João M.M. Rodrigues, Alice Dias, João F. Mano
CICECO - Aveiro Institute of Materials, Department of Chemistry
University of Aveiro (Portugal)
jrodrigues@ua.pt; jmano@ua.pt

http://dx.medra.org/10.17374/CI.2026.108.3.67

CHEMICAL DESIGN OF NATURAL BIOMATERIALS

Natural-derived polymers have attracted considerable attention due their abundance in nature and intrinsic properties such as biodegradability and bioavailability. Their bioactivity and applications are strongly influenced by their chemical structure. However, inherent limitations can restrict broader use. Precise chemical modifications can introduce functional groups and tailor physicochemical, mechanical, and biological properties, enabling the development of multifunctional biomedical devices.

Introduction

Synthetic polymers have played a major role in biomaterials fabrication due to the precise control they offer over chemical structure, low batch-to-batch variability, and ease of sourcing. However, Nature is a rich source of inspiration, offering structural concepts and materials that can improve human health while preserving ecosystems and supporting environmental sustainability. In particular, biopolymers derived from plants and animals, such as polysaccharides and proteins, have evolved to mediate biological interactions, inherently providing bioactivity, biocompatibility and biodegradability [1]. They represent low-cost, renewable building blocks for biomedicine and biotechnology, and their inherent biofunctionality, unique physicochemical and biological properties enable the development of a wide range of multifunctional devices for healthcare applications [2].

Polysaccharides (*e.g.*, alginate, chitosan, hyaluronic acid, laminarin, pullulan) and animal-derived proteins (*e.g.*, collagen, gelatin, silk fibroin) can be obtained from natural resources such as plants, fungus, seaweeds, and animals, or sourced from industry by-products, thereby aligning biomedicine and biotechnology with circular-economy principles.

Beyond plant- and animal-derived materials, human-derived proteins and tissues are emerging as truly adequate alternative protein sources to bioengineering platforms for cell culture that recapitulate the physiological environment found in real human tissues and organs. For example, blood-derived proteins, such as human platelet lysates (hPL) and platelet-rich plasma, are rich in growth factors essential for tissue repair. When derived from a patient's own blood, these materials uniquely combine bioactivity with immunological safety and can be formulated as biomaterial systems for personalized therapeutic applications [3]. Perinatal tissues, including chorionic or amniotic membrane (hAM), placenta (hPC) or umbilical cord, representing another underexploited resource, are commonly discarded after birth. These tissues are rich in biologically potent extracellular matrix (ECM) components with remarkable regenerative and immunomodulatory properties. Such sustainable sources are not associate to any ethical issues, as hPL can be even obtained from expired blood fraction units, and hPC is considered medical waste [4].

However, to enhance their natural properties or to impart specific functionalities, appropriate chemical modification strategies must be applied according to the unique structural characteristics of natural polymers, thereby enhancing their biological activities and elevate surface, mechanical/rheological, stimuli responsiveness and processability characteristics.

Precise chemical modification of biopolymers into advanced biofunctional materials

Chemical modification of biopolymer structures can significantly enhance properties such as water solubility, mechanical properties, bioactivity, and the overall processability and functional per-

formance of the resulting biomaterial. Moreover, the translational potential of biopolymers is closely linked to development of competitive alternatives to existing commercial materials. To be viable, these materials must be prepared through simple, straightforward, green, and cost-effective synthetic routes. Owing to the presence of reactive chemical functionalities, such as hydroxyl (-OH), amine (-NH_2), carboxyl (-COOH), or thiol (-SH) groups, biopolymers can be selectively modified using targeted chemical strategies to exploit their intrinsic reactivity and introduce defined functional or biofunctional moieties. Such modifications enable precise tuning of material properties, creating new opportunities for the development of advanced functional biomaterials for biomedical applications, such as hydrogels for tissue engineering or microparticles for drug delivery [5].

