabiee SM, Jahanshahi MJ. Synthesis and characterization of hydroxyapatite/chitosan nanocomposite materials for medical engineering applications. Composites Part B: Engineering. 2012 Jun 1;43(4):1881-6.
83. Mohandas A, Anisha BS, Chennazhi KP, Jayakumar R. Chitosan–hyaluronic acid/VEGF loaded fibrin nanoparticles composite sponges for enhancing angiogenesis in wounds. Colloids and Surfaces B: Biointerfaces. 2015 Mar 1;127:105-13.
84. Indrani DJ, Budiyanto E. Preparation and characterization of porous hydroxyapatite and alginate composite scaffolds for bone tissue engineering. International Journal of Applied Pharmaceutics. 2017 Dec;9(Special Issue 2):98-102.
85. Cheung HY, Lau KT, Lu TP, Hui D. A critical review on polymer-based bio-engineered materials for scaffold development. Composites Part B: Engineering. 2007 Apr 1;38(3):291-300.

86. Bouhadir KH, Lee KY, Alsberg E, Damm KL, Anderson KW, Mooney DJ. Degradation of partially oxidized alginate and its potential application for tissue engineering. Biotechnology progress. 2001;17(5):945-50.
87. Anjum S, Arora A, Alam MS, Gupta B. Development of antimicrobial and scar preventive chitosan hydrogel wound dressings. International journal of pharmaceutics. 2016 Jul 11;508(1-2):92-101.
88. Kondo S, Kuroyanagi Y. Development of a wound dressing composed of hyaluronic acid and collagen sponge with epidermal growth factor. Journal of Biomaterials Science, Polymer Edition. 2012 Jan 1;23(5):629-43.
89. Baoyong L, Jian Z, Denglong C, Min L. Evaluation of a new type of wound dressing made from recombinant spider silk protein using rat models. Burns. 2010 Sep 1;36(6):891-6.
90. Chen G, Sato T, Ohgushi H, Ushida T, Tateishi T, Tanaka J. Culturing of skin fibroblasts in a thin PLGA–collagen hybrid mesh. Biomaterials. 2005 May 1;26(15):2559-66.
91. Kamoun P. Mental retardation in Down syndrome: a hydrogen sulfide hpothesis. Medical Hypotheses. 2001 Sep 1;57(3):389-92.
92. WHO, Infectious Diseases Kill over 17 Million People a Year: WHO Warns of Global Crisis (n.d.), https://www.who.int/news/item/01-01-1996-infectiousdiseases-kill-over-17-million-people-a-year-who-warns-of-global-crisis. (Accessed 14 December 2020).
93. Sulaiman N, Abid SK, Chan SW, Nazir U, Mahmud NP, Latib SK, Hafidz HF, Shahlal SA, Sapuan SH, Fernando T. Geospatial dashboards for mapping and tracking of novel coronavirus pandemic. InProc. Int. Conf. Ind. Eng. Oper. Manag 2020 Dec 10 (Vol. 59, pp. 2336-2348).
94. Jiao J, Duan C, Xue L, Liu Y, Sun W, Xiang Y. DNA nanoscaffold-based SARS-CoV-2 detection for COVID-19 diagnosis. Biosensors and Bioelectronics. 2020 Nov 1;167:112479.
95. Setyawati MI, Kutty RV, Tay CY, Yuan X, Xie J, Leong DT. Novel theranostic DNA nanoscaffolds for the simultaneous detection and killing of Escherichia coli and Staphylococcus aureus. ACS applied materials & interfaces. 2014 Dec 24;6(24):21822-31.
96. Liu M, Zhang Q, Brennan JD, Li Y. Graphene-DNAzyme-based fluorescent biosensor for Escherichia coli detection. MRS Communications. 2018 Sep;8(3):687-94.
97. Xu Y, Wang H, Luan C, Liu Y, Chen B, Zhao Y. Aptamer-based hydrogel barcodes for the capture and detection of multiple types of pathogenic bacteria. Biosensors and Bioelectronics. 2018 Feb 15;100:404-10.
