

Natural biological macromolecules for designing hydrogels as health care and antiaging solutions [†]

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Abstract: Recent advances in the development of strategies for chemical adaptation of biomacromolecules, such as polysaccharides, proteins and lipids, have allowed the design of functional hydrogels suitable for the current requirements in the biomedical and health care fields. Hydrogels are three-dimensional hydrophilic materials that have the ability to absorb and retain a large volume of water and are produced from a lower fraction of precursor macromolecules. They can be made from both natural and synthetic materials and can have different degrees of stiffness and elasticity, depending on the projected application. Hydrogels are biocompatible, and therefore can be safely used in various applications, including contact lenses, dressings, medical devices and tissue engineering scaffolds. Also, they are effective targeted delivery systems for various drugs (antibiotics, analgesics, chemotherapeutics). Due to the protection effect regarding high temperatures, acidic environments and enzymatic degradation provided for a wide range of unstable macromolecules, including peptides and proteins, the hydrogels can be considered as promising delivery vehicles. Hydrogels can be designed as adaptable natural extracellular matrices, with different degrees of rigidity and porosity. They can be functionalized with a wide variety of bioactive molecules, such as growth factors, proteins and peptides, very useful in tissue engineering applications, including cartilage and bone regeneration, neural tissue engineering and wound healing. As antiaging therapy systems, they can be combined with plant extracts or can include a multitude of bioactive compounds, such as collagen, hyaluronic acid, vitamins, enzymes, amino acids or probiotics. The versatility and unique properties of bio-hydrogels are challenging and determine their study and application in many fields, such as health care and antiaging solutions. The aim of this research is to give an insight about the current status of polysaccharide-based hydrogels for applications in biomedical domain. This will highlight new strategies to develop novel bio-materials which might help in improving the human health.

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1. Introduction

Aging is a natural and irreversible evolution due to a gradual degradation of physiological and biological functions that occurs with the advancing age of a person. On the biological level, there is a molecular and cellular degeneration due to both internal and external factors and which manifests itself by diminishing physical and mental capacity, as well as by increasing the risk of some diseases. Antiaging focuses on health care solutions that can prevent, delay or reverse the aging process with the goal of extending life span while maintaining physical beauty, physical body and mental functionality, for an active life [1]. To this end, to improve the health and longevity of the global population, food and health policies have been elaborated and some therapies have been developed against degenerative aging processes and for the prevention of major diseases associated with aging. Many natural antiaging products and different administration systems of

bioactive compounds have been proposed to combat harmful processes such as oxidative stress, hormonal deficiencies or inflammation [2]. Among them, hydrogels are interesting and potential materials as effective platforms for the delivery of antiaging agents.

Biomaterials based on hydrogels are cross-linked networks with 3D architectures, which contain a small fraction of precursor organic macromolecules and can absorb large amounts of water or other fluids, due to some hydrophilic components in their structure (such as amino groups, carboxyl, hydroxyl or ethers) [3].

Hydrogels can be obtained both from natural polymeric materials and from synthetic polymeric materials or from a combination of them [4]. They can have different degrees of rigidity and elasticity, depending on the designed application. Hydrogels can be synthesized by physical, chemical or both polymer crosslinking methods (Figure 1) [5], at the same time, by simple mixing, solution casting, free radical polymerization, bulk polymerization, gamma and UV irradiation, or using the interpenetrating network formation route [6-9].