Chemical grafting represents one of the most straightforward and commonly employed approaches for functionalizing biopolymers without compromising their intrinsic properties. Laminarin (LAM-OH), a low-molecular-weight branched polysaccharide composed by glucose units, was chemically modified at its primary hydroxyl groups through a modular and flexible functionalization strategy, resulting in the incorporation of defined functional groups, namely, allyl, carboxylic acid, amine, thiol, and aldehyde moieties, into its backbone, yielding LAM-C=C, LAM-NH_2, LAM-COOH, LAM-SH and LAM-C=O (Fig. 1) [6].
A new library of LAM-derivatives was established, opening new avenues for adapting these strategies to the modification of other biopolymers. Moreover, to enhance cell adhesion within polysaccharides backbone, where intrinsic cell-adhesive motifs are absent, additional functionalization strategies can be implemented, including the incorporation of the cell-adhesive RGD tripeptide (Arg-Gly-Asp). At a macroscopic scale, chemical modification permits to process matrices capable of accommodating cells and directing their fate in 3D. Two examples of structures that can be obtained from natural-derived polymers are highlighted, namely hydrogels and cryogels.

Hydrogels are highly hydrated, interconnected polymer networks with the ability to replicate key features of native tissues. Their high-water content supports the diffusion of nutrients and signaling molecules, while significant progress has been made in tailoring their properties, such as mechanical strength, which can be precisely tuned to match those of target tissues [5]. By modifying natural polymers with photocrosslinkable moieties, such

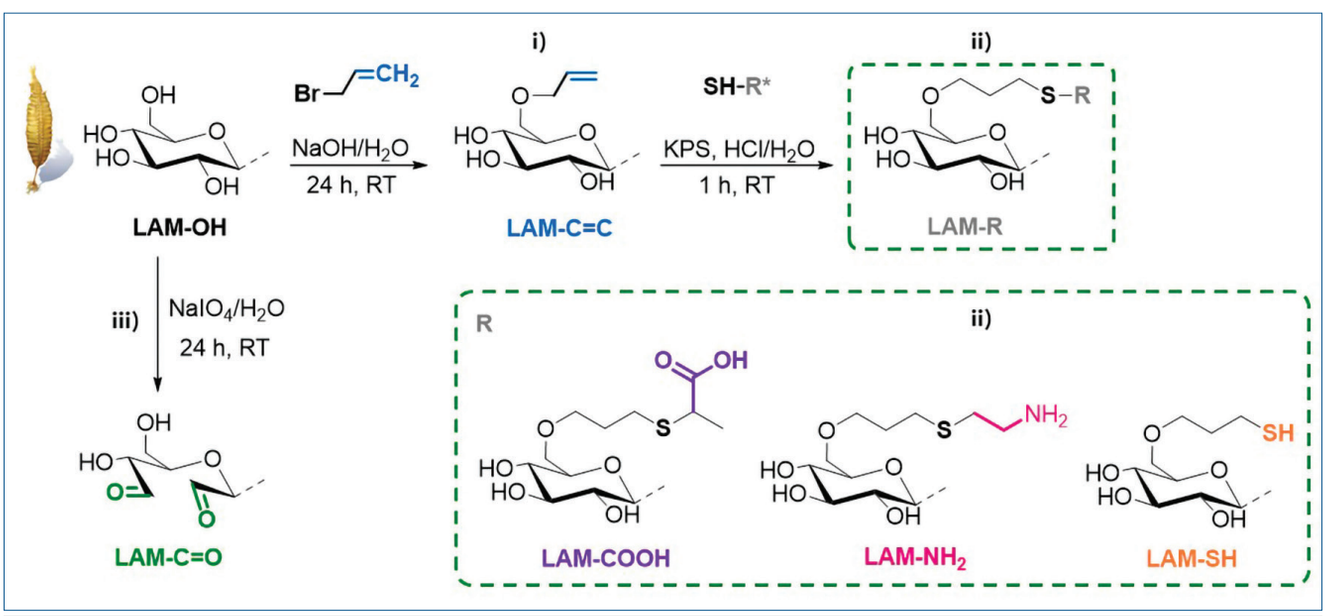

Fig. 1 - Schematic representation of the modified LAM–OH derivatives, functionalized through i) nucleophilic substitution, ii) thiol-Michael addition, and iii) oxidation. Adapted from [6]

