WISELEAF SCIENTIFIC VENTURES

BIODEGRADABLE POLYMERS IN DRUG DELIVERY AND TISSUE ENGINEERING

Natural and bioderived polymer in drug delivery and regeneration

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Abstract

A polymer is a large macromolecule made up of repeating subunits or chains of branched and unbranched monomers, connected through covalent chemical bond. These polymers are categorised into natural, synthetic, semi-synthetic polymers. They can be tailored for many applications including drug delivery, Implantable devices, tissue engineering and regenerative medicine. Natural and bio-derived polymers like collagen, gelatin, fibrin, agar and chitosan are obtained from renewable sources and have properties like biocompatibility, non-toxic nature, biodegradability and flexible nature which make them favorable in biomedical research.

They have found widespread applications in drug delivery systems and regeneration. In drug delivery system, due to their controlled and targeted release, they improve the stability of the drug and reduce side effects. A natural polymer, carageen is formulated for sustained release in many pharmaceutical industries. Various polymer-based carriers such as hydrogels, films, and scaffolds have been developed for delivering drugs, proteins, genes, and growth factors effectively. In the field of regeneration, it is used for bone tissue regeneration, cardiovascular tissue regeneration, skin tissue regeneration and wound healing.

Latest innovation in 3D-bioprinting, nanotechnology, anti-cancer drug delivery methods demonstrate the expanding potential of these biomaterials in modern therapeutics. Despite their advantages, they face many challenges such as limited mechanical strength, low stability, scale-up and manufacturing concerns. This chapter focuses on the classification of biological properties, preparation techniques and use of natural and bioderived polymers in drug delivery and regeneration.

Key words: Drug delivery, Regeneration, Natural and Bioderived polymer

1. Introduction

1.1 Overview of Biomaterials

These are natural or synthetic materials designed to function safely within the human body. Biomaterials can assist in medical treatments by replacing, repairing, or enhancing the function of tissues and organs. In recent years, biomaterials have played a major role in healthcare, diagnostics and treatment of various diseases. Successive generations of biomaterials have been produced aiming to improve their biocompatibility and mitigating the defects of previous generations. They can be used in various fields, such as in medical and implant devices, artificial lenses & cornea, and in many other applications. The implant device can be of many types, including orthopedic, cardiovascular, ophthalmological, and sensory implants. For ophthalmological implants, extensive research has been done on contact lenses, including artificial lenses and corneal implants. The biomaterials employed in the treatment of cardiac diseases have revolutionized the field of cardiovascular implants. The use of polymeric stents coated with anti-inflammatory drugs instead of metallic stents has reduced the chances of in-stent retinosis in the treatment of atherosclerosis [1]. In certain patients, artificial shape memory based artificial blood vessels have been grafted instead of stent or natural blood vessels because of weak and unsuitable blood vessels. The main aim of designing advance biomaterial is to overcome the limitation of earlier material and enhance their safety, efficacy and user comfort [1].

1.2 Importance of Natural and Bioderived Polymers

Natural polymers are organic compounds, mainly extracted from natural sources like plants and microbes, as compared to synthetic polymers that are chemically derived or modified. They are extensively used to make biomaterials due to their qualities, such as biocompatibility, biodegradability, mechanical properties, and their versatility. Despite their advantages, they also have certain limitations like low mechanical strength, flexibility, uncontrollable degradation rate, and difficulty in large-scale production. Bioderived polymers are obtained through fermentation or controlled chemical modification of naturally occurring polymers to improve their physicochemical and biological properties. Despite their advantages, they also

have certain limitations like low mechanical strength, flexibility, uncontrollable degradation rate, and difficulty in large-scale production.

Around the mid-20th century, most of the commercial polymers were made from petroleum-derived products that showed hazardous effects. Around the 1980s, their effects reached a critical point, and natural and derived polymers were introduced, and production began at industrial levels [4,5]. They were used in the commercial industry thereafter and solved many problems related to the agriculture and construction industries.

In recent years, extensive research has been done on these materials due to their unique biological properties that allow cell attachment, proliferation, differentiation, and tissue repair; examples include polymers like chitosan, cellulose, collagen, gelatin, etc. Chitosan is commonly used in drug delivery and wound healing because of its biocompatibility and antimicrobial properties [11]. Collagen is mainly used as a scaffold material for skin regeneration. Gelatin is commonly used in regenerative therapies due to its ability to enhance cell interaction and growth. Cellulose, because of its high functionality, biocompatibility and degradability, is commonly used in skincare and other healthcare products. The extensive application of natural polymers in tissue engineering (TE) is primarily due to their uncanny similarity to the natural extracellular matrix.

1.3 Application of Natural and Bioderived polymers

Natural and bio-derived polymers have become indispensable materials in the field of biomedicine because of their diverse physicochemical properties. These can be used to make antimicrobial coatings, gauze, tapes, and targeted drug delivery. A patch named biomass-energetic chitosan microneedle array (CSMNA) that facilitates wound healing was developed by Chi et al. [19]. The microneedle's structure also helps deliver the drug-carrying agent to the target location. Natural polymers have properties such as biocompatibility, non-toxicity and stimuli-based degradation, which make them suitable for drug delivery and regeneration. There are several advantages of using these materials for tissue regeneration, including the structure and composition of polymers that can be easily tailored, it promotes cellular functions like cell proliferation and differentiation. In the case of a scaffold implant, no additional surgery is required because the biodegradable nature of bio-derived polymers allows new tissue to

develop over time, encouraging tissue regeneration. Polysaccharides and protein-based materials are quite similar in nature, making these materials minimally invasive in nature as compared to synthetic materials.

Today, most contact lenses are composed of hydrogel or silicone hydrogel materials as opposed to the earlier generation's cellulose acetate butyrate and silicone elastomer-based lenses. These hydrogel-based contact lenses are soft and elastic in nature, which allows proper gaseous exchange [16]. Hydrogels are also being researched extensively for their use in drug delivery. Different natural polymers can be used to make hydrogels; examples include chitosan, gelatin, alginate, hyaluronic acid, cellulose, and starch derivatives. Hydrogels are 3D, hydrophilic polymeric structures with great potential for retaining biological fluids while maintaining their structural integrity. This property renders it for drug administration, wound healing, and tissue regeneration. They have excellent biocompatibility, degradability, non-toxic degradation products, and a flexible nature, which enables their widespread application in fields like cell culture, cell delivery systems, wound healing, and as drug carriers [16].

Natural polymers like collagen, chitosan and keratin can act as scaffolds for cell migration and differentiation during healing processes, wound healing, and tissue repair. They provide structural support to the proliferating cells and enable the formation of new granular tissue (Figure 1). Collagen is the most abundant component of the extracellular matrix (ECM) that helps in the formation of a supportive structure, while hyaluronic acid and alginate are responsible for maintaining moisture and a conducive environment, respectively. It has been found that keratin works well in reducing scarring, especially in areas where scarring may impair functionality. Chitosan ensures a sterile environment and reduces microbial growth during wound healing owing to its antimicrobial nature.

