BIOLOGY AND MEDICAL BIOLOGY

NATURAL COMPONENTS AS THE STRUCTURE OF HYDROGELS FOR CELLULAR THERAPY AND TISSUE ENGINEERING

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ABSTRACT

Hydrogels are a class of dimensional hydrophylic polymer networks capable of absorbing and retaining large amounts of water. Natural and synthetic components can serve as a material for the hydrogel production. Hydrogels have unique physico-chemical properties, which are determined by the material composition and concentration, its density, crosslinking methods, and production approaches. This review article describes natural materials used for the production of hydrogels having different properties.

The natural components of hydrogels are collagen, elastin, gelatin, chitosan, dextran, hyaluronic acid, alginate, silk fibroin and glycosaminoglycans. These components are considered biodegradable and biocompatible, since they do not have a toxic effect on tissues. Natural materials provide good cell adhesion, the spread of bioactive signals as well as they affect the behavior of cells in vitro and in vivo. To obtain hydrogels, physical and chemical methods of crosslinking are used, which determine the properties of the final product. Also, hydrogels can be further modified by various active molecules, growth factors that increase their biological functionality. To date, hydrogels made of natural materials are widely used in ophthalmology, neurosurgery, in the treatment of skin wounds, in various cardiovascular pathologies, in restoring the volume of circulating blood, some cartilage defects, targeted delivery of pharmacological drugs, active molecules, etc. Thus, hydrogels produced from natural components are an extremely promising material for cellular technologies and tissue engineering.

Key words: *hydrogel, natural materials, cellular technologies, tissue engineering*

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ПРИРОДНЫЕ КОМПОНЕНТЫ КАК СТРУКТУРА ГИДРОГЕЛЕЙ ДЛЯ КЛЕТОЧНОЙ ТЕРАПИИ И ТКАНЕВОЙ ИНЖЕНЕРИИ

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РЕЗЮМЕ

Гидрогели – объёмные сетевые структуры, материалом для изготовления которых являются как природные, так и синтетические компоненты. Это гидрофильные полимеры, способные поглощать и удерживать значительное количество воды. Благодаря уникальным физико-химическим свойствам, программируемым в зависимости от цели дальнейшего применения, гидрогели широко используются в биомедицинской сфере. Данная обзорная статья посвящена природным материалам для создания гидрогелей с различными характеристиками.

К природным материалам для изготовления гидрогелей относятся коллаген, эластин, желатин, хитозан, декстран, гиалуроновая кислота, альгинат, фиброин шёлка, гликозаминогликаны. Являясь компонентами внеклеточного матрикса, натуральные материалы считаются наиболее физиологическими или биосовместимыми и не оказывают токсического воздействия на организм. Другим не менее важным параметром считается биодеградируемость, которую необходимо учитывать при выборе компонентов для изготовления гидрогелей. Природные материалы обеспечивают хорошую клеточную адгезию, распространение биоактивных сигналов, а также способны влиять на поведение клеток in vitro и in vivo. Для синтезирования гидрогелей используют физические и химические методы сшивания, с помощью которых задаются определённые свойства гидрогелей. Кроме того, гидрогели могут быть дополнительно модифицированы различными активными молекулами, факторами роста, повышающими их биофункциональность. На сегодняшний день гидрогели из природных материалов широко используются в офтальмологии, нейрохирургии, при лечении кожных ран, при различных сердечно-сосудистых патологиях, в восстановлении объёма циркулирующей крови, некоторых хрящевых дефектов, целенаправленной доставке фармакологических препаратов, активных молекул и во многом другом. Таким образом, гидрогели из природных компонентов являются крайне перспективным материалом в клеточных технологиях и тканевой инженерии.

Ключевые слова: *гидрогель, природные материалы, клеточные технологии, тканевая инженерия*

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INTRODUCTION

Hydrogels are three-dimensional networks consisting of hydrophilic polymers crosslinked through covalent bonds or held together by physical intramolecular and intermolecular interactions, with water as the dispersion medium. They can be characterized by such physical parameters as size, modulus of elasticity and viscosity, swelling and degradation rate. For this reason, hydrogels are unique viscoelastic materials.

Hydrogels have the ability to absorb up to 90 % of water and are considered superabsorbent materials [1]. As a result of their ability to absorb water, hydrogels have a wide range of applications in various fields, among which medicine is one of the leading ones. The high hydrophilicity of hydrogels is explained by the presence of hydrophilic particles such as carboxyl, amide, amino and hydroxyl groups distributed along the backbone of the polymer chains. Water uptake by the hydrogel occurs until there is a balance between the osmotic forces that stimulate water into the hydrogel matrix and the cohesive forces of polymer bonds within the hydrogel that prevent excessive water uptake. In other words, the higher the degree of crosslinking of a particular hydrogel, the lower the degree of swelling [2].

Due to their unique properties, hydrogels are given close attention, numerous scientific studies are being conducted by researchers around the world, and practical applications of biohydrogels are carried out. As a result, hydrogels from natural components are extremely promising materials in the cellular technologies and tissue engineering.

