Hyaluronic Acid as a Component of Natural Polymer Blends for Biomedical Applications: A Review

Alina Sionkowska 1,*, Magdalena Gadomska 1, Katarzyna Musiał 1 and Jacek Piątek 2 *

1 Department of Biomaterials and Cosmetics Chemistry, Faculty of Chemistry, Nicolaus Copernicus University in Toruń, Gagarin 7, 87-100 Toruń, Poland; 291013@student.umk.pl (M.G.); musialk.97@gmail.com (K.M.)
2 Health Sciences Faculty, President Stanisław Wojciechowski State University of Applied Sciences in Kalisz, Nowy Świat 4 st., 62-800 Kalisz, Poland; drpiatek@interia.eu
*
Correspondence: alinas@umk.pl

Academic Editors: Adam Gadomski and Piotr Bełdowski
Received: 9 August 2020; Accepted: 2 September 2020; Published: 4 September 2020

Abstract: In this review, we provide a report on recent studies in the field of research on the blends of hyaluronic acid with other natural polymers, namely collagen and chitosan. Hyaluronic acid has attracted significant interest in biomedical and cosmetic applications due to its interesting properties. In recent years, blends of hyaluronic acid with other polymers have been studied for new materials development. New materials may show improved properties that are important in the biomedical applications and in cosmetic preparations. In this review paper, the structure, preparation, and properties of hyaluronic acid blends with collagen and chitosan have been discussed and examples of new materials based on such blends have been presented. A comparison of the currently available information in the field has been shown. Future aspects in the field of hyaluronic acid blends and their applications in the biomedical and cosmetic industry have also been mentioned.

Keywords: hyaluronic acid; polymer blends; biopolymers; biomaterials; chitosan; collagen

1. Introduction

Hyaluronic acid (HA) belongs to the glycosaminoglycan compounds, which are members of the polysaccharides family. The molecule of HA is consisting of alternating units of N-acetyl-D-glucosamine and glucuronic acid. HA is a part of almost every tissue in vertebrates [1]. The molecular weight of HA is very high, up to several millions. The structure of HA is shown in Figure 1. HA is not covalently bonded to proteins, but it is widely distributed mainly in the connective tissue. Chemically, hyaluronic acid is a hydrophilic macromolecule with -COOH and -OH functional groups. The solubility of HA in water is high, and it forms highly viscous solutions. Such solutions show unique viscoelastic properties. HA can form intramolecular hydrogen bonding, which leads to three-dimensional structures. Hyaluronic acid can trap water within its structure and can form gels. The amount of trapped water is approximately 1000 times of the weight of HA. HA is a part of the following tissues: articular cartilage, the nucleus pulposus, skin, the cervix, and the glycosylcalyx of endothelial cells. The solutions and gels of HA are commonly used as a dermal filler. After injection, it is possible to restore skin volume and to minimize the appearance of wrinkles. HA is a very effective and safe ingredient of cosmetic formulation.

The role of hyaluronic acid in the body is strictly connected with its properties. HA is synthesized by a class of integral membrane proteins known as HA synthases [2]. These proteins lengthen HA by repeated addition of glucuronic acid and N-acetyl-D-glucosamine groups to the growing sugar. The half-life of HA in human tissues ranges from one day in skin tissues up to 70 days in some parts of the eye. HA plays an important role in ECM (extracellular matrix) by several specific and non-specific interactions. It is also helpful for the growth of epithelial tissue cells, eosinophil, macrophages, and a few animal tissues cells. The role usually depends on the molecular weight of HA. For example,
low weight HA is essential in healing and scar formation, whereas high molecular weight HA may support the tissue integrity. HA due to water absorption provides flexibility to the animal tissue and lubrication in muscular connective tissues.

Hyaluronic acid is widely used in biomaterials. For example, HA has been extensively investigated for wound dressing applications. HA can be cross-linked by a variety of physical and chemical methods because of the presence of several functional groups. HA can be used in tissue repair because it is able to promote mesenchymal and epithelial cell migration and differentiation. Biological properties make HA very good material for tissue engineering. From an aqueous solution of HA, one can fabricate 3D porous materials. The properties of 3D HA materials, as well as the properties of HA hydrogels, can be modified by HA concentration and by crosslinking process [3–7]. The crosslinking process makes materials more resistant to enzymatic degradation. HA hydrogels are widely used for skin rejuvenation due to its ability to moisturize the skin [8]. Moreover, HA in intradermal injection has been used as a dermal filler. HA is also an ingredient in cosmetic creams and gels for the treatment of different types of diseases [9–12]. HA in the form of hydrogel works as a collagen stimulator [13–15]. The film-forming properties of HA can also be used for hair treatment [16].

Hyaluronic acid is widely used not only in cosmetics. HA is also used for drug delivery, coatings and implantation of organs, and for several therapeutic purposes due to its ability to modify cellular behavior. The properties of hyaluronic acid can be modified not only by chemical and physical crosslinking methods. Hyaluronic acid can be blended with another polymer and/or a biopolymer. Blending the polysaccharides with the less expensive synthetic polymers is one of the approaches to reduce the cost of materials. Polymer scaffolds for biomedical applications can be made of blends of hyaluronic acid with synthetic polymers and/or another natural polymer. The aim of this review is to show the current research on the blends of hyaluronic acid with collagen and chitosan. However, it should be emphasized that hyaluronic acid can also be blended with several other polymers and biopolymers [17–20].

2. Blends of Hyaluronic Acid and Collagen

Hyaluronic acid can be used for modification of collagen properties. Collagen is a structural protein that provides fundamental structural and mechanical support in human and animal bodies. Collagen-based materials are widely applied in the biomedical field, for example, it can be used in tissue regeneration/engineering and for new materials fabrication. The example of collagen application is a preparation of artificial skin, bone graft substitutes (collagen composites with inorganic particles), dental implants, artificial tendons and blood vessels, corneal implants, regeneration of nerves, cartilage, and several other tissues [21].

The investigation of the properties of the blends based on collagen and hyaluronic acid has been already initiated and several interesting biomaterials based on such blends have been proposed [22–41]. Several research groups have studied interactions between collagen and HA and the possibility of new materials formation based on such a blend. The possible interactions between collagen and hyaluronic acid are shown in Figure 2.
Polymer-polymer interactions, such as hydrophobic and electrostatic interactions, have been studied in a hyaluronic acid and collagen mixture, and new matrices based on the blends have been obtained by Taguchi et al. [22]. Matrices with polymer–polymer interactions could be obtained upon their immersion in water at 37 °C with no collagen denaturation. The material obtained showed high swelling properties [22]. Collagen–hyaluronic acid membranes for applications in regenerative medicine can be obtained by self-assembly [23]. The lyophilized matrices show multipore structures and can be useful in the preparation of cartilage regenerative scaffolds [24]. Porous collagen/hyaluronic acid matrices have been crosslinked by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) [25]. Such scaffolds can be used for dermal tissue regeneration. Porous sponges based on the blends of collagen and hyaluronic acid have been fabricated by employing a combination of freezing, lyophilizing, and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC) crosslinking methods [26]. Porous hybrid scaffolds based on collagen and hyaluronic acid have also been prepared by a novel overrun process performed by Lee et al. [27]. The above-mentioned authors showed that the scaffolds with uniform dual-pore structure with porosity higher than scaffolds prepared by the conventional freeze-drying method can be prepared. In this work, the bubble injection and recrystallization have been used. The mechanical strength and biodegradation kinetics were controlled by choosing the adequate preparation method and the collagen/hyaluronic acid composition. The porous collagen/hyaluronic acid scaffolds could be functionalized with biotin by incorporating avidin. A nano-fibrous assembly of collagen–hyaluronic acid for controlling cell-adhesive properties has been studied by Fujie et al. [28]. Hybrid scaffolds composed of hyaluronic acid and collagen in a 3D form were prepared and evaluated for cartilage regeneration by Kim et al. [29]. The time of degradation of the hybrid scaffolds in vitro increased with increasing collagen concentration. Moreover, the cell growth in the hybrid scaffolds increased with increasing collagen concentration after a period of 2 weeks of the cell culture.

