TABLE OF CONTENTS

INTRODUCTION

Biomaterials are a class of biocompatible materials specifically designed to interact with biological systems (Biobaku-Mutingwende, 2021; Malviya and Sundram (eds.), 2023), with multifunctionality referring to their ability to simultaneously perform multiple functions, such as stimulating tissue regeneration, preventing infections, or enabling the controlled release of therapeutic agents (Swartjes, 2017). In this thesis, the studied biomaterials are based on natural polymers and natural bioactive molecules, two classes of compounds with high potential for the development of advanced therapeutic systems.

Over the past decades, numerous strategies have been developed involving the incorporation of natural bioactive molecules into polymer matrices, aiming to improve their stability, solubility and release control. Polymeric systems used for this purpose include hydrogels, liposomes, emulsions or nanoparticles (Hu M. et al., 2022; Li Q. et al., 2021; Siraj et al., 2021). Among these, hydrogels have attracted particular interest due to their three-dimensional structure, ability of absorbing large amounts of water without dissolving, thus mimicking the mechanical and viscoelastic characteristics of biological tissues (Dragan & Dinu, 2020; Zheng and Xiao, 2023; Zheng B.-D. et al., 2023).

Recent research has shown that encapsulating polyphenols and terpenes/essential oils (EOs) in polysaccharide-based hydrogels is a promising approach for: (i) preventing their oxidation and volatilization, (ii) improving their stability and water solubility , (iii) extending their shelf life, (iv) increasing their bioavailability and effectiveness, and (v) enabling controlled release into the body (Ding et al., 2022; Madamsetty et al., 2023; Sudheer et al, 2023). Consequently, hybrid hydrogels based on polysaccharides/polyphenols or polysaccharides/EOs in various forms (films/membranes, microparticles, fibers) have emerged as innovative systems for numerous applications, including drug delivery, tissue engineering, wound treatment, food packaging and/or even functional foods (Ghiorghita, **Platon** et al., 2024).

The literature data indicate that the preparation of previously studied hydrogels often involves heating precursor mixtures to temperatures above 50 °C for gelation, the use of photoinitiators and UV irradiation, or chemical cross-linking agents, or intensive processing to obtain the final materials. Considering these aspects, for the preparation of the hybrid hydrogel/bioactive compound systems presented in this PhD thesis, the cryogelation technique was chosen, a simple method that avoids heating and thus preserves the bioactivity of phytocompounds. This technique also uses water as a solvent, resulting in a reduced environmental impact and allowing easy purification of the biomaterials. Another advantage of the studies described in the thesis is also the use of small amounts of low toxicity cross-linking agents, where applicable. In terms of properties, compared to hydrogels, cryogels possess higher porosity, a higher degree of pore interconnection, contributing to a more efficient and uniform encapsulation of bioactive compounds, as well as lower density and high mechanical strength regardless of the stabilization method (physical or chemical cross-linking). The cryogelation technique allows for gel formation using very low concentrations of reactants, as cross-linking occurs in the unfrozen microphase rather than throughout entire mass, as in conventional gelation performed at room temperature. In addition, the originality of this thesis also derives from the fact that the plant extracts used are obtained from indigenous species of spontaneous flora or cultivated in the historical region of Moldova, which are scarcely studied in the literature as components of hydrogel-type biomaterials.

In this context, the main **scientific objectives** of the PhD thesis entitled "*Design of novel multifunctional biomaterials based on polymers and different natural bioactive molecules*" were:

- Preparation and characterization of *Vaccinium myrtillus* L.*,* *Ribes nigrum* L. and *Rubus fruticosus* L. extracts to select the appropriate one for inclusion in Xn-based biomaterials;
- Preparation and characterization of *Hypericum perforatum* L. extract;
- Preparation of cryogels based on Xn, and CS, respectively and optimization of preparation/composition conditions by analyzing morphological, mechanical, swelling and antimicrobial properties;
- Development of hybrid biomaterials by including the selected phytocompounds/plant extracts into the prepared matrices;
- Structural andmorphological characterization, as well as evaluation of the mechanical and swelling properties of the hybrid biomaterials;
- Investigating specific properties of biomaterials containing bioactive compounds (such as stability, response to pH variations, antioxidant and antimicrobial properties, controlled release of active ingredients, and cytocompatibility).

The PhD thesis "*Design of novel multifunctional biomaterials based on polymers and different natural bioactive molecules*" is structured in two parts comprising, 6 chapters, as follows:

Part I (**Chapter I**) provides a comprehensive analysis of the current state of research on hybrid biomaterials based on polysaccharides and bioactive compounds, highlighting the preparation methods, functional properties, and main application areas (such as wound healing, drug delivery, functional foods and food packaging).

Part II (Chapter II-VI) presents the original research contributions, describing the development and characterization of innovative cryogel-type biomaterials with multiple functionalities and potential applications in biomedical and food fields. **Chapter II** report the extraction and characterization of *Vaccinium myrtillus* L.*,* *Ribes nigrum* L. and *Rubus fruticosus* L. extracts, as well as the preparation and characterization of Xn-based hybrid cryogel biomaterials incorporating these anthocyanin-rich extracts. The stability, pH responsiveness, and food freshness monitoring abilities are also highlighted. **Chapter III** presents the optimization of the preparation conditions for CS-based cryogel biomaterials, followed by the incorporation of curcumin (CCM) into selected matrices and assessment of their properties, including the matrix's capability for controlled CCM release. **Chapter IV** discusses the extraction and characterization of *Hypericum perforatum* L. extract, and the optimization of preparation conditions for obtaining CS-based cryogels functionalized with thiourea capable of incorporating *Hypericum perforatum* L. extract. **Chapter V** aims to develop cryogels based on double-cross-linked CS and a volatile terpenoid (thymol), highlighting both preparation strategies and biomaterial characteristics. **Chapter VI** includes the materials and methods used in the studies. The thesis ends with a presentation of **the general conclusions** derived from the preformed studies, along with perspectives for future research, bibliography, and dissemination activities carried out during the doctoral program.

PART II. ORIGINAL CONTRIBUTIONS

CHAPTER II. MULTIFUNCTIONAL CRYOGEL BIOMATERIALS BASED ON XANTHAN AND EXTRACTS RICH IN ANTHOCYANIN MONOMERS

II.2. Extraction and chemical characterization of anthocyanin-rich extracts

Firstly, the aim was to obtain polyphenolic extracts from three berry species known for their high anthocyanin content: bilberries (*Vaccinium myrtillus* L.*, **Af***), blackcurrants (*Ribes nigrum* L.*, **C***) and blackberries (*Rubus fruticosus* L., ***MB*** and ***MS***). Following extraction,the polyphenolic extracts were characterized using chemical and chromatographic methods, as well as *in vitro* antioxidant activity assays. Their stability of the extracts was also evaluated over time and across different pH levels. The phytochemical analysis showed that the ***Af*** extract exhibited the highest polyphenolic content (803 mg gallic acid equivalents/100 g fresh weight), featuring a rich profile of flavonoid glycosides (e.g., rutoside, hyperoside, etc.), phenolic acids (e.g., chlorogenic acid), and anthocyanins (e.g., ***cyanidin-3-glucoside, C3G***). The *in vitro* antioxidant activity of ***Af*** extract demonstrated its strong scavenging ability, achieving over 80% inhibition of 2,2-diphenyl-picryl-hydrazil (DPPH) after 5 minutes (EC50 = 46.16 μg/mL). Based on these results, the ***Af*** extract was selected for further experiments.

II.3. Hybrid biomaterials based on xanthan and Vaccinium myrtillus L. extract

Given the limited stability of the ***Af*** extract in aqueous solutions—ranging from 2 to 12 days depending on pH—encapsulation within polymeric matrices was considered essential to preserve its bioactive properties. Therefore, the second part of the experimental work focused on the development and characterization of hybrid systems based on Xn and the ***Af*** extract**.** To assess the impact of formulation strategy and composition on the properties of the resulting biomaterials, Xn/poly(vinyl alcohol) (PVA) cryogels were obtained by freeze-thaw cycles (**CG/S1.x**) (**Figure II.10A**). Chemically cross-linked Xn-based cryogels with 1,4-butanediol-diglycidyl ether (1,4-BDGE), dried either by freeze-drying (**CG/S2a.x**) or in the oven (**CG/S2b.x**) were also prepared (**Figure II.10B**).

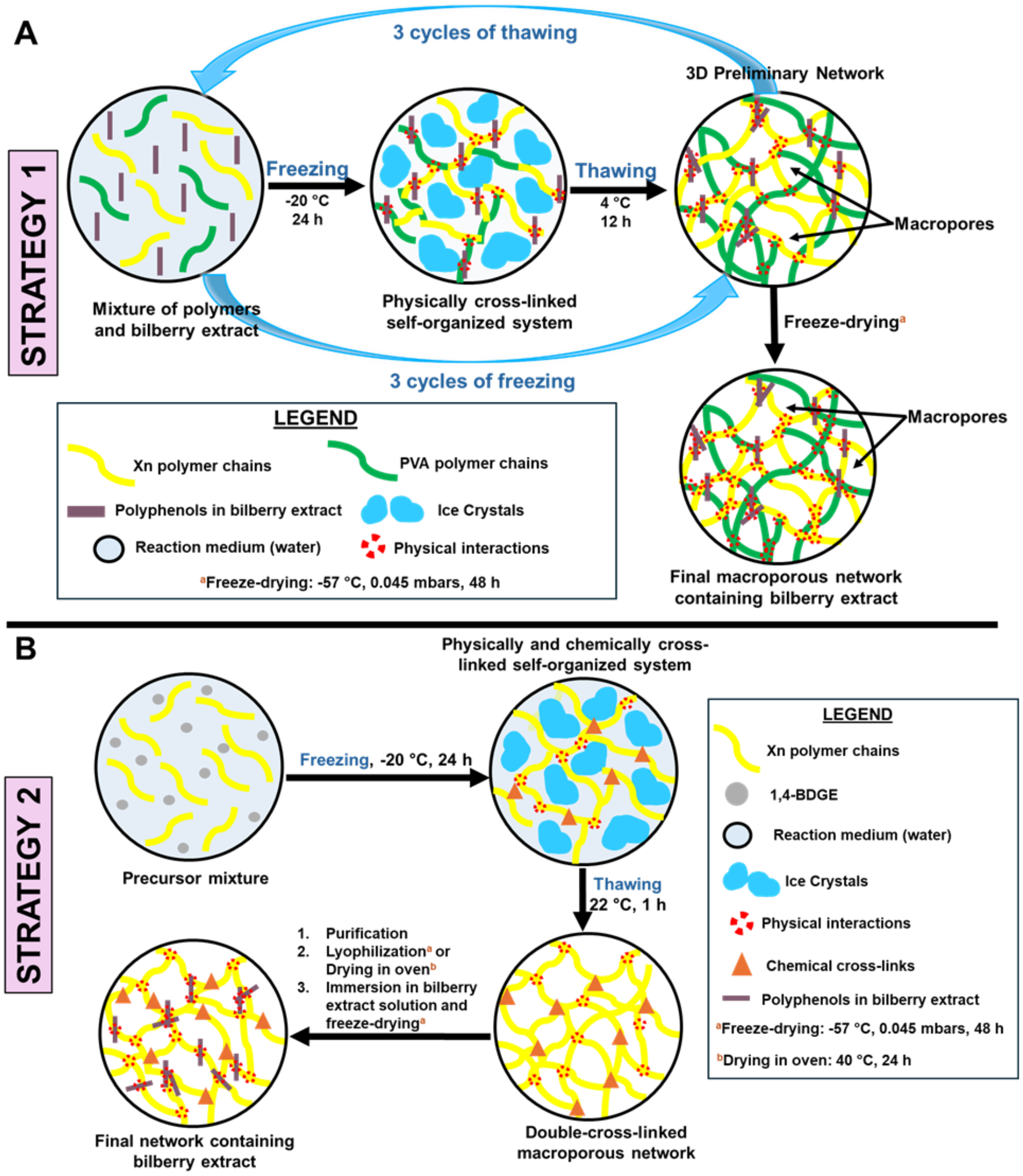


Figura II.10. Schematic representation of the steps taken to obtain hybrid cryogels based on Xn and *Vaccinium myrtillus* L. extract (A) **strategy 1**: the mixture of polymers (Xn and PVA) and ***Af*** extract was subjected to three successive freeze-thaw cycles, followed by freeze-drying; (B) **strategy 2**: the precursor mixture of Xn and the cross-linking agent, 1,4-BDGE, was frozen, thawed, purified, and dried either by freeze-drying or in an oven. Subsequently, the Af extract was absorbed into the matrix, followed by a final freeze-drying step.

