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Proceeding Paper

Natural Biological Macromolecules for Designing Hydrogels as Health Care and Anti-aging 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 for 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 using 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 such as antibiotics, analgesics, and chemotherapeutics. Due to the protection effect with regards to high temperatures, acidic environments and enzymatic degradation which affect 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, and they are very useful in tissue engineering applications, including cartilage and bone regeneration, neural tissue engineering, and wound healing. As anti-aging 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 anti-aging solutions. The aim of this research is to provide an insight regarding the current status of polysaccharide-based hydrogels for applications in the biomedical domain. This will highlight new strategies to develop novel biomaterials which might help in improving human health.

Keywords: macromolecules; hydrogels; health care; anti-aging

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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 molecular and cellular degeneration due to both internal and external factors which manifests as diminishing physical and mental capacity, as well as increased risk of some diseases. Anti-aging 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 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 anti-aging products and different administration systems of bioactive compounds have been proposed to combat harmful processes such as oxidative stress, hormonal deficiencies, and inflammation [2]. Among them, hydrogels are interesting and potential materials as effective platforms for the delivery of anti-aging 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 hydrophilic components in their structure (such as amino groups, carboxyl, hydroxyl, or ethers) [3].

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

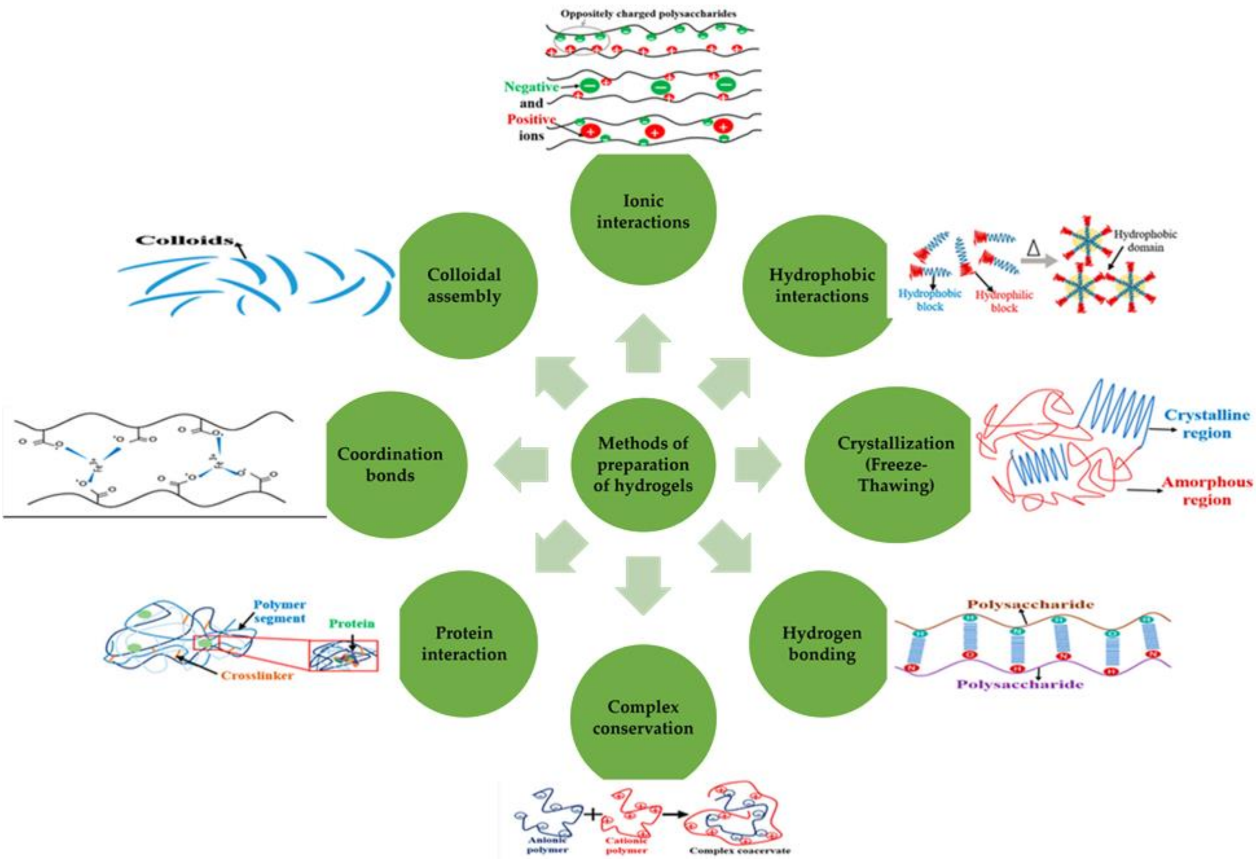

Figure 1. The methodologies employed for synthesizing hydrogels [5].

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 highlights are: 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 using 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 through functionalizing bio-hydrogels with various bioactive compounds, including unstable macromolecules such as peptides and proteins or with different growth factors particularly effective in anti-aging 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 bioactivities, for example proteins and 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 anti-aging solutions or in areas such as health care. The aim of this research is to provide insight into the current status of macromolecule-based hydrogels for multiple biomedical applications (Figure 2). This will highlight new strategies for the development of new biomaterials which could help improve human health, quality of life, or in anti-aging therapies.

