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From Nature to Novelty: A Critical Review of Gum-Based Bio-Functional Materials

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Abstract
This comprehensive review and critical analysis explore the expanding role of natural gums in the field of biomaterials, highlighting their biocompatibility, biodegradability, and functional versatility for extensive modification. Emphasizing recent advances, this paper examines novel fabrication technologies that have significantly enhanced the performance of gum-based bio-functional materials, with a focus on their applications in tissue engineering, drug delivery, and beyond. Through a detailed evaluation of current research, this review provides a thorough overview of innovative synthesis and processing methods, while offering a critical assessment of their potential benefits and limitations for future development.

Key words: biomaterials – biomedical applications – natural gums – scaffolds – tissue engineering

1 Introduction

In the realm of biomaterials, gum-based materials have emerged as a versatile and promising class of compounds for various applications [1,2], particularly in the fields of drug delivery [3,4,5], tissue engineering [6,7,8,9], and regenerative medicine [10,11]. Other applications not strictly related to the human body include water purification [12] and the creation of coatings [13].

Gum-based materials are a heterogeneous group of polysaccharides that can be classified based on their source and chemical structure. Each type of gum exhibits distinct physicochemical properties, which can be further tailored through chemical modifications to suit specific applications.

- Tragacanth gum is a natural polysaccharide (Figure 1) derived from *Astragalus* plants, commonly found in India, Turkey, and Iran.
  It is available in two main forms: flakes and ribbons, with ribbons providing higher viscosity. This gum is valued for its thickening, emulsifying, and stabilizing properties, and is widely used in food, pharmaceuticals, and cosmetics.
  It is odorless, tasteless, and considered safe, as it is non-mutagenic, non-allergenic, and non-carcinogenic. Its composition, primarily made of galacturonic acid with side chains of sugars like xylose and fucose, can vary depending on the plant's origin, environment, and growing conditions [1].

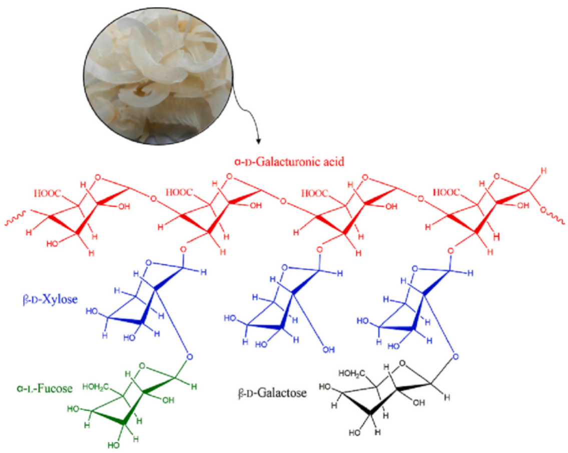

Figure 1: Chemical structure of tragacanth gum. [1]

- Xanthan Gum is a high molecular weight polysaccharide produced by the fermentation of *Xanthomonas* bacteria [7]. It is valued for its unique rheological properties, such as high viscosity at low concentrations and pseudoplastic behavior [7]. These characteristics make it a versatile ingredient in pharmaceutical applications, including drug delivery systems and tissue engineering. Xanthan gum has been found to be biocompatible and has been utilized to improve the mechanical strength and thermal stability of biomaterials.
- Gellan Gum is a linear polysaccharide (Figure 2) produced by the microbial fermentation[1] of *Sphingomonas elodea* (formerly *Pseudomonas elodea*). It has properties similar

[1] Microbial fermentation is a metabolic process where microorganisms, like bacteria or yeast, convert sugars into energy, often producing byproducts such as acids, gases, or alcohol.

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to the Natural Extracellular Matrix (ECM)[2], making it a promising material for tissue engineering. Gellan gum forms strong, flexible gels with excellent biocompatibility, low cytotoxicity[3] and biodegradability [6,14].