The gel fraction yield (GFY) values increased with increasing ***Af*** extract content, rising from 78.41% to 87.64%, indicating an increase in the stability of the physically cross-linked cryogels upon extract incorporation. This improvement is attributed to the reinforcement of the 3D network through hydrogen bonds and/or π-π interactions between the functional groups of Xn, PVA and those of the compounds identified in the ***Af*** extract (e.g., rutoside, chlorogenic acid, hyperoside, *C3G*). In the case of double-cross-linked matrices, the drying method significantly affected the *GFY* values, with oven-dried samples exhibiting higher values. The successful incorporation of the ***Af*** extract was confirmed by FTIR analysis. SEM analysis revealed a porous morphology in the case of freeze-dried cryogels (**Figure II.15**) whereas oven-dried samples (**CG/S2b.x, Figure** Eroare! În document nu există text cu stilul precizat.**1**) showed a continuous structure, indicating that oven drying led to the collapse of the pores formed by cryogelation. The average pore sizes and pore wall thicknesses were dependent on material composition. Increasing the extract content resulted in more compact pore walls and a significant decrease in the average pore size, from 132.53 µm (**CG/S1.0**) to 42.66 µm (**CG/S1.3**). These changes are directly linked to the increased density of physical interactions determined by the polyphenolic compounds present in the ***Af*** extract.

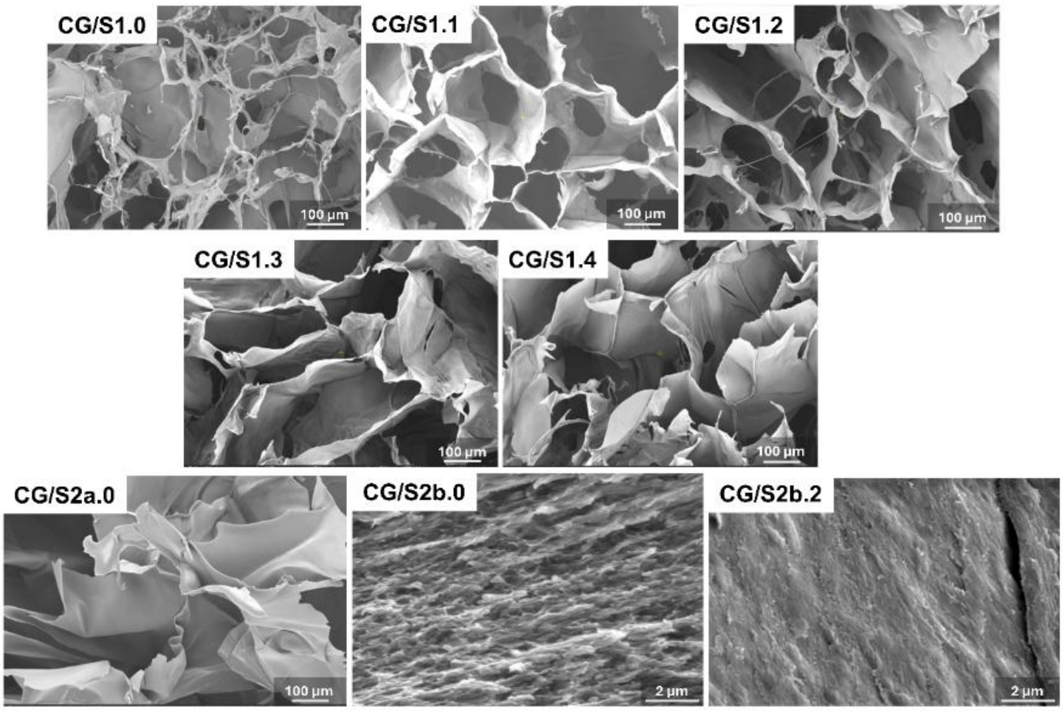


Figure Eroare! În document nu există text cu stilul precizat.**1.** SEM micrographs of Xn-based cryogels with various compositions.

Increasing the amount of the ***Af*** extract in the biomaterial formulation influenced their mechanical properties. In freeze-dried cryogels, this resulted in network stiffening, and enhanced compressive strength, increasing from 215 kPa (**CG/S1.0**) to 247 kPa (**CG/S1.4**). The double-cross-linked matrices exhibited even higher compressive strength values, ranging from 340 to 498 kPa, due to the additional reinforcement provided by chemical cross-linking. Furthermore, the incorporation of the extract increased the hydrophobic character of the cryogels, as reflected by the rise in contact angle values from 75° (**CG/S1.0**) to 87° (**CG/S1.2**), and reduced the swelling ratio from 53 to 39. The Xn-based biomaterials were able to preserve the antioxidant activity of the ***Af*** extract, with **CG/S1.4** demonstrating 93% inhibition of DPPH radicals. Additionally, the presence of the extract significantly enhanced the antibacterial activity of the materials, achieving 100% inhibition against standard strains of *Salmonella typhimurium*, *Escherichia coli,* and *Listeria monocytogenes*.

Another key finding was the improved stability of the extract following its incorporation into Xn-based biomaterials. This was evidenced by the relatively constant values of the colorimetric parameters observed over 42 days under acidic or alkaline pH conditions , **Figure II.25**), and up to 50 days under ambient conditions (**Figure II.26**).

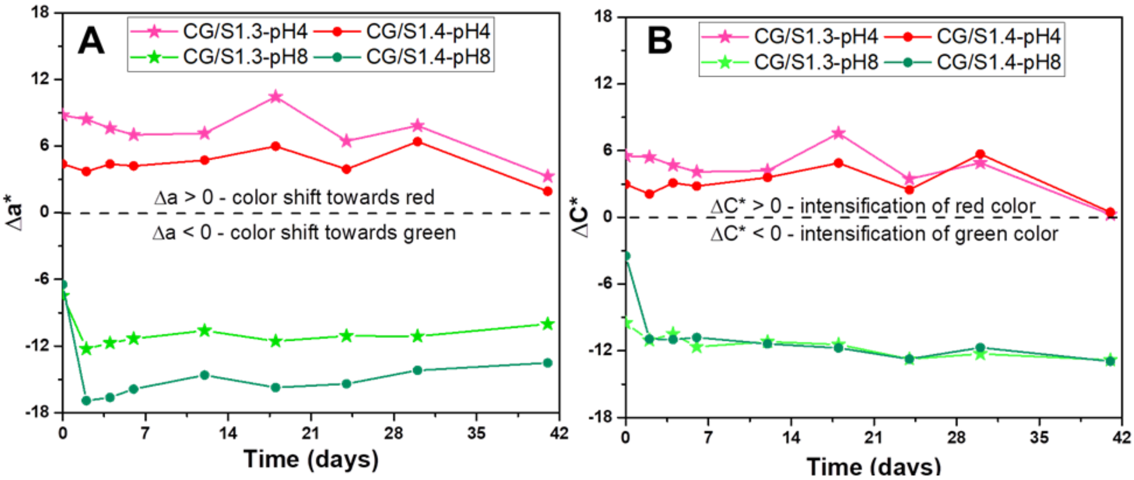


Figure Eroare! În document nu există text cu stilul precizat.**.2.** Color variation on the red-green color axis, a* (A) and chromaticity C* (B) for Xn cryogels containing different concentrations of BLB extract at pH = 4 and pH = 8.

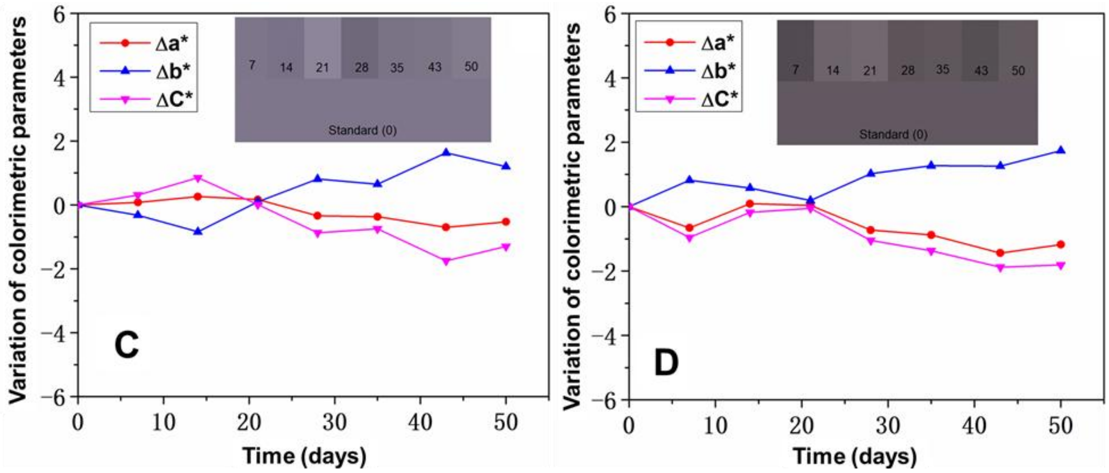


Figure Eroare! În document nu există text cu stilul precizat.**.3.** Color variation on the red-green (a*), yellow-blue (b*) and chromaticity color axis for cryogels CG/S1.2 (C) and

CG/S2b.1 (D) (inset: simulated color palette with measurements recorded at 7, 14, 21, 28, 35, 43, 50 days).

The chemically cross-linked cryogel **CG/S2a.1** showed a rapid colorimetric response (within < 1 h) and a detectable color change (ΔE > 5) upon exposure to ammonia concentrations ranging from 50 to 200 ppm (**Figure II.27A**), demonstrating its potential as a freshness indicator for protein-rich foods. Additionally, the cryogel displayed reversible color changes: from pink to blue upon exposure to ammonia vapors, and back to pink when exposed to acetic acid vapors (**Figure II.27D**). This reversible behavior was maintained even after four consecutive exposure cycles to acidic and alkaline conditions, confirming its reusability and chromogenic stability.