This article objectives are to provide an analytical review of natural components for the manufacture of hydrogels and to identify their advantages and disadvantages.

Classification of hydrogels. Hydrogels can be categorized into natural, synthetic and semi-synthetic based on their origin. Natural hydrogels include collagen, silk fibroin, dextran, hyaluronic acid and derivatives of natural materials such as chitosan, alginate and other hydrogels derived from decellularized tissues [3]. Hydrogels from natural materials are considered to be the most physiological because they are components of the extracellular matrix. However, their final microstructure and properties are difficult to control. Mechanical properties and dependence on polymerisation or gelation conditions are often poorly understood by manufacturers, and, because of their natural origin (bovine fibrinogen, collagen from rat tail), composition from one batch to another can vary considerably. As a result of the above reasons, hydrogels from natural materials are often combined with synthetic materials to create composite polymers, which are currently under active research. Depending on the stability characteristics in physiological environment, hydrogels can be non-biodegradable and biodegradable.

Biocompatibility and biodegradability are two important parameters that require special attention when selecting a polymer. [4]. We should also note that biocompatible materials are not always biodegradable and vice versa, which once again emphasises the importance of proper material selection.

Biocompatibility is a specific material property, which consists in the absence of toxic or other harmful effects against biological tissues and systems, whereas biologically incompatible materials are capable of causing tissue reactions that include necrosis, dystrophic calcification, significant fibrosis, and foreign body reaction.

Biodegradation, i. e. the alteration of the physical, chemical and biochemical properties of a material under the influence of the biological environment, generally involves two steps:

1. Water penetrates into the polymer matrix, interacts with chemicals by hydrolysis, shortening the polymer chain length, as a result leading to molecular weight reduction, fragment metabolism and volume erosion.

2. Polymer surface erosion occurs when the rate at which water molecules penetrate the matrix is slower than the rate at which the polymer transforms into water-soluble materials.

A polymeric material biodegradation may take place either in the surface layer accessible to the liquid environment, when the material properties do not change before the surface layer is destroyed, or in the volume of the polymeric product, where the rate of the liquid biological environment exceeds the rate of polymer degradation [5]. An advantage of biodegradable polymers is the ability of most of them to allow good cell adhesion and proliferation *in vivo*, to persist for a certain time due to their tunable properties (permeability, elasticity, stiffness and chemical reactivity) and then degrade without harmful effects on the body [6].

A vital role in the formation and degradation of hydrogel structure belongs to cross-linkages, due to which polymer stabilisation (cross-linking) takes place, which in turn leads to multidimensional expansion of polymer chains, thereby resulting in the formation of stable network structures. Based on the types of cross-links, hydrogels can be divided into two groups: chemically cross-linked and physically cross-linked [7].

Chemical crosslinking of hydrophilic polymers, which includes free-radical polymerisation, polyaddition and polycondensation, and radiation polymerisation, is one of the main methods for hydrogel production. Chemical crosslinking involves the interaction of a hydrophilic polymer solution with a bifunctional crosslinking agent. Both natural and synthetic hydrophilic polymers are considered suitable for the preparation of hydrogels using this method. For example, albumin and gelatin-based hydrogels have been developed using dialdehyde or formaldehyde as crosslinking agents. High water content hydrogels based on cross-linking of functionalized polyethylene glycol and lysine-containing polypeptide have also been developed by this method [2].

Free radical polymerisation is used to obtain hydrogels from natural materials, provided that these polymers have suitable functional groups or are function-

alised with radical polymerisable groups. For example, this method has been used to develop various chitosan-based hydrogels [8]. The essence of the method is that radicals react with monomers, turning them into active forms that interact with a large number of other monomers, resulting in the formation of polymer matrices. This method can be used for both in-solution and bulk preparation. Solution polymerization is preferential for the synthesis of large quantities of hydrogels, in which case water is the most commonly used solvent. Bulk polymerisation proceeds faster than solution polymerisation with no need for solvent removal, which is time-consuming in many cases.

Physical cross-linking techniques include ionic interaction, hydrogen bonding and hydrophobic association.

During ionic interaction, polyelectrolyte attachment to polivalent ions of opposite charge is performed to form polyelectrolyte complexes in which bonds are formed between pairs of charged sites along the polymer chains. In this manner, for example, polymerization of alginate, which consists of glucuronic and mannuronic acids residues that are cross-linked with calcium ions, occurs [9].

A hydrogen bond between the polymer chains may also participate in the formation of a hydrogel, such as carboxymethylcellulose, with hydrogen bonds formed during dispersion in hydrochloric acid. The mechanism involves replacing sodium with hydrogen in an acidic solution to stimulate the creation of hydrogen bonds. Reducing the pH of the aqueous polymer solution is a prerequisite. Factors such as polymer concentration, polymer molar ratio, solvent type, solution temperature and the degree of connection between polymer functionalities also play an important role.

A hydrophobic association based on hydrophobic interactions is another way to produce hydrogels [10]. Both polymers and copolymers form structures which are separated by hydrophobic microdomains that act as associated cross-linking points throughout the polymer structure and are surrounded by hydrophilic water-absorbing regions. Nevertheless, this method is hardly used despite its low cost mainly as a result of poor interfacial adhesion.