Multifunctionalized hydrogel scaffolds based on hyaluronic acid–tyrosine and human-like collagen have been fabricated by Liu et al. [30]. The crosslinking of this blend with 1,4-butanediol diglycidyl ether led to the formation of materials that can be considered as soft-tissue fillers. It has been shown that the material showed good mechanical properties, biological stability, and biocompatibility.

An extracellular matrix can be mimicked by biopolymer blends in several forms. An injectable hydrogel composed of type I collagen and hyaluronic acid has been designed to mimic the extracellular matrix for vascular cells growing and wound closure by Ying et al. [31]. The preparation of the collagen/hyaluronic acid hydrogel was performed through in situ couplings of phenol moieties of collagen I-hydroxybenzoic acid and hyaluronic acid–tyramine through horseradish peroxidase. The porous hydrogel was obtained using the above procedure that contributed to the exchange of gas, medium, and nutrition. The injectable hydrogel plays an important role in soft-tissue filling and repair. Such an injectable hydrogel based on hyaluronic acid and human-like collagen was proposed by Zhang et al. [32]. Collagen and HA were crosslinked with 1,4-butanediol diglycidyl ether to form a three-dimensional network. An in vivo injection showed that there was little inflammatory response...
to such a hydrogel after 1, 2, and 4 weeks. This hydrogel can also be considered as a promising biomaterial for soft-tissue filling and repair. Collagen/hyaluronic acids hydrogels can be used as an efficient and controlled gene delivery biodegradable materials [33]. Biomaterial-based gene delivery can find numerous tissue engineering applications or can be a tool to examine tissue formation.

Collagen/hyaluronic acid blends can be used as an artificial dermis [34]. The efficacy of an artificial dermis composed of hyaluronic acid and collagen with or without epidermal growth factor, both in vitro and in vivo, have been studied by Mineo et al. [34]. It was found that such artificial dermis induced excellent wound bed formation acceptable for autologous skin grafting. Collagen/hyaluronic acid blends have been studied as wound dressing by several research groups as well [35–37]. A modified collagen/hyaluronic acid mixture has been studied as an injectable composite filler for soft-tissue reconstruction and may be a suitable candidate as an injectable dermal filler for tissue augmentation in humans [38].

Another procedure in the fabrication of new materials based on biopolymer blends is electrospinning. A nanofibrous hyaluronic acid/collagen hybrid scaffold has been fabricated by electrospinning by a number of research groups [39, 40]. The two above mentioned substances formulated interpenetrating polymer networks, which have been studied for their implementation as a tissue-engineered heart valve. The review concerning this approach has been prepared by Nazir [41]. In the above-mentioned review, the comparison of the existing experimental approaches and recent technical challenges in this field have been demonstrated.

3. Blends of Hyaluronic Acid and Chitosan

Chitosan is a polysaccharide, which is obtained from chitin. It shows cationic polyelectrolyte properties. In chitosan structure, there are 2-acetamido-2-deoxy-β-D-glucopyranose units and the deacetylated form of these units, 2-amino-2-deoxy-β-D-glucopyranose. Chitosan is widely used in biomedical, pharmaceutical, and cosmetic applications. This biopolymer is biocompatible with high charge density. It is also non-toxic and shows good mucoadhesion [42]. Chitosan materials can be modified by the addition of hyaluronic acid to form new materials based on such binary blends. Hyaluronic acid and chitosan can form nanoparticles, hydrogels, microspheres, sponges, and films, all with a wide range of biomedical applications. In the scientific literature, there are several papers regarding an investigation of interactions between chitosan and HA [43–60].

The degree of miscibility of chitosan with hyaluronic acid was analyzed by us by a viscometric method and atomic force microscopy [43]. The studies indicated that chitosan/hyaluronic acid blends were miscible at the weight fraction of chitosan w(Chitosan) ≥ 0.5 in 0.1 mol dm⁻³ CH₃COOH/0.2 mol dm⁻³ NaCl and 0.1 mol dm⁻³ HCl at 25 degrees C. The influence of the type of solvent on the structure of chitosan, hyaluronic acid, and their blend films was investigated as well [44]. It was found that the surface roughness of chitosan, hyaluronic acid and their blended films was altered by mixing. The structure of chitosan blends with hyaluronic acid depends on the blend composition and on the solvent used for preparing the blend. Moreover, very important in miscibility were also the chitosan degree of acetylation and its molecular weight [45]. The possible interactions between chitosan and hyaluronic acid are shown in Figure 3. The interactions between hyaluronic acid and chitosan depend on pH and ionic strength [46]. Due to the strong charge complementarity between both of the biopolymers, electrostatic self-assembly may take place at very acidic pH but is almost unobservable at high ionic strength.

Based on the blends of hyaluronic acid and chitosan the hydrogels have been investigated for applications in tissue engineering to cartilage regeneration [47, 48]. The potential of chitosan–hyaluronic acid dialdehyde hydrogels for in vivo cartilage regeneration has been studied as well [50]. In the above-mentioned study, the gel alone for cartilage regeneration as well as a combination of chondrocytes and gel for cartilage repair were studied. It was found that there was no significant enhancement in the quality of regenerated cartilage in the presence of encapsulated chondrocytes. Hyaluronic acid and chitosan have been proposed for the preparation of coacervate-based scaffolds for cartilage tissue
engineering [50]. Such coacervates were used also to encapsulate bone marrow stem cells. Injectable and body temperature-sensitive hydrogels based on chitosan and hyaluronic acid for pH-sensitive drug release have been proposed by Zhang et al. [51]. It was shown that the mechanical properties, as well as the gelation temperature, can be modified by changing the HA content. The drug release possibility of such materials can also be modified by the blend composition. It was stated that the carboxyl group in hyaluronic acid can form the hydrogen bonds with the protonated amine in chitosan, which promotes the increase in mechanical strength of the hydrogels and depresses the initial burst release of drugs from the hydrogel. Hyaluronic acid/chitosan polyelectrolyte multilayers were used for surface modification of titanium alloys for biomedical applications [52]. Hyaluronic acid and chitosan-based materials can also be used as a new dressing generation for wound care [53]. Chitosan and hyaluronic acid have been used for the preparation of composite fibers by electrospinning and subsequent coating [54]. The electrospun nanofibers were also obtained from an aqueous complex coacervate solution composed of chitosan and hyaluronic acid [55]. Electrospun nanofibers can be used in biomedical applications. Chitosan and hyaluronic acid have also been studied as a promising biomaterial for injectable tissue engineering as thermogels that undergo temperature-dependent-so-gel transition [56]. Preparation of one pot tripeptide network hydrogel of chitosan and hyaluronic acid formed by triazole linkage, metal-coordination, and polyion complexation was proposed by Engkagul et al. [57]. It was shown that the salt-containing water system favors polyion complex formation of chitosan and hyaluronic acid without precipitation. The mechanical properties and morphologies can be controlled by simply varying the biopolymers mole ratios. The obtained hydrogels showed biocompatibility based on studies with chondrocyte cells. Chitosan–hyaluronic acid polyelectrolyte multilayer scaffolds were fabricated with statistically significant stiffness variances by Erickson et al. [58] to characterize the effect of scaffold stiffness on morphology, proliferation, drug resistance, and gene expression in human glioblastoma cells. Chitosan–hyaluronic acid blends have also been used for the fabrication of wound-healing materials [59,60]. New materials in the form of membranes composed of chitosan and chitosan–hyaluronic acid containing new arginine derivatives with thiazolidine-4-one scaffold have been prepared using the ionic cross-linking method by Iacob et al. [60]. The properties of chitosan and HA allow for several modifications of both of these biopolymers, so probably in the future, several new materials based on chitosan and HA blends will be proposed.