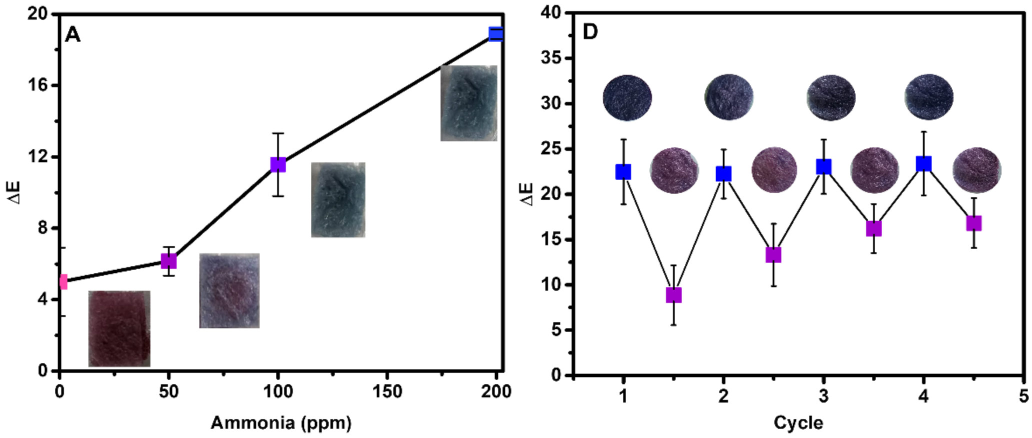


Figure Eroare! În document nu există text cu stilul precizat..**4**. (A) Color difference (ΔE) of **CG/S2a.1** after one hour of exposure to ammonia vapors of various concentrations. (D) Color reversibility of the **CG/S2a.1** cryogel under alternating exposure to alkaline and acidic vapors.

When cryogel **CG/S2a.1** was placed in contact with two *Carassius gibelio* (Prussian carp) specimens —stored for 24 h at 25 °C and 4 days at 4 °C, respectively a visible color change from pink to blue was observed, attributed to the diffusion of volatile amines released by the decaying meat (**Figure II.28**).

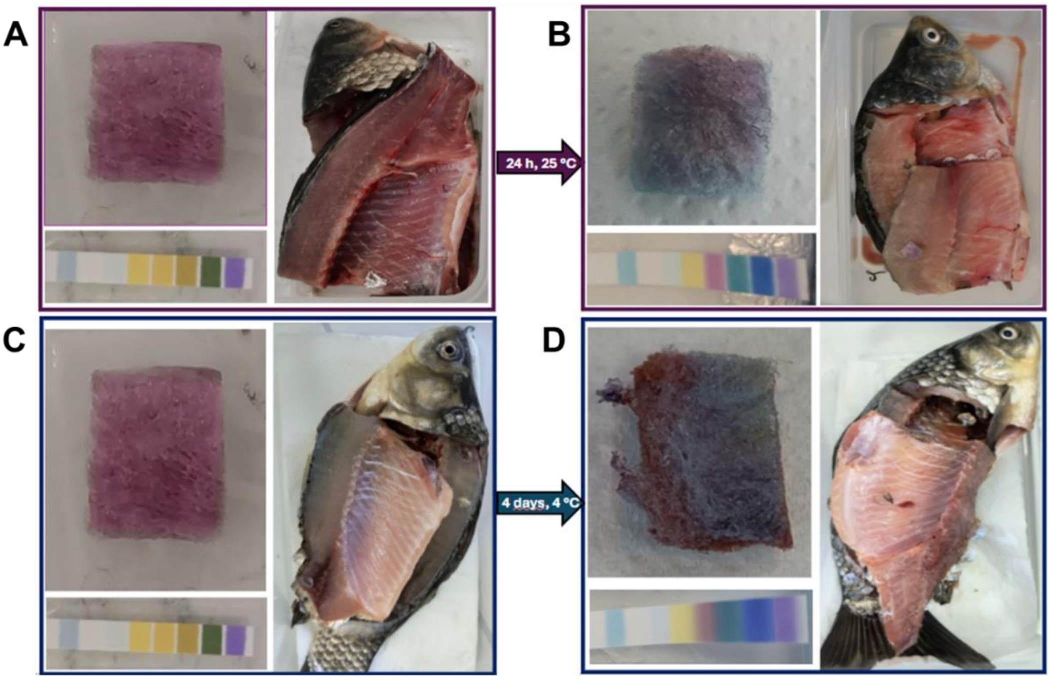


Figure II.28. (A–D) Visual appearance of cryogel **CG/S2a.1**, pH indicator paper, and *Carassius gibelio* before (A, C) and after storage: 24 h at 25 °C (B) and 4 days at 4 °C (D).

In conclusion, the bilberry extract was successfully encapsulated in physically or double cross-linked Xn-based biomaterials. These hybrid biomaterials exhibit a combination of mechanical robustness, structural stability, and multifunctional properties—antioxidant, antimicrobial, and chromogenic—highlighting their potential as pH-sensitive sensors for smart food packaging applications.

CHAPTER III. MULTIFUNCTIONAL CRYOGEL BIOMATERIALS BASED ON CHITOSAN AND CURCUMIN

III.2. Cryogels based on chitosan cross-linked with glutaraldehyde

In this study, CS sponges cross-linked with glutaraldehyde (GA) were prepared either by cryogelation or conventional gelation at room temperature. The properties of the obtained gels were influenced by CS concentration, the cross-linking ratio, and gelation temperature (**Platon** et al., 2023).

The influence of different CS concentrations and preparation conditions on the gel-forming ability, *GFY* and density values are shown in **Tabel III.1**.

Table Eroare! În document nu există text cu stilul precizat..1. Preparation conditions, appearance, *GFY* (%) and density of porous CS-GA hydrogels.

Sample code	CS, %	[a] GA, %	[b]GA, μmoli	[c]T, °C	Appearance	[d]*GFY*, %	[e]Density (g/cm^3)
CG0.5GA5	0.5	5	0.14	−20	Opaque, light yellow	86	0.00932
CG0.5GA7.5	0.5	7.5	0.22	−20		89	0.01066
CG0.5GA10	0.5	10	0.29	−20		89	0.01327
CG1GA5	1	5	0.14	−20	Opaque, light yellow	86	0.01287
CG1GA7.5	1	7.5	0.22	−20		86	0.01357
CG1GA10	1	10	0.29	−20		87	0.01422
CG2GA5	2	5	0.14	−20	Opaque, dark brown	97	0.01531
CG2GA7.5	2	7.5	0.22	−20		97	0.01972
CG2GA10	2	10	0.29	−20		87	0.02145
HG0.5GA10	0.5	10	0.29	21	No gel		
HG1GA10	1	10	0.29	21	No gel		
HG2GA10	2	10	0.29	21	Transparent, light yellow	94	

[a] represents the concentration of GA stock solutions, [b] is the amount of GA in μmoles added to the calculated reaction mixture per 1 mmol of NH$_2$ groups, [c] gelation temperature; [d, e] – average values.

The *GFY* values for cryogels ranged from 86% to 89%, indicating high gelation efficiency even at low CS concentrations (0.5%) and minimal cross-linker amounts (0.14

μmoles). This demonstrates that cryogelation allows gel formation under low reactant concentrations, which is not possible in the case of conventional gelation at room temperature.

FTIR spectroscopy confirmed the successful cross-linking of CS with GA, while SEM analysis revealed a heterogeneous porous morphology with interconnected, honeycomb-like pores. The relationship between composition and pore size was most evident in samples ***CG2GA5***, ***CG2GA7.5*** and ***CG2GA10***. These showed a trend toward smaller pore sizes (30-50 μm) with increasing cross-linking ratio and CS concentration attributed to a higher number of cross-linking points. In contrast, the ***HG2GA10*** sample, prepared at room temperature, exhibited poorly defined pores due to gelation occurring throughout the entire reaction system. The swelling behavior studies provided information on the stability of the gels over time, in both pH 2 and PBS solutions and provided insight into swelling equilibrium. The ***CG0.5GA10*** cryogels exhibited low stability, disintegrating after about 30 min in pH 2, and after about 1 hour in PBS.

Cryogels prepared from 1% and 2% CS solutions showed excellent mechanical properties (**Figure III.6**). Notably, ***CG2GA10*** maintained its original shape after 10 successive compression-relaxation cycles. In contrast, the hydrogel obtained at room temperature exhibited poor mechanical performance, due to its disorganized internal structure.

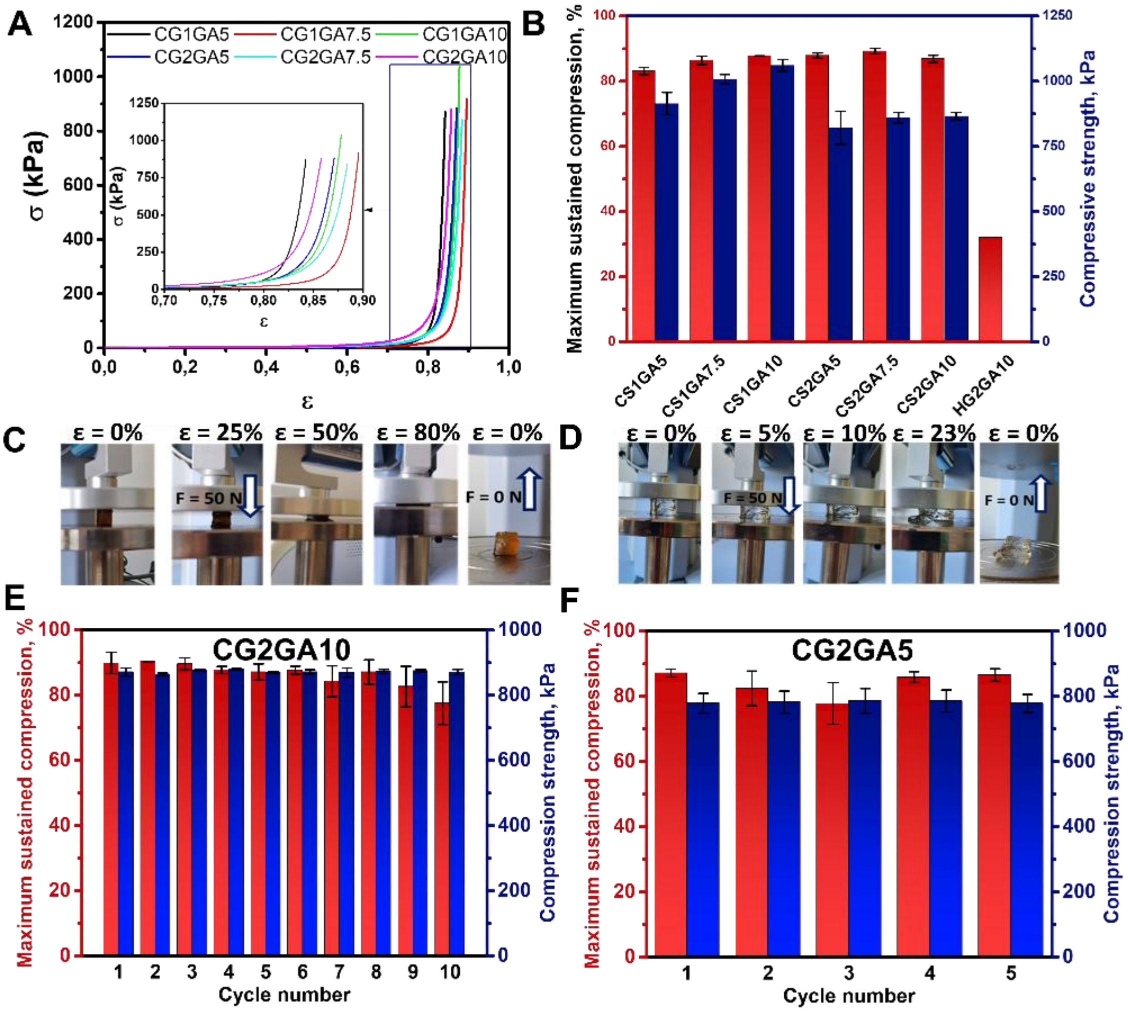


Figure Eroare! În document nu există text cu stilul precizat.**.5.** Stress-strain curves for CS-GA cryogels with different compositions (A); Maximum sustained compression (red) and compressive strength (blue) for different CS-GA cryogel formulayions (B); Optical images of the behavior of samples ***CG2GA10*** (C) and ***HG2GA10*** (D) during the application and removal of the compression force; Maximum sustained compression and compressive strength over multiple compression-relaxation cycles for ***CG2GA10*** (E) and ***CG2GA5*** (F) (**Platon** et al., 2023).