Ionizing radiation techniques are also effective methods for the synthesis of hydrogels. Ionizing radiations, such as electron beams and γ-rays, are high energy and can ionize simple molecules in both air and water. In the process of irradiation of the polymer solution, reactive regions are formed along the polymer filaments, which eventually lead to the formation of a large number of cross-links [11]. The advantages of this method are simplicity, high speed, absence of catalysts to start the polymerization reaction and the possibility to control the process by varying the irradiation dose [12]. However, this method shall not be applied if the polymers decompose under ionising irradiation.

Meanwhile, hydrogels physically obtained are not homogeneous since the clusters formed by intermolecular or hydrophobic/ionic-bonded areas create inhomogeneities in the structure, the destruction of which can occur when conditions change, such as ionic strength, pH, temperature, directional force, addition of dissolved substances.

Material property also appears to depend on its supramolecular structure. This term can be defined as "the way macromolecules are packed in the space of distinguished elements, the size and shape of such elements and their mutual arrangement in space". Porous hydrogels comprise a dispersed system consisting of cell-pores interconnected through a polymer framework phase, promoting cell migration and improving the available surface area for cell-cell interaction with surrounding tissues. Some other parameters such as pore volume, pore size distribution, pore opening size, pore wall roughness, surface functionality, polymer structure and porous interconnectivity are also important [2].

As a function of pore size, pores can be divided into micropores (less than 2 nm), mesapores (2–50 nm) and macropores (greater than 50 nm). Therefore, the experiments have determined that the optimal pore size for angiogenesis and osteogenesis is 50–100 μm [13], 100–200 μm is necessary for cartilage regeneration [14] and 200–300 μm for regeneration of damaged skin [15].

Hydrogels of natural origin can be classified into three groups: **protein-based** materials (collagen, fibrin, elastin, gelatin, silk fibroin), **polysaccharides** (alginate, chitosan, glycosaminoglycans) and **decellularised tissue materials**. Natural gels are typically formed from proteins and extracellular matrix components, which makes them biocompatible, bioactive and promising materials for biomedical applications. Animal extracts, collagen from pig tissue or rat tails, while fibroin is extracted from insects, serves as the source of proteins.

Collagen. Collagen is generally an insoluble fibrillar protein with an elongated filamentous shape of molecules that forms the basis of connective tissue, provides its strength and elasticity, and plays an important role in cell signaling and modulation of cell behavior. A variety of collagen types are now widely available from tendons, skin, intestines, corneas and blood vessels of some mammalian animals as well as marine organisms and fish [16]. Biologically, collagen has low antigenicity and inflammatory response, yet high biocompatibility and biodegradability. Over 29 forms of collagen are available in mammalian tissues, of which only collagens types I, II, and III are considered true fibrillar proteins. Type I collagen is the most abundant fibrillar protein, accounting for 90 % of the collagen in the body. Collagen comprises a complex hierarchical four-level structure in which the primary structure is an amino acid triplet sequence Gly-X-Y, where Gly is represented by glycine, forming up to 30 % of the total amino acid content of collagen, and X-Y are proline and hydroxyproline, respectively. Its secondary structure comprises repeats of a given amino acid triplet chain, which are then assembled into a triple helix to form a tertiary level of organisation, where each chain contains about 1000 amino acids. Collagen fibres themselves constitute the quaternary structure of collagen and are formed by self-assembled fibres

[17]. It is also worth noting that the structural and mechanical properties of collagen fibrils are related to Ca^{2+} concentrations, which is associated with chelation between collagen molecules and Ca^{2+}. While the mechanical properties of collagen are ideal in native tissues, in collagen I-based biomaterials, mechanical strength is insufficient due to the lack of covalent (disulfide) bonds present in collagen types III, IV, VI, VII, and XVI. As a result, crosslinking by physical, chemical and biological methods is basically used to increase the mechanical properties of the material. Alternatively, the different collagen molecular forms in the body are able to form complexes that can also improve mechanical properties through transmembrane receptors, the main ones being the α1β1 and α2β1 integrins, which provide interactions between cells and the extracellular matrix. These integrins have been identified on activated T-cells, platelets, vascular, epithelial cells and fibroblasts [18]. Signaling through α1 contributes to the regulation of extracellular matrix composition, proliferation. Concurrently, a survival signal, considered unique among collagen-binding integrins, passes through α1 [19]. Integrin α2β1 has the ability to mediate cell adhesion, spreading on fibrillar sheath I and is the only collagen-binding integrin in platelets, and recognises type IV, VI and XII collagens [20]. To date, however, the exact mechanism of collagen recognition by integrins is currently not fully identified.