![Figure 3. Possible interactions between chitosan and hyaluronic acid (HA) in blends.](image)

**Figure 3.** Possible interactions between chitosan and hyaluronic acid (HA) in blends.

### 4. Ternary Blends of Hyaluronic Acid, Collagen, and Chitosan

More than two polymers blending is a new trend in polymer science. In the most recently published literature, there are reports on ternary blends prepared using three different polymers. Although it is not easy to investigate the interactions between three different macromolecules, some attempts have been made to understand the chemical and physical forces acting on the molecular level. New materials based on ternary biopolymer blends have also been proposed. There are only a few papers in the scientific literature regarding hyaluronic acid blends with other natural polymers and synthetic polymers where interactions between biopolymers in mixtures have been scarcely described. Nevertheless, the interactions between collagen, hyaluronic acid, and chitosan in mixtures

...
and materials based on collagen/hyaluronic acid/chitosan blend have been studied within the last 5 years [61–76] and new materials have been proposed.

In Figure 4, the scheme of preparation of the materials based on hyaluronic acid, collagen, and chitosan is shown.

**Figure 4.** Scheme of preparation of the materials based on hyaluronic acid, collagen, and chitosan.

Collagen, hyaluronic acid, and chitosan possess specific properties that can be used to produce man-made blends that confer unique structural and mechanical properties. Miscibility of the components is an important aspect, which determines the properties of the ternary blend. The interaction between three natural polymers, namely collagen, hyaluronic acid, and chitosan, have been studied by viscometric measurements and FTIR spectroscopy [43,62]. The viscometric study showed that collagen/hyaluronic acid blends were miscible in any composition. In the case of ternary blends, the polymeric components were partially miscible. The mechanical properties of chitosan/collagen/hyaluronic acid films, such as tensile strength and Young’s modulus depend on the blend composition. The addition of chitosan to the collagen/hyaluronic acid blend led to an increase in tensile strength by approximately 50%. The results of FTIR analysis showed intermolecular interactions between functional groups of biopolymers [62].

The interactions in chitosan blends with hyaluronic acid and collagen have been studied in solution by the viscometric method and by atomic force microscopy and FTIR for films made of the blends. The surface properties have been measured by contact angle measurements. The results showed that chitosan/hyaluronic acid blends were miscible at the weight fraction of chitosan w(ch) ≥ 0.5. In the case of ternary blends, the polymeric components showed miscibility with collagen at a weight fraction smaller than 0.2. The wettability of chitosan/hyaluronic acid and chitosan/hyaluronic acid/collagen blend films was bigger than those for the chitosan and collagen films. The morphology of ternary blends has also been altered in comparison to films made of single biopolymers. Atomic force microscopy (AFM) results showed that microdomains appeared in the form of globular agglomerates. The differences between surface properties of films made of single components and the surface properties of films made of ternary blends can be a consequence of interactions between collagen, chitosan, and HA [42,63]. The possible interactions between above-mentioned biopolymers have been presented in Figure 5.

Based on chitosan, hyaluronic acid, and collagen blends, thin films and 3D sponges have been prepared [63–67]. The properties of blend films have been investigated by contact angle measurements and atomic force microscopy. The former measurements showed that chitosan films are more polar after the addition of hyaluronic acid and collagen. The AFM results showed that the addition of chitosan to hyaluronic acid led to an increase in surface roughness [64].
The addition of chitosan to collagen/HA mixture led to the alterations of surface roughness, hydrophilicity, and thermal properties of those binary blends. Thermal stability of binary blends increased after the addition of chitosan. The surface free energy has been also altered after mixing of three biopolymers. Polar and dispersive components of surface free energy, which were calculated for the binary and ternary blends showed that more hydrophilic films were produced by HA and chitosan addition to collagen. All the above observations suggest that collagen interacts with hyaluronic acid and chitosan. The interactions between three macromolecules led to the change in the surface properties of polymer films [65]. Surface properties of ternary blends are very important as biopolymer films made of the ternary blend can be applied for example in cosmetic preparations [66]. The hair protection capability of collagen/chitosan/hauluronic was studied using SEM microscopy and the mechanical testing of hair coated with the blends. It was found that the addition of hyaluronic acid to a collagen/chitosan blend improves the mechanical resistance of biopolymeric films. Samples with hyaluronic acid addition were more stable in an aqueous environment and provided higher surface roughness. Films based on chitosan, collagen, and hyaluronic acid can be successfully crosslinked by dialdehyde starch [67]. It was found that the addition of dialdehyde starch had an influence on mechanical properties of the films. The films crosslinked with dialdehyde starch were less elastic and more resistant to rupture than those without such treatment. The roughness of the samples decreased after the crosslinking with dialdehyde starch (Figure 6) and the surface free energy increased. The film-forming properties of the mixture of collagen, hyaluronic acid, and chitosan crosslinked with dialdehyde starch can be used in medicine and in cosmetic preparations.

3D porous composites based on blends of chitosan, collagen, and hyaluronic acid were obtained through the lyophilization process, and the properties of the scaffolds were studied [68]. SEM images of such 3D composites are shown in Figure 7. Biological properties are also significant, especially for those materials that are dedicated to biomedical application. Natural polymers have been widely used in biomedicine and separately have been proposed as the in vitro extracellular matrix materials. However, the interactions of tricomponent–biopolymer composites with cells is not well studied yet. Biological properties of new materials obtained based on ternary blends should be investigated. For each blend, the proliferation rate of selected cells incubated with biomaterials should be studied. Hyaluronic acid addition to chitosan/collagen blend also modified the properties of 3D composites based on those biopolymers. The results showed that mechanical properties and thermal stability of chitosan/collagen blends were improved. Biological properties of 3D materials can be sufficient for biomedical applications, as it was found that materials were non-toxic and the cell morphology was not significantly altered [68].
Molecules 2020, 25, x FOR PEER REVIEW 8 of 17

(a) (b)

Figure 6. AFM images of the surface of unmodified and samples modified with dialdehyde starch (DAS): (a) collagen, (b) collagen + DAS, (c) chitosan, (d) chitosan + DAS. [67], Copyright 2020. Reproduced with permission from Elsevier Ltd. (DAS = dialdehyde starch).

(c) (d)