Antimicrobial activity tests showed that the cryogels possess remarkable antibacterial properties against both Gram-positive (*S. aureus*, *L. monocytogenes*) and Gram-negative (*E. coli*, *S. typhimurium*) bacterial strains.

III.3. Hybrid biomaterials based on chitosan and curcumin

Curcumin (CCM) was loaded into the cryogels, and FTIR analysis confirmed its successful incorporation. The morphological analysis revealed a reduction in pore size, indicating structural changes following CCM loading. For the evaluation of biomedical applicability, the CCM release kinetics were investigated in simulated gastrointestinal media. The experimental data were fitted with Higuchi, Korsmeyer–Peppas, and first-order kinetic models (**Figure III.14**).

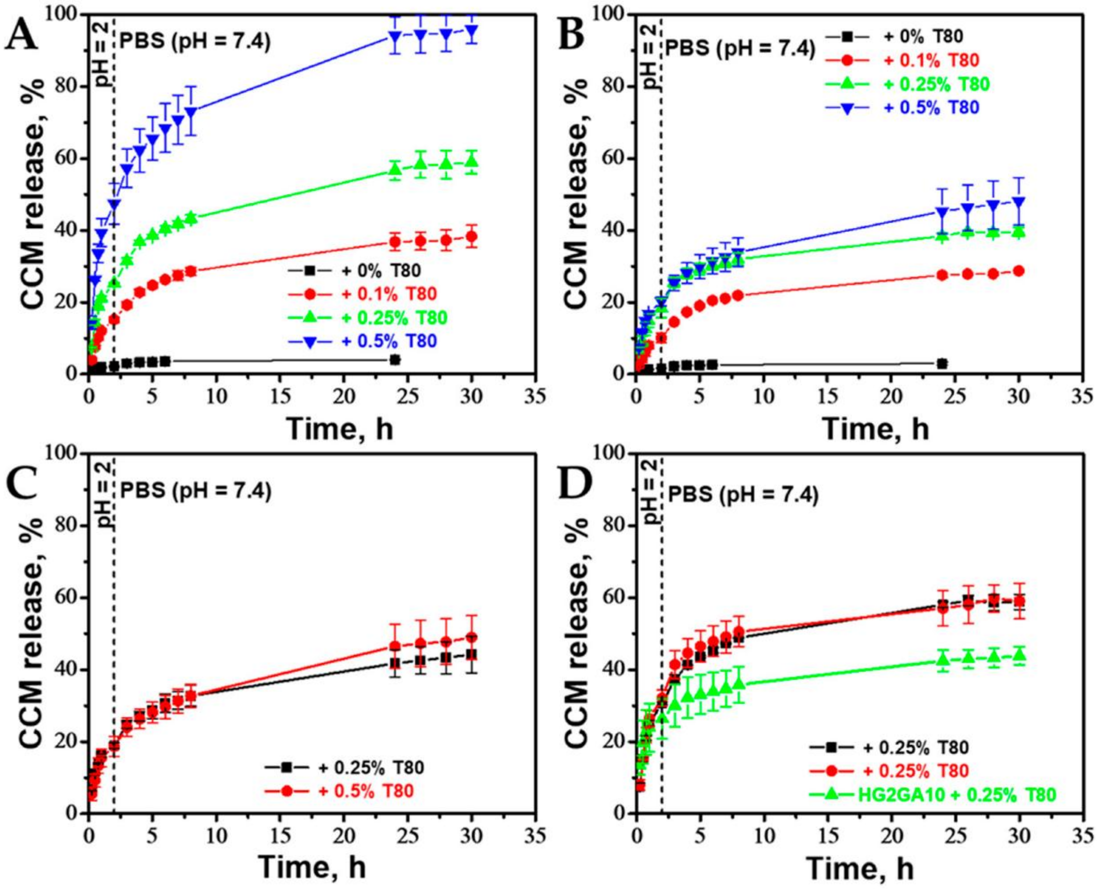


Figure III.14. Release kinetics of CCM (at 37 °C in pH 2 and PBS from (A) CG2GA5 sponges with different T80 concentrations, (B) CG2GA10 sponges with different T80 concentrations, (C) CG2GA7.5 cryogels with different T80 concentrations, and (D) CG0.5GA10, CG1GA10, and HG2GA10 sponges with 0.25 wt. % T80 (**Platon** et al., 2023).

Based on the values of the diffusion exponent (n_r) from the Korsmeyer-Peppas equation, a pseudo-Fickian diffusion-controlled release mechanism was identified. In conclusion, the cryogelation technique allows the design of CS-based gels at low reactant concentrations. The encapsulation of CCM in GA cross-linked CS-based cryogels represents a promising strategy for preserving the bioactivity of this polyphenol. These hybrid biomaterials also offer controlled and prolonged CCM release, enhancing their potential for biomedical applications.

CHAPTER IV. MULTIFUNCTIONAL CRYOGEL BIOMATERIALS BASED ON CHITOSAN DERIVATIVES AND *HYPERICUM PERFORATUM* L. EXTRACT

In this study, novel macroporous hybrid cryogel constructs comprising thiourea-containing chitosan (CSTU) derivative and a *Hypericum perforatum* L. extract (HYP_E), were prepared (**Platon** et al., 2024).

IV.2. Cryogels based on chitosan functionalized with thiourea

The first objective was to optimize the preparation conditions for biopolymer matrices by modifying CS with thiourea and cross-linking with formaldehyde (FA) (**Figure IV.2**) (Ghiorghita, Lazar, **Platon** et al., 2023). Structural characterization (FTIR; ^{13}C-NMR – **Figure IV.4**), along with morphological (SEM), mechanical, and antibacterial analyses 9against *S. aureus* and *E. coli*) led to the selection of optimal design parameters for these biomaterials.

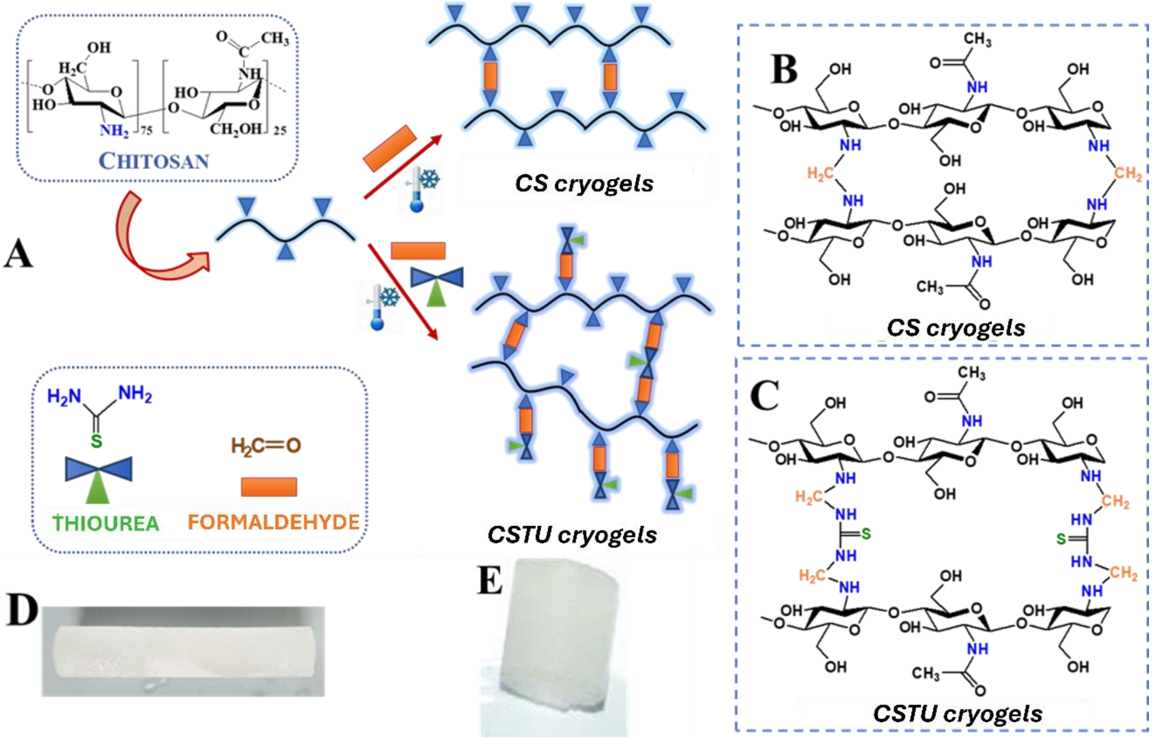


Figura Eroare! În document nu există text cu stilul precizat..**6.** Schematic representation of the preparation principle of FA-cross-linked CS and CSTU cryogels (A). Chemical structures of CS (B) and CSTU (C) cryogels showing the cross-linking with FA and modification with thiourea. Optical images of CS cryogel, as monolith (D) and in wet state (E) (Ghiorghita, Lazar, **Platon** et al., 2023)

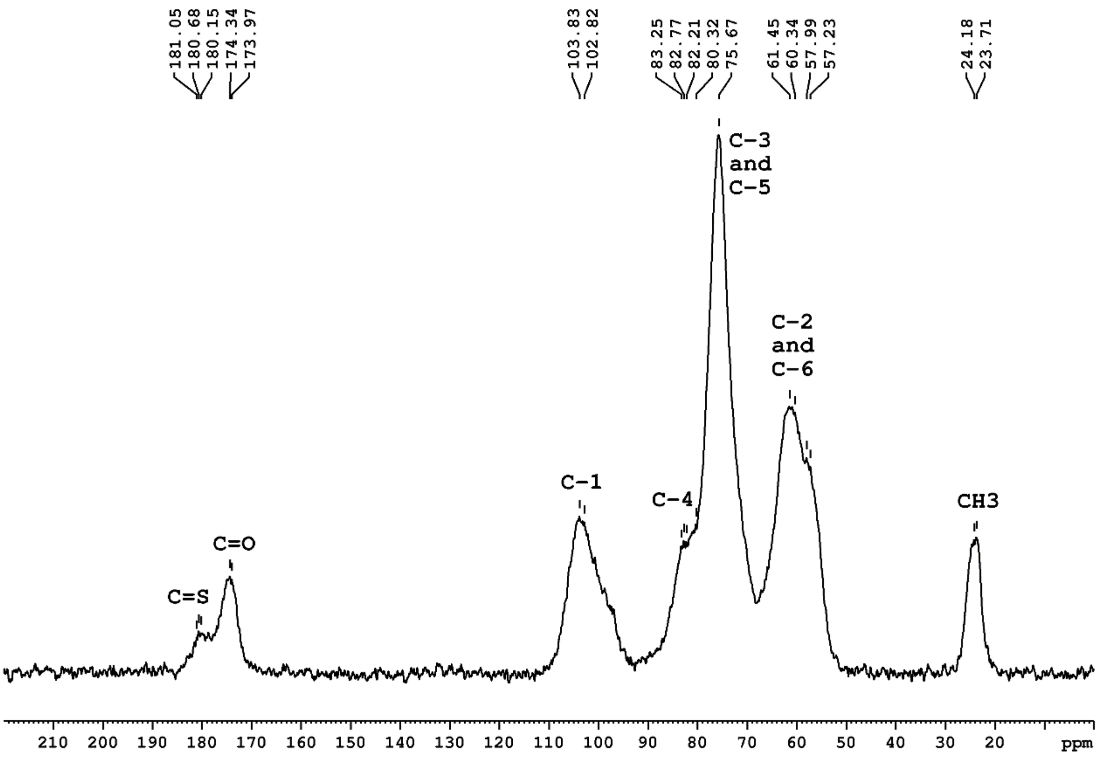


Figure Eroare! În document nu există text cu stilul precizat..**7.** ^{13}C CP-MAS spectrum of **CSTU2.5** cryogel.

