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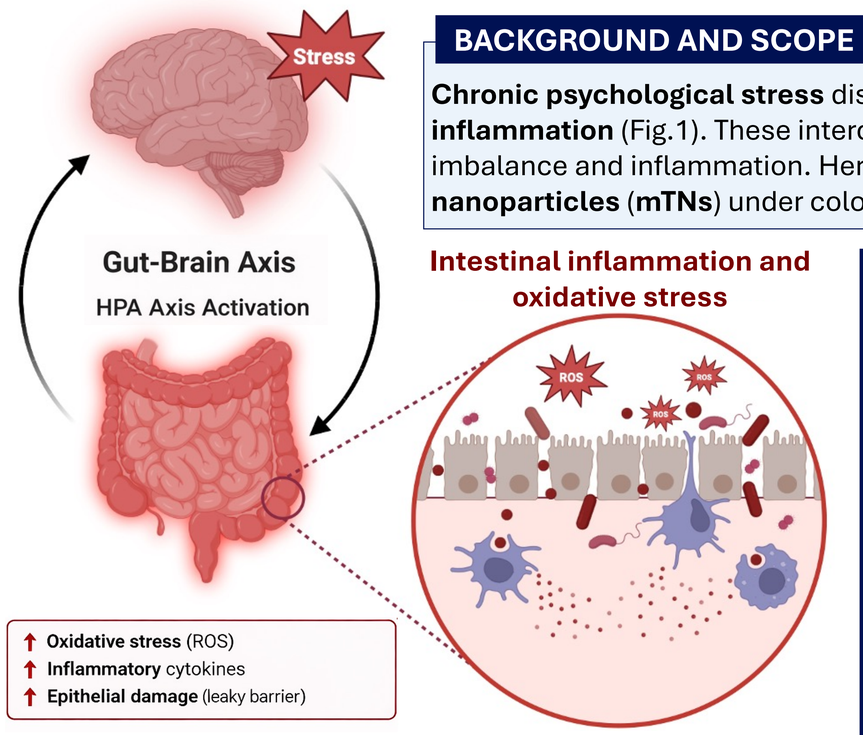
Dual-Crosslinked Alginate Hydrogel for Sustained Antioxidant Nanoparticles Delivery in Colon-Targeted Therapy

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BACKGROUND AND SCOPE

Chronic psychological stress disrupts **gut homeostasis** via activation of the HPA axis, leading to **oxidative stress**, **epithelial damage**, and persistent **intestinal inflammation** (Fig.1). These interconnected processes play a key role in colon-related disorders, yet current therapies often fail to effectively target both oxidative imbalance and inflammation. Here, we develop a **dual-ion crosslinked sodium alginate** (**SA**)**-based hydrogel** for the **sustained delivery** of **mineral-tannic acid nanoparticles** (**mTNs**) under colon-mimicking conditions, enabling combined **redox** and **inflammatory modulation** for **colon-targeted therapy**.