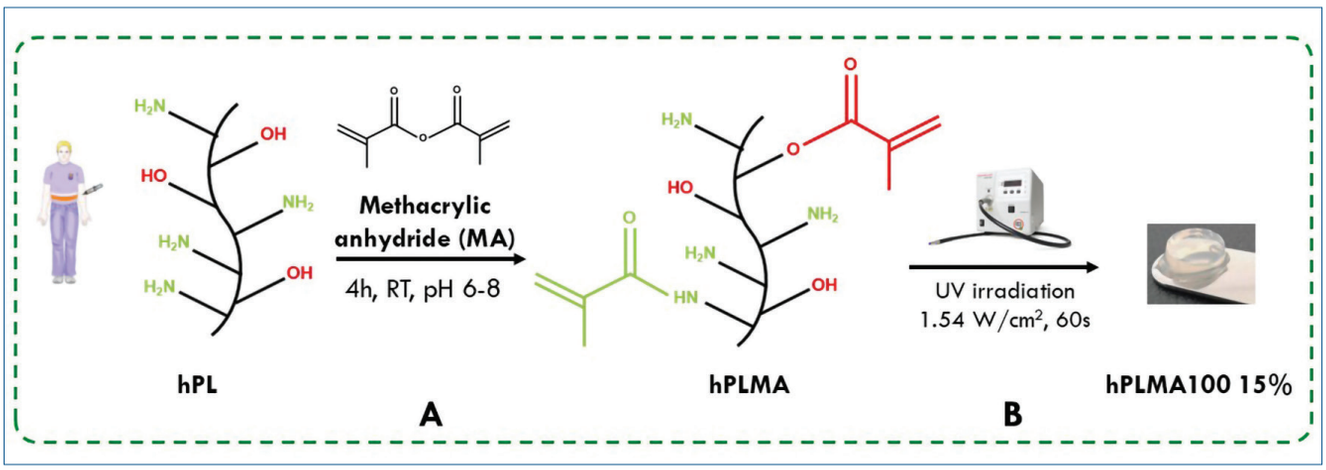

Fig. 2 - A) Reaction of hPL with methacrylic anhydride, achieving hPLMA;
B) photocrosslinked hPLMA hydrogels formed from hPLMA100 at 15% (w/v). Adapted from [6, 7]

as methacryloyl groups, liquid precursor solutions can be polymerized in the presence of a photoinitiator upon light exposure, enabling rapid and controlled gelation. Similarly, hPL functionalized with photocrosslinkable groups to obtain human methacryloyl platlet lysates (hPLMA), can form hydrogels upon exposure to light in the presence of a photoinitiator (Fig. 2) [7]. By controlling the degree of substitution or the solution concentration, tunable mechanical properties can be achieved.
Among many applications, hydrogels have been used to develop 3D disease models [8, 9], adhesive hydrogel for drug release [10] and cell encapsulation [11]. As 3D polymeric network, hydrogels frequently have limited porous nanostructure, which limits cell migration and molecular diffusion.

Cryogels have emerged as a superior alternative to hydrogels offering interconnected porosity, cell migration, mechanical stability, and injectability. Cryogels are formed via crosslinking under subzero conditions, where ice crystal acts as porogens, creating a 3D network in the semi-frozen phase. Upon thawing, a highly interconnected macropo-