IV.3. Preparation and chemical characterization of *Hypericum perforatum* L. extract

Hypericum perforatum L. extract was obtained through maceration using 70% ethanol. Using thin-layer chromatography (TLC) and reversed-phase high-performance liquid chromatography (RP-HPLC), hyperforin, adhyperforin, hypericin, pseudohypericin, rutoside, hyperoside, isoquercitrin, quercetin, apigenin-7-*O*-glucoside, biapigenin, kaempferol glycosides, chlorogenic acid, and various other phenolic acids were identified in the composition of HYPE. The total polyphenolic content was 330,8 mg GAE/g dry extract. Antioxidant assays determined the extract concentration capable of inhibiting over 90% of DPPH free radicals.

IV.4. Hybrid biomaterials based on chitosan derivatives and *Hypericum perforatum* L. extract

Hybrid cryogels were prepared by incorporating the HYPE extract during the CSTU gel preparation stage (**Figure IV.15**). All compositions achieved *GFY* values above 90%, indicating an excellent conversion of components into gels (**Platon** et al., 2024).

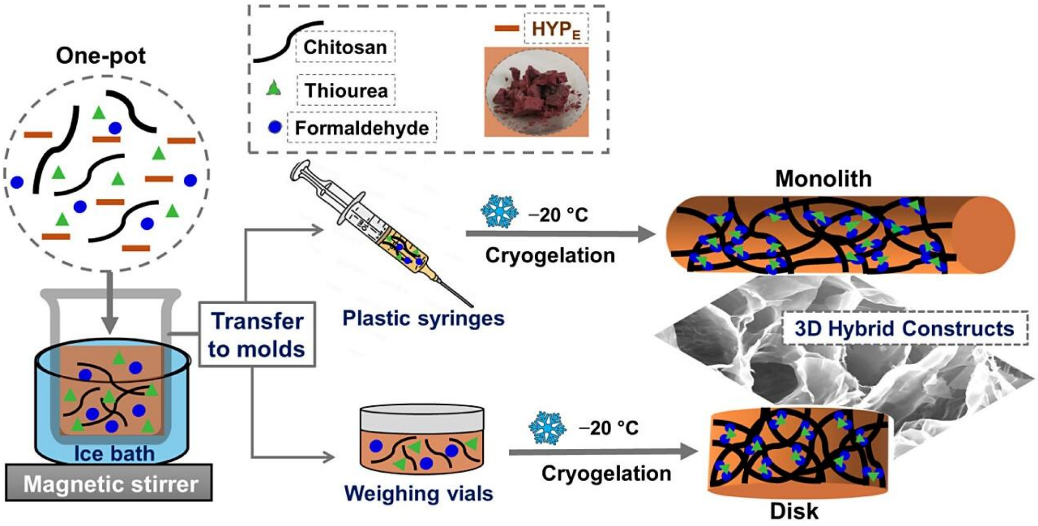


Figure Eroare! În document nu există text cu stilul precizat..**8.** Schematic diagram of the preparation process of the HYP$_x$ hybrid cryogel constructs.

Optical images of hybrid cryogels, both in disc and monolith form, confirmed the inclusion of HYP$_E$ in the 3D polymer network (**Figure IV.16**).

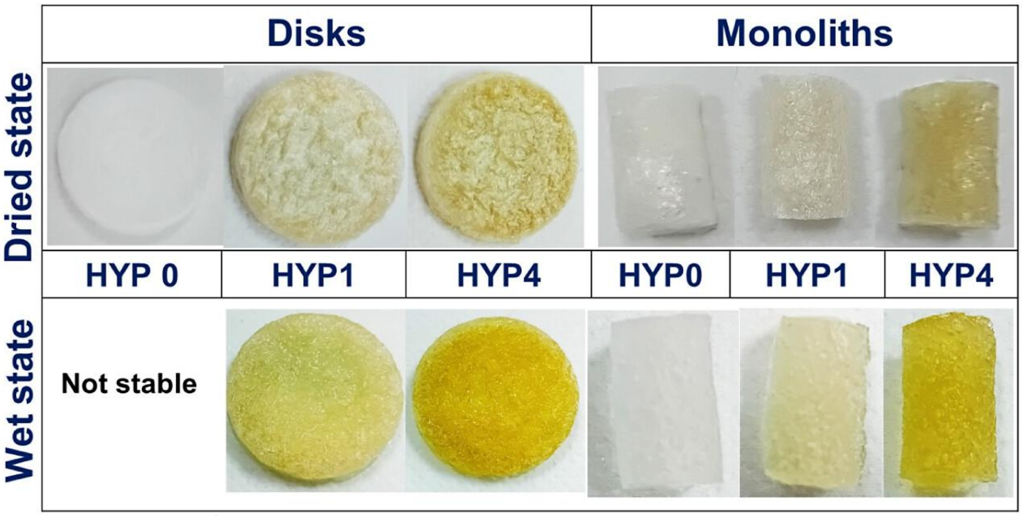


Figure Eroare! În document nu există text cu stilul precizat..**9**. Optical images of dry or wet cryogels, prepared in the form of monoliths or discs and containing different amounts of HYP$_E$.

Structural (FTIR, ^{13}C-NMR) and morphological analysis confirmed successful incorporation of the extract and preservation of the porous structure characteristic of hydrogels prepared by cryogelation and dried by freeze-drying. The pore size of the **HYP0** cryogels ranged from 70 to 120 µm, while the incorporation of HYP$_E$ reduced pore size to about 40 – 90 µm, indicating strong interaction between HYP$_E$ components and CS functional groups.

Regardless of HYP_E content, the hybrid cryogels maintained low density (0.0180 g/cm3 to 0.0264 g/cm3; (**Eroare! Fără sursă de referință.B**)) and approximately 98% porosity, classifying them as ultralight materials, i.e. aerogels. Swelling studies proved their superabsorbent character, with swelling capacities ranging from 14266% and 31605% in pH 2 (**Figure IV.22B**).

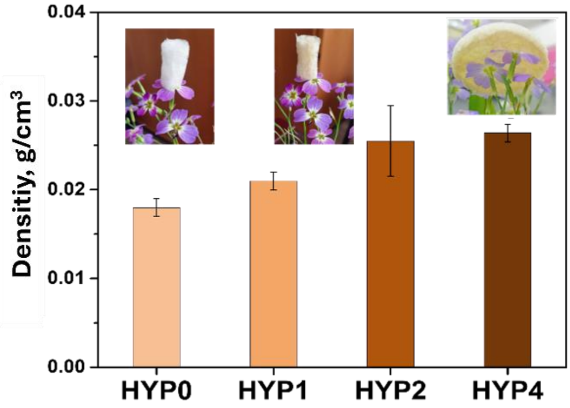


Figure IV.18B. Density of cryogels with different contents of HYP_E; the insets illustrate the optical images of freeze-dried cryogels placed on *Oxalis* flowers to indicate their ultralight properties (**Platon** et al., 2024).

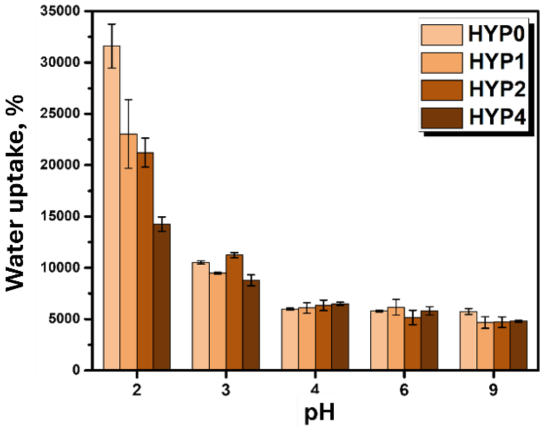


Figure IV.22B. Swelling capacity after 24 h at different pH values (**Platon** et al., 2024).

Uniaxial compression tests confirmed the rigidity of the dry cryogel network and the outstanding elasticity of the samples in the swollen state (**Figure IV.23**). The physical interactions between HYP_E and the three-dimensional polymer newtork contributed to enhanced compressive strength. Cryogels showed the ability to return to their original shape after the removal of the force applied due to reversible water movement within the matrix (**Figure IV.23H**).

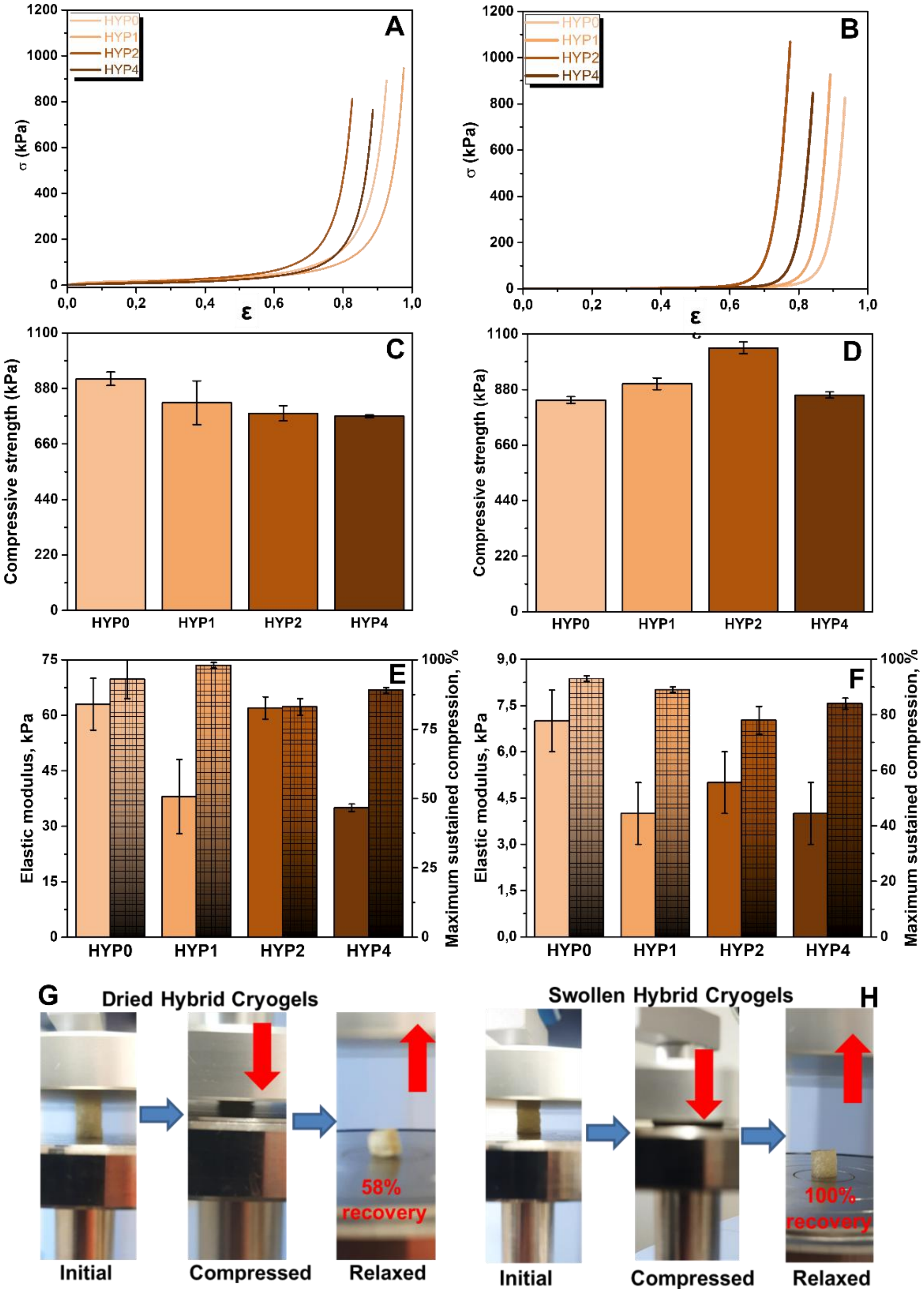


Figure Eroare! În document nu există text cu stilul precizat.**.10.** Stress-strain curves (A,B), compressive strength (C, D), elastic modulus and maximum sustained compression (E, F) of hybrid cryogels in both dried (A, C, E, G) and swollen (B, D, F, H) states. Optical images of dried (G) and swollen (H) hybrid cryogels (sample **HYP4**) before and after 100% compression demonstrating 58% shape recovery for the dry sample and 100% for the swollen sample (**Platon** et al., 2024).