Figure 7. SEM images of (a) CTS/Coll; (b) CTS/Coll/5HA composites. [68], Copyright 2020. Reproduced with permission from Elsevier Ltd. (CTS = chitosan; Coll = collagen; HA = hyaluronic acid).
Three-dimensional porous polymer-based matrices can be used for fabrication composite materials containing inorganic particles. Such materials have potential in bone repair and in bone tissue engineering. It seems that 3D porous composites based on blends of chitosan, collagen, and hyaluronic acid can also be considered as a matrix for the incorporation of inorganic particles [69–76]. Additional crosslinking of such composites may offer materials with good biocompatibility and mechanical properties, which can be proper in bone tissue engineering. For example, the calcium phosphate in situ precipitation in 3D porous scaffolds based on chitosan, collagen, and hyaluronic acid crosslinked by EDC/NHS (N-(3-dimethylamino propyl)-N’-ethylcarbodiimide hydrochloride/N-hydroxysuccinimide) was proposed [69]. It has been shown that the properties of 3D composites crosslinked by EDC/NHS were altered by hyaluronic acid addition. The following parameters of the scaffold were improved: mechanical properties, thermal stability, and porosity. SEM images showed that precipitation was homogeneously carried out in the whole volume of samples. Attachment of SaOS-2 cells to all the modified materials was more efficient in comparison to results obtained in unmodified control, and proliferation of these cells was markedly increased on scaffolds with precipitated calcium phosphate. The obtained materials can be potentially used in tissue engineering and regenerative medicine. Not only films but also 3D scaffolds based on chitosan, collagen, and hyaluronic acid can be successfully crosslinked by dialdehyde starch [70]. Such crosslinked matrixes can also be used for calcium phosphate in situ precipitation. The mechanical properties, porosity, and density of the materials were improved after such a crosslinking process. Calcium phosphate was deposited in the scaffolds at the Ca/P ratio similar to 2. SEM images showed the homogeneous structure, with interconnected pores. The crosslinker addition and inorganic compound precipitation improved the biocompatibility of the scaffolds. It is much easier and faster is to prepare the polymer/inorganic particles composites by the simple addition of such particles to polymer matrices. It is known that collagen and hydroxyapatite form a complex structure of bone tissue. To produce an artificial bone tissue the powder of nano-hydroxyapatite has been added to the mixture of chitosan, collagen, and hyaluronic acid. After mixing all the above-mentioned components and lyophilization process, the porous 3D composite was obtained. The addition of hydroxyapatite (Hap) caused an improvement of mechanical and thermal properties of ternary biopolymer blend. All the composites showed a porous structure with interconnected pores, which can be appropriate for bone tissue engineering [71,72]. Calcium ions can be released from the composite during its degradation in water [71]. Scaffolds can also be crosslinked by dialdehyde starch and by tannic acid [72]. The compressive modulus, as well as the porosity for the scaffolds crosslinked by dialdehyde starch, was higher than for those crosslinked by tannic acid. However, crosslinking with tannic acid led to material with better biocompatibility than those for materials after crosslinking by dialdehyde starch. Nevertheless, the results showed that both scaffolds can provide the support required in tissue engineering and regenerative medicine [72]. Collagen, chitosan, and hyaluronic acid blends can be also crosslinked with genipin [73]. The above mentioned three biopolymers were used to prepare injectable and in situ gelating biomimetic hybrid materials for potential use in bone tissue engineering. The surface-modified silica particles were introduced to the solutions of biopolymers and after crosslinking with genipin the bioactive phase was formed. Hybrids of various compositions were obtained, and their physicochemical and biological properties were studied. The in vitro cell culture studies showed that the materials developed are biocompatible as they support MG-63 cells adhesion, proliferation as well as alkaline phosphatase (ALP) expression [73].

Although the biological properties in vivo of single natural polymers are widely researched, the behavior and influence of tricomponent–biopolymer composites on cell morphology, differentiation, and function in living organisms are not yet well known. For collagen/chitosan/hyaluronic acid composites, the adhesion and proliferation of human osteosarcoma SaOS-2 cells on the scaffolds have been studied and the biocompatibility of the chosen scaffolds has been further studied by their in vivo implantation into the subcutaneous tissue of rabbits [74]. The obtained results suggest that the stability of such scaffolds is rather low. The X-ray images of the tissues surrounding the scaffolds showed both
the control scaffolds without hydroxyapatite (HAp) and those with 50% wt. HAp addition underwent degradation after 6 months. The scaffolds containing 80% wt. of HAp remained in the implanted place, which may suggest that it can be useful in tissue engineering. Biological properties and tissue response show that the material can be considered as a scaffold of soft and hard tissues.

Collagen, chitosan, and hyaluronic acid in the form of thin films can be used as a matrix for drug incorporation [63,75]. Polymeric blends based on the above-mentioned biopolymers in the form of thin films with the addition of gentamicin sulphate were obtained. Microbiological tests were performed to evaluate the diffusion of the drug from matrices. The results showed that thin films based on collagen, chitosan, and hyaluronic acid enriched in gentamicin sulphate inhibit the growth of both Gram-negative bacteria (E. coli and P. aeruginosa) and Gram-positive (S. aureus) ones [75]. The procoagulant properties of hyaluronic acid–collagen/chitosan complex film have also been studied [76,77].

Collagen, chitosan, and hyaluronic acid in a 3D form can be used as a matrix for magnetic particles incorporation [78]. It was found that 3D composites made of collagen, chitosan, and hyaluronic acid with magnetic particles are hydrophilic and characterized by a high swelling ability; nevertheless, they are rigid and lack flexibility. With the increasing content of magnetic particles in the polymer blend, the Young's modulus decreases. The 3D material with magnetite particles can be used in biomedical applications, e.g., tissue repair and drug delivery.

5. Possible Application of New Materials Based on the Blends of Hyaluronic Acid with Other Natural Polymers

New materials based on the blends of HA, collagen, and chitosan can be prepared in several forms. Film-forming properties can be useful for the preparation of wound-healing materials [2,63–67,79,80]. Mechanical properties of such materials can be modified by chemical and physical crosslinking [67,72,73,81,82]. Such modification may help in stimulating epithelium cells to proliferate, which are often needed to produce materials with improved biological properties for tissue engineering [81,82]. The properties of the materials based on the blends can be simply modified by changing the weight ratio of the components in the blend. Thin films can be also used in tissue engineering, as usually, materials obtained have been biocompatible.

New materials based on the blends of above-mentioned biopolymers can be used as a topical formulation, which can offer some potential for the delivery and localization of medication to the skin [83]. Some antibacterial properties can be reached by incorporation silver nanoparticles and/or other bioactive agents into formulation [75,84,85]. The penetration through the skin can be adjusted by a properly selected molecular weight of HA [86]. A cosmetic formulation, such as a cream for the treatment of skin disorders and dehydration caused, for example, during radiotherapy and other treatments, may contain a blend of HA, collagen, and chitosan.

Polymer blends can be also turned into 3D structures, such as foams and scaffolds [68–72,87–89]. In such 3D structures, inorganic particles can be incorporated, and in such a way, one can obtain materials, which can mimic a bone tissue [72,74]. Incorporation of magnetic particles into the biopolymer blends can lead to new materials, which can be used in biomedical applications, such as: tissue repair, drug delivery, magnetic resonance imaging (MRI), hyperthermia, magnetofection, and cellular therapy [78,90–93]. 3D scaffolds based on biopolymer blends with magnetic properties can be inserted directly into an injured site. In such a way, it can help to control the orientation of new collagen fibers formed around the applied scaffold. Such new materials can also be used in new generation therapy and as matrices for the delivery of compounds with magnetic properties [78].

Within the last 5 years, several articles have been published that show that it is still of interest within scientific groups to research the blends of hyaluronic acid with other biopolymers [85,94–102]. For example, new materials were prepared based on the mixtures of hyaluronic acid and carboxymethyl cellulose [94]. Interpenetrating polymer networks based on collagen, hyaluronic acid, and chondroitin sulfate as scaffolds for brain tissue engineering was studied by Li et al. [95]. Hyaluronic acid–pullulan injectable hydrogels incorporated with biomimetic hydroxyapatite spheres were studied by Ghorbani et al. [96]. Water-insoluble silk fibroin/hyaluronic acid scaffolds were proposed by Guan et al. [97]. Polycaprolactone/
gelatin/hyaluronic acid blends have been studied for usage as electrospun scaffolds by Unal et al. [98]. Ternary blends of silk fibroin, hyaluronic acid, and heparin were also studied for potential soft-tissue engineering [99]. A novel biomaterial made of alginate, hyaluronic acid, halloysite nanotube, and polyvinylidene fluoride has been proposed for printing cartilage scaffolds [100]. The hydrogel composed of hyaluronic acid and alginate as a potential bio-ink for 3D bioprinting of articular cartilage engineering constructs has been also proposed [101]. Next potential bio-ink was proposed by enzymatically crosslinked hyaluronic acid–gelatin hybrid hydrogels [102]. There are much more examples of ongoing research on hyaluronic acid and its blends with other biopolymers. This fact suggests that it is increasing interest in the creation of new materials based on such blends. Apart from experimental study on HA materials there are also studies regarding molecular dynamic simulation of this macromolecule behavior in the presence of water and other molecules [103,104].

The application of biopolymer blends for preparation of biomedical materials has been summarized graphically in Figure 8.