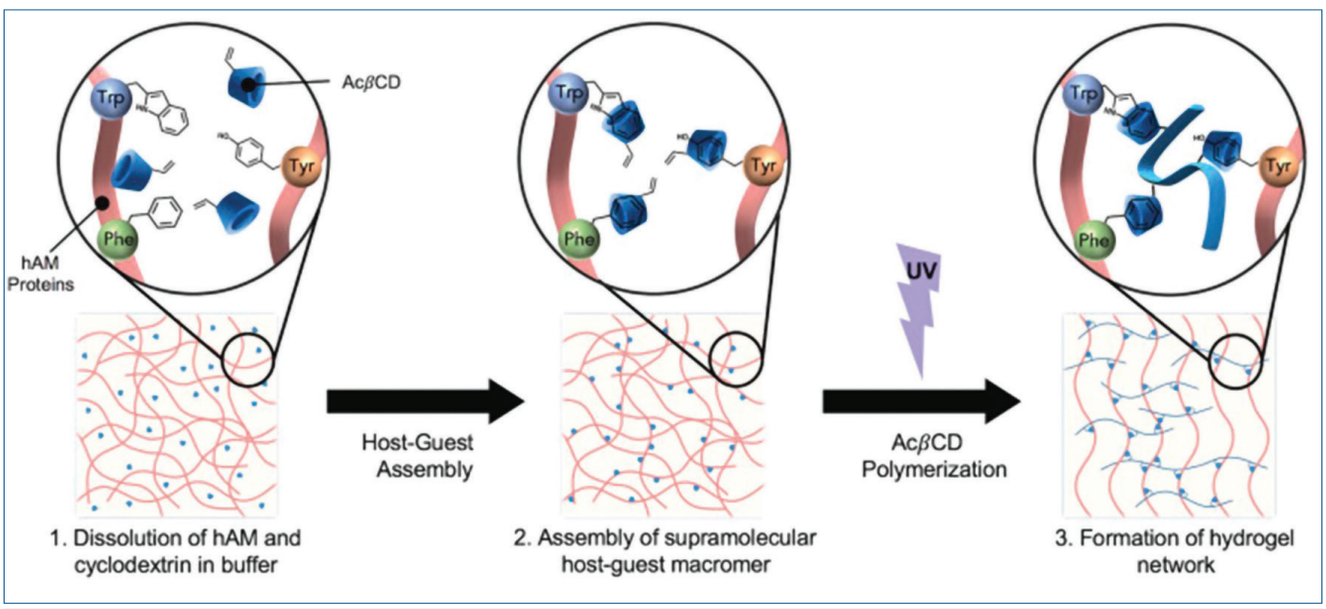

Fig. 3 - Schematic representation of the formation of the hAM-AcβCD
host-guest macromer and subsequent polymerization into hydrogels. Adapted from [16]