The antioxidant activity of the extract decreased after incorporation into the CSTU-based matrices (**Figure IV.24A**). However, antimicrobial testing revealed a synergistic effect, consisting in an increase of inhibition diameters and a broadening of the spectrum (**Figure IV.24B**).

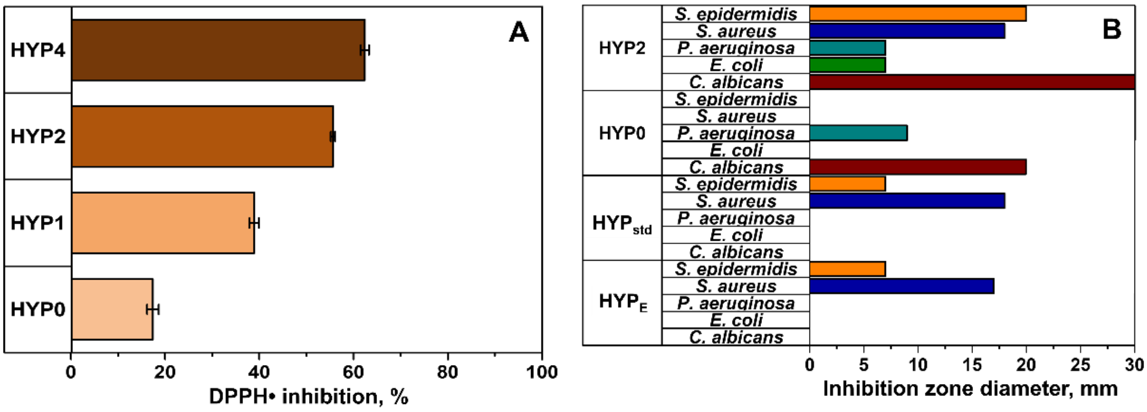


Figure Eroare! În document nu există text cu stilul precizat..**11.** (A) DPPH radical scavenging activity of CSTU/HYP$_E$ hybrid cryogels; (B) Antimicrobial activity of HYP$_E$, HYP$_{std}$ extracts, and hybrid cryogels (**Platon** et al., 2024).

Biocompatibility testing using the NHDF cell line showed cell viability above 85% for both CSTU and HYP$_E$-containing cryogels (**Figure IV.25**).

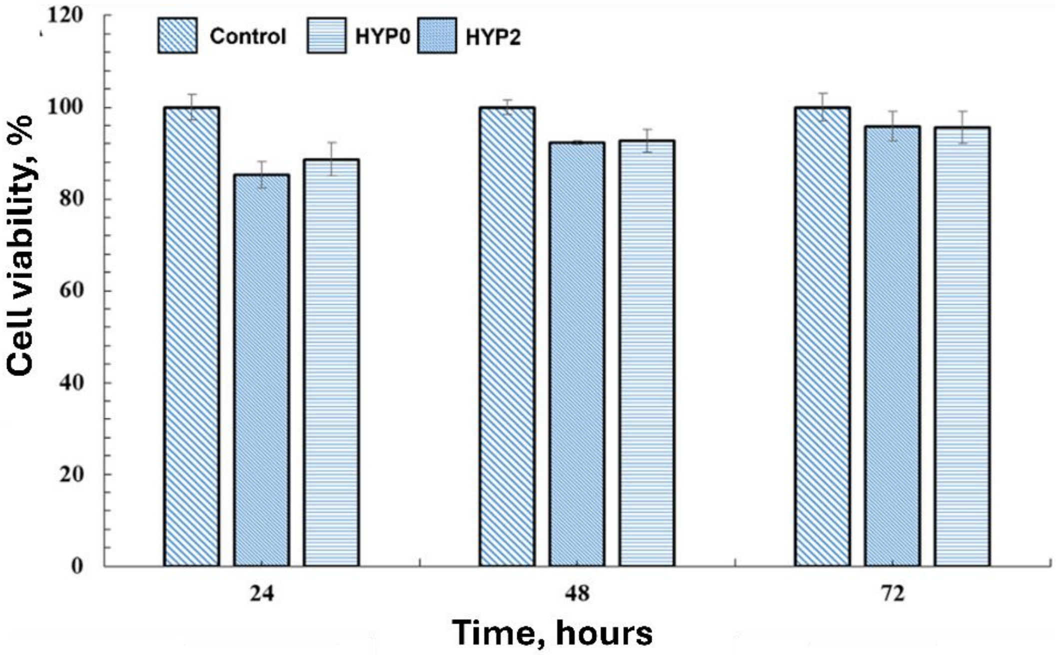


Figure Eroare! În document nu există text cu stilul precizat..**12.** Cell viability (%) of NHDF cells in direct contact with **HYP0** and **HYP2** cryogels, measured by MTT assay (**Platon** et al., 2024).

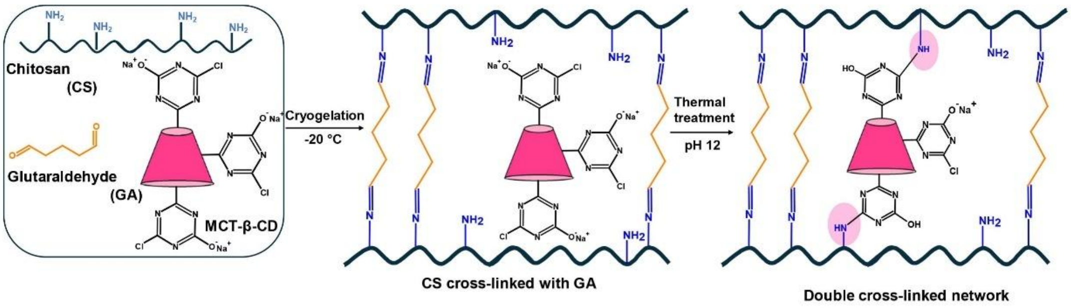
In conclusion, the successful incorporation of the St. John's wort extract in the FA-cross-linked CSTU matrices was achieved. These hybrid biomaterials exhibit multifunctional properties, including superabsorbency, excellent mechanical performance, antioxidant and antimicrobial effects, cytocompatibility, highlighting their potential for biomedical applications.

CHAPTER V. MULTIFUNCTIONAL CRYOGEL BIOMATERIALS BASED ON DOUBLE CROSS-LINKED CHITOSAN AND THYMOL

V.2. Cryogels based on chitosan and cavasol

This chapter presents the preparation strategies for porous cryogel composites composed of CS and monochlorotriazinyl-β-cyclodextrin (MCT-β-CD or cavasol), in the form of monoliths. Network stabilization was achieved by double cross-linking of CS with GA and MCT-β-CD, using two techniques: either by initial mixing of the reactants or by successive cross-linking, first with GA and then with MCT-β-CD (**Figure V.1**). In both methods, the GA cross-linking was performed under cryogelation conditions, while MCT-β-CD cross-linking was carried out by thermal treatment, with optimal conditions identified as 1 h at 70 °C and 3 h at 80 °C (Dragan, **Platon** și colab., 2025).

1st Strategy



2nd Strategy

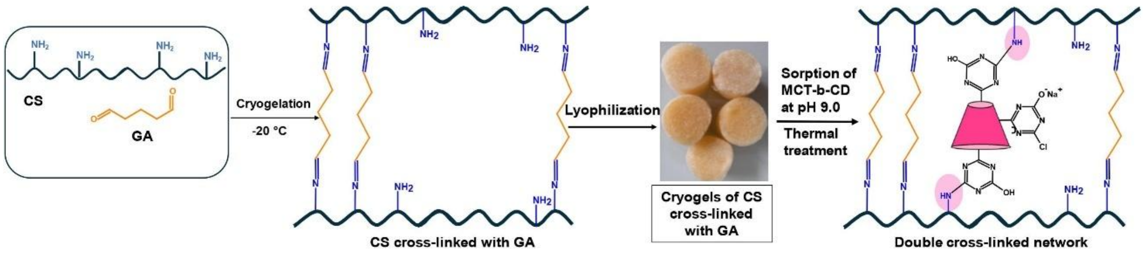


Figure V.1. Schematic representation of the strategies used for the fabrication of CS-based cryogels as hosts for thymol (Dragan, **Platon** et al., 2025).

Successful cross-linking with MCT-β-CD of CS-composite cryogels was confirmed through FTIR spectroscopy (**Figure V.3**), ^{13}C-NMR (**Figure V.4**) EDX analysis and morphological evaluation by SEM.

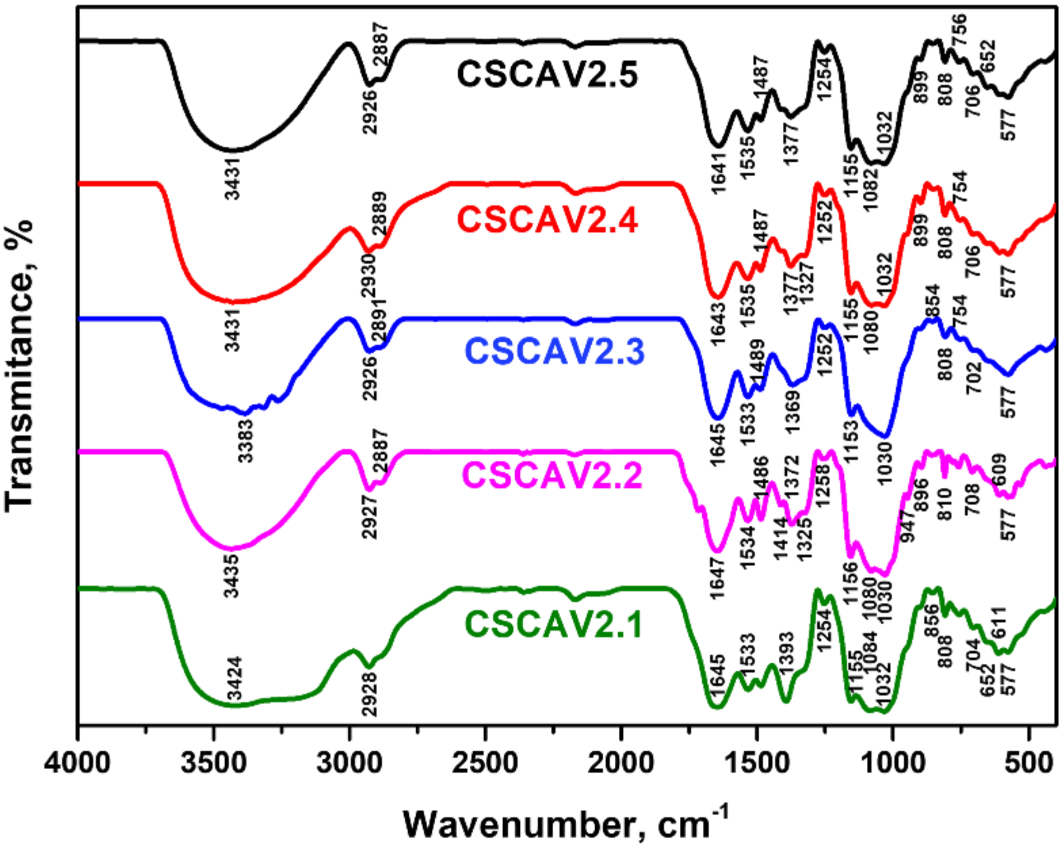


Figure Eroare! În document nu există text cu stilul precizat.**.13.** FTIR spectra of CS-based biocomposites prepared by strategy 2 (Dragan, **Platon** et al., 2025)

The average pore size ranged from 73 μm to 149 μm, depending on the preparation strategy, reactant concentrations, and thermal conditions. The mechanical properties of CSCAV biocomposites were evaluated by uniaxial compression measurements. The results showed that all biocomposites can sustain a deformation of more than 74 %, characteristic for porous materials obtained by the cryogelation process. The compressive strength was higher in the case of composites obtained by successive cross-linking, reaching values of up to 294 kPa (**CSCAV2.3**).