The collagen hydrogel properties are both affected by the collagen source (rat tail tendon, cattle skin, pig skin, etc.) and the extraction method. Nowadays, collagen hydrogels are generally synthesised by extraction at low pH values using acetic acid. The acid-dissolved collagen is then neutralized with concentrated (10×) phosphate-buffered saline (PBS), Hanks' balanced salt solution, or cell culture medium, followed by the addition of neutralizing agents (NaOH, HEPES) and other reagents (water, 1 × medium, 1 × PBS) to initiate fibril self-assembly at a temperature close to physiological pH and polymerization of 37 °C. An increase in pH around the isoelectric point at low ionic strength, however, can improve linear viscoelastic properties and transparency [21]. Notwithstanding, for physiological encapsulation, the pH of hydrogels is limited between 7.4 and 8.4 to maintain cell viability. The collagen obtained in this way largely retains the telopeptide regions that are sites for cross-linking, and in fact this extraction co-isolates a small number of multimers with intact cross-linking sites [22].

A combination of salt precipitation with enzymatic extraction exists along with acid extraction of collagen. In this case, digestion with pepsin results in completely cleaved terminal non-helical regions that contain intermolecular cross-links, and collagen acquires a soluble form [17].

The orientation of collagen fibrils plays an important role for some tissues. For instance, for nerve tissue [23] and cornea [24], the fibrils need to be previously aligned, for which microstructuring techniques have been developed using magnetic nanoparticles that, under the influence of an external magnetic field, promote correct fibrillar orientation.

Collagen hydrogels have found wide application in cell technology and regenerative medicine owing to their high bioeffectiveness. However, the biggest advantage of collagen hydrogel is that cells and bioactive components can be incorporated directly into it already during the manufacturing process [16]. At the same time, lowering the gelation temperature promotes the formation of a smaller number but longer and thicker collagen fibrils, while fibrils polymerized at higher temperatures form a smaller number of bundles that are furthermore less ordered, which affects the mechanical and structural properties of the hydrogel.

Collagen-based hydrogels with good optical characteristics and mechanical properties were obtained by ionic leaching method by adding NaCl. The hydrogel obtained in this way has found wide application in tissue engineering of the eye cornea [25].

Although type I collagen is the most abundant protein in the body, tissues such as articular cartilage and vitreous fluid contain predominantly type II collagen, which exhibits poor mechanical properties without cross-linking and is difficult to make structurally strong. In order to improve mechanical properties, type I and type II collagens are copolymerised to produce gels with a lower void content and high elastic modulus, which have potential as a framework for articular cartilage engineering [26].

A limitation in the use of collagen as a biomaterial is that when the vascular endothelium is damaged, the collagen located in the vascular wall under the endotheliocytes activates platelets, promoting their adhesion on the damaged surface. Afterwards, through the system of interrelationship of blood coagulation factors and formation of active complexes, a fibrin clot is formed [27]. Moreover, the high cost of pure collagen limits its availability as a cost-effective approach for large-scale biomaterial utilisation [28]. However, despite the drawbacks, hydrogels that include collagen have found worthy applications in regenerative medicine.

Elastin. The key fibrillar protein of the extracellular matrix is elastin, which is synthesized by fibroblasts, endotheliocytes and contains glycine, alanine, valine, and leucine in its composition. Due to the alternation of hydrophobic and hydrophilic domains within the structure, this protein is important for the elasticity and stability of many vertebrate tissues, including large arteries, lungs, ligaments, tendons, skin and elastic cartilage [29]. The elastin precursor, tropoelastin, in combination with microfibrils, contributes to tissue structural integrity and biomechanics through constant flexibility, which allows for repetitive cycles of stretching and relaxation dependent on a hydrated environment. It should be noted that the elastin monomer is capable of increasing in length by a factor of eight. A large number of hydrophobic radicals prevent the creation of a stable globule; as a result, elastin polypeptide chains do not form regular secondary and tertiary structures, but have the property of self-assembly with stable cross-links under physiological conditions, forming a stable molecule [3].

Being a native extracellular matrix protein, elastin is non-immunogenic. As a result of their biological activity and physicochemical properties, elastin and related peptides are ideal candidates to be used as biomedical materials including scaffolds, hydrogels and drug delivery systems in tissue engineering [30]. For instance, good results were obtained by using elastin and elastin-like peptides in the healing of such wounds as trophic foot ulcers in diabetes mellitus, burn wounds, etc. [31]. Elastin dressings mimic the extracellular matrix, providing a natural environment that regulates cell proliferation, migration, differentiation and an adequate overall healing process.

The mechanical properties of elastin-based biomedical materials can be improved by combining the latter with natural or synthetic polymers. Thus, polymers that combine repeating sequences of silk and elastin units are described. Silk-elastin promotes the migration of fibroblasts and macrophages and induces collagen production by fibroblasts, accelerating the formation of granulation tissue more than 3-fold [32]. By varying the sequence ratio, the solubility and material strength of the silk-elastic polymer can be controlled, and its self-gel forming ability is convenient for wound coverage, promoting moisture retention.

Silk-elastin-like polymers, which are in liquid state at room temperature and form hydrogels after injection into the body, are considered to be good candidates as polymer matrices for gene delivery. The mechanism of DNA binding and release with polymers is based on ion exchange [33]. At pH = 7.4, the primary amines of lysine and arginine residues are protonated and interact with negatively charged DNA phosphates. An increase in the ionic strength of the buffer leads to a rise in the concentration of counterions and a weakening of the interaction between DNA phosphates and amino groups, resulting in the release of bound DNA.