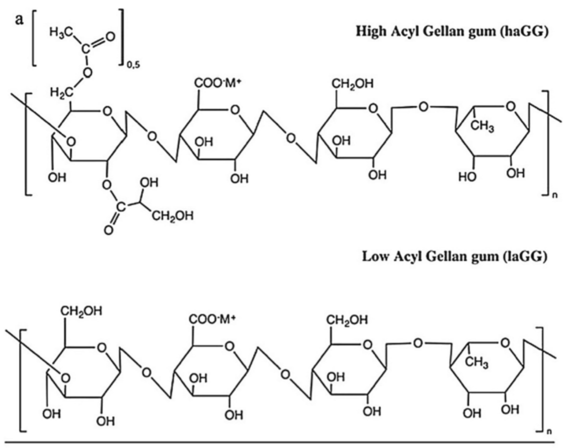

Figure 2: Chemical structure of high acyl gellan gum (ha GG) and low acyl gellan gum (la GG). [6]

- Cashew Gum (from the exudate of the *Anacardium occidentale L.* plant) [15] is a polysaccharide exudate that has gained attention for its biocompatibility and biodegradability. It has been explored for use in biomedical applications, including as a supportive material for enhancing or replacing damaged tissues (Figure 3).

Figure 3: Representative visual aspect of cashew gum before (left) and after (right) purification by dissolution in water followed by precipitation with ethanol, centrifugation, filtration, and milling. [15]

- Guar Gum, derived from the seeds of *Cyamopsis tetragonolobus* [16], is a non-ionic polysaccharide with numerous biomedical applications. It is appreciated for its stability across a broad pH range, low cost, non-toxicity, and hydrophilicity [4]. Guar gum has been used in the formulation of matrix tablets for oral drug delivery, hydrogels, microspheres, and nanoparticles for targeted drug delivery, as well as in transdermal and ocular drug delivery systems [8].
- Locust Bean Gum (also known as Carob Gum) is a natural galactomannan[4] extracted from the seeds of the carob tree [13,17]. It is used as a thickening, gelling, and stabilizing agent in food and pharmaceutical industries. In drug delivery, locust bean gum has been explored for its ability to control drug release and as a component in the formulation of sustained-release matrices.

General properties and characteristics of gum-based materials include their biocompatibility [18,19], biodegradability [4,20], non-toxicity, and ability to form hydrogels [1,7,14,16,18,21,22]. These properties make them ideal candidates for use in tissue engineering scaffolds [17], where they can mimic the native extracellular matrix and provide a conducive environment for cell growth and tissue integration.

Furthermore, their rheological properties, such as shear-thinning behavior and pseudoplasticity [7,10,15], make them suitable for applications in drug delivery systems, where they can be used to develop hydrogels, nanoparticles, and microparticles for controlled release of therapeutic agents.

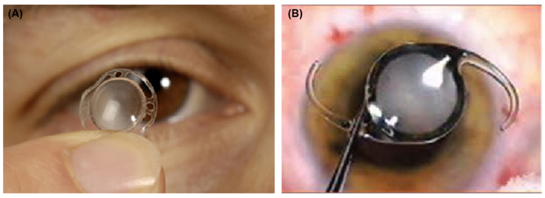

Figure 4: Ophthalmologic applications of biomaterials (A) artificial cornea hip and (B) intraocular lenses. [2]

The versatility of gum-based materials is further highlighted by their ability to be chemically modified to improve properties such as mechanical strength, thermal stability, and biocompatibility. These modifications, including the addition or removal of functional groups, crosslinking, or blending with other polymers, result in materials with tailored characteristics to meet specific biomedical needs and will be further discussed in the following section.

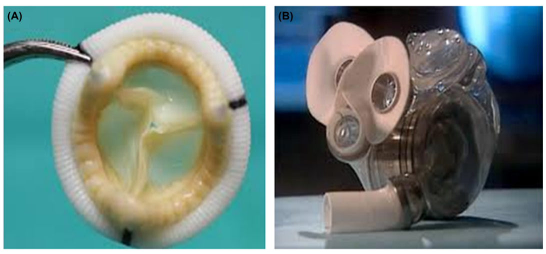

Figure 5: Cardiovascular applications of biomaterials (A) heart valve and (B) artificial heart. [2]

[2] The ECM is a complex network of proteins and other molecules that surrounds and supports the cells within tissues and organs. It provides structural support, facilitates communication between cells, and regulates various cellular functions, such as growth, migration, and differentiation.