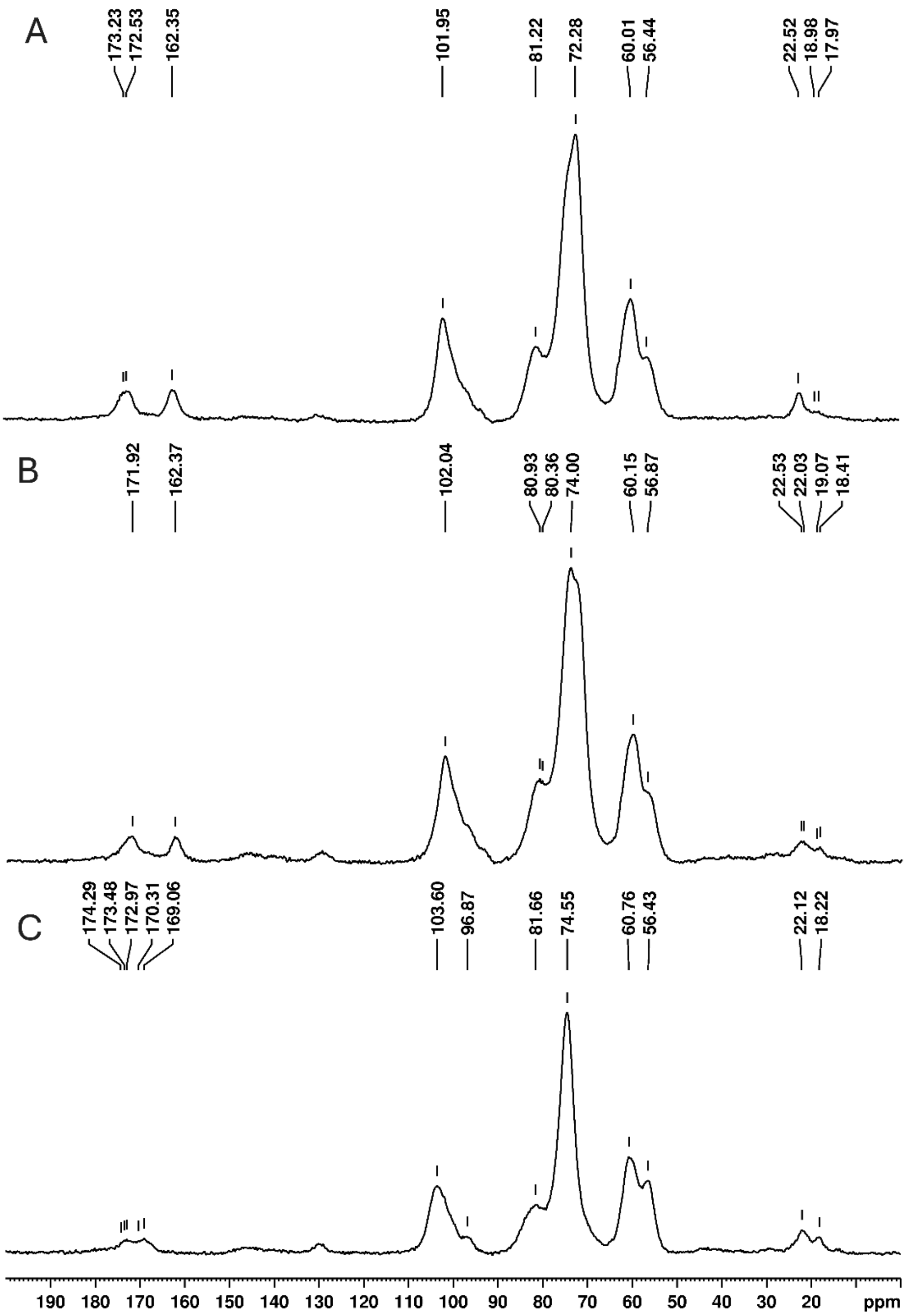


Figure Eroare! În document nu există text cu stilul precizat.**.14.** ^{13}C CP-MAS spectra of **CS207_5%GA** (A), **CSCAV.1.3** (B) and **CSCAV.2.3** (C), recorded at 100,6 MHz (Dragan, **Platon** et al., 2025).

V.3. Hybrid biomaterials based on double-cross-linked chitosan and thymol

Porous CS-based biocomposites were able to incorporate thymol, a terpenoid with remarkable antioxidant properties (**Figure V.8A**). The hybrid CSCAV/thymol biomaterials showed excellent DPPH free radical scavenging properties, exceeding 85% inhibition (**Figure V.8B** and **C**). **CSCAV1.3** cryogel with thymol retained over 50% antioxidant activity even after 15 days of storage (**Figure V.8D**).

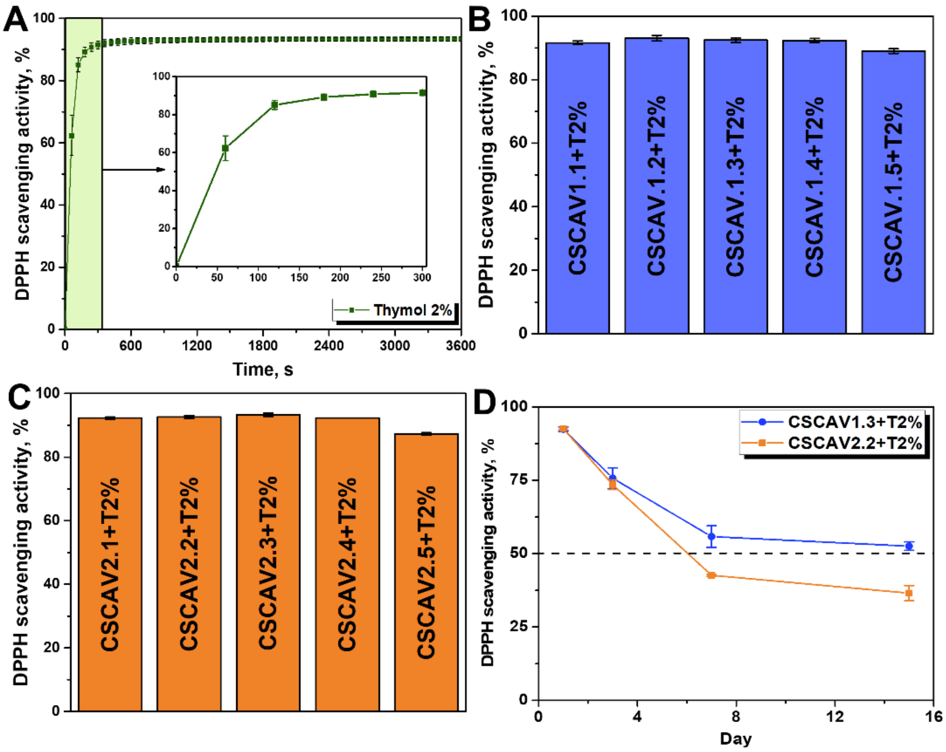


Figure V.8. Antioxidant activity of thymol (A) and biocomposites prepared by strategy 1 (B) and strategy 2 (C) respectively; DPPH radical scavenging activity of biocomposites over time (D) (Dragan, **Platon** et al., 2025).

Composites with or without thymol demonstrated increased antibacterial efficacy against *S. aureus* (up to 100%), regardless of the preparation strategy. In contrast, the antibacterial activity of thymol-free cryogels against *E. coli* ranged from 40 % (**CSCAV1.3**) to 63 % (**CSCAV1.4**), while all thymol-containing composites obtained by strategy 1 had an antibacterial efficacy of 100 % (Dragan, **Platon** et al., 2025).

In conclusion, the developed CS-based biocomposites, stabilized via double cross-linking and functionalized with thymol, exhibit a highly porous internal structure, excellent mechanical strength, superior swelling ability, and notable antioxidant and antimicrobial performance. These multifunctional properties highlight the potential of these materials for biomedical applications.

CONCLUSIONS

1. Multifunctional cryogel biomaterials based on xanthan and anthocyanin-rich extracts

This chapter presents the preparation, properties, and potential applications of hybrid cryogel biomaterials based on xanthan (Xn) and anthocyanin-rich extracts.

- Extracts from three berry species (bilberries, blackcurrants, and blackberries) were obtained and analyzed in terms of their phytochemical profiles, antioxidant activity, and stability.
- Phytochemical analyses revealed that the bilberry extract (***Af)*** has the highest polyphenolic content and the strongest antioxidant activity against the DPPH free radicals.
- The ***Af*** extract exhibited **limited stability** in aqueous solutions (2-12 days, depending on pH), which emphasizes **the need** for its encapsulation **in polymer matrices**.
- Xn and PVA-based cryogels were obtained by freeze-thaw cycles, as well as Xn-based cryogels cross-linked with 1,4-butanediol diglycidyl ether (1,4-BDGE), dried either by freeze-drying or in the oven.
- Structural (FTIR) and morphological (SEM) analyses confirmed the successful incorporation of the ***Af*** extract and revealed a porous architecture.
- The increase in the amount of extract positively influenced the mechanical and rheological properties of cryogels, leading to network stiffening and improvements in compressive strength and elastic modulus.
- The incorporation of the extract accentuated the hydrophobic character of the cryogels (by increasing the contact angle values) and reduced their swelling capacity.
- The Xn-based matrices preserved the **antioxidant activity** of the ***Af*** extract, and its presence had a beneficial role on the ability to **inhibit bacterial growth,** reaching an efficiency of 100% against *Salmonella typhimurium*, *Escherichia coli* and *Listeria monocytogenes*.
- Encapsulation of the ***Af*** extract in Xn-based biomaterials significantly **improved its stability**, as demonstrated by relatively constant colorimetric parameters during **42 days** (under acidic or alkaline pH conditions) and up to **50 days** under normal conditions.
- Xn/ ***Af*** -based biomaterials also showed a **rapid and easily detectable response to different concentrations of ammonia**.