Their self-assembly under physiological conditions and thermosetting behavior of these polymers along with their biodegradability, biocompatibility and well-defined composition as a result of their indivudual design make them also attractive for controlled drug delivery [34].

By adding elastin to a mixture of gelatin and cellulose acetate, the structure of the fibre is altered and the rate of degradation of the framework is reduced, supporting fibroblast attachment and proliferation *in vitro* [35]. Fibroblast and keratinocyte proliferation is also promoted by mixing elastin with collagen and polycaprolactone. Improved flexibility caused by elastin also promotes cell infiltration and earlier neovascularisation. And, skin substitutes such as Matriderm and Glyaderm have bovine elastin in their composition, which increases the biomechanical stability and elasticity of remodelled tissue in treated wounds [30].

Elastin-based biomaterials have also been applied to regenerate damaged myocardium, create heart valves, and biostents to restore normal heart function or minimise various injuries [36, 37].

Moreover, the biomaterial, which has elastin in its composition, has shown good mechanical properties in vascular transplantology, both for tearing and suture preservation, at the same time providing effective blood circulation as well as the formation of endothelial cell layer [38].

Elastin-based biomaterials can be easily stored and are relatively inexpensive to produce. However, although elastin is a natural component of the extracellular matrix and is biocompatible and appropriately biodegradable, it is not often used for hydrogel production due to its ability to calcify [39, 40].

Fibrin. Fibrin, one of the main proteins involved in hemostasis, is also actively involved in the natural process of repairing damaged tissues. Fibrin gels have been considered to be an alternative to collagen since the cells cultured in fibrin gel produce more collagen and elastin than cells cultured in collagen gel [41]. Fibrin gels offer advantages such as their outstanding biocompatibility and reconfigurable porosity, providing sufficient surface area and space for cell adhesion, proliferation and regeneration of the extracellular matrix.

At present, fibrin hydrogels are widely used in clinics as haemostatic sealants, biological glues, and various dressings [42].

A hydrogel based on fibrin, fibrinogen and autologous blood with thrombin are being used for biological lung volume reduction, a new method of endobronchial treatment for patients with severe emphysema aimed at reducing the volume of the target lung lobe [43].

Good results have been made possible by attaching synthetic materials to fibrin hydrogels. For instance, a composite of fibrin and polylactic-co-glycolic acid ensures slow drug release and, as a consequence, promotes spinal cord regeneration. By increasing the elastic modulus with the addition of polylactide, earlier regeneration of bone and cartilage tissue occurs [44].

Fibrin-based hydrogels are also used in cardiac tissue engineering. Specifically, a fibrin-based composite material consisting of aligned microfilaments uniformly distributed throughout the hydrogel has been developed [45]. Nevertheless, often the main obstacle for fibrin gels without the addition of other agents is in the low mechanical strength, but combining hydrogels with stable and solid materials significantly improves the physical properties, allowing these limitations to be overcome.

Gelatin. Gelatin is a natural and inexpensive polymer, being biodegradable and having minimal immunogenicity, which make it remain one of the best materials for tissue engineering. Gelatin is also used in the food and pharmaceutical industries, in the manufacture of cosmetics and photographic films as a stabiliser, thickener, emulsifier and film former, and their mechanical properties depend on the supramolecular structure. The polymer is manufactured from the skin and bones of cattle and some fish species [46] by hydration of collagen, with gelatin type A treated with acids (pH = 1–3), gelatin type B – with alkaline solutions. As compared to type B gelatin, type A gelatin has more carboxil groups present, making it more pre-

ferable for creating framework materials. As an example, the addition of type A gelatin to collagen films increased film viscosity, tensile strength and elongation at break, while type B gelatin does not possess such properties [47]. At the same time, the stability of gelatin at high temperatures and a wide pH range makes it convenient to attach synthetic and natural polymers to the gelatin base. Specifically, a gelatin-based hydrogel with the addition of methacrylate promotes prolonged cell survival during transplantation as a consequence of efficient cell proliferation, adhesion and migration in an ischaemic environment. As an experimental result, this hydrogel induced blood flow restoration and neovascularisation in a mouse hind limb ischaemia model [48]. Another group of scientists combined gelatin with nanographene oxide in order to improve mechanical and biomedical properties. The manufactured hydrogel demonstrated unique properties such as moderate roughness, suitable pore size, temperature-dependent viscoelasticity and controlled biodegradation. The hydrogel showed outstanding interactions with bone marrow mesenchymal stem cells and rat chondrocytes. Furthermore, an *in vivo* study showed better formation of healthy hyaline cartilage after microfracture [49].