98. Zhang P, Liu H, Li X, Ma S, Men S, Wei H, Cui J, Wang H. A label-free fluorescent direct detection of live Salmonella typhimurium using cascade triple trigger sequences-regenerated strand displacement amplification and hairpin template-generated-scaffolded silver nanoclusters. Biosensors and Bioelectronics. 2017 Jan 15;87:1044-9.
99. Mobed A, Hasanzadeh M, Babaie P, Aghazadeh M, Mokhtarzadeh A, Rezaee MA. Cetyltrimethyl ammonium bromide modified gold nanostructure supported by chitosan as a novel scaffold for immobilization of DNA and ultra-sensitive bioassay of legionella pneumophila. Microchemical Journal. 2019 Sep 1;149:103961.
100. World Health Organization. Promoting cancer early diagnosis. World Health Organization. Available online: https://www. who. int/activities/promoting-cancer-early-diagnosis (accessed on 2 April 2023). 2021.
101. Goossens N, Nakagawa S, Sun X, Hoshida Y. Cancer biomarker discovery and validation. Translational cancer research. 2015 Jun;4(3):256.

102. Zhang K, Lv S, Zhou Q, Tang D. CoOOH nanosheets-coated g-C3N4/CuInS2 nanohybrids for photoelectrochemical biosensor of carcinoembryonic antigen coupling hybridization chain reaction with etching reaction. Sensors and Actuators B: Chemical. 2020 Mar 15;307:127631.
103. Yu Z, Cai G, Liu X, Tang D. Pressure-based biosensor integrated with a flexible pressure sensor and an electrochromic device for visual detection. Analytical Chemistry. 2021 Jan 25;93(5):2916-25.
104. Magi-Galluzzi C. Prostate cancer: diagnostic criteria and role of immunohistochemistry. Modern Pathology. 2018 Jan 1;31:12-21.
105. Brunnström H, Johansson A, Westbom-Fremer S, Backman M, Djureinovic D, Patthey A, Isaksson-Mettävainio M, Gulyas M, Micke P. PD-L1 immunohistochemistry in clinical diagnostics of lung cancer: inter-pathologist variability is higher than assay variability. Modern Pathology. 2017 Oct 1;30(10):1411-21.
106. Trümper LH, Bürger B, Von Bonin F, Hintze A, Von Blohn G, Pfreundschuh M, Daus H. Diagnosis of pancreatic adenocarcinoma by polymerase chain reaction from pancreatic secretions. British journal of cancer. 1994 Aug;70(2):278-84.
107. Husarik DB, Steinert HC. Single-photon emission computed tomography/computed tomographyfor sentinel node mapping in breast cancer. InSeminars in nuclear medicine 2007 Jan 1 (Vol. 37, No. 1, pp. 29-33). WB Saunders.
108. Song S, Naeim F. New applications of flow cytometry in cancer diagnosis and therapy. InCancer Diagnostics: Current and Future Trends 2004 (pp. 199-232). Totowa, NJ: Humana Press.
109. Wu L, Qu X. Cancer biomarker detection: recent achievements and challenges. Chemical Society Reviews. 2015;44(10):2963-97.
110. Hasanzadeh M, Rahimi S, Solhi E, Mokhtarzadeh A, Shadjou N, Soleymani J, Mahboob S. Probing the antigen-antibody interaction towards ultrasensitive recognition of cancer biomarker in adenocarcinoma cell lysates using layer-by-layer assembled silver nano-cubics with porous structure on cysteamine caped GQDs. Microchemical Journal. 2018 Dec 1;143:379-92.
111. Hassanpour S, Hasanzadeh M, Saadati A, Shadjou N, Soleymani J, Jouyban A. A novel paper based immunoassay of breast cancer specific carbohydrate (CA 15.3) using silver nanoparticles-reduced graphene oxide nano-ink technology: A new platform to construction of microfluidic paper-based analytical devices (μPADs) towards biomedical analysis. Microchemical Journal. 2019 May 1;146:345-58.