[3] Cytotoxicity refers to the quality of being toxic to cells. It is the degree to which a substance or material can damage or kill cells.

[4] Galactomannan is a type of polysaccharide composed of mannose and galactose sugars.

2 Material Design

Generally, the design phase is paramount, dictating the success of biomedical applications.

The choice of base material is critical, with natural gums such as xanthan gum, gellan gum, and guar gum often prioritized. These gums are chosen for their biocompatibility, biodegradability, and the ability to mimic the ECM. The selection process is informed by the intended application, with different gums exhibiting unique properties that lend themselves to specific uses [9,11,22,23].

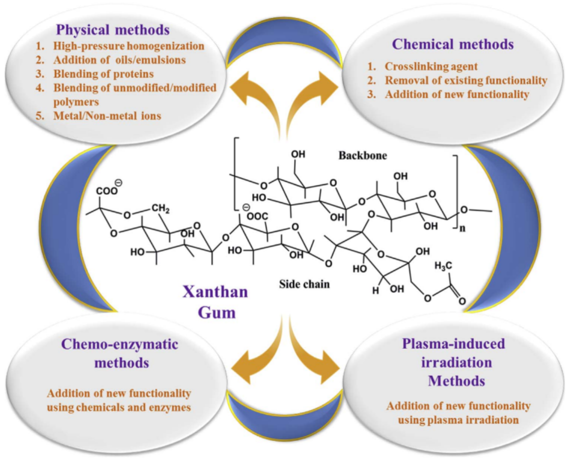

Figure 6: Common methods of modification of xanthan gum polymer chains used in tissue engineering. [7]

Once a base material is selected, it often undergoes physicochemical modification to enhance its properties. This can involve altering the gum's molecular structure [7,24], adding functional groups, or blending with other polymers to improve mechanical strength or thermal stability [10,20].
For instance, carboxymethylation, sulfation, and esterification are common modification techniques that can improve a gum's solubility and bioactivity:

- Carboxymethylation is a chemical modification process in which a carboxymethyl group ($-CH_2-COOH$) is introduced into a molecule. This process typically involves the substitution of a hydrogen atom with a carboxymethyl group. This modification improves properties like solubility, bioavailability, and interaction with other molecules; in specific, carboxymethylation of cellulose or guar gum can enhance their water solubility. [23]
- Sulfation is a chemical process in which a sulfate group ($-SO_3$) is introduced into a molecule, typically replacing a hydrogen atom.
  This modification alters the physical and chemical properties of the substance, in particular can improve functionalities such as water solubility, anticoagulant activity, or interaction with proteins and cells. [23]
- Esterification is a chemical reaction in which an alcohol reacts with an acid to form an ester and water. Typically, this involves the interaction between a carboxylic acid and an alcohol, where the hydroxyl group ($-OH$) from the acid combines with the hydrogen from the alcohol's hydroxyl group, releasing water (H_2O) and forming an ester linkage ($-COOR$).
  In this case esterification of natural polymers can enhance their solubility, hydrophobicity, and thermal stability. [3,21,23]

The design process is further refined based on the material's intended application. In drug delivery, gums are formulated into systems that can encapsulate therapeutic agents [1], with the release rate controlled by the gum's physicochemical properties. In tissue engineering, the design focuses on creating scaffolds that support cell adhesion and proliferation, often involving the development of hydrogels with tunable mechanical properties [18,25].

Ensuring biocompatibility is a central tenet of material design. This involves assessing how the material interacts with biological systems, avoiding harmful effects such as toxicity or immune responses. Cytotoxicity tests are routinely conducted to ensure the safety of gum-based materials [6,14,19,26].