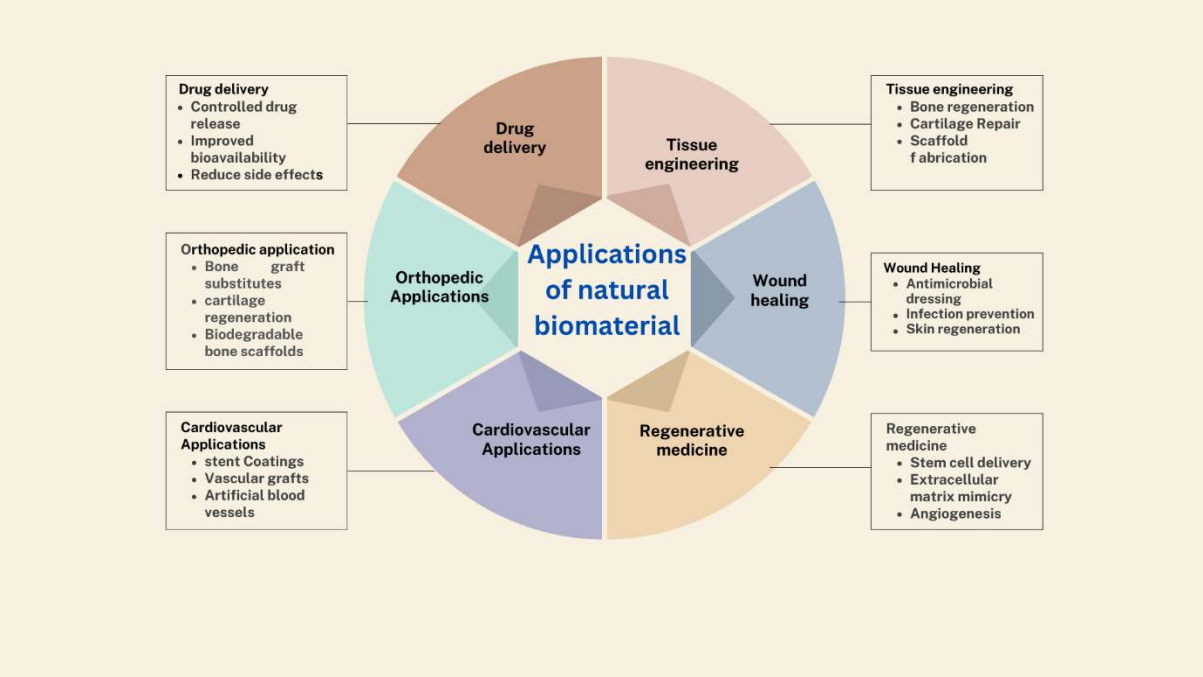

Figure 1. Schematic representation of the major applications of natural biomaterials, including drug delivery, tissue engineering, wound healing, regenerative medicine, cardiovascular applications, and orthopaedic applications, representing their roles in tissue engineering and regenerative medicine.

Natural biopolymers play a pivotal role in bone tissue engineering, where they are fabricated into hydrogels, microspheres, and nanofibrous scaffolds. Bio-composites like hydroxyapatite have also been developed that help in the bone healing process by acting as a scaffold for the formation of lost bone tissue.

2. Classification of Natural and Bioderived Polymer

Natural and bioderived polymers can be categorized on the basis of their origin. These materials are produced from plants, animals, or microorganisms and are commonly used in biomedical applications due to their biocompatibility, biodegradability, low toxicity, and ability to facilitate tissue engineering, wound healing, and regenerative medicine applications (Table.1).

2.1 Plant-Sourced Polymers

Plant-based polymers are natural materials extracted from plants that can be used to make biomaterials for controlled drug release systems and TE scaffolds, as they are non-toxic, biodegradable, and long-lasting. As opposed to synthetic polymers, natural plant-based

polymers require minimal chemicals and less energy during production and are devoid of human-related pathogens making them an attractive choice for biomedical application [12]. Due to their porous nature, mechanical and structural properties, they are suitable for cell growth and tissue repair.

Plant-derived polymers include materials such as lignin, cellulose, hemicellulose, pectin, amylopectin, inulin, guar gum, alginate, etc.

Cellulose is usually derived from plants, algae, bacteria, and certain other marine sources such as tunicates (sea squirts) and ascidians. The monomeric unit composed of glucose, linked by β(1→4) glycosidic bonds. Cellulose microfibrils can be arranged into either microcrystalline cellulose (MCC) or cellulose nanocrystals (CNCs). These diverse structures allow the formation of various types of scaffolds with different properties and structure. As these cellulose-based polymers create a favorable environment for tissue regeneration, they are widely employed in bone, skin, and muscle regeneration [14].

Lignin is a type of complex aromatic polymer, formed from three phenylpropane precursors: coniferyl, sinapyl, and p-coumaryl alcohols. These precursors polymerize into guaiacyl, syringyl, and p-hydroxyphenyl units [14]. It is commonly found in plant cell wall, rice husk, wheat straw and has antimicrobial, antioxidant and biocompatible properties. Pure lignin usually has low flexibility, but after modifications it can be used to form hydrogels, nanofibers, and nanoparticles.

Alginate is a linear, anionic polysaccharide that is abundantly found in the cell walls of phaeophyceae. It is composed of β-D-mannuronic and α-L-guluronic acid residues [19]. Alginate is a hydrocolloid extracted from the seaweeds, including kelps and brown algae and from some capsular bacteria. It readily forms hydrogels in the presence of divalent cations. It is one of the most extensively studied biomaterials because of its gentle gelation, non-toxicity, and excellent moisture-retention properties. Bacterial alginates are extracted using *Pseudomonas aeruginosa*, *P. putida, P. fluorescens* and *Azotobacter vinelandii* [19]. Commercial alginate is predominantly derived from *Laminaria digitata*, *Macrocystis pyrifera*, *Ascophyllum nodosum*, *Ecklonia maxima*, *Saccharina japonica*, *Lessonia nigrescens*, and several species of *Sargassum* and *Ecklonia*.

Alginate is used in agriculture for coating of fruits, vegetables, and seeds, as well as a carrier for biocontrol agents that promote plant development [12].

Structurally, starch consists of amylose and amylopectin joined together by α-1,4- and α-1,6-glycosidic bonds. Starch, either in its original form or after modifications, is commonly used as a coating material and serves as biodegradable films and coatings. An increased amylose ratio in starch is highly desirable for producing coatings with favorable characteristics [12].

2.2 Animal-Sourced Polymer

Animal-sourced biopolymers, as their name implies, are naturally occurring polymers procured from animals and have applications in TE, drug delivery, and regenerative medicine. Some of the animal-based polymers include polymers like chitosan, chitin, silk fibroin, spider silk (spidroin), collagen, gelatin, keratin, casein, chondroitin sulphate, glycogen and hyaluronic acid.