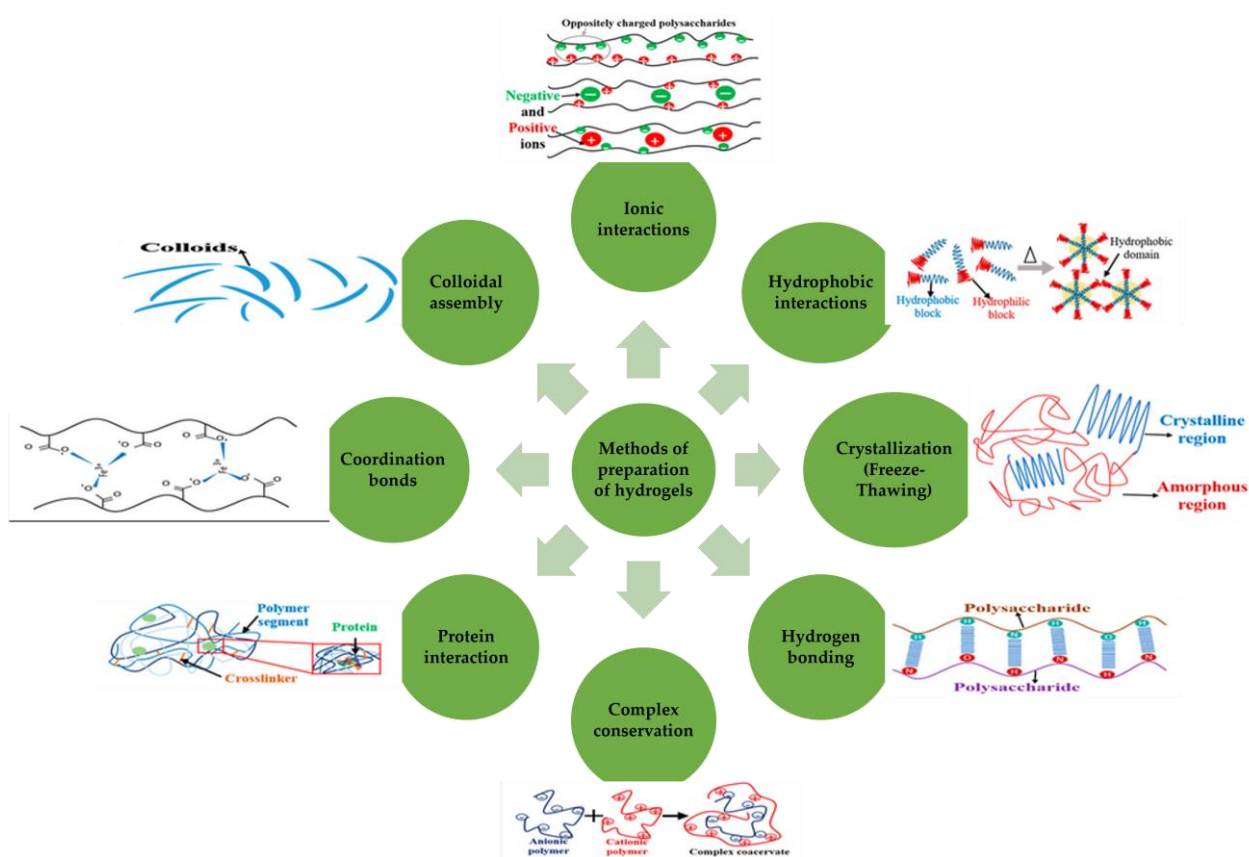


Figure 1. The methodologies employed for synthesizing the hydrogels [5].

Hydrogels can be classified based on their surface charge as (i) ionic (anionic or cationic), (ii) amphoteric (containing both acidic and basic groups), (iii) zwitterionic (containing anionic and cationic groups), or (iv) neutral [10].

Natural hydrogels contain polymers from natural sources and have a high potential to be used in numerous biomedical and health care applications, due to their superior biological properties compared to synthetic polymers. Among the characteristics of natural hydrogels, some can be highlighted such as: non-toxicity, biocompatibility, biodegradability, good mechanical properties, porosity, elasticity, and ease of production at low prices, with huge possibilities to be customized and functionalized to be implemented as solutions for different requirements. Hydrogels can be effective delivery systems for phytochemicals contained in various extracts, for potential applications in dermatology and cosmetology. For example, hydrogels loaded with *Cornus mas L.* plant extracts showed

strong antioxidant properties as well as a beneficial effect on skin cell viability *in vitro*. In addition, they increased skin hydration and prevented transepidermal water loss [11]. Hydrogels can be used as materials to fill the tissue space created by disease, accident or wrinkles and produce therapeutic effects with minimal invasion. Hydrogels are injected into tissues with the aim of carrying drugs, biological macromolecules and cells to reconstruct or regenerate damaged tissues [12].