Gelatin-based hydrogel with added polyurethane with customisable mechanical properties and degradation rate gives the ability to print a complex structure such as a nose-shaped design. The stability of the hydrogel structure was maintained by two-step formation via Ca^{2+}-chelating and thermal gelation at 37 °C without toxic cross-linking reagent. Mesenchymal stem cells incubated with gelatin-polyurethane hydrogel have demonstrated good viability, high motility and proliferation rate [50]. In addition, the hydrogel, which includes gelatin, also increases cell viability during cryopreservation [51].

Solutions of gelatin derivatives are also used for rapid replenishment of circulating blood volume as a result of their iso-oncotic properties. Such solutions are excreted through the excretory system unchanged. In addition, gelatin solutions, as opposed to other colloids, do not affect coagulation and are therefore considered safe in cases of haemorrhage and thrombocytopenia [52]. The gelatin addition to alginate hydrogel improves the mechanical characteristics of the latter, increasing gelation time, swelling ratio, degradation rate, and pore size uniformity [53].

The potential of gelatin as a vascular scaffolding material is being actively studied. As opposed to collagen fibres, gelatin hydrogels have higher tensile strength (8–12 MPa), which makes it convenient to use gels for vascular tissue regeneration [28].

Different conformations of gelatin molecules can be achieved by varying the temperature, solvent, and pH; new materials based on gelatin are still being developed.

Fibroin. Silk fibroin, a protein produced by silkworms, spiders and scorpions, is widely used as a frame material for tissue regeneration [54]. The resulting protein is treated with solvents such as lithium bromide, formic acid, ionic liquids and a triple solvent system $CaCl_2$ – ethanol – water to remove sericin, which glues silk fibers. Water-soluble silk I and insoluble silk II can be classified. By means of an annealing process, silk I transforms into crystalline silk II, in which Young's modulus and tensile strength are both increased [55].

As compared to biomaterials such as collagen, silk fibroin has exceptional mechanical strength, impact toughness and thermal stability [56]. It is also worth remembering that for many decades, silk fibroin has also been used as a suture material.

As a consequence of its good mechanical properties, low immune response, minimal thrombogenicity and appropriate biodegradability, silk fibroin has been used in vascular engineering [28, 57], skin regeneration [56], bone repair [58, 59], nerve, ligament and cartilage recovery [60].

Hydrogels combining the properties of silk and elastin have been used for the controlled release of molecules including vitamin B12 and cytochrome as well as DNA [61].

Silk fibroin is widely used in 3D bioprinting technology, where silk is applied as a backbone obtained by a methacrylation process using glycidyl methacrylate. The mechanical and rheological properties of the hydrogel were found to be unique in experimental studies and are modulated by varying the silk fibroin content. This material has enabled the creation of complex organ structures including heart, blood vessels, brain, trachea and ear with excellent structural stability and can be used for tissue and organ engineering depending on specific biological requirements.

Dextran. Among the natural materials there are also polysaccharides such as dextran, alginate, chitosan and hyaluronic acid. Dextran itself is a non-toxic hydrophilic homopolysaccharide consisting of linear residues (α-1,6-linked d-glucopyranose) with a low percentage of α-1,2-, α-1,3- and α-1,4-linked side chains. Alternately, as a bacterially derived biopolymer, dextran can be synthesised from sucrose of *Leuconostoc mesenteroides* with dextransucrase or from maltodextrins with dextrinase. This polymer chain of glucosyl links may also be synthesised using dextransucrase by transferring the D-glucosyl unit from sucrose to acceptor molecules [62].

Dextran types of different sizes and structures are synthesised depending on the dextransucrase produced by the strain, and their solubility depends on the structure of the branched bonds. As an example, dextrans with more than 40 % branching on α-1,3-linkages is considered insoluble in water, whereas the presence of 95 % linear linkages makes it water-soluble and suitable for biomedical and pharmaceutical applications. A dextran, however, is susceptible to enzymatic degradation by dextranase, which exists in mammalian tissues including humans [63].

As compared to other polysaccharides having functional groups, dextran contains only hydroxyl groups, and new derivatives may be generated by incorporating functionalities without compromising its basic properties. Degree of substitution of dextran derivatives refers to the number of substituted hydroxyl groups per unit

and generally affects the properties of its derivatives, hence dextran can be designed by chemical modification for various purposes. Specifically, this polysaccharide is used to reduce vascular thrombosis by binding to erythrocytes, platelets and vascular endothelium, increasing their electronegativity, reducing erythrocyte aggregation and platelet adhesiveness by decreasing clotting factor VIII. Dextran-coated platelets are more evenly distributed in the thrombus and bound by coarse fibrin, facilitating thrombolysis, in which, by inhibiting α2-antiplasmin, dextran activates plasminogen. At the same time, larger dextrans, remaining in the blood vessels, can act as powerful osmotic agents to eliminate hypovolaemia. Increased volume causes hemodilution, which improves blood flow and further increases the patency of microanastomoses [64]. In addition, dextran is also capable of inhibiting the adhesion of leukocytes to the endothelium by attenuating the IL-8 release without preventing the endotheliocyte activation. As a result, the anti-inflammatory effect is realized [65]. Dextran prevents ischaemic-reperfusion injury in organ transplantation by being able to capture reactive oxygen species and reduce excessive platelet activation [66]. Soluble dextran-haemoglobin complexes synthesised by dialdehyde and alkylation methods can be used to replenish the for circulating blood volume in emergency situations. Chemically modified dextran with altered hydrophilicity (hydrophobicity), sensitivity to temperature, pH and ionic strength is being widely used for drug delivery [67].