Collagen is one of the main structural proteins found in skin, tendons, ligaments, organic matrix of bones and other connective tissue. There are nearly 29 types of collagen, mostly consisting of glycine, proline, hydroxyproline, and lysine, which imparts remarkable tensile strength. Collagen exhibits a triple helix structure, made up of one supplementary chain and two homologous chains, and is stabilized by hydrogen bonding [18]. Its primary sources of extraction are porcine, marine, bovine, and some avian tissues. Collagen closely mimics the native extracellular matrix structure and is widely used in drug delivery, wound healing, regeneration of skin, bone, nerve, corneal tissues, and scaffolds for tissue engineering. Gelatin, which is extracted by partial hydrolysis of collagen has molecular weight of 15-400kD. It has excellent water-retaining capacity, biodegradability and gel-forming capacity that qualify it for drug delivery, capsule formation, wound healing, electrospun nanofibers, and bioink for 3D bioprinting [18].

Chitin and chitosan are natural polysaccharides obtained from exoskeletons of crustaceans, particularly crabs and shrimp shells. Chitin is a naturally occurring, nitrogen-containing polysaccharide composed of N-acetyl-D-glucosamine units linked by β-(1→4) linkages. They are non-toxic, biocompatible, biodegradable, and have antimicrobial properties, and are suitable for wound healing, TE, scaffold formation, and drug delivery [11].

Glycogen cannot be easily obtained from plants, so it is sourced from two primary sources bovine livers or marine mollusks such as oysters and mussels. It is a highly branched glucose polymer and serves as stored energy molecule. Its densely branched structure, enables the formation of hydrogels with good swelling, water retention, and self-healing properties. Although less researched, glycogen demonstrated promising results in controlled drug release, hydrogel fabrication, and TE applications.

Hyaluronic acid is a glycosaminoglycan found in vertebrate connective and epithelial tissues. It is a macromolecule polymer composed of glucuronic acid and *N*-acetylglucosamine linked via glycosidic bonds. One of the study reveals that it interacts with the CD44 receptors and regulates cell movement, adhesion, and proliferation, making it an ideal biomaterial for hydrogel scaffold design [20]. Hyaluronic acid can be degraded easily in its raw form; hence, chemical modifications such as coating with hydroxyapatite and microparticles are required to improve the strength and bioactivity. These enhancements make its structure more porous and suitable for biomineralization and cell activity [20].

Overall, animal-based polymers are essential for regeneration and drug delivery systems as they support living cells and make them suitable for a wide range of clinical applications.

2.3 Microbial-Sourced Polymers

Microbial-based polymers are the macromolecules synthesized by microorganisms like bacteria and fungi through process like fermentation among many others [17]. Unlike synthetic polymers that require large amount of toxic chemicals and very controlled environment during production, these microbial polymers usually require mild fermentation and are suitable for various biomedical applications like wound healing, tissue regeneration, and bone healing etc. They can be broadly divided into: polysaccharides, polyster, and polyamides. Examples of polysaccharides includes materials like xanthan gum, curdlan, gellan gum, welan gum, pullulan, bacterial cellulose etc. Gellan gum has been investigated for oral, nasal, ocular, and gastric drug delivery systems.

Xanthan gum is a natural polymer extracted from the aerobic gram-negative bacterium *Xanthomonas campestris* by fermentation. Chemically, its backbone is made up of a linear chain of 1,4-linked β-D glucose. To every alternate glucose a trisaccharide side chain consisting

of β-D-mannose-β-D-glucuronic acid - α-D-mannose is attached, connected to the backbone through an α-(1→3) glycosidic linkage. The mannose residue at the end is partially pyruvylated, with a pyruvate group forming a cyclic acetal linkage at the C-4 and C-6 positions while the internal mannose residue is acetylated at C-6 position [12]. The unique molecular architecture of xanthan gum enables the formation of highly viscous solutions. It provides great stability over a broad range of pH, temperature, and ionic conditions. These physicochemical properties, along with its non-toxic, biodegradable, and biocompatible nature, have led to its extensive application in pharmaceutical formulations, controlled drug delivery systems, TE scaffolds, and hydrogel-based biomaterials.

Acacia gum is a natural exudate polysaccharide extracted from the sap of *Acacia senegal* and *Acacia seyal*. This polysaccharide has a branched structure of galactose and arabinose residues. Acacia gum enhances the growth of beneficial gut bacteria. It has been explored for its prebiotic potential by Rawi et al [12] and its application as dietary fibre supplement. Furthermore, it has extensive applications in the pharmaceutical, cosmetic, and food industries owing to its excellent thickening, emulsifying, and stabilizing properties.

Pullulan is an extracellular polysaccharide that consists of maltotriose units with α-1,6 glycosidic linkage. It is derived as a water-soluble polysaccharide from the fungus *Aureobasidium pullulans.* It has good tensile strength and enhanced adhesion time. Due to its unique characteristic of being impermeable to oxygen, it is often used as a substitute for blood plasma [12]. Other pullulan-producing microorganisms are *Rhodotorula bacarum, Tremella mesenterica, Teloschistes flavicans, Cyttaria hariotii, and Cyttaria darwinii* [12].

Polyester and polyamide include materials such as Polyhydroxyalkanoates (PHAs) and Poly-γ-glutamic acid (γ-PGA), respectively. PHAs are extracted from microorganisms such as *Cupriavidus necator* and *Bacillus* species. γ-PGA is extracted from *Bacillus subtilis* and related *Bacillus* species. PHAs, are biodegradable plastics synthesized by microorganisms. They have over 150 structural variations, and the diversity arises from the varying carbon counts in their monomers. PHAs are usually divided into short chain length (scl-PHAs) such as poly(3-hydroxybutyrate); medium chain length (mcl-PHAs) such as poly(3-hydoxyhexanoate), and long chain length (lclPHAs) such as Poly(3-hydroxypentadecanoate) [12]. They are

biodegradable, biocompatible, and have excellent mechanical properties, allowing their use in controlled drug delivery (CDD) systems, tissue regeneration, and wound care products. Continued research on large-scale production of microbial polymers is expected to further expand their role in future biomedical applications.

3. Physicochemical Properties

The physicochemical properties of natural polymers represent their physical and chemical properties. These properties influence their performance in clinical applications, making them suitable for use in CDD and tissue regeneration.

3.1 Biocompatibility

This property refers to the ability of a biomaterial to function effectively within a biological system while maintaining compatibility with surrounding tissues, without releasing any toxins during its degradation. It reduces the risk of chronic inflammation, toxicity, fibrosis, and immune rejection, which makes them acceptable for implants and biomedical purposes. [7]. Natural and bioderived polymers are biocompatible, mimicking the composition of the extracellular matrix, making them suitable for promoting cellular proliferation, adhesion, and neo-tissue formation.

3.2 Biodegradability and Bioactivity

Biodegradability refers to the ability of natural and bio-derived biopolymers, to undergo controlled degradation into non-toxic, biologically compatible by-products through enzymatic activity, hydrolysis, or other physiological processes. The degradation pattern of a biomaterial is influenced by various factors, including its chemical composition, molecular weight, crystallinity, degree of cross-linking, porosity, hydrophilicity, and the physiological environment in which it is implanted. Initially, bioinert materials such as titanium and ceramics were considered ideal for implants as they elicit minimal biological responses, but do not actively participate in neo-tissue formation. With advances in material sciences, the paradigm has now shifted towards bioderived and natural polymers as they dynamically interact with the surroundings and promote cell adhesion, proliferation, angiogenesis, and tissue remodelling with a controlled degradation rate.