Depending on the chemical structure, natural polymers can be classified into: (i) polysaccharides (chitin, chitosan, alginate, cellulose, polysaccharide gums, carrageenan, starch), (ii) proteins (collagen, gelatin, fibrin, gelatin, silk, keratin), (iii) polynucleotides (DNA, RNA), (iv) polyphenols (lignin), and (v) glycosaminoglycans (hyaluronic acid, heparin, heparan sulfate, chondroitin sulfate A and B) [13]. Due to their natural origin, hydrogels synthesized from natural polymers, and especially from polysaccharides and proteins, are comparable to the extracellular matrix and are biocompatible. In order to improve the mechanical properties of hydrogels (mechanical strength and flexibility), the crosslinking of natural polymers is used by grafting with monomers or mixing with different synthetic polymers.

Advanced materials based on natural hydrogels with a high-water absorption capacity and good mechanical properties can be prepared by a composite design strategy that mainly employs natural (and less synthetic) polymers with physicochemical properties established in advance, such as biological activities, biodegradability, solubility, crystallinity, surface and textural properties [14]. The design strategy can be raised to the next level by functionalizing bio-hydrogels with various bioactive compounds, including unstable macromolecules such as peptides and proteins or with different growth factors particularly effective in antiaging or tissue engineering applications [15,16]. A new generation of biomaterials is represented by natural super-porous hydrogels, which allow water to enter in the 3D network of material and with-it different bio actives for example proteins, peptides, can generate intelligent bio-hydrogels that respond to external stimuli, such as pH, temperature or the presence of specific molecules, with applications in biomedicine [17].

The versatility and unique properties of bio-hydrogels are challenging and determine their study and application as antiaging solutions or in areas such as health care. The aim of this research is to provide insight into the current status of macromolecules-based hydrogels for multiple biomedical applications (Figure 2). This will highlight new strategies for the development of new biomaterials that could help improve human health, quality of life or in antiaging therapies.

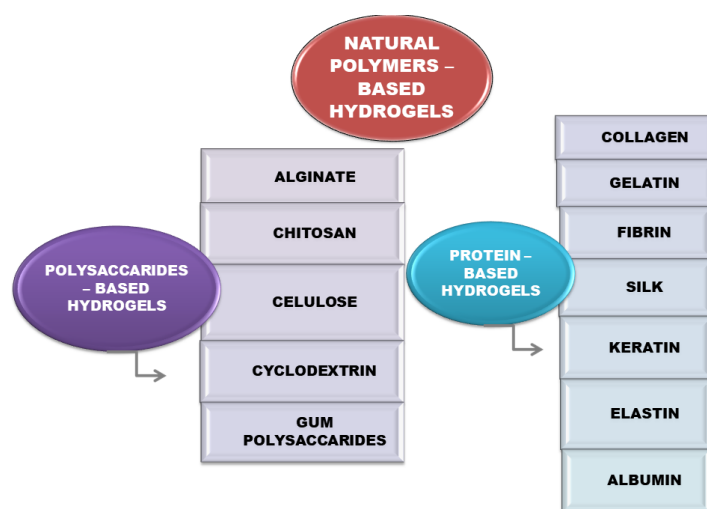


Figure 2. Classification of natural polymers-based hydrogels.

2. Polysaccharide-based hydrogels

In nature, there is a huge diversity of polysaccharides with different types of glycosidic bonds, which determine unique physical and chemical properties that result in extraordinary functional versatility. Polysaccharide-based hydrogels can be successfully used as therapeutic biomacromolecule delivery platforms in a wide range of fields, including as health care and antiaging solutions.

2.1. Alginate

Alginate is currently extracted from brown algae such as *Laminaria hyperborean* and *Lessonia* and contains homopolymer blocks of β -D-mannuronic acid and α -L-guluronic acid and free functional hydroxyl and carboxyl groups. It has a very low solubility in water, and forms a viscous aqueous solution in the presence of monovalent cations such as sodium and potassium. Alginate with high molecular weight forms very viscous solutions, but for antiaging applications, the one with low molecular weight is mainly used, to be able to form hydrogels that include proteins or cells [18].