- Biomaterials based on Xn and ***Af*** extract were successfully tested as **freshness indicators** for protein-rich foods, such as Prussian carp (Carassius gibelio).

2. **Multifunctional cryogel biomaterials based on chitosan and curcumin**

In this chapter, the preparation of novel systems was investigated based on chitosan (CS) cross-linked with glutaraldehyde (GA) by the cryogelation method, respectively conventional gelation at room temperature.

- FTIR spectroscopy confirmed the successful cross-linking of CS with GA, while SEM analysis revealed a porous, honeycomb-like structure.
- The swelling behavior study provided information on the stability of the gels over time, as well as on the kinetics of the swelling equilibrium.
- The optimal preparation parameters were identified for obtaining **cryogels with excellent mechanical properties** and **the ability to return to their initial shape** after 10 successive compression-relaxation cycles.
- The superior morphological and mechanical properties of cryogels compared to conventional hydrogels **were highlighted**.
- **Antimicrobial tests** have shown that cryogels have remarkable antibacterial properties against both Gram-positive (*Staphylococcus aureus, Listeria monocytogenes*) and Gram-negative (*Escherichia coli, Salmonella typhimurium*) bacterial strains.
- The incorporation of curcumin into biomaterials led to a reduction in pore size, and the release mechanism of curcumin followed a pseudo-Fickiandiffusion model.
- The cryogel biomaterials were able **to maintain the antioxidant activity** of curcumin.

3. **Multifunctional cryogel biomaterials based on chitosan and *Hypericum perforatum* L. extract**

In this study, cryogels based on thiourea (TU)-functionalized CS were developed for the incorporation of *Hypericum perforatum* L. (HYP_E) extract.

- The preparation conditions for the biopolymer matrices were optimized by modifying CS with TU and cross-linking with formaldehyde. The resulting materials were characterized structurally (FTIR, ^{1}H-NMR, ^{13}C-NMR), morphologically (SEM), mechanically, and their antimicrobial properties were assessed.
- *The Hypericum perforatum* L. extract was obtained and analyzed both qualitatively and quantitatively.

- The optimal extract concentration required to inhibit over 90% of DPPH free radicals was determined.
- The incorporation of the extract into the biomaterials did not alter theporous internal structure characteristic of cryogels.
- The **superabsorbent character** of the prepared materials has been proven. The swelling capacity of cryogels with HYP_E was higher than that of commercial wound dressings based on natural or synthetic polymers.
- The materials exhibited both rigidity in the dry state and elasticity upon hydration, highlighting their mechanical adaptability.
- The presence of the HYP_E extract in biomaterials led to an increase in compressive strength.
- Cryogels exhibited **the ability to return to their initial shape** after the removal of applied mechanical stress.
- A synergism between the biopolymer matrix and the extract was observed, resulting in larger inhibition zones and **a broader antimicrobial spectrum**.
- Both the extract and the prepared cryogels showed **cytocompatibility** with human fibroblasts.

4. Multifunctional cryogel biomaterials based on cross-linked double chitosan and thymol

This chapter describes the preparation strategies employed to develop porous cryogel composites based on chitosan and a derivative of β-cyclodextrin (MCT-β-CD).

- Network stabilization was achieved using two cross-linking agents for chitosan and following two strategies: either by initial mixing of the reactants or by sequential cross-linking.
- The successful incorporation of MCT-β-CD into the CS composite cryogels was confirmed by structural (FTIR, ^{13}C-NMR) and elemental (EDX) analyses; morphological analysis (SEM) revealed a well-defined porous internal structure.
- It was found that the preparation strategy influenced the mechanical properties of the prepared biomaterials, with the sequential method yielding materials with superior **compressive strength**.
- The incorporation of thymol into the prepared biomaterials reduced its volatility and endowed the materials with excellent **antioxidant activity**.

- Thymol-loaded cryogels demonstrated an enhanced **antibacterial efficacy** against *Staphylococcus aureus* and *Escherichia coli.*

FUTURE PERSPECTIVES

The results obtained in this PhD studies provide a foundation for further exploration of the designed biomaterials in biomedical and food-related applications:

- The outstanding properties of hybrid biomaterials based on xanthan and anthocyanin monomers from bilberries could support the development of smart food packaging systems with commercial potential, contributing to improved food sustainability and safety.
- The inclusion of St. John's wort extract into biopolymeric biomaterials can be used in the development of wound dressings or other medical devices intended for the treatment of dermopathologies, having beneficial effects on wound healing.
- Cryogelation emerges as a promising technique for developing advanced controlled-release pharmaceutical systems, and stabilizing highly volatile compounds, with potential applications in both the pharmaceutical and food industries.

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SCIENTIFIC ACTIVITY

Papers published in ISI-rated scientific journals during the PhD program:

1. **Platon, I.-V.**; Ghiorghita, C.-A.; Lazar, M.M.; Raschip, I.E.; Dinu, M.V., **2023**. Chitosan Sponges with Instantaneous Shape Recovery and Multistrain Antibacterial Activity for Controlled Release of Plant-Derived Polyphenols. *International Journal of Molecular Sciences,* 24(5), 4452. https://doi.org/10.3390/ijms24054452 (FI$_{2023}$ = 4.9; Q1);
2. Ghiorghita, C.-A.; Lazar, M. M.; **Platon, I.-V.**; Humelnicu, D.; Doroftei, F.; Dinu, M.V., **2023**. Feather-weight cryostructured thiourea-chitosan aerogels for highly efficient removal of heavy metal ions and bacterial pathogens. *International Journal of Biological Macromolecules,* 235. https://doi.org/10.1016/j.ijbiomac.2023.123910 (FI$_{2023}$ = 7.7; Q1);
3. Ghiorghita, C.-A., **Platon, I.-V.**, Lazar, M.M., Dinu, M.V., Aprotosoaie, A.C., **2024**. Trends in polysaccharide-based hydrogels and their role in enhancing the bioavailability and bioactivity of phytocompounds. *Carbohydrate Polymers*, 334, 122033. https://doi.org/10.1016/j.carbpol.2024.122033 (FI$_{2023}$ = 10.7; Q1);
4. **Platon, I.-V.;** Ghiorghita, C.-A.; Lazar, M.M.; Aprotosoaie, A.C.; Gradinaru, A.C.; Nacu, I.; Verestiuc, L.; Nicolescu, A.; Ciocarlan, N.; Dinu, M.V., **2024**. Highly Compressible, Superabsorbent, and Biocompatible Hybrid Cryogel Constructs Comprising Functionalized Chitosan and St. John's Wort Extract. *Biomacromolecules*, 25 (8), 4615-5388 https://doi.org/10.1021/acs.biomac.4c00496 (FI$_{2023}$ =5.5; Q1);
5. Dragan, E.S.; **Platon, I.-V.**; Nicolescu, A.; Dinu, M.V. **2025.** Structural, mechanical, antioxidant and antibacterial properties of double cross-linked chitosan cryogels as hosts for thymol. *International Journal of Biological Macromolecules,* 304, 140968 https://doi.org/10.1016/j.ijbiomac.2025.140968 (FI$_{2023}$ = 7.7; Q1);
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1. **Platon, I.-V.;** Raschip, I.E.; Aprotosoaie, A.C.; Gradinaru, A. C.; Dinu, M.V. *Development of bioactive hydrogels containing Thymus vulgaris essential oil by ice template-assisted freeze-drying technique.* ICMPP – Open Door to The Future. Scientific Communications of Young Researchers (MacroYouth) - 2nd edition – Iași, 19.11.2021.
2. Dinu, M.V.; Lazar, M.M.; Raschip, I.E.; Ghiorghita, C.-A.; **Platon, I.-V..** *Recent advances in multicomponent polymer systems with controlled 3D architectures.* Congresul Internațional al Universității „Apollonia" din Iași – Iași, 28.02-02.03.2022
3. **Platon, I.-V.**; Ghiorghita, C.-A.; Lazar, M.M; Dinu, M.V. *A one-pot approach to prepare elastic, but robust macroporous chitosan hydrogels functionalized with thiourea.* ICMPP – Open Door to The Future. Scientific Communications of Young Researchers (MacroYouth) – Iași, 18.11.2022
4. **Platon, I.-V.;** Ghiorghita, C.-A.; Lazar, M.M; Raschip, I.E.; Aprotosoaie, A.C.; Dinu, M.V. *Optimizarea bioactivitatii curcuminei prin încapsulare în hidrogeluri poroase pe bază de chitosan.* Congresul Național de Farmacie 2023 – Cluj-Napoca, 27-29.09.2023
5. **Platon, I.-V.;** Ghiorghita, C.-A.; Lazar, M.M; Raschip, I.E.; Dinu, M.V. *Innovative polysaccharide-based sponges with instantaneous shape recovery and multistrain antibacterial activity for controlled release of curcumin.* ICMPP – Open Door to The Future. Scientific Communications of Young Researchers (MacroYouth) – Iași, 17.11.2023
6. **Platon, I.-V.;** Ghiorghita, C.-A; Aprotosoaie, A.C.; Lazar, M.M; Dinu, M.V. *New biomaterials based on chitosan functionalized with thiourea and Hypericum perforatum L. extract for biomedical applications.* Congresul Internațional „Pregătim viitorul promovând excelența!" al Universității Apollonia – Iași 27.02– 01.03.2025

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1. **Platon, I.-V.**; Ghiorghita, C.-A.; Lazar, M.M; Raschip, I.E.; Dinu, M.V. *Textural and mechanical features of porous chitosan-based hydrogels*. International Conference on Rheology – Iași, 26.05.2022, Iași
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3. **Platon, I.-V.**; Aprotosoaie, A.C.; Raschip, I.E.; Dinu, M.V. *Plant-derived polyphenols: chemical structure and biological activity.* PSE Meeting 2022 - Natural Products in Drug Discovery and Development – Advances and Perspectives – Iași, 19-22.09.2022
4. **Platon, I.-V.**; Ghiorghita, C.-A., Lazar, M.M.; Humelnicu, D.; Dinu, M.V. *Chitosan and thiourea-chitosan ultra-lightweight macroporous hydrogels as efficient sorbents for removal of Ag(I) and Pb(II) ions*. ICCE 2022 - International Conference on Chemical Engineering – Iași, 15-17.10.2022
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Research projects (team member):

- Immobilization of anthocyanins in polysaccharide-based materials for obtaining smart ecological food packaging, project PN-III-P1-1.1-TE-2021-1683 (TE 6/2022), team member (research assistant-PhD student) during 2022-2024.
- New adsorbent materials based on metal ion-rich composites with applications in waste minimization and sustainable circular economy, project PN-III-P1-1.1-TE-2021-0771 (TE 3/2022), team member (research assistant-PhD student) during 2022-2024

Patents applied for: 3

Patent Name/Patent Application	**Registration number**	**Authors**
Procedeu de obţinere a unor criogeluri superabsorbante pentru păstrarea umidităţii solului	Application No.: a00520 / Date of Registration: 21-09-2023	Claudiu-Augustin Ghiorghiţă; Maria Marinela Lazăr; **Ioana-Victoria Platon**; Maria Valentina Dinu
Procedeu de obtinere a unor ambalaje ecologice inteligente	Application No.: a00205 / Date of Registration: 24-04-2024	Irina Elena Răschip; Nicușor Fifere; **Ioana-Victoria Platon**; Maria Valentina Dinu
Biocompozite poroase pe bază de chitosan pentru controlul bioactivităţii terpenelor şi terpenoidelor volatile	Application No.: a00342 / Date of Registration: 19-06-2024	Ecaterina Stela Dragan, Maria Valentina Dinu, **Ioana-Victoria Platon**