Chitosan, a deacetylated derivative of chitin, is an excellent example of biodegradable and bioactive materials that naturally degrade with the help of lysozyme into non-toxic chito-oligosaccharides and glucosamine. These degradation products possess antimicrobial, anti-inflammatory, and immunomodulatory properties, thereby accelerating wound healing, stimulating collagen deposition, and supporting tissue regeneration [6,11].

Table 1. Classification of natural and bio-derived polymers based on their origin, properties, and their corresponding biological sources.

S.No.	Origin	Biopolymer	Source	Properties	Biomedical application
1.	Plant-based polymer	Cellulose	Pine wood, bamboo, cotton	Biocompatible Biodegradable Good mechanical strength	Formation of scaffolds Bone regeneration Skin regeneration
		Lignin	Plant cell wall, rice husk, wheat straw	Antimicrobial Antioxidant biocompatible	Formation of hydrogels Tissue repair Formation of nano-fibres
		Alginate	Wild-type Alginate Expressors include *Pseudomonas aeruginosa* and *Azotobacter vineland* recombined into *Escherichia coli*	moisture retaining Drug delivery antimicrobial	Wound healing Colon-targeted formulations.
		Starch	Wheat, rice, beans, lentils	Biodegradable Non-toxic	Film-forming increased amylose ratio present in starch
			Seeds of *Cyamopsis tetragonoloba*	Hydrophilic high viscosity	Controlled drug delivery hydrogels
2	Animal-based polymer	Chitin and chitosan	Crabs and shrimp shells	Antimicrobial Non-toxic	Tissue engineering Scaffold formation Drug delivery system
		Collagen	Marine collagen obtained from fishes like salmon and tuna and bovine animals	Biocompatible biodegradable	Wound healing Tissue engineering Drug delivery

		Gelatine	Hydrolysed Collagen	Excellent film forming ability Hydrophilic biocompatible	Used as drug delivery carrier Wound dressing
		Glycogen	Genera *Streptomyces, Rhizobium*	Highly branched self-healing hydrogel formation	Drug delivery Hydrogels fabrication Tissue engineering applications.
		Hyaluronic acid	Human cartilage, skin of pigs	Biodegradable Hydrophilic	Improves mineral deposition Provide suitable environment
		Silk fibroin	Silkworm (*Bombyx mori*) cocoon	Excellent mechanical strength, biocompatible	Bone, cartilage, skin regeneration
		Heparin	Porcine intestinal mucosa, bovine lung	Anticoagulant, bioactive	Vascular grafts, drug delivery
3	Microbial-based polymer	Dextran	*Leuconostoc sp., including L. pseudomesenteroides, L. mesenteroides and L. citreum*	Excellent water retention capacity biocompatibility biodegradability.	Acts as a hydrogel-forming material for drug delivery systems Controlled drug release formulations Tissue engineering scaffolds.
		Xanthan gum	Gram-negative aerobic bacterium *Xanthomonas campestris*	Excellent thickening agent Water soluble biocompatible	Acts as a stabilising agent, thickener, and gelling agent in the pharmaceutical and cosmetic industries.
		Acacia gum	Extracted from the sap of different Acacia tree varieties like *Acacia seyal* and *Acacia senegal*.	Stabilizing agent biodegradable	Enhances the division of advantageous gut bacteria

		PHA	*Cupriavidus necator*, *Bacillus* spp.	Biodegradable Biocompatible	Sutures Wound healing
		γ-PGA	*Bacillus subtilis*	Non-toxic High water retention capacity	Hydrogels Biodegradable implants
		Pullulan	Polymorphic fungus *Aureobasidium pullulans*	Water soluble excellent tensile strength	Used as a substitute for blood plasma improves stability
		Bacterial cellulose	*Komagataeibacter xylinus* (formerly *Acetobacter xylinum)*	High purity, high tensile strength, water retention	Wound dressings cartilage skin regeneration

3.3 Mechanical Properties

Mechanical properties of a biomaterial determine its ability to withstand external and internal forces while maintaining its structural integrity and functional performance under physiological conditions. It includes properties such as strength, elasticity, toughness, and structural stability of a material. The required properties of a material will depend upon the targeted tissue; for example, substantial mechanical strength and compressive strength are required for bone scaffolds and cartilage replacements to prevent deformation or fracture of the scaffold. On contrary, biomaterials designed for cartilage, skin, blood vessels, or neural tissues should be flexible and elastic enough. Natural biomaterials may possess inherently poor mechanical strength, which can be overcome strategically using fabrication, composite formation, cross-linking, and reinforcement [3].

3.4 Surface Properties and Interactions with Cells

Surface properties of a biomaterial include surface chemistry, topography, surface roughness and charge characteristics, which influence the interactions between the material and living systems. These properties ensures protein binding, cell growth, cell adhesion and maturation. Favorable surface properties support proper interaction between cells and help in tissue repair; otherwise, it may lead to reduced cell adhesion, increased probability of bacterial infection, and immune rejection. For example, bacterial cellulose, mirroring the structure of the ECM, helps in cell attachment and fastens the wound healing rate [2,14].

4. Manufacturing Methods for Bioderived Polymers

These polymers can be manufactured with various methods and some of the prominent one's are mentioned below.

4.1 Crosslinking Methods

Crosslinking is a conventional fabrication technique used for preparing natural polymer-based scaffolds. Different conventional preparation methods have been designed to fabricate polysaccharide-based tissue scaffolds [21]. Multiple crosslinking strategies including ionic crosslinking, genipin crosslinking, EDC/NHS crosslinking, and photo-crosslinking, are widely employed to enhance the performance of biopolymer-based scaffolds for biomedical application.

Photo crosslinking is a commonly used covalent crosslinking technique due to its convenience, rapid gel formation, and accurate spatial and time-resolved control. It utilizes a light-sensitive initiator that forms free radicals after exposure to UV light, inducing polymerization and developing a favourable three-dimensional hydrogel network. As compared to non-covalent crosslinking, photo crosslinked hydrogels demonstrate enhance mechanical stability, consistent network structure and permanent covalent bonding. This method is suitable for both synthetic and chemically functional biopolymer such as alginate, hyaluronic acid, chitosan etc. Because of their high biocompatibility, and flexibility in fabricating, numerous hydrogel morphologies, photo crosslinked hydrogels are used in CDD, TE, wound repair, cell culture, and regenerative therapy.[23]

Ionic interaction is employed for hydrogel network formation and requires the addition of multivalent ions to the polymer solution for promoting hydrogel formation, at room

temperature and near neutral pH. This immediate crosslinking technique is commonly used for alginate, where carboxylic groups of neighboring polymer chains bind with multivalent cations to create an ionically crosslinked gel network. Polysaccharides, like gellan gum, can also be crosslinked by metal ions. Calcium is the most commonly used crosslinking ion, and calcium chloride ($CaCl_2$) is favoured due to its excellent solubility and fast gelation.