Mechanical properties are tailored to match the physiological conditions of the application site. For example, the elasticity of a gum-based hydrogel used for cartilage repair must mimic the mechanical behavior of native cartilage. This requires careful adjustment of the gum's chemical cross-linking density [16,17].

Innovative designs also incorporate responsiveness to environmental stimuli, such as pH or temperature changes, which can trigger drug release or gel formation. This is particularly useful in smart drug delivery systems and tissue engineering scaffolds that require dynamic performance [8,26].
The design must also account for sterilization methods that ensure the material is safe for medical use without compromising its properties. This can involve gamma irradiation, autoclaving[1], or chemical treatments like exposure to ethanol [15].

Finally, the material design must be translatable to large-scale production while maintaining consistency in quality and performance. This involves optimizing the extraction, purification, and modification processes for industrial application [8].

2.1 Characterization Techniques

At the core of material characterization lies the assessment of the molecular and supramolecular structures. The information gleaned from these analyses is crucial for optimizing material performance and ensuring biocompatibility.
The most mentioned techniques are:

- Fourier-Transform Infrared Spectroscopy (FTIR) is invaluable for identifying the presence and composition of functional groups within a material. By analyzing the infrared absorption spectrum, it's possible to deduce the molecular structure and the types of chemical bonds present. [12,27,28]
- X-ray Diffraction (XRD) is employed to probe the crystalline structure of materials. It provides data on unit cell dimensions, crystal lattice orientations, and the degree of crystallinity, which are critical factors in determining mechanical properties. [24,26,28]
- Scanning Electron Microscopy (SEM) offers high-resolution imaging of the surface morphology and microstructure of materials. This visual data is essential for evaluating the

[1] Autoclaving is a sterilization process that uses high-pressure saturated steam to eliminate microorganisms such as bacteria, viruses, fungi, and spores.

topography and porosity, which can significantly influence cell-material interactions. [12,26]
- Transmission Electron Microscopy (TEM) allows for the observation of finer details, such as nanoscale features and defects, that may not be resolvable with SEM. This technique is particularly useful for analyzing the dispersion of nanoparticles or the structure of thin films. [27]
- Dynamic Light Scattering (DLS) is a technique used to measure the size distribution and dynamics of particles in suspension or polymers in solution. It works by analyzing the scattering of light caused by particles moving in a liquid due to Brownian motion. [27]

Moreover, the stability and integrity of a biomaterial under varying temperatures and mechanical stresses are vital for its performance.
Regarding this topic, the following techniques are commonly used:

- Thermogravimetric Analysis (TGA) measures the change in mass of a material as a function of temperature. This analysis is crucial for understanding thermal stability and degradation mechanisms. [16]
- Differential Scanning Calorimetry (DSC) is used to study the heat capacity of materials and detect phase transitions, such as melting points and glass transitions, which are pivotal for processing and application.
- Dynamic Mechanical Analysis (DMA) evaluates the viscoelastic properties of materials under dynamic conditions. This analysis is essential for predicting how a material will behave under mechanical stress over time. [28]

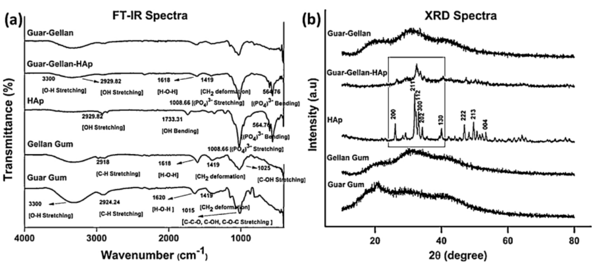

Figure 7: (a) FT-IR spectra, and (b) XRD Spectra of guar gum, gellan gum, hydroxyapatite, guar gum-gellan gum-hydroxyapatite composite, and guar gum-gellan gum composite respectively. [20]

3 Novel Fabrication Technologies

Novel fabrication technologies have emerged to address the increasing demand for advanced materials with tailored properties for specific applications. These innovative techniques allow for better control over the structure, mechanical properties, and biological performance of the resulting biomaterials.
Presented below is a curated selection of technologies identified as the most commonly used and studied.