![Figure 8. Potential applications of biopolymer blends base of HA, collagen, and chitosan.](image)

6. Conclusions

Hyaluronic acid is widely studied for its use in biomedical fields. This biopolymer can be modified in several ways, especially blending it with another biopolymer may lead to new interesting biomaterials. The preparation of a hyaluronic acid blend with other polymers and/or biopolymers is neither a closed nor a completed topic, as there are many polymers and biopolymers that can be studied as a component of such the blends. In regenerative medicine, there is still an increasing need for new materials for cell-based transplantation, tissue engineering, drug delivery, and gene therapy. There is also a need to design new wound dressing materials and hydrogels for cosmetic applications. New materials based on the blends of hyaluronic acid with collagen, chitosan as well as with other biopolymers may fulfill the gap between the demand for biomaterials for tissue regeneration and the supply. The potential of newly designed materials using biopolymer blends may be huge; nevertheless, the detailed biological study of any kind of such materials is required.

Author Contributions: Conceptualization, A.S.; data curation, A.S.; formal analysis, A.S.; funding acquisition, A.S.; investigation, A.S.; methodology, A.S.; resources, A.S.; supervision, A.S.; writing—original draft, A.S., M.G., K.M., J.P.; writing—review and editing, A.S., M.G., K.M., and J.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.
References

1. Schante, C.; Zuber, G.; Herlin, C.; Vandamme, T. Chemical modifications of hyaluronic acid for the synthesis of derivatives for a broad range of biomedical applications. *Carbohydr. Polym.* 2011, 85, 469–489. [CrossRef]

2. Vasvani, S.; Kulkarni, P.; Rawtani, D. Hyaluronic acid: A review on its biology, aspects of drug delivery, route of administrations and a special emphasis on its approved marketed products and recent clinical studies. *Int. J. Biol. Macromol.* 2020, 151, 1012–1029. [CrossRef]

3. Al-Sibani, M.; Al-Harrasi, A.; Neubert, R.H.H. Effect of hyaluronic acid initial concentration on cross-linking efficiency of hyaluronic acid-based hydrogels used in biomedical and cosmetic applications. *Pharmazie* 2017, 72, 81–86.

4. Luo, Y.; Kirker, K.R.; Prestwich, G.D. Cross-linked hyaluronic acid hydrogel films: New biomaterials for drug delivery. *J. Control. Release* 2008, 69, 169–184. [CrossRef]

5. Berko, S.; Maroda, M.; Bondar, M.; Eros, G.; Hartmann, P.; Szentner, K.; Szabo-Revesz, P.; Kemeny, L.; Borbely, J.; Csanyi, E. Advantages of cross-linked versus linear hyaluronic acid for semisolid skin delivery systems. *Eur. Polym. J.* 2013, 49, 2511–2517. [CrossRef]

6. Masters, K.S.; Shah, D.N.; Leinwand, L.A.; Anseth, K.S. Crosslinked hyaluronic acid scaffolds as a biologically active carrier for valvular interstitial cells. *Biomaterials* 2005, 26, 2517–2525. [CrossRef]

7. Kim, I.L.; Mauck, R.L.; Burdick, J.A. Hydrogel design for cartilage tissue engineering: A case study with hyaluronic acid. *Biomaterials* 2011, 32, 8771–8782. [CrossRef] [PubMed]

8. Bukhari, S.N.; Roswandi, N.L.; Waqas, M.; Habib, H.; Hussain, F.; Khan, S.; Sohail, M.; Ramli, N.A.; Thu, H.E.; Hussain, Z. Hyaluronic acid, a promising skin rejuvenating biomimic: A review of recent updates and pre-clinical and clinical investigations on cosmetic and nutricosmetic effects. *Int. J. Biol. Macromol.* 2018, 120, 1682–1695. [CrossRef] [PubMed]

9. Ievdokimova, N.I. Hyaluronic acid, receptor CD44, and their role in diabetic complications. *Ukr. Kyi Biokhimichnyi Zhurnal* 2008, 80, 5–44.

10. Papakonstantinou, E.; Roth, M.; Karakiulakis, G. Hyaluronic acid: A key molecule in skin aging. *Dermatoenocrinol* 2012, 4, 253–258. [CrossRef] [PubMed]

11. Narurkar, V.A.; Fabi, S.G.; Bucay, V.W.; Tedaldi, R.; Downie, J.B.; Zeichner, J.A.; Butterwick, K.; Taub, A.; Kadoya, K.; Makino, E.T.; et al. Rejuvenating hydrator: Restoring epidermal hyaluronic acid homeostasis with instant benefits. *J. Drugs Dermatol.* 2016, 15, 24–37.

12. Pavicic, T.; Gauglitz, G.G.; Lersch, P.; Schwach-Abdellauk, K.; Malle, B.; Korting, H.C.; Farwick, M. Efficacy of cream-based novel formulations of hyaluronic acid of different molecular weights in anti-wrinkle treatment. *J. Drugs Dermatol.* 2011, 10, 990–1000. [PubMed]

13. Brandt, F.; Bassichis, B.; Bassichis, M.; O’Connell, C.; Lin, X. Safety and effectiveness of small and large gel-particle hyaluronic acid in the correction of perioral wrinkles. *J. Drugs Dermatol.* 2011, 10, 982–987. [PubMed]

14. Rzany, B.; Cartier, H.; Kestemont, P.; Trevidic, P.; Sattler, G.; Kerrouche, N.; Dhuan, J.C.; Ma, M.Y. Full-face rejuvenation using a range of hyaluronic acid fillers: Efficacy, safety, and patient satisfaction over 6 months. *Dermatol. Surg.* 2012, 38, 1153–1161. [CrossRef]

15. Streit, M.; Brand, C.U.; Braathen, L.R. Soft tissue augmentation for treatment of wrinkles and scars of the face. *Ther. Umsch.* 1999, 56, 212–218. [CrossRef]

16. Sionkowska, A. The potential of polymers from natural sources as components of the blends for biomedical and cosmetic applications. *Pure Appl. Chem.* 2015, 87, 1075–1084. [CrossRef]

17. Xie, H.; Chen, X.; Shen, X.; He, Y.; Chen, W.; Luo, Q.; Ge, W.; Yuan, W.; Tang, X.; Hou, D.; et al. Preparation of chitosan-collagen-alginate composite dressing and its promoting effects on wound healing. *Int. J. Biol. Macromol.* 2018, 107, 93–104. [CrossRef]

18. Vieira, S.; Strymecka, P.; Stanaszek, L.; Silva-Correia, J.; Drela, K.; Fiedorowicz, M.; Malysz-Cymborska, L.; Rogujski, P.; Janowski, M.; Reis, R.L.; et al. Methacrylated gellan gum and hyaluronic acid hydrogel blends for image-guided neurointerventions. *J. Mat. Chem. B* 2020, 8, 5928–5937. [CrossRef]

19. Ronca, A.; D’Amora, U.; Raucci, M.G.; Lin, H.; Fan, Y.J.; Zhang, X.D.; Ambrosio, L. A Combined Approach of Double Network Hydrogel and Nanocomposites Based on Hyaluronic Acid and Poly (ethylene glycol) Diacrylate Blend. *Materials* 2018, 11, 2454. [CrossRef]
20. Pokorny, M.; Rassushin, V.; Wolf, L.; Velebný, V. Increased Production of Nanofibrous Materials by Electroblowing from Blends of Hyaluronic Acid and Polyethylene Oxide. *Polym. Eng. Sci.* 2016, 56, 932–938. [CrossRef]

21. Sionkowska, A.; Skrzyński, S.; Śmiechowski, K.; Kołodziejczak, A. The review of versatile application of collagen. *Polym. Adv. Technol.* 2017, 28, 4–9. [CrossRef]

22. Taguchi, T.; Tanaka, J. Swelling behavior of hyaluronic acid and type II collagen hydrogels prepared by using conventional crosslinking and subsequent additional polymer interactions. *J. Biomater. Sci. Polym. Ed.* 2002, 13, 43–52. [CrossRef] [PubMed]