Although ionic crosslinking is a simple and widely employed technique for fabricating alginate-based hydrogels, it is associated with several limitations such as relatively low mechanical strength, limited structural stability, and the possibility of gradual leaching of cross-linking metal ions after implantation. These factors may compromise the long-term mechanical performance and biological stability of the hydrogel under physiological conditions. Therefore, to produce hydrogels with the required mechanical resilience and biological performance for TE and CDD, careful optimization of the polymer and cross-linker concentrations is crucial. [24].

4.2 Nanoparticles fabrication

Ionic gelation is one of the most extensively used methods for the fabrication of biopolymeric nanoparticles. It is simple, mild, and does not require the use of organic solvents or harsh processing conditions as compared to other conventional techniques [25]. It utilizes the electrostatic interactions between oppositely charged polymers and cross-linking agents, which eventually results in the formation of nanosized particles under specific cconditions[29].

Among many other polymers, chitosan is mostly used in ionic gelation because of its biodegradability, low toxicity, and mucoadhesive properties. Acidic media cause protonation of the amino group in chitosan, which results in the polymer interacting with multivalent anions such as sodium tripolyphosphate (TPP) and forming cross-linked nanoparticles[25,27]. The process generally involves dissolving chitosan in dilute acetic acid. After which TTP is added in a controlled manner along with continuous stirring, this leads to the formation of spherical nanoparticles through ionic interactions. Several parameters during the process of fabrication, strongly influence the characteristics of the resulting nanoparticles. The pH of the chitosan solution is considered one of the most important factors as its affecting the amount of protonation and therefore the extent of ionic cross-linking [25,28]. Increasing pH usually

produces larger particles with lower surface charge due to reduced protonation of chitosan chains. The concentration of chitosan and TPP, mixing speed, and addition rate of the cross-linker drastically affect the particle size and colloidal stability[29].

Nanoprecipitation is one of the simplest and most widely used technique for the fabrication of polymeric nanoparticles. It is also known as the solvent displacement method[1]. It is a continuous, replicable and energy-efficient method that does not require complex instrumentation. In this method, a polymer and the drug are mixed in an organic solvent like acetone or ethanol. Add the organic phase dropwise to the aqueous phase. In this phase also add a stabilizer or a surfactant is added to the mixture and constantly stirred. The addition of the solvent to the aqueous medium leads to the precipitation of the polymer and the formation of nanoparticles. Nanoprecipitation yields particles of a given size, which depends on several parameters such as polymer concentration, solvent to antisolvent ratio, addition rate and stirring conditions. Recent studies have further studied the use of nanoprecipitation in developing advanced nanomedicines. Temozolomide-loaded PLGA nanoparticles made by nanoprecipitation have small particle size, high encapsulation efficiency, and higher anticancer activity against glioblastoma cells [32]. Curcumin-loaded PLGA nanoparticles have improved drug stability and longer drug release properties for cancer therapy[33]. Quercetin-loaded chitosan nanoparticles made using this approach had high antioxidant activity and improved bioavailability [34]. Furthermore, surface-functionalized nanoparticles made by nanoprecipitation have shown high potential for targeted drug and gene delivery applications.

4.3 3D & Bioprinting Technologies

3D printing is a layer-wise fabrication method used to architect three-dimensional structures from digital designs. The introduction of cell-containing scaffolds enabled the advancement of bioprinting for fabricating tissue-engineered constructs and drug delivery systems. Several bioprinting methods, such as inkjet, extrusion-driven and laser-based have been designed. Bioprinting enables excellent reproducibility and accurate control during scaffold fabrication. A suitable bioink should demonstrate favourable mechanical and biological properties, such as biocompatibility, biodegradability and suitable geometric structure[31]

3D bioprinting allows the fabrication of tissue architect ex vivo or in situ using favourable bioinks with excellent biocompatibility, structural integrity, and suitable mechanical and rheological characteristics. Hydrogels are commonly used as bioinks due to their highly aqueous environment, which resembles the extracellular matrix (ECM) and promotes cell encapsulation. Throughout bioprinting, polymer dispersion is transformed into three-dimensional structures by crosslinking, which plays an important role in regulating the physicochemical properties of the construct along with cell behavior. The main 3D bioprinting methods include extrusion process, inkjet, laser-based bioprinting, and photopolymerised-based [24].

5. Application of Natural Polymers in Drug Delivery Systems

Drug delivery refers to the combined approaches used to deliver therapeutic drugs to the target site, usually present inside the body to ensure the therapeutic effect [35]. These systems regulate the dosage of the drug related based on location and time of drug delivery. They try to improve the effectiveness of the drugs due to their controlled, targeted, and sustained release. This reduces the toxicity of the drug and its cost by only releasing drugs at the required site and in minimal amounts. In traditional drug administration methods, the chances of toxicity and side effects are high due to their less specific administration methods that can lead to drug leakage to healthy body tissues. Advanced drug delivery systems have been developed over time that further increase the efficiency, safety, and quality of drug delivery. Some intelligent delivery systems have also been developed in recent years that release drugs only when stimulated by a particular stimulus. These stimuli can include changes in pH, temperature, enzymes, and many other biomarkers [37]. The use of naturally derived polymers in drug delivery is due to their low toxicity, biodegradability, and their resemblance to the natural tissue. They can be used to form nanoparticles, hydrogels, microspheres, and scaffolds for drug delivery purpose.

5.1 Controlled/Sustained Release of Pharmaceuticals

Polymeric drug delivery is a device or specific formulation that allows the release of a therapeutic agent into the body, in an effective and controlled way by maintaining the release rate, time, and place of delivery[36]. The emergence of these drug delivery system was due to

the limitations of the conventional systems, which require repetitive administration and frequent changes in drug concentration. These controlled drug release systems allowed for maintenance of constant drug concentrations and reduced the need for repetitive administration while increasing the efficiency and efficacy of the drug[35].

There are several mechanisms involved in drug release, including diffusion-controlled release, degradation-controlled release, surface erosion-controlled release, and the combined mechanism. In the diffusion-controlled mechanism, the drug slowly diffuses out of the polymer matrix into the surrounding environment with the help of water molecules that penetrate the polymer and allow for its diffusion from higher to a lower concentration. In the degradation-controlled mechanism, the drug is released eventually as the polymeric bonds undergo enzymatic or hydrolytic cleavage. In the surface erosion-controlled mechanism, first the surface of the polymer undergoes hydrolysis, followed by the rest. In the combined mechanism, the release of Drug occurs due to the combined effect of diffusion, degradation, and erosion[36]. Among all these mechanisms, the combined mechanism is the most commonly used for drug delivery.

Advantages of these polymeric drug delivery systems include targeted delivery, reduced systemic toxicity, reduced administration, sustained release, and ability to carry proteins, peptides and nucleic acids[35]. Some examples include polymers like chitosan used for oral delivery, gene delivery, wound healing and pulmonary delivery. Hyaluronic acid is non-immunogenic, used in hydrogel formation and in targeted drug delivery through CD44 receptor [22].