2.2. Chitosan

Chitosan is obtained by deacetylation of chitin (extracted from the endoskeletons of marine crustaceans), the second most abundant biopolymer in the natural environment after cellulose. It has unique biological attributes such as biocompatibility, non-toxicity, biodegradability, bioadhesiveness, antimicrobial and antifungal activity, remarkable affinity for proteins, antitumor and hemostatic activity. Insoluble in water, but soluble in weak acids, chitosan forms hydrogels by itself or in combination with other compounds [19]. Chitosan-based hydrogels can be used in cosmetics as hair products in the form of films, having hair fixing properties, as shampoos, conditioners, rinse agents, in hair dyes, as humectants to increase the water content in the upper layers of the skin in moisturizing cosmetic products, or as biofilms in oral care products.

2.3. Cellulose

Cellulose is the most abundant biopolymer found and comes from green and renewable resources in nature. Its derivative, the one often used in multiple applications, carboxymethyl cellulose, is a biocompatible, biodegradable, non-toxic and cheap polymer. It is used as a base, together with other natural ingredients, in obtaining products for the protection and care of the skin and protection. Bio hydrogels based on carboxymethyl cellulose used as skin masks, for example, contain various natural extracts rich in phenolic compounds and flavonoids with antioxidant activity, cytocompatibility and excellent broad-spectrum antimicrobial activity [20].

2.4. Gum polysaccharides

Recent advances in the development of composite bio-hydrogels based on natural polymers have led to the reconsideration of the potential of acacia gum, guar gum, xanthan gum, and tragacanth gum, to design effective materials through ecological approaches for use in natural platforms as effective delivery systems of pharmacologic agents for health care applications, cosmetics and antiaging [21-23].

The excellent biocompatibility of natural polysaccharides led to obtaining biohydrogels as viable alternatives to synthetic materials and their use in numerous biomedical applications. Thus, hydrogels have been developed as wound dressings for the treatment of chronic and infected wounds, as scaffolds for tissue engineering, or as drug delivery systems [24,25].

3. Protein-based hydrogels

Hydrogels based on protein are biocompatible and biodegradable and easy to synthesize. In addition, they have many advantages over those based on other polymers,

because they can incorporate unnatural amino acids, obtaining protein/nonprotein hybrids. In this way, the characteristics of hydrogels can be easily adjusted by changing the sequence of amino acids, for multiple applications such as antiaging, cosmetics, drug delivery systems, tissue engineering and regenerative medicine [26].

3.1. Collagen

Collagen is the most abundant of the extracellular matrix protein found in mammals. Collagen-based biomaterials have great potential for cosmetic and antiaging applications, due to their abundance, possible biodegradability, advantageous biocompatibility, low immune response, and good absorption. However, it also has some disadvantages, such as poor mechanical strength, low elasticity, poor dimensional and thermal stability. Therefore, to overcome the limitations, different crosslinking methods with other substances are used [27].

3.2. Gelatin

Gelatin is made from collagen, including by converting waste products such as cartilage, bone and skin. It is biodegradable, non-toxic, cheap and can be easily combined with other substances, obtaining sustainable materials. Gelatin-based hydrogels are often used in various innovative applications, such as bone reconstruction or targeted drug delivery [28,29].

3.3. Fibrin-based hydrogels

Fibrin is an important blood component responsible for hemostasis. Fibrin-based hydrogels are widely used in various applications such as tissue engineering, as a biological scaffold for stem or primary cells in the design of various tissues and regenerative medicine. Due to their tunable mechanical properties and nanofibrous structural properties, these hydrogels can be used for potential pancreas tissue engineering and musculoskeletal applications [30].

3.4. Silk

Silk protein is an extremely fascinating natural material, used extensively in the biomedical domain due to its biocompatibility, immunogenicity, slow degradation rate, non-nontoxicity and elastic properties. Hydrogels-based natural silk proteins have been widely investigated [31]. Silk protein have proved to exhibit cell adhesion and proliferation of the skin, being broadly used for chronic wound healing [32].

3.5. Keratin

Keratin is a durable fibrous protein being a structural component of hair, feathers, nails, horns, hooves and claws. Hydrogel-based keratin have been broadly studied for their possible applications in biomedical engineering and regenerative medicine (drug delivery, regeneration, hemostasis, and cell culture [33].