Hydrogels can comprise a variety of functionalities, protecting bioactive molecules from being modified. In order to obtain hydrogels with different physical and biological properties including swelling, degradation rate, mechanics, crosslinking density, and biocompatibility, the dextran was introduced with allyl isocyanate, chloroacetic acid ethylamine, and maleic anhydride. Polyethylene glycol diacrylate was introduced as cross-linking agent [68]. In order to improve cell encapsulation by cross-linking glycidyl methacrylate dextran (Dex-GMA) and dithiothreitol (DTT) derivatives in physiological conditions by means of thiol-Michael addition reaction, a hydrogel was prepared and its mechanical properties, gelation process and degree of swelling may be adjusted by changing the pH of phosphate buffer solution [69].

Chitosan. One of the most abundant natural polysaccharides in the world after cellulose is chitin derived from cell walls of the crustacean, insect and fungus exoskeletons, which is used for the chitosan manufacture by deacetylation. Chitosan is a bioactive polymer with a wide range of applications as a result of its functional properties such as antibacterial activity, nontoxicity, ease of modification and biodegradability [70]. One of the advantages of chitosan is the ability to form films, in the process of which formation chitosan powder is mixed with acid solution, poured into a container and dried at room temperature, thermostatically. Among the disadvantages of chitosan-based hydrogels are their limited solubility in some solvents, and poor mechanical properties, which are minimised by chemical or physical modification [71].

Chitosan has a wide range of applications in medical fields. Similar to dextran, it is used for a controlled drug delivery, in tissue engineering, as a blood anticoagulant, an antimicrobial agent and a biomaterial for bone regeneration [72].

For the delivery of drugs and other active molecules, chitosan has unique properties such as *in situ* gelation, mucoadhesion, hydrophilic nature and enhanced permeability. The process of controlled drug release is also known to be dependent on external parameters (temperature, pH). As a consequence of their good biocompatibility and similarity to the extracellular matrix, chitosan hydrogels may serve as promising candidates for targeted delivery of cells, providing them with protection from the immune response and promoting increased cell viability. Additionally, through the reversible bonds of hydrogels, the embedded cells can not only proliferate and migrate but also adjust their morphology.

By considering the temperature sensitivity, which depends on the concentration, molecular weight and degree of deacetylation of chitosan, when using chitosan/αβ-glycerophosphate hydrogel, it was found that the optimum molecular weight was 1360 kDa, gelation temperature was 37 °C, and the percentage of deacetylated chitosan was 75 %, while no gel formation occurred when these characteristics were changed [73].

Chitosan hydrogel modified with 3-(3,4-dihydroxyphenyl)-propionic acid and polyethylene glycol based on sebacic acid modified with p-hydroxybenzaldehyde were prepared as a hemostatic preparation. Along with antibacterial properties, cytocompatibility and sufficient extensibility, the synthesized hydrogel showed a rapid haemostatic effect, due to which the volume of blood loss from the liver in mice was reduced by almost 90 % compared to the control group [74].

Hyaluronic acid. Hyaluronic acid is a polyanionic natural polymer that is a linear polysaccharide composed of glucuronic acid and N-acetylglucosamine. It is the most versatile macromolecule present in the connective tissue of all vertebrates. As a consequence of their good physicochemical properties, hyaluronic acid preparations are used in osteoarthritis surgery, eye surgery, plastic surgery, tissue engineering and drug delivery [75]. When chemically modified, hyaluronic acid can be converted into many physical forms – viscoelastic solutions, hydrogels, fibers, macroporous and fibrillar sponges. The chemical modifications target three functional groups: glucuronic acid carboxylic acid, primary and secondary hydroxyl groups, and N-acetyl group. Carboxylates have been modified by carbodiimide-mediated reactions, esterification and amidation; hydroxyls were subjected to etherification, divinyl sulfone crosslinking, esterification and bis-epoxide crosslinking.

To produce hyaluronic acid-based hydrogels, radical polymerization is used, which includes the formation of a radical under the action of an initiation source (light, temperature, redox reaction) that reacts with a reactive group on the hyaluronic acid macromer to generate kinetic

chains. More often photoinitiated polymerisation is used, the advantage of which is temporal and spatial control [76].

Acrylates and methacrylates are the most common reactive groups for application in radical polymerisation, since they react rapidly with radicals. Among the simplest and most widely used hyaluronic acid modification reactions is the reaction of the acid with methacrylic anhydride to form methacrylated hyaluronic acid, which has been successfully applied to seal corneal tears [77]. As an alternate method of modifying hyaluronic acid, glycidyl methacrylate and hyaluronic acid are reacted to form conjugates, with methacrylation occurring over a long period of time at room temperature. Obtaining tightly cross-linked gels is provided by photocrosslinking, which may also be used to obtain a range of complex fluids from flowable to viscoelastic [78]. Such modifications yield stable and enzymatically degradable hydrogels. In some cases, however, biodegradation needs to be slowed down to limit cell migration and cell-to-cell contacts, or for a system with individualised temporal properties. To that end, hyaluronic acid macromers have been synthesised to form hydrogels that are both hydrolytically and enzymatically degradable by introducing hydrolytically degradable esters (lactic acid, caprolactone) between the hyaluronic acid backbone and the photoreactive groups [79].