5.2 Targeted Drug Delivery Methods

These methods are developed to transfer pharmaceuticals agents specifically to the site of action, which enhances their clinical effectiveness (Figure.2). The biological properties and flexible nature of natural polymers have made them suitable for this system. They can be developed into various drug delivery systems such as microspheres, capsules, nanoparticles, beads, films, hydrogels, nanofibers, and polymer conjugates for site-specific and controlled drug release[26].

Microspheres are spherical drug carriers made up of polymers, such that they can be used for controlled and sustained drug release. Their use arises due to their ability for their extended drug release period that can maintain constant drug concentration. Tablet and capsule-based drug delivery systems are usually created using the wet granulation method and are among the most widely used pharmaceutical formulations. To improve the drug delivery period, they can be incorporated with biopolymers like alginate and chitosan. Nanoparticle-based drug delivery systems are among the most popular delivery systems. Due to their large surface area, small size and excellent drug-carrying capacity, they are used to carry macromolecules across nasal, ocular, tracheal and oral routes to improve efficiency. Nanofibers have a highly porous structure that makes them attractive for drug delivery. Chemical and surface modification can further increase their drug loading capacity and bioactivity. Electrospun nanofibers are highly effective for wound healing, drug release and transversal drug release. In a bead-based delivery system, biopolymeric beads are used for drug delivery. Due to their structural stability, they are exploited heavily for delivery of sensitive drugs. They are frequently used for oral drug delivery applications. Film-based drug delivery systems use films that get attached to biological surfaces and provide extended drug release. They can be used heavily for buccal, sublingual, peritonial oral, and transdermal applications [26,35].

Hydrogel-based drug delivery systems have acquired significant interest due to their good biological properties and excellent water absorption capacity while preserving their structure. Natural polymer-based hydrogels developed from materials such as chitosan, alginate, HA, chitin, and cellulose derivatives have been widely explored for controlled and site-specific drug delivery. These hydrogels can incorporate a wide range of therapeutic agents, including antitumor drugs, antibiotics, and biologically active compounds, and systematically release them in response to external stimuli such as pH, making them potential platforms for modern pharmaceutical applications [26,28].

Conjugate-based drug delivery systems have been broadly studied as nano-conjugates that can allow both passive and active targeting of therapeutic agents to targeted sites. so, that the medicine can work more efficiently and cause less toxicity to the nearby healthy cells. For example, folate–chitosan nanoparticles enhance specific site delivery of doxorubicin to cancer

cells with less toxicity to normal tissues. Polymers integrate with graphene oxide, or multi-shell carbon nanotubes, to improve drug incorporation, biological compatibility and protein binding. Similarly, alginate–chitosan interaction enhances the entire productivity of drug delivery systems [22,35].

5.4 Response to Stimuli for Drug Delivery

Smart or stimuli-responsive materials are being extensively worked on recently due to their ability to alter their physicochemical nature in response to certain changes in their environment. They can respond to internal and external stimuli like pH and redox potential, temperature, light and magnetic field. These physicochemical changes upon encounter with a specific stimulus make them a suitable option for controlled drug release and tissue regeneration [26].

The pH-stimulated biomaterial usually contains ionisable groups that further undergo protonation or deprotonation upon changes in the environmental pH. Due to variation in the pH level in different organs, materials can be designed such that they release a specific drug at a certain pH only, ensuring targeted delivery of drugs. Examples include materials like chitosan used to make pH-sensitive hydrogels for wound dressing and drug release and hyaluronic acid-based self-healing hydrogels [28].

Thermoresponsive bioderived materials are smart materials that undergo reversible changes in physicochemical properties or their conformational structure in response to temperature. Some examples include materials like gelatin, chitosan/β-Glycerophosphate Hydrogels, cellulose derivatives and Elastin-Like Polypeptides (ELPs). Gelatin is an extensively researched upon thermoresponsive material, as they exhibit reverse sol-gel transitions. They are highly recommended for the production of injectable scaffolds and for drug delivery. Although chitosan alone is not thermoresponsive, when combined with β-glycerophosphate it forms an injectable hydrogel [27]. It remains liquid during administration and gels at body temperature, enabling minimally invasive drug delivery. Derivatives like methyl cellulose show gelation with changes in temperature and are used in ocular drug delivery and tissue scaffolds. Stimuli-based materials also include light-responsive bioderived materials like gold nanoparticles synthesized in collagen protein hydrogel. These light-responsive materials can be further divided on the basis of the photochemical reaction involved: photoisomerization, photothermal,

photocleavage, or photopolymerization [37]. Collagen-based photothermal hydrogels combine the advantages of collagen with light-triggered controlled drug release and tissue regeneration. Magnetic-responsive biomaterial scaffolds combine biopolymers with magnetic nanoparticles for drug administration and tissue reconstruction [28].

6. Natural and Bioderived Polymers in Tissue Regeneration (TE)

6.1 Overview of TE

TE is an interdisciplinary field and a continuously growing area of medical science that aims to restore or regenerate affected tissues and organs. Instead of depending only on traditional treatments such as organ transplantation, this method integrates living cells, biomaterials, and bioactive molecules to help the body restore its own tissues. The primary aim is to rebuild both the structure and normal function of affected tissues. [41]

Scaffolds play an important role in tissue engineering. A scaffold serves as a short-term framework where cells can adhere, proliferate, and slowly form new tissue. As the new tissue forms, the scaffold gradually breaks down within the body. The scaffold material should be biologically compatible, biodegradable, and sufficiently strong to maintain the developing tissue [56].

Recent advances in tissue engineering have created new opportunities for the treatment of bone, skin, hepatic, and vascular defects (Figure 2). Even though many of these technologies are under laboratory-based and clinical studies, they have shown positive results in enhancing tissue healing and regeneration. With ongoing advances in biomaterials, scaffold design, and cell therapies, tissue engineering is expected to become an essential part of upcoming regenerative medicine [19].