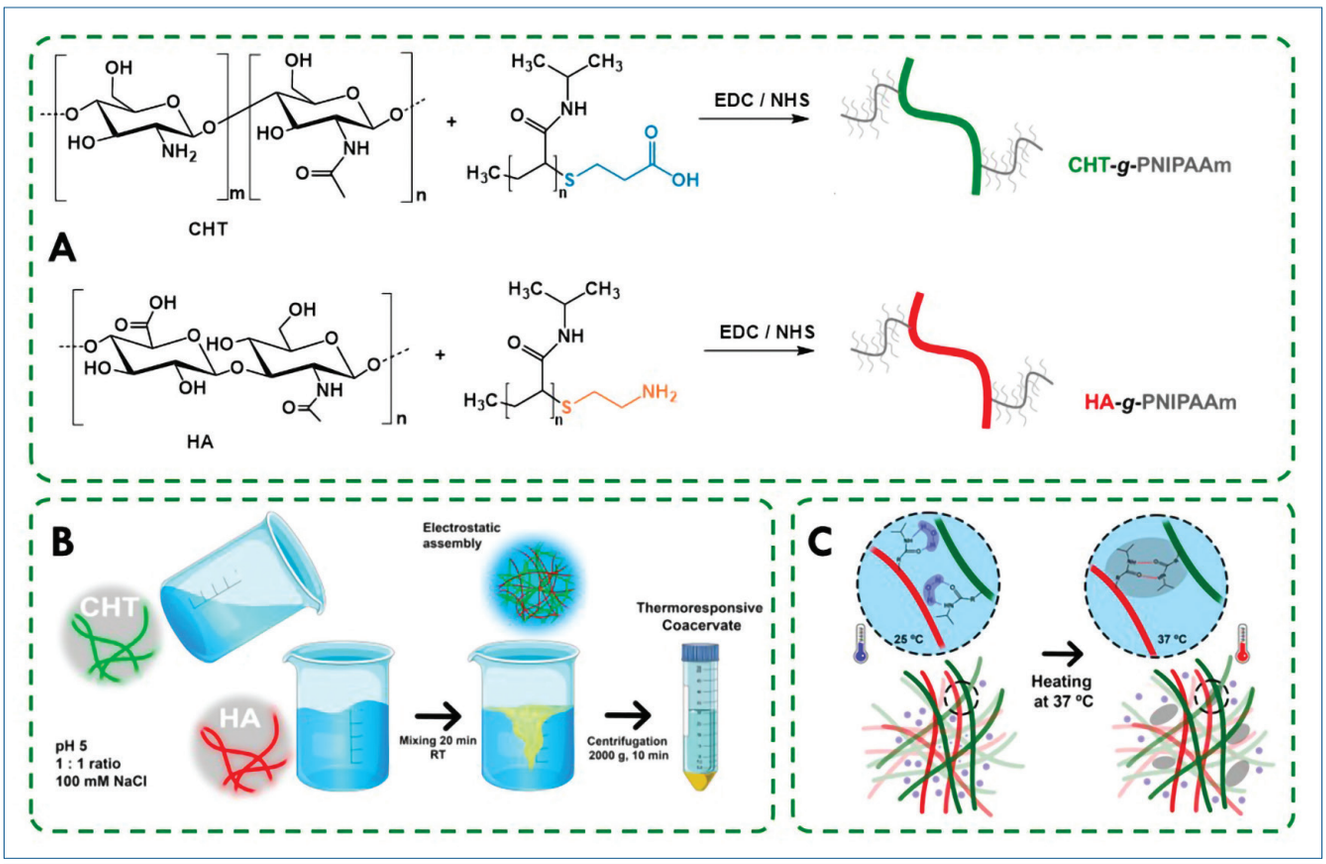

Fig. 4 - A) Chemical route to obtain CHT-g-PNIPAAm and HA-g-PNIPAAm through EDC/NHS coupling chemistry; B) assembling thermoresponsive coacervate; C) temperature-dependent behavior of PNIPAAm chains below and above the lower critical solution temperature (LCST). Adapted from [17]

rous structure is obtained, enabling the material to maintain structural integrity under mechanical stress (*e.g.*, injection) and recover its shape after deformation. This architecture facilitates efficient solutes diffusion and mass transport of nanoparticles, microorganisms, and cells [12]. Integrating cryogels into 3D bioprinting, overcomes the structural limitations of traditional hydrogels [13, 14]. This technique is particularly powerful when combined with human-derived matrices, as it allows the fabrication of "shape-memory" scaffolds exhibiting injectability properties [15].

Covalent chemistry is widely used into preparation of biomaterials. However, materials assembled through *supramolecular interactions* have achieved significant success in replicating the viscoelastic and dynamic properties of the ECM. In this context, dynamic hydrogels were produced through the supramolecular assembly of decellularized hAM, mediated by host-guest interactions between the hydrophobic pendant groups from the hAM proteins and the hydrophobic cavity of the acryloyl-β-cyclodextrin (AcβCD) [16]. Subsequent photopolymerization of AcβCD let the formation of soft hydrogels exhibiting tunable stress relaxation and strain-stiffening behaviour (Fig. 3).

A novel class of biomaterials, referred to as "smart" materials, which respond to different stimuli such as temperature, pH, or light wavelengths, are emerging as promising platforms for biomedical applications. Poly(N-isopropylacrylamide) (PNIPAm), a synthetic polymer, is known for its sharp phase transition near physiological temperature ~31.8 °C), at which it undergoes a reversible shift from a hydrated, swollen state to a collapsed, hydrophobic conformation. By combining the synergistic properties of natural and synthetic polymers, a thermoresponsive complex coacervate was engineered through the electrostatic interactions of

oppositely charged modified polysaccharides with PNIPAm chains through EDC/NHS chemistry (Fig. 4). The resulting biopolymeric-derived coacervate exhibits pronounced shear-thinning behavior and undergoes a rapid sol-gel transition at physiological temperature **[17]**.