23. Chung, E.J.; Jakus, A.E.; Shah, R.N. In situ forming collagen-hyaluronic acid membrane structures: Mechanism of self-assembly and applications in regenerative medicine. *Acta Biomater.* 2013, 9, 5153–5161. [CrossRef] [PubMed]

24. Taguchi, T.; Ikoma, T.; Tanaka, J. An improved method to prepare hyaluronic acid and type II collagen composite matrices. *J. Biomed. Mater. Res.* 2002, 61, 330–336. [CrossRef] [PubMed]

25. Park, S.N.; Lee, H.J.; Lee, K.H.; Suh, H. Biological characterization of EDC-crosslinked collagen-hyaluronic acid matrix in dermal tissue restoration. *Biomaterials* 2003, 24, 1631–1641. [CrossRef]

26. Lin, Y.K.; Liu, D.C. Studies of novel hyaluronic acid-collagen sponge materials composed of two different species of type I collagen. *J. Biomater. Appl.* 2007, 21, 265–281. [CrossRef]

27. Lee, S.J.; Kim, S.Y.; Lee, Y.M. Preparation of porous collagen/hyaluronic acid hybrid scaffolds for biomimetic functionalization through biochemical binding affinity. *J. Biomed. Mater. Res. B Appl. Biomater.* 2007, 82B, 506–518. [CrossRef]

28. Fujie, T.; Furutate, S.; Niwa, D.; Takeoka, S. A nano-fibrous assembly of collagen-hyaluronic acid for controlling cell-adhesive properties. *Soft Matter* 2010, 6, 4672–4676. [CrossRef]

29. Kim, H.J.; Kim, K.K.; Park, I.K.; Choi, B.S.; Kim, J.H.; Kim, M.S. Hybrid scaffolds composed of hyaluronic acid and collagen for cartilage regeneration. *Tissue Eng. Regen. Med.* 2012, 9, 57–62.

30. Liu, Y.; Fan, D. Novel hyaluronic acid-tyrosine/collagen-based injectable hydrogels as soft filler for tissue engineering. *Int. J. Biol. Macromol.* 2019, 141, 700–712. [CrossRef]

31. Ying, H.Y.; Zhou, J.; Wang, M.Y.; Su, D.D.; Ma, Q.Q.; Lv, G.Z.; Chen, J.H. In situ formed collagen-hyaluronic acid hydrogel as biomimetic dressing for promoting spontaneous wound healing. *Mater. Sci. Eng. C-Mater. Biol. Appl.* 2019, 101, 487–498. [CrossRef] [PubMed]

32. Zhang, J.J.; Ma, X.X.; Fan, D.D.; Zhu, C.H.; Deng, J.J.; Hui, J.F.; Ma, P. Synthesis and characterization of hyaluronic acid/human-like collagen hydrogels. *Mater. Sci. Eng. C-Mater. Biol. Appl.* 2014, 43, 547–554. [CrossRef] [PubMed]

33. Segura, T.; Chung, P.H.; Shea, L.D. DNA delivery from hyaluronic acid-collagen hydrogels via a substrate-mediated approach. *Biomaterials* 2005, 26, 1575–1584. [CrossRef] [PubMed]

34. Mineo, A.; Suzuki, R.; Kuroyanagi, Y. Development of an artificial dermis composed of hyaluronic acid and collagen. *J. Biomater. Sci. Polym. Ed.* 2013, 24, 726–740. [CrossRef]

35. Kondo, S.; Niiyama, H.; Yu, A.; Kuroyanagi, Y. Evaluation of a wound dressing composed of hyaluronic acid and collagen sponge containing epidermal growth factor in diabetic mice. *J. Biomater. Sci. Polym. Ed.* 2012, 23, 1729–1740. [CrossRef]

36. Kondo, S.; Kuroyanagi, Y. Development of a wound dressing composed of hyaluronic acid and collagen sponge with epidermal growth factor. *J. Biomater. Sci. Polym. Ed.* 2012, 23, 629–643. [CrossRef]

37. Yu, A.; Niiyama, H.; Kondo, S.; Yamamoto, A.; Suzuki, R.; Kuroyanagi, Y. Wound dressing composed of hyaluronic acid and collagen containing EGF or bFGF: Comparative culture study. *J. Biomater. Sci. Polym. Ed.* 2013, 24, 1015–1026. [CrossRef]

38. Kim, Z.H.; Lee, Y.; Kim, S.M.; Kim, H.; Yun, C.K.; Choi, Y.S. A composite dermal filler comprising cross-linked hyaluronic acid and human collagen for tissue reconstruction. *J. Microbiol. Biotechnol.* 2015, 25, 399–406. [CrossRef]

39. Kim, T.G.; Chung, H.J.; Park, T.G. Macroporous and nanofibrous hyaluronic acid/collagen hybrid scaffold fabricated by concurrent electrospinning and deposition/leaching of salt particles. *Acta Biomater.* 2008, 4, 1611–1619. [CrossRef]