Alginate. Alginates – salts of alginic acid – are considered to be no less promising natural materials. Alginic acid is a viscous rubber-like substance, a polysaccharide which is extracted from red, brown, green algae and bacterial source. Alginates are unbranched polysaccharides composed of 1-4-linked β-d-mannuronic acid and its C-5 epimer α-l-guluronic acid.

Alginate biosynthesis may be divided into four stages:

1. Synthesis of mannuronic acid precursor.
2. Cytoplasmic membrane transfer and polymerization into polymannuronic acid.
3. Periplasmic transfer and modification.
4. Export through the outer membrane.

Alginate modification, which can only be carried out in stage 3, depends on solubility, reactivity and characteristics. Alginates can be dissolved in aqueous, organic or mixed media, and the degree of solubility can influence the substitution pattern of the derivatives. The modification occurs at two eOH positions (C-2 and C-3) or at a single eCOOH position (C-6). The difference in reactivity can be easily applied to selectively modify either of these two types [80]. To improve the physicochemical properties, chemical modification is used to increase the ionic strength of the gel, enhance biodegradation, and introduce new properties. In this process, the alginate is being processed by acetylation, phosphorylation, sulfation, hydrophobic modification, attachment of cellular signalling molecules, covalent cross-linking and copolymerisation.

Alginates can be characterised by such biological activities as antimicrobial and haemostatic action, antitoxic and anti-radiation action, hypolipidemic effect, suppression of the activity of facultative flora, and slowing down the rate of glucose absorption from the small intestine. Alginates are an important polysaccharide family for producing hydrogels at moderate pH and temperature conditions which are suitable for sensitive biomolecules such as proteins, nucleic acids [80]. Additionally, complex monosaccharide compositions and the ability to create controlled sequences make alginates a promising material for a variety of applications. Currently, alginates are used as wound dressings [81], have a significant impact in the progression of cystic fibrosis, but more important is the use of alginate cross-linking in the manufacture of hydrogels for the encapsulation of cells and islets of Langerhans in the treatment of diabetes mellitus. Specifically, a thermosensitive sodium alginate/poloxamer 407 (hydrophilic nonionic surfactant of copolymer class)/ pluronic F-127/polyvinyl alcohol hydrogel with the addition of amikacin was developed for wound healing. This hydrogel had good tensile strength and mechanical properties while maintaining elasticity and flexibility due to sufficient cross-linking between hydrogel components. A microscopic investigation revealed a rough surface with sufficient pore size, the presence of which promoted wound oxygenation to accelerate the healing process, provided a moist environment to intensify re-epithelialisation and granulation tissue formation, as well as supported longer release of encapsulated drugs [82]. Similar results were obtained by other researchers who designed a sodium alginate/H_2S hydrogel with $CaCl_2$ as cross-linking agent.The pore size was approximately 50–90 μm, which was suitable for cell penetration and migration; the hydrogel mass increased by more than 120 %. Meanwhile, it has been observed that the release kinetics of the encapsulated substance depends on the pH of the surrounding solution, and release is faster in an acidic environment than in a neutral one [83].

As the majority of hydrogels based on natural materials, alginate gels are used for controlled drug delivery as they have great potential to create drug carriers with adaptive behavior and adjustable properties. To achieve this, the hydrogels were cross-linked by simultaneous photopolymerisation of vinyl groups and photodimerisation of anthracene with the addition of doxorubicin. The involvement of anthracene in the gel leads to reversible crosslinking control and transition between gel/sol states [84].

Alginate/polyacrylamide hydrogel is a potential candidate material for vascular remodelling, which has mechanical strength, resistance to enzymatic degradation and anti-calcification ability, and can inhibit platelet adhesion, aggregation and activation, promote endothelial cell adhesion and proliferation. Additionally, it is able to stimulate the secretion of NO and PGI2, which are important factors, involved in vascular remodelling and repair [85].

CONCLUSION

Currently, naturally occurring polymers are increasingly being used as raw materials for the preparation of hy-

drogels. These are mainly caused by the absence of negative impact on the environment, as well as by the biofunctionality of the derivative products. As a general rule, these polymers allow the production of hydrogels that have desirable properties such as biocompatibility, biodegradability, and non-cytotoxicity. Hydrogels made from natural components show decent results in such biomedical fields as aesthetic medicine, tissue engineering, drug screening, oncological pathology therapy, and others. As a result, natural materials in the basis of hydrogels occupy one of the key places and are promising components in the improvement of existing compositions and the development of new ones.

Conflict of interest

The authors of this article declare no conflicts of interest.

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