112. Luo Z, Zhang L, Zeng R, Su L, Tang D. Near-infrared light-excited core–core–shell UCNP@ Au@ CdS upconversion nanospheres for ultrasensitive photoelectrochemical enzyme immunoassay. Analytical chemistry. 2018 Jun 25;90(15):9568-75.
113. Luo Z, Qi Q, Zhang L, Zeng R, Su L, Tang D. Branched polyethylenimine-modified upconversion nanohybrid-mediated photoelectrochemical immunoassay with synergistic effect of dual-purpose copper ions. Analytical chemistry. 2019 Feb 22;91(6):4149-56.
114. Qiu Z, Shu J, Liu J, Tang D. Dual-channel photoelectrochemical ratiometric aptasensor with up-converting nanocrystals using spatial-resolved technique on homemade 3D printed device. Analytical chemistry. 2018 Dec 13;91(2):1260-8.
115. Yu Z, Tang Y, Cai G, Ren R, Tang D. Paper electrode-based flexible pressure sensor for point-of-care immunoassay with digital multimeter. Analytical chemistry. 2018 Dec 20;91(2):1222-6.

116. Aggarwal R, Romero GR, Friedl V, Weinstein A, Foye A, Huang J, Feng F, Stuart JM, Small EJ. Clinical and genomic characterization of Low PSA Secretors: a unique subset of metastatic castration resistant prostate cancer. Prostate cancer and prostatic diseases. 2021 Mar;24(1):81-7.
117. Lu N, Pei H, Ge Z, Simmons CR, Yan H, Fan C. Charge transport within a three-dimensional DNA nanostructure framework. Journal of the American Chemical Society. 2012 Aug 15;134(32):13148-51.
118. Chen X, Zhou G, Song P, Wang J, Gao J, Lu J, Fan C, Zuo X. Ultrasensitive electrochemical detection of prostate-specific antigen by using antibodies anchored on a DNA nanostructural scaffold. Analytical chemistry. 2014 Aug 5;86(15):7337-42.
119. Leamon CP, Low PS. Folate-mediated targeting: from diagnostics to drug and gene delivery. Drug discovery today. 2001 Jan 1;6(1):44-51.
120. Fales AM, Crawford BM, Vo-Dinh T. Folate receptor-targeted theranostic nanoconstruct for surface-enhanced Raman scattering imaging and photodynamic therapy. Acs Omega. 2016 Oct 1;1(4):730-5.
121. Soleymani J, Hasanzadeh M, Somi MH, Jouyban A. Differentiation and targeting of HT 29 cancer cells based on folate bioreceptor using cysteamine functionalized gold nano-leaf. Materials Science and Engineering: C. 2020 Feb 1;107:110320.
122. Soleymani J, Hasanzadeh M, Shadjou N, Somi MH, Jouyban A. Spectrofluorimetric cytosensing of colorectal cancer cells using terbium-doped dendritic fibrous nano-silica functionalized by folic acid: a novel optical cytosensor for cancer detection. Journal of pharmaceutical and biomedical analysis. 2020 Feb 20;180:113077.
123. Soleymani J, Hasanzadeh M, Somi MH, Shadjou N, Jouyban A. Highly sensitive and specific cytosensing of HT 29 colorectal cancer cells using folic acid functionalized-KCC-1 nanoparticles. Biosensors and Bioelectronics. 2019 May 1;132:122-31.
124. Soleymani J, Hasanzadeh M, Somi MH, Shadjou N, Jouyban A. Probing the specific binding of folic acid to folate receptor using amino-functionalized mesoporous silica nanoparticles for differentiation of MCF 7 tumoral cells from MCF 10A. Biosensors and Bioelectronics. 2018 Sep 15;115:61-9.
125. Gu C, Guo C, Li Z, Wang M, Zhou N, He L, Zhang Z, Du M. Bimetallic ZrHf-based metal-organic framework embedded with carbon dots: Ultra-sensitive platform for early diagnosis of HER2 and HER2-overexpressed living cancer cells. Biosensors and Bioelectronics. 2019 Jun 1;134:8-15.