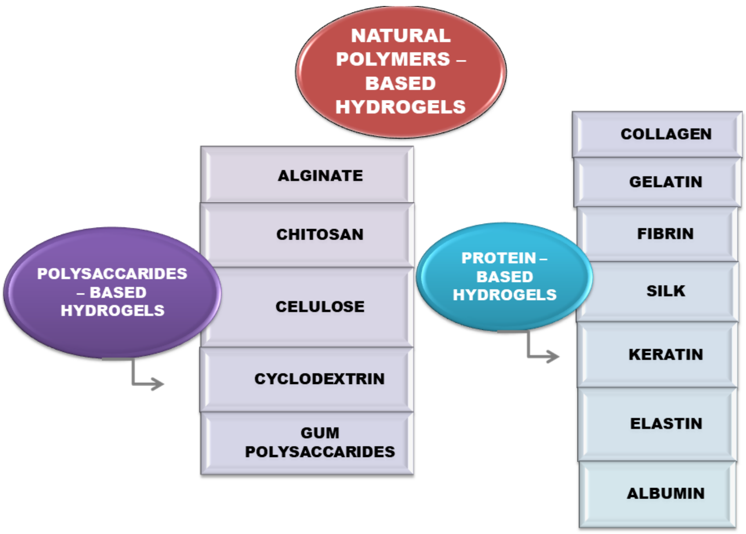

Figure 2. Classification of natural polymer-based hydrogels.

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 anti-aging 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 anti-aging applications, a 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 alone or in combination with other compounds [19]. Chitosan-based hydrogels can be used in cosmetics as hair products such as shampoos, conditioners, rinse agents, and hair dyes in the form of films which have hair fixing properties, 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. The derivative 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, to obtain products for the protection and care of the skin. 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 applications in health care, cosmetics, and anti-aging [21–23].

The excellent biocompatibility of natural polysaccharides led to obtaining bio-hydrogels as viable alternatives to synthetic materials and their use in numerous biomedical applications. Thus, these 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/non-protein hybrids. The characteristics of hydrogels can be easily adjusted through changing the sequence of amino acids for multiple applications such as anti-aging, cosmetics, drug delivery systems, tissue engineering, and regenerative medicine [26].

3.1. Collagen

Collagen is the most abundant of the extracellular matrix proteins found in mammals. Collagen-based biomaterials have great potential for cosmetic and anti-aging 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 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

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-toxicity, and elastic properties. Silk protein-based hydrogels have been widely investigated [31]. Silk proteins have been shown to exhibit cell adhesion and proliferation in skin, and is broadly used for chronic wound healing [32].

3.5. Keratin

Keratin is a durable fibrous protein which is a structural component of hair, feathers, nails, horns, hooves, and claws. Keratin-based hydrogels have been broadly studied for possible applications in biomedical engineering and regenerative medicine, including 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 in 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 carrier of drugs or therapeutic molecules, 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.

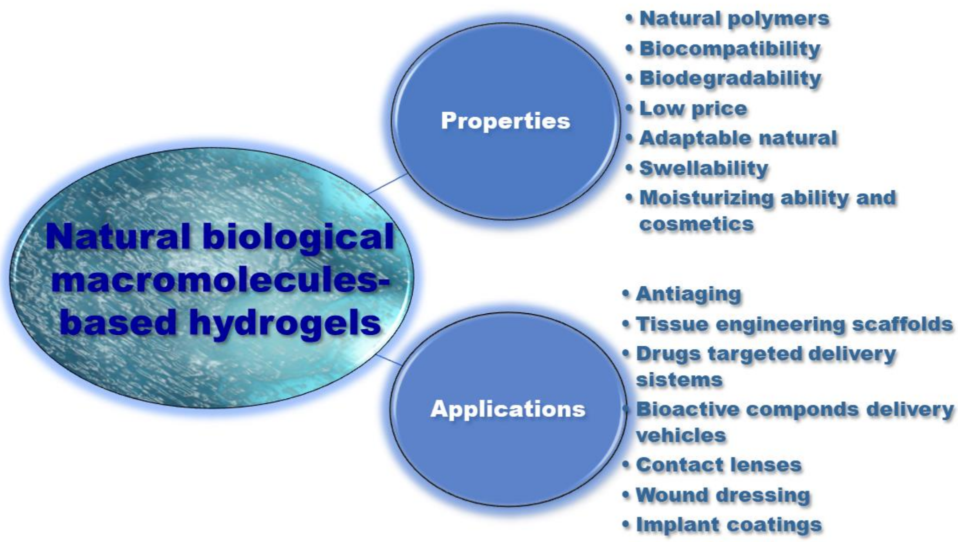

Figure 3. Properties and applications of natural biological macromolecule-based hydrogels.

4. Future Perspectives

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

Still, when comparing the outcomes and the current knowledge regarding the use of hydrogels in cosmetics and anti-aging therapies, the existing small number of publications constitutes a significant problem. Future perspectives of applications of hydrogels in cosmetics and anti-aging therapies can be comparable to those used in biomedical fields.

Lately, significant attention has been given to 'smart hydrogels' which have the capability to exhibit dramatic changes as a response to variations in the surrounding tissue. In cosmetics, for skin or hair treatment, some physical, chemical, or biochemical stimuli can be used for 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 anti-aging 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. The future development of biopolymers using modifications and/or blending of two or more biopolymers could result in new hydrogel development for cosmetic applications. Biopolymer-based hydrogels are used for the development of new cosmetic products to be exploited as "beauty masks". These hydrogels have a huge market, being highly sought after, and have been used in products recently.

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