Concluding perspective and future outlook

The broad range of chemical modification strategies available for extending the functionality of biopolymers represents a powerful strategy for improving their physicochemical and biological properties across different applications. These modifications can confer enhanced bioactivity, stimuli responsiveness, the introduction of crosslinkable moieties or active groups, dynamic and bioinstructive behavior, and improved mechanical properties. Moreover, alongside the use of natural biopolymers, there is a continued drive towards the development of efficient, cost-effective, and environmentally sustainable chemical methodologies, with a particular focus on the use of renewable resources, minimizing toxic waste, and the adoption of green synthesis techniques, including enzymatic processes and solvent-free methods. Nevertheless, despite substantial academic progress, the translation of these technologies into industrial-scale applications remains constrained by persistent challenges.

Acknowledgments

This work was developed within the scope of the project CICECO-Aveiro Institute of Materials, UID/50011/2025 (DOI 10.54499/UID/50011/2025) & LA/P/0006/2020 (DOI 10.54499/LA/P/0006/2020) & UID/PRR/50011/2025 (DOI 10.54499/UID/PRR/50011/2025), financed by national funds through the FCT/MCTES (PIDDAC). J.M.M.R. acknowledge FCT for the individual Assistant Researcher contract (2023.07239.CEECIND/CP2840/CT0004, DOI 10.54499/2023.07239.CEECIND/CP2840/CT0004) under the Scientific Employment Stimulus - Individual Call.

References

[1] G. Satchanska, S. Davidova *et al., Polymers*, 2024, **16**, 1159.

[2] M.M.A. Sacramento, J. Borges *et al., Frontiers in Bioengineering and Biotechnology*, 2022, **10**, 1041102.

[3] S.C. Santos, Ó.E. Sigurjonsson *et al., Tissue Engineering Part B: Reviews*, 2018, **24**, 454.

[4] I.A. Deus, J.F. Mano *et al., Acta Biomaterialia*, 2020, **110**, 1.

[5] V.G. Muir, J.A. Burdick, *Chemical Reviews*, 2021, **121**, 109908.

[6] A.M.S. Costa, J.M.M. Rodrigues, *et al., Journal of the American Chemical Society*, 2020, **142**, 19689.

[7] S.C. Santos, C.A. Custódio *et al., Advanced Healthcare Materials*, 2018, **7**, 1800849.

[8] M. Zargarzadeh, M.C. Gomes *et al., Advanced Functional Materials*, 2023, **33**, 2214372.

[9] C.F. Monteiro, I.A. Deus *et al., Advanced Functional Materials*, 2024, **34**, 2315940.

[10] K.R. Amaral, A.S. Silva *et al., Advanced Healthcare Materials*, 2023, **12**, 2301513.

[11] M.M. Maciel, N.H. Besheli *et al., Biotechnology Journal*, 2024, **19**, 2300469.

[12] A. Memic, T. Colombani *et al., Advanced Therapeutics*, 2019, **2**, 1800114.

[13] E.J. Castanheira, L.P. Monteiro *et al., ACS Materials Letters*, 2025, **7**, 1152.

[14] E.J. Castanheira, J.R. Maia *et al., Materials Today Nano*, 2024, **28**, 100519.

[15] J.P. Sousa, I.A. Deus *et al., Biomaterials Science*, 2024, **12**, 4393.

[16] B. Ladeira, M. Gomes *et al., Biomaterials*, 2025, **320**, 123270.

[17] L.P.G. Monteiro, M. Carreira *et al., Small*, 2026, e13642.

Progettazione chimica di biomateriali naturali

I polimeri di origine naturale hanno suscitato notevole interesse grazie alla loro abbondanza in natura e alle loro proprietà caratteristiche, quali biodegradabilità e biodisponibilità. La loro bioattività e le loro applicazioni sono fortemente influenzate dalla struttura chimica. Tuttavia, limitazioni intrinseche possono ostacolarne un impiego più ampio. Modificazioni chimiche mirate consentono di introdurre gruppi funzionali e di modulare le proprietà fisicochimiche, meccaniche e biologiche, favorendo lo sviluppo di dispositivi biomedici multifunzionali.