126. Guo C, Su F, Song Y, Hu B, Wang M, He L, Peng D, Zhang Z. Aptamer-templated silver nanoclusters embedded in zirconium metal–organic framework for bifunctional electrochemical and SPR aptasensors toward carcinoembryonic antigen. ACS applied materials & interfaces. 2017 Nov 29;9(47):41188-99.
127. Zhou N, Su F, Guo C, He L, Jia Z, Wang M, Jia Q, Zhang Z, Lu S. Two-dimensional oriented growth of Zn-MOF-on-Zr-MOF architecture: A highly sensitive and selective platform for detecting cancer markers. Biosensors and Bioelectronics. 2019 Jan 1;123:51-8.
128. Park CS, Ha TH, Kim M, Raja N, Yun HS, Sung MJ, Kwon OS, Yoon H, Lee CS. Fast and sensitive near-infrared fluorescent probes for ALP detection and 3d printed calcium phosphate scaffold imaging in vivo. Biosensors and Bioelectronics. 2018 May 15;105:151-8.
129. Xue C, Zhang S, Li C, Yu X, Ouyang C, Lu Y, Wu ZS. Y-shaped backbone-rigidified triangular DNA scaffold-directed stepwise movement of a DNAzyme walker for sensitive microRNA imaging within living cells. Analytical chemistry. 2019 Dec 3;91(24):15678-85.

130. Wang D, Chai Y, Yuan Y, Yuan R. Precise regulation of enzyme cascade catalytic efficiency with DNA tetrahedron as scaffold for ultrasensitive electrochemical detection of DNA. Analytical chemistry. 2019 Feb 13;91(5):3561-6.
131. Amado LC, Saliaris AP, Schuleri KH, St. John M, Xie JS, Cattaneo S, Durand DJ, Fitton T, Kuang JQ, Stewart G, Lehrke S. Cardiac repair with intramyocardial injection of allogeneic mesenchymal stem cells after myocardial infarction. Proceedings of the National Academy of Sciences. 2005 Aug 9;102(32):11474-9.
132. Berry MF, Engler AJ, Woo YJ, Pirolli TJ, Bish LT, Jayasankar V, Morine KJ, Gardner TJ, Discher DE, Sweeney HL. Mesenchymal stem cell injection after myocardial infarction improves myocardial compliance. American Journal of Physiology-Heart and Circulatory Physiology. 2006 Jun;290(6):H2196-203.
133. Gaynor J, Adams DC, Sams AE. Effect of intraarticular injection of autologous adipose-derived mesenchymal stem and regenerative cells on clinical signs of chronic osteoarthritis of the elbow joint in dogs. Veterinary therapeutics: research in applied veterinary medicine. 2008;9:192-200.
134. Koh YG, Jo SB, Kwon OR, Suh DS, Lee SW, Park SH, Choi YJ. Mesenchymal stem cell injections improve symptoms of knee osteoarthritis. Arthroscopy: The Journal of Arthroscopic & Related Surgery. 2013 Apr 1;29(4):748-55.
135. Chen FM, Sun HH, Lu H, Yu Q. Stem cell-delivery therapeutics for periodontal tissue regeneration. Biomaterials. 2012 Sep 1;33(27):6320-44.
136. Kost J, Langer R. Responsive polymeric delivery systems. Advanced drug delivery reviews. 2012 Dec 1;64:327-41.
137. Marler JJ, Upton J, Langer R, Vacanti JP. Transplantation of cells in matrices for tissue regeneration. Advanced drug delivery reviews. 1998 Aug 3;33(1-2):165-82.
138. Florence AT, Jani PU. Novel oral drug formulations: their potential in modulating adverse effects. Drug safety. 1994 Mar;10:233-66.
139. Sokolsky-Papkov M, Agashi K, Olaye A, Shakesheff K, Domb AJ. Polymer carriers for drug delivery in tissue engineering. Advanced drug delivery reviews. 2007 May 30;59(4-5):187-206.