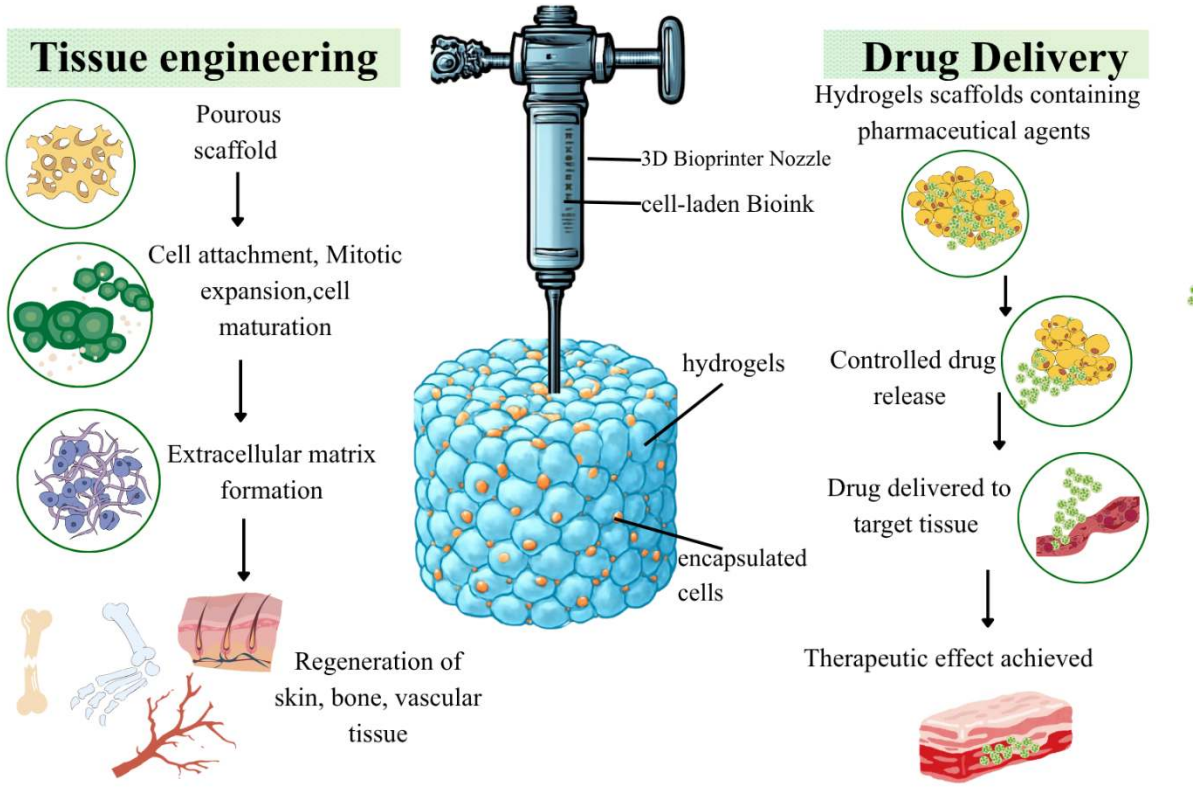

Figure 2. Applications of natural and bio-derived biopolymers in tissue engineering and drug delivery.

6.2 Role of Scaffolds in Tissue Engineering

Scaffolds are 3D structures that act as a framework for cell attachment and proliferation. In tissue engineering, scaffolds play an important role in mimicking the natural tissue environment by providing both mechanical support and a biological environment. A scaffold should have qualities like biocompatibility, biodegradability, porosity, proper mechanical strength, and the ability to allow adequate nutrient and oxygen transport [56,57].

Recent advancements have improved the scaffold design from simple supporting structures to bioactive platforms capable of interacting with surrounding cells. The design of a scaffold plays an essential function in determining cell tissue maturation. Maintaining pore size according to the required tissue can improve regeneration. For example, highly porous scaffolds are ideal for bone tissue fabrication as they promote vascularization and differentiation [55,57].

Scaffolds are also made from natural polymers such as collagen, fibrin, silk fibroin and keratin. Natural polymers have excellent biocompatibility and closely resemble the ECM, whereas synthetic polymers have better mechanical strength and controlled degradation rates. Hybrid scaffolds integrating natural and synthetic biomaterials have emerged as promising platforms in the field of regenerative medicine [3,56].

Silk fibroin-based porous scaffolds have shown great results in bone, cartilage, neural, and skin tissues reconstruction. This is due to their excellent mechanical properties and controllable biodegradation [23]. Fibrin scaffolds have been used in skin wound healing and in nerve regeneration. This is due to their ability to promote cell adhesion, migration, and differentiation [24]. Type II collagen scaffolds are also used for cartilage tissue engineering [25].

6.3 Vascular Tissue Regeneration

Cardiovascular diseases (CVDs) remain one of the leading causes of mortality worldwide. Hence, the growing demand for methods to repair or replace damaged blood vessels. Although autografts are currently considered the clinical standard for small-diameter vessel replacement, their application is restricted by limited availability. Therefore, vascular tissue engineering has emerged as a promising substitute for developing vascular tissues that closely resemble the biological and structural nature of native blood vessels.

The main method of vascular tissue engineering involves the fabrication of a biocompatible scaffold having appropriate mechanical strength, porosity, and the ability to support vascular cell adhesion, proliferation, and differentiation. After scaffold development, vascular cells are added to the construct, where they gradually synthesize the extracellular matrix proteins and the scaffold degrades simultaneously. The construct then matures in a bioreactor before implantation. It usually has structural and functional characteristics similar to native vessels[55].

Several electrospun scaffolds have shown expected outcomes for vascular regeneration. Heparin-modified poly(ε-caprolactone) hydrogel tubular scaffolds have shown successful vascular regeneration and reduced aneurysm, followed by implantation in rat abdominal aortas [52]. Carbon nanotube/polycaprolactone/gelatin composite scaffolds have mechanical properties similar to native blood vessels while increasing cellular multiplication [43].

Multilayer polycaprolactone vascular scaffolds that are designed to replicate the multilayer structure of arterial walls have demonstrated considerable effect for cardiovascular tissue engineering [40].

6.4 Bone Tissue Regeneration

Bone tissue engineering has gained considerable attention compared to conventional bone grafting techniques and has revolutionized the treatment of extensive bone defects [47,48]. This approach involves the use of biomaterial scaffolds, cells, and biologically active molecules to create a cellular microenvironment that resembles native bone tissue and promotes regeneration [47]. An ideal scaffold should possess excellent biocompatibility, biodegradability, a porous structure, and adequate mechanical strength. Furthermore, it should support cell attachment, proliferation, and differentiation [33,34]. Among the various materials used for scaffold fabrication, natural polymers such as cellulose and starch, along with bioceramics including hydroxyapatite and β-tricalcium phosphate, have gained considerable attention because of their favorable biological properties and osteoconductive potential [48,50].

Recent advances in additive manufacturing and smart biomaterials have enabled the development of patient-specific and stimuli-responsive scaffolds capable of regulating cellular behavior and promoting osteogenesis [47,49]. For example, three-dimensional (3D)-printed polycaprolactone (PCL)/hydroxyapatite scaffolds have demonstrated enhanced bone regeneration in animal models [50]. Similarly, eggshell-reinforced PCL scaffolds and nano-hydroxyapatite-containing electrospun scaffolds have exhibited significant osteogenic potential and improved bone-forming ability [48 50]. Moreover, advanced in situ printing technologies that directly deposit bone graft materials at the defect site during surgery represent another promising strategy for future clinical translation and personalized bone regeneration therapies [47].

6.5 Skin Tissue Regeneration

Skin, the largest organ and acts as the first line of defense against any injury, microbial infection, UV radiation, and excessive water loss. Including its protective role, it is also responsible for functions like thermoregulation, immune response, and vitamin D synthesis

among many others. Structure of skin is mainly composed of three layers: the outer epidermis, the dermis and the hypodermis that is made up of adipose tissue [43].