40. Fischer, R.L.; McCoy, M.G.; Grant, S.A. Electrospinning collagen and hyaluronic acid nanofiber meshes. *J. Mater. Sci. Mater. Med.* 2012, 23, 1645–1654. [CrossRef]
41. Nazir, R. Collagen—hyaluronic acid based interpenetrating polymer networks as tissue engineered heart valve. *Mater. Sci. Technol.* **2016**, *32*, 871–882. [CrossRef]
42. Crini, G. Historical review on chitin and chitosan biopolymers. *Environ. Chem. Lett.* **2019**, *17*, 1623–1643. [CrossRef]
43. Lewandowska, K.; Sionkowska, A.; Grabska, S. Chitosan blends containing hyaluronic acid and collagen: Compatibility behaviour. *J. Mol. Liq.* **2015**, *212*, 879–884. [CrossRef]
44. Kayitmazer, A.B.; Koksal, A.F.; Iyilik, E.K. Complex coacervation of hyaluronic acid and chitosan: E properties. *Polym. Adv. Technol.* **2018**, *29*, 2919–2924. [CrossRef]
45. Lalevee, G.; Sudre, G.; Montembault, A.; Meadows, J.; Malaise, S.; Crepet, A.; David, L.; Delair, T. Polyelectrolyte complexes via desalting mixtures of hyaluronic acid and chitosan—Physicochemical study and structural analysis. *Carbohydr. Polym.* **2016**, *154*, 86–95. [CrossRef] [PubMed]
46. Kayitmazer, A.B.; Koksal, A.F.; Iyilik, E.K. Complex coacervation of hyaluronic acid and chitosan: Effects of pH, ionic strength, charge density, chain length and the charge ratio. *Soft Matter.* **2015**, *11*, 8605–8612. [CrossRef]
47. Monteiro do Nascimento, M.H.; Lombello, C.B. Hyaluronic acid and chitosan based hydrogels for cartilage tissue engineering. *Polim. Cienc. Tecnol.* **2016**, *26*, 360–370.
48. Park, H.; Choi, B.; Hu, J.L.; Lee, M. Injectable chitosan hyaluronic acid hydrogels for cartilage tissue engineering. *Acta Biomater.* **2013**, *9*, 4779–4786. [CrossRef]
49. Neethu, M.; Mohanan, P.V.; Sabareeswaran, A.; Prabha, N. Chitosan-hyaluronic acid hydrogel for cartilage repair. *Int. J. Biol. Macromol.* **2017**, *104*, 1936–1945.
50. Acar, O.K.; Kayitmazer, A.B.; Kose, G.T. Hyaluronic acid/chitosan coacervate-based scaffolds. *Biomacromolecules* **2018**, *19*, 1198–1211. [CrossRef]
51. Zhang, W.; Jin, X.; Li, H.; Zhang, R.R.; Wu, C.W. Injectable and body temperature sensitive hydrogels based on chitosan and hyaluronic acid for pH sensitive drug release. *Carbohydr. Polym.* **2018**, *186*, 82–90. [CrossRef] [PubMed]
52. Valverde, A.; Perez-Alvarez, L.; Ruiz-Rubio, L.; Olivenza, M.A.P.; Blanco, M.B.G.; Diaz-Fuentes, M.; Vilas-Vilela, J.L. Antibacterial hyaluronic acid/chitosan multilayers onto smooth and micropatterned titanium surfaces. *Carbohydr. Polym.* **2019**, *207*, 824–833. [CrossRef] [PubMed]
53. Viganì, B.; Rossi, S.; Sandri, G.; Bonferoni, M.C.; Caramella, C.M.; Ferrari, F. Hyaluronic acid and chitosan-based nanosystems: A new dressing generation for wound care. *Expert Opin. Drug Deliv.* **2019**, *16*, 715–740. [CrossRef] [PubMed]
54. Bazmandeh, A.Z.; Mirzaei, E.; Ghasemi, Y.; Kouhbanani, M.A.J. Hyaluronic acid coated electrospun chitosan-based nanofibers prepared by simultaneous stabilizing and coating. *Int. J. Biol. Macromol.* **2019**, *138*, 403–411. [CrossRef] [PubMed]
55. Sun, J.F.; Perry, S.L.; Schiffman, J.D. Electrospinning Nanofibers from Chitosan/Hyaluronic Acid Complex Coacervates. *Biomacromolecules* **2019**, *20*, 4191–4198. [CrossRef]
56. Lee, E.J.; Kang, E.; Kang, S.W.; Huh, K.M. Thermo-irreversible glycol chitosan/hyaluronic acid blend hydrogel for injectable tissue engineering. *Carbohydr. Polym.* **2020**, *244*, 116432. [CrossRef]
57. Engkagul, V.; Sereemaspun, A.; Chirachanchai, S. One pot preparation of chitosan/hyaluronic acid-based triple network hydrogel via in situ click reaction, metal coordination and polyion complexation in water. *Carbohydr. Polym.* **2018**, *200*, 616–623. [CrossRef]
58. Erickson, A.E.; Levengood, S.K.L.; Sun, J.L.; Chang, F.C.; Zhang, M.Q. Fabrication and Characterization of Chitosan—Hyaluronic Acid Scaffolds with Varying Stiffness for Glioblastoma Cell Culture. *Adv. Healthc. Mater.* **2018**, *7*, 1800295. [CrossRef]
59. Xu, H.T.; Ma, L.; Shi, H.F.; Gao, C.Y.; Han, C.M. Chitosan—hyaluronic acid hybrid film as a novel wound dressing: In vitro and in vivo studies. *Polym. Adv. Technol.* **2007**, *18*, 869–875. [CrossRef]
60. Iacob, A.T.; Dragan, M.; Ghetu, N.; Pieptu, D.; Vasile, C.; Buron, F.; Routier, S.; Giusca, S.E.; Caruntu, I.D.; Profire, L. Preparation, Characterization and Wound Healing Effects of New Membranes Based on Chitosan, Hyaluronic Acid and Arginine Derivatives. *Polymers* **2018**, *10*, 607. [CrossRef]
61. Mitura, S.; Sionkowska, A.; Jaiswal, A. Biopolymers for hydrogels in cosmetics: Review. *J. Mater. Sci. Mater. Med.* **2020**, *31*, 50. [CrossRef] [PubMed]
62. Lewandowska, K.; Sionkowska, A.; Grabska, S.; Kaczmarek, B.; Michalska, M. The miscibility of collagen/hyaluronic acid/chitosan blends investigated in dilute solutions and solids. J. Mol. Liq. 2016, 220, 726–730. [CrossRef]

63. Sionkowska, A.; Kaczmarek, B.; Markiewicz, E. L-ascorbic acid release from polymeric matrixes based on blends of chitosan, collagen and hyaluronic acid. Mol. Cryst. Liq. Cryst. 2016, 640, 46–53.

64. Sionkowska, A.; Lewandowska, K.; Grabska, S.; Kaczmarek, B.; Michalska, M. Physico-chemical properties of three-component mixtures based on chitosan, hyaluronic acid and collagen. Mol. Cryst. Liq. Cryst. 2016, 640, 21–29. [CrossRef]

65. Lewandowska, K.; Sionkowska, A.; Grabska, S.; Kaczmarek, B. Surface and thermal properties of collagen/hyaluronic acid blends containing chitosan. Int. J. Biol. Macromol. 2016, 92, 371–376. [CrossRef]

66. Sionkowska, A.; Kaczmarek, B.; Michalska, M.; Lewandowska, K.; Grabska, S. Preparation and characterization of collagen/chitosan/hyaluronic acid thin films for application in hair care cosmetics. Pure Appl. Chem. 2017, 89, 1829–1839. [CrossRef]

67. Sionkowska, A.; Michalska-Sionkowska, M.; Walczak, M. Preparation and characterization of collagen/hyaluronic acid/chitosan film crosslinked with dialdehyde starch. Int. J. Biol. Macromol. 2020, 149, 290–295. [CrossRef]

68. Sionkowska, A.; Kaczmarek, B.; Lewandowska, K.; Grabska, S.; Pokrywcznska, M.; Kloskowski, T.; Drewa, T. 3D composites based on the blends of chitosan and collagen with the addition of hyaluronic acid. Int. J. Biol. Macromol. 2016, 89, 442–448. [CrossRef]

69. Kaczmarek, B.; Sionkowska, A.; Kozłowska, J.; Osyczka, A. M. New composite materials prepared by calcium phosphate precipitation in chitosan/collagen/hyaluronic acid sponge cross-linked by EDC/NHS. Int. J. Biol. Macromol. 2018, 107, 247–253. [CrossRef]

70. Kaczmarek, B.; Sionkowska, A.; Osyczka, A. M. The application of chitosan/collagen/hyaluronic acid sponge cross-linked by dialdehyde starch addition as a matrix for calcium phosphate in situ precipitation. Int. J. Biol. Macromol. 2018, 107, 470–477. [CrossRef]

71. Sionkowska, A.; Kaczmarek, B. Preparation and characterization of composites based on the blends of collagen, chitosan and hyaluronic acid with nano-hydroxyapatite. Int. J. Biol. Macromol. 2017, 102, 658–666. [CrossRef] [PubMed]

72. Kaczmarek, B.; Sionkowska, A.; Osyczka, A. M. The comparison of physic-chemical properties of chitosan/collagen/hyaluronic acid composites with nano-hydroxyapatite cross-linked by dialdehyde starch and tannic acid. Polym. Test. 2017, 62, 171–176. [CrossRef]

73. Lewandowska-Lancucka, J.; Gilarska, A.; Bula, A.; Horak, W.; Latkiewicz, A.; Nowakowska, M. Genipin crosslinked bioactive collagen/chitosan/hyaluronic acid injectable hydrogels structurally amended via covalent attachment of surface-modified silica particles. Int. J. Biol. Macromol. 2019, 136, 1196–1208. [CrossRef] [PubMed]

74. Kaczmarek, B.; Sionkowska, A.; Gόlnyska, M.; Polkowska, I.; Szponder, T.; Nehrbass, D.; Osyczka, A. M. In vivo study on scaffolds based on chitosan, collagen, and hyaluronic acid with hydroxyapatite. Int. J. Biol. Macromol. 2018, 118, 938–944. [CrossRef] [PubMed]

75. Michalska-Sionkowska, M.; Kaczmarek, B.; Walczak, M.; Sionkowska, A. Antimicrobial activity of new materials based on the blends of collagen/chitosan/hyaluronic acid with gentamicin sulfate addition. Mater. Sci. Eng., C Mater. Biol. Appl. 2018, 86, 103–108. [CrossRef]

76. Hu, Y.; Wu, Y.; Cai, J.; Ma, S.; Wang, X. The procoagulant properties of hyaluronic acid-collagen (i)/chitosan complex film. J. Biomater. Sci. Polym. Ed. 2009, 20, 1111–1118. [CrossRef]