a. Microwave-assisted synthesis [11,29] is highlighted as a rapid and efficient method for the fabrication of hydrogels from natural gums. This technique offers several advantages, such as reduced reaction times, lower energy consumption, and improved product homogeneity.
For instance, the synthesis of an adsorbent hydrogel from acacia gum phthalate and pectin for the removal of mefenamic acid from water demonstrates the effectiveness of this approach. The hydrogel prepared via microwave-assisted free-radical polymerization showed excellent adsorption capacity and was suitable for environmental remediation applications.

b. Three-dimensional bioprinting [8,21,25] is revolutionizing the field of tissue engineering by enabling the creation of complex, biomimetic scaffolds with high precision.
Bioinks based on natural gums, such as gellan gum and guar gum, are used to fabricate 3D structures that closely mimic the native extracellular matrix. These hydrogels support cell attachment, proliferation, and differentiation, making them ideal for tissue regeneration applications.
The development of self-healing, injectable hydrogels cross-linked with borax and integrated with silver nanoparticles for biomedical applications also underscores the potential of 3D bioprinting in creating biomaterials with unique properties.

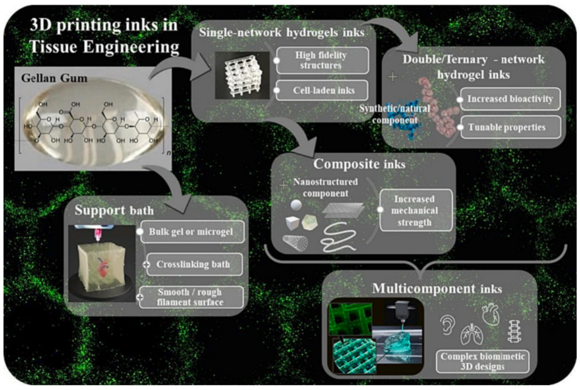

Figure 8: Gellan Gum as one of 3D printing inks in Tissue Engineering. [6]

c. The emulsion solvent diffusion [27,30] is employed to create gum-based nanoparticles with controlled size and morphology, which is crucial for drug delivery applications. The formation of nanoparticles through emulsion solvent diffusion allows for the encapsulation of therapeutic agents, improving their solubility, stability, and targeted delivery.

d. Supercritical fluid technology [27] is utilized for the fabrication of nanoparticles with well-defined characteristics. This green technology operates under conditions of high pressure and temperature, allowing for the formation of nanoparticles without the use of organic solvents. This results in bio-functional materials with enhanced biocompatibility and reduced toxicity.

e. Electrospinning [2,31] is a versatile technique used to produce nanofibers from gum-based polymers. These nanofibers can be fabricated into mats or scaffolds with high surface area to volume ratios, making them suitable for applications such as wound dressings and drug delivery systems. The technique allows for control over fiber diameter and orientation, which can be tailored to specific applications.

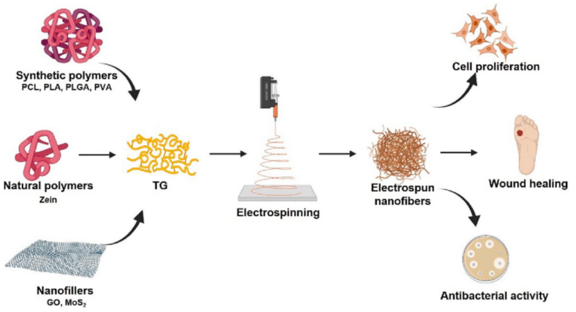

Figure 9: Tragacanth gum based nanofibrous delivery systems for wound healing and antibacterial activity. [1]

f. Polyelectrolyte complexation [2,32] is a method used to create hydrogels and nanoparticles through the interaction of gum-based polyanions with polycations. This method is advantageous for its simplicity and the ability to form complexes with tunable properties.