Skin regeneration is a highly regulated biological process involving four phases: haemostasis, inflammation, remodelling and proliferation [43,44]. During this process the inflammatory phase is responsible for removal of pathogens and damaged cells, fibroblasts synthesize the extracellular matrix components, endothelial cells promote angiogenesis and eventually leads to the restoration of the epithelial barrier. Conventional wound management approaches include gauze dressings, skin grafts and flap reconstruction. But they have many disadvantages, including pain during dressing removal, permanent scarring, infections, and limited tissue availability. In recent years, several methods like growth factor delivery, stem cell therapy and use of electrically conductive biomaterials have been worked on to improve tissue regeneration [42,44].

Recent studies have further shown the potential of tissue-engineered approaches for skin regeneration. Collins and Birkinshaw explained the application of hyaluronic acid-based scaffolds and highlighted their ability to mimic the native extracellular matrix and hence, supports cellular proliferation, and tissue repair [45]. Su et al. developed scaffolds loaded with hyaluronic acid and epidermal growth factor that enhanced skin wound healing and tissue regeneration in vivo [46]. This research indicates that combining biomaterials with bioactive molecules can drastically improve the regenerative capacity of damaged skin.

7. Recent trends

Regenerative engineering and drug delivery has been revolutionized during the last few years due to the development of bio-derived polymers and materials. They provide structural support, controlled drug release, less toxicity, biocompatibility, and also participate actively in the required process. Among these developments, smart hydrogels, nanocomposite scaffolds, bio fabrication technologies like 3D printing, and targeted drug and gene delivery have attracted significant attention in the recent years. The combination of some desirable properties like controlled degradation, environmental responsiveness, and improved mechanical and biological performance makes these materials promising options for future drug delivery and tissue regeneration.

7.1 Smart and Stimuli Responsive Hydrogels

Smart hydrogels are advanced materials that is made up of a 3D structure of polymeric interaction. These polymers can undergo changes in their chemical or physical properties when stimulated by a specific signal. These stimuli can be internal or external such as pH, temperature, light, enzymes, electric and magnetic fields and so on. They have garnered rather special attention in the field of regenerative medicine and drug delivery due to their biological and structural properties that closely resemble the natural extracellular matrix. Smart hydrogels, unlike conventional one's release drugs only when they come in contact with a specific microenvironment, ensuring more efficiently drug delivery and less systemic toxicity [61-63].

Natural polymers such as chitosan, cellulose derivative, alginate, gelatine, and hyaluronic acid, are extensively used for developing stimuli-responsive hydrogels due to their excellent biocompatibility and biodegradability. Thermoresponsive chitosan/β-glycerophosphate hydrogels remain in a liquid state during injection and gets converted into gels at normal body temperature, making them suitable for minimally invasive drug delivery and injectable tissue scaffolds [61,62]. Likewise, pH-responsive chitosan hydrogels make use of the differences in physiological pH to release therapeutic molecules at the target site only [63]. Self-healing hyaluronic acid hydrogels have been used in cartilage and skin regeneration because of their ability to recover their structure after mechanical damage and due to their nature to promote cell migration and proliferation [62].

Recent works have also focused on multifunctional hydrogels that simultaneously deliver drugs, growth factors, and stem cells to the target location in the body [66]. Photo responsive hydrogels containing gold nanoparticles allow controlled release upon stimulationfrom a light source, while magnetic-responsive hydrogels containing iron oxide nanoparticles can help in reducing cellular irregularities and enhance tissue regeneration under an external magnetic field. These properties make smart hydrogels promising candidates for personalized medicine, precision drug delivery, and regenerative therapies [69].

7.2 Nanocomposite Scaffold and Nanocarriers

Nanocomposite scaffolds represent one of the most rapidly advancing areas in the field of regenerative therapies and controlled drug release. These scaffolds are made by mixing nanoscale materials like hydroxyapatite nanoparticles, graphene oxide, carbon nanotubes, bioactive glass, and metallic nanoparticles into natural polymer matrices. This significantly improves the mechanical strength, electrical conductivity, surface roughness, and biological activity of scaffolds along with biodegradability and biocompatibility [64,65]. Nanocomposite technology was mainly developed to overcome the limitations of natural polymers like mechanical strength and their uncontrollable degradation. Nano-hydroxyapatite reinforced collagen and cellulose scaffolds closely resemble the mineral composition of bone and enhance the differentiation of nearby bone cells and mineral deposition. Likewise, graphene oxide mixed into gelatine and chitosan matrices increases cell attachment, proliferation, and formation of new blood vessels due to its large surface area and excellent mechanical properties. Carbon nanotube/polymer composite scaffolds have also proven to improve the electrical conductivity and mechanical behaviour of scaffold, making them suitable for vascular, neural, and cardiac tissue engineering. Nanocarriers made by using chitosan, cellulose, and alginate can carry antibiotics, anticancer drugs, proteins, and growth factors and release them in a regulated manner when converted to an encapsulation form [68]. Silver nanoparticle-loaded chitosan scaffolds present antimicrobial activity and can support wound healing and local drug delivery at the same time [64,65].

The combination of nanotechnology with natural polymers has therefore enabled the development of a multifunctional material that combine mechanical support, biological activity, and therapeutic delivery within a single polymer.

7.3 Advanced Targeted and Gene Delivery Systems

The recent advancements in the field of natural and bioderived polymers-based controlled drug release systems are focused more on targeted and gene delivery. It ensures precise delivery of pharmaceuticals to the required tissues. Natural polymers like chitosan, HA, alginate, and pullulan are increasingly being worked upon as nanocarriers. It is due to their properties like low toxicity, biodegradability, and ability to protect sensitive biomolecules from uncontrollable degradation [65]. Targeted delivery systems use specific receptors in the body to ensure the

delivery of drugs to a precise location. HA-based nanoparticles target CD44 receptors that are overexpressed in numerous cancer cells, improves the effectiveness of anticancer drugs while minimizing the damage to healthy tissues. pH-sensitive and enzyme-responsive nanoparticles can release therapeutic agents in tumors or inflamed tissues [69].

Chitosan nanoparticles have shown excellent potential as non-viral vectors for the delivery of DNA, messenger RNA, and small interfering RNA. These carriers protect nucleic acids by enzymatic breakdown and facilitate cellular uptake [22]. Several multifunctional polymeric systems also capable of co-delivering drugs and genes have shown promising results in cancer therapy and regenerative medicine. Alginate microfibers and hydrogel-based delivery systems have also been worked upon because they can capture cells, proteins, and therapeutic molecules, making them suitable for TE and in personalized medicine. The combination of nanotechnology, gene therapy, and natural polymers is expected to contribute significantly in the coming years to the development of next-generation therapeutic systems [68].

8. Conclusion

Natural and bioderived polymers have become an important part of modern drug delivery and regenerative medicine because they replicate the body's natural environment closely and have excellent biocompatibility and biodegradability. Their ability to be made into hydrogels, scaffolds, nanoparticles, and targeted delivery systems has generated new outcomes for increasing therapeutic effectiveness and tissue repair. With advancements in materials like smart biomaterials, nanotechnology, and biofabrication techniques, these polymers will eventually play an even more important role in shaping the future of personalized medicine and regenerative therapies.

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