3.6. Elastin

Elastin-like polypeptides (ELPs) are natural proteins that have been extensively studied for biomedical applications. ELPs have been revealed to be biocompatible and non-immunogenic with potential use for drug delivery and tissue engineering [34].

3.7. Albumin

Hydrogels prepared using albumin as the elementary component have outstanding properties, such as biocompatibility, biodegradability, non-immunogenicity, and good mechanical properties. Albumin can bind to many active biomolecules such as fatty acids, vitamins, drugs, hormones, and ions in cells or tissues. For this reason, albumin-based

hydrogels can be used as a drug carrier or therapeutic molecule and as a scaffold for tissue engineering [35].

In summary, the main properties of natural biological macromolecules for designing hydrogels used in biomedical fields and their applications are represented in Figure 3.

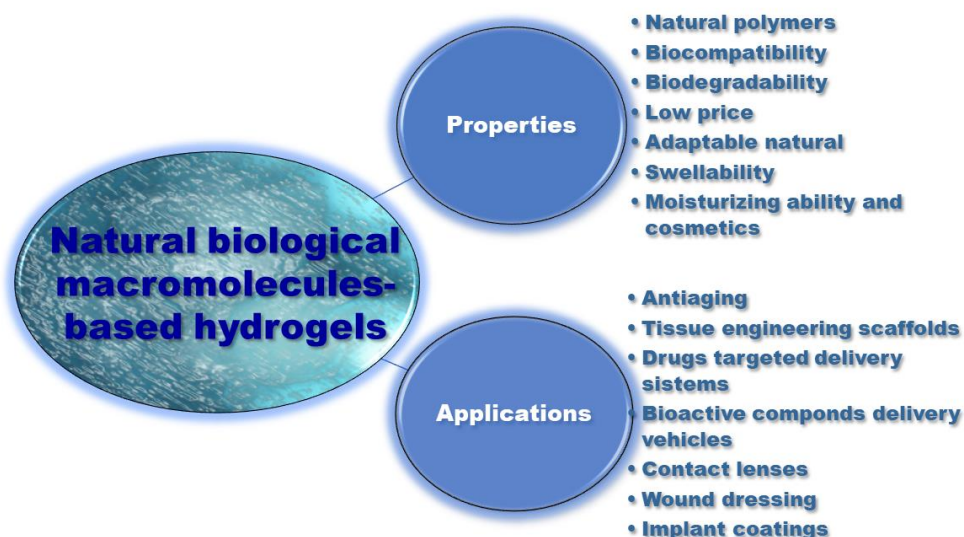


Figure 3. Properties and applications of natural biological macromolecules-based hydrogels.

4. Future Perspectives

The use of natural hydrogels has gained further attention in the last years due to the advances in their eco-friendly synthesis, modification, characterization and their potential applications in numerous fields. Nevertheless, there are still some challenges to overcome, such as the improvement in the adsorption/absorption ability, water retention capacity and mechanical properties. Emerging cost-effective and scalable manufacture approaches is a key for commercialization and extensive usage.

Still, when comparing the outcomes and the current knowledge regarding the use of hydrogels in cosmetics and antiaging therapies, the existing small number of publications constitute a main problem. Future perspectives of applications of hydrogels in cosmetics and antiaging therapies can be comparable to those used for biomedical fields.

Lately, a significant attention has been drawn to the 'smart hydrogels' which have the capability to exhibit dramatic changes as a response to variations in the surrounding. In cosmetics for skin or hair treatment some physical, chemical or biochemical stimuli can be used for the stimuli-sensitive hydrogels applications.

5. Conclusions

Plentiful hydrogel assemblies have been synthesized and characterized for health care and cosmetic applications. In particular, the noteworthy features of the hydrogel networks for applications in cosmetics and antiaging comprise an excellent swelling ability and a good mechanical strength. Biodegradability also constitutes an advantage of these materials. The incorporation or encapsulation of active ingredients into the hydrogel structure can lead to novel cosmetic products progress. The future development of biopolymers by modification and/or blending of two or even more biopolymers can result in new hydrogels development for cosmetic applications. Biopolymer-based hydrogels are used for the development of new cosmetic products, to be exploited as "beauty masks". They have a huge market, being highly sought after and used products recently.

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