77. Wu, Y.; Hu, Y.; Cai, J.; Ma, S.; Wang, X. Coagulation property of hyaluronic acid –collagen/chitosan complex film. J. Mater. Sci. Mater. Med. 2008, 19, 3621–3629. [CrossRef]

78. Sionkowska, A.; Grabska, S. Incorporation of magnetite particles in 3D matrices made from the blends of collagen, chitosan, and hyaluronic acid. Adv. Polym. Technol. 2018, 37, 2905–2914. [CrossRef]

79. Highley, C. B.; Prestwich, G. D.; Burdick, J. A. Recent advances in hyaluronic acid hydrogels for biomedical applications. Curr. Opin. Biotechnol. 2016, 40, 35–40. [CrossRef]

80. Shaharudin, A.; Aziz, Z. Effectiveness of hyaluronic acid and its derivatives on chronic wounds: A systematic review. J. Wound Care 2016, 25, 585–592. [CrossRef]
81. Genasetti, A.; Vigetti, D.; Viola, M.; Karousou, E.; Moretto, P.; Rizzi, M.; Bartolini, B.; Clerici, M.; Pallotti, F.; De Luca, G.; et al. Hyaluronic and human endothelial cell behaviour. *Connect. Tissue Res.* **2008**, *49*, 120–123. [CrossRef] [PubMed]

82. Miyake, S.; Chomoucka, J.; Drbohlavova, J.; Huska, D.; Adam, V.; Kizek, R.; Hubalek, J. Magnetic nanoparticles and hyaluronic acid. *Adv. Drug Deliv. Rev.* **2020**, *162*, 257–275. [CrossRef] [PubMed]

83. Jayakumar, R.; Kuttan, G.; Kuttan, R. Improvement of mechanical properties and biostability of biodegradable nanocomposites. *Mater. Sci. C Mater. Eng. C* **2020**, *141*, 116107. [CrossRef] [PubMed]

84. Yang, S.; Zhu, B.; Yin, P.; Zhao, L.; Wang, Y.; Fu, Z.; Dang, R.; Xu, J.; Zhang, J.; Wu, N. Integration of Human Umbilical Cord Mesenchymal Stem Cells-Derived Exosomes with Hydroxyapatite-Embedded Hyaluronic Acid-Alginate Hydrogel for Bone Regeneration. *ACS Biomater. Sci. Eng.* **2020**, *6*, 1590–1602. [CrossRef]

85. Makvandi, P.; Ali, G.W.; Della Sala, F.; Abdel-Fattah, W.I.; Borzacchiello, A. Hyaluronic Acid-Based Theranostic Sci-fi Scaffolds for Brain Tissue Engineering. *Acta Biomater.* **2020**, *96*, 1–11. [CrossRef] [PubMed]

86. Ghorbani, F.; Zamanian, A.; Behnamghader, A.; Joupari, M.D. Bioactive and biostable hyaluronic acid/nanofibrillar collagen based injectable nanocomposite: A biomimetic antibacterial scaffold for bone tissue regeneration. *Mater. Sci. C Mater. Eng. C* **2020**, *140*, 110195. [CrossRef]

87. Chomoucka, J.; Drbohlavova, J.; Huska, D.; Adam, V.; Kizek, R.; Hubalek, J. Magnetic nanoparticles and targeted drug delivering. *Pharm. Res.* **2010**, *27*, 144–149. [CrossRef]

88. Ito, A.; Shinkai, M.; Honda, H.; Kobayashi, T. Medicinal application of functionalized magnetic nanoparticles. *J. Biosci. Bioeng.* **2005**, *99*, 1–11. [CrossRef] [PubMed]

89. Dias, A.M.; Hussain, A.; Marcelo, R.; Rouque, A.C. An iron oxide magnetic colloids modified with polysaccharides. *Int. J. Mol. Sci.* **2011**, *12*, 272–293. [CrossRef] [PubMed]

90. Jayakumar, R.; Chennazhi, K.P.; Srinivasan, S.; Nair, S.V.; Furuike, T.; Tamura, H. Hyaluronic acid microbeads from orodispersible hyaluronic acid film by carboxymethyl cellulose addition. *Food Sci. Biotechnol.* **2020**, *29*, 142–155. [CrossRef]

91. Chomoucka, J.; Drbohlavova, J.; Huska, D.; Adam, V.; Kizek, R.; Hubalek, J. Magnetic nanoparticles and targeted drug delivering. *Pharm. Res.* **2010**, *27*, 144–149. [CrossRef]

92. Jayakumar, R.; Kuttan, G.; Kuttan, R. Improvement of mechanical properties and biostability of biodegradable nanocomposites. *Mater. Sci. C Mater. Eng. C* **2020**, *141*, 116107. [CrossRef] [PubMed]

93. Chomoucka, J.; Drbohlavova, J.; Huska, D.; Adam, V.; Kizek, R.; Hubalek, J. Magnetic nanoparticles and targeted drug delivering. *Pharm. Res.* **2010**, *27*, 144–149. [CrossRef] [PubMed]

94. Ito, A.; Shinkai, M.; Honda, H.; Kobayashi, T. Medicinal application of functionalized magnetic nanoparticles. *J. Biosci. Bioeng.* **2005**, *99*, 1–11. [CrossRef] [PubMed]

95. Dias, A.M.; Hussain, A.; Marcelo, R.; Rouque, A.C. An iron oxide magnetic colloids modified with polysaccharides. *Int. J. Mol. Sci.* **2011**, *12*, 272–293. [CrossRef] [PubMed]

96. Jayakumar, R.; Chennazhi, K.P.; Srinivasan, S.; Nair, S.V.; Furuike, T.; Tamura, H. Hyaluronic acid microbeads from orodispersible hyaluronic acid film by carboxymethyl cellulose addition. *Food Sci. Biotechnol.* **2020**, *29*, 142–155. [CrossRef]

97. Chomoucka, J.; Drbohlavova, J.; Huska, D.; Adam, V.; Kizek, R.; Hubalek, J. Magnetic nanoparticles and targeted drug delivering. *Pharm. Res.* **2010**, *27*, 144–149. [CrossRef] [PubMed]

98. Ito, A.; Shinkai, M.; Honda, H.; Kobayashi, T. Medicinal application of functionalized magnetic nanoparticles. *J. Biosci. Bioeng.* **2005**, *99*, 1–11. [CrossRef] [PubMed]

99. Dias, A.M.; Hussain, A.; Marcelo, R.; Rouque, A.C. An iron oxide magnetic colloids modified with polysaccharides. *Int. J. Mol. Sci.* **2011**, *12*, 272–293. [CrossRef] [PubMed]
101. Antich, C.; de Vicente, J.; Jimenez, G.; Chocarro, C.; Carrillo, E.; Montanez, E.; Galvez-Martin, P.; Marchal, J.A. Bio-inspired hydrogel composed of hyaluronic acid and alginate as a potential bioink for 3D bioprinting of articular cartilage engineering constructs. *ACTA Biomater.* 2020, 106, 114–123. [CrossRef] [PubMed]

102. Phuong, L.T.; Son, J.Y.; Lee, Y.; Ryu, S.B.; Park, K.M.; Park, K.D. Enzymatically Crosslinkable Hyaluronic Acid-Gelatin Hybrid Hydrogels as Potential Bioinks for Tissue Regeneration. *Macromol. Res.* 2020, 28, 400–406.

103. Andrysiak, T.; Beldowski, P.; Siódmiak, J.; Weber, P.; Ledzinski, D. Hyaluronan-chondroitin sulfate anomalous crosslinking due to temperature changes. *Polymers* 2018, 10, 560. [CrossRef] [PubMed]

104. Dédainaitė, A.; Wieland, D.C.F.; Beldowski, P.; Claesson, P.M. Biolubrication synergy: Hyaluronan–Phospholipid interactions at interfaces. *Adv. Coll. Interf. Sci.* 2019, 274, 102050. [CrossRef]

© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).