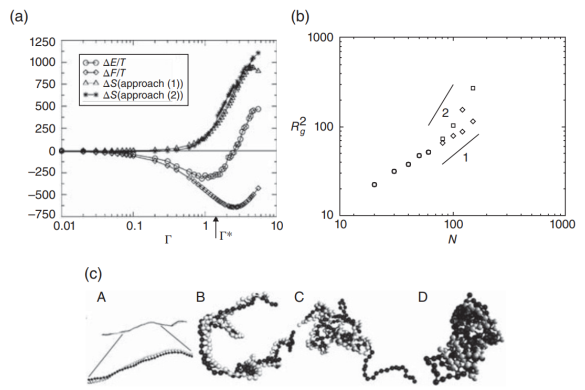

Figure 10: Insights on thermodynamics and structure of polyelectrolyte complexes from computer simulations. [32]

g. Solvent casting [2], followed by particulate leaching[1], is a technique used to produce porous scaffolds from gum-based polymers. This method allows for control over the porosity and interconnectivity of the scaffolds, which is essential for tissue engineering applications where cell infiltration and nutrient diffusion are critical.

h. Freeze-drying [22], or lyophilization, is a common technique used to create porous scaffolds with well-defined structures. By freezing a hydrogel and then removing the solvent under vacuum, a porous scaffold is formed.

4 Critical Analysis

The domain of gum-based biomaterials is burgeoning with research, promising a wealth of applications in tissue engineering, drug delivery, and regenerative medicine. However, a critical analysis reveals several challenges and limitations that must be addressed to fully realize the potential of these biomaterials.

While many natural gums are lauded for their biocompatibility, the immune response they elicit remains a concern. For instance, the authors in [7] emphasize the importance of understanding the immunological response to xanthan gum. This is crucial because, despite its non-toxic nature, it may still stimulate immune responses that could hinder its long-term performance in biomedical applications.

The authors in [1] underscores the problem of variability in physicochemical properties based on the source of extraction and environmental conditions. The heterogeneity of natural gums can lead to batch-to-batch inconsistencies, which is detrimental for the development of standardized medical products.

The mechanical properties of gum-based hydrogels are critical for their use as tissue scaffolds. The authors in [6] points out the need for mechanical reinforcement of these hydrogels. Often, the gels lack the necessary strength required for load-bearing applications, such as in bone tissue engineering.

The hydrophilic nature of gums can limit the release of water-soluble drugs. The authors in [7] discusses this limitation, noting that while it aids in cell adhesion and proliferation, it can also lead to poor control over drug release kinetics.

The paper [24] highlights the challenges associated with processing gum-based materials, where complex fabrication techniques are often required to achieve the desired material properties.

Controlling the degradation rates of gum-based biomaterials is essential for applications in tissue engineering and drug delivery. In [9], the difficulty in tailoring the degradation profiles of gum-based scaffolds is mentioned, which could lead to either too rapid or too slow degradation, affecting the integration and functionality of the scaffold within biological systems.

Many gums require chemical modification to improve their properties, but the toxicity of these modifiers can be a concern. The authors in [11] discusses the use of chemically modified gums for environmental remediation, but the potential toxicity of these derivatives, especially phthalates, is a concern that needs to be addressed.

The scalability of gum production and the cost of purification and modification processes can hinder widespread adoption. This is touched upon in [15], where the scalability of cashew tree gum production for industrial applications is noted as a significant challenge.

Lastly, the environmental impact of gum harvesting and production processes should not be overlooked. The authors in [8] discusses the use of natural gums in bioscaffolds, but there is a need for sustainable harvesting practices and minimal environmental impact throughout the gum lifecycle.

In conclusion, while gum-based biomaterials present a promising avenue for research and development, critical challenges must be addressed to ensure their safety, efficacy, and scalability. Continued research and innovation are vital to overcome these hurdles and to unlock the full potential of these versatile materials in biomedical applications.

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[1] In this process, particles (like salts or sugars) are mixed into a polymer or other matrix material. After the matrix solidifies, the particles are leached out (dissolved and removed) using a solvent, leaving behind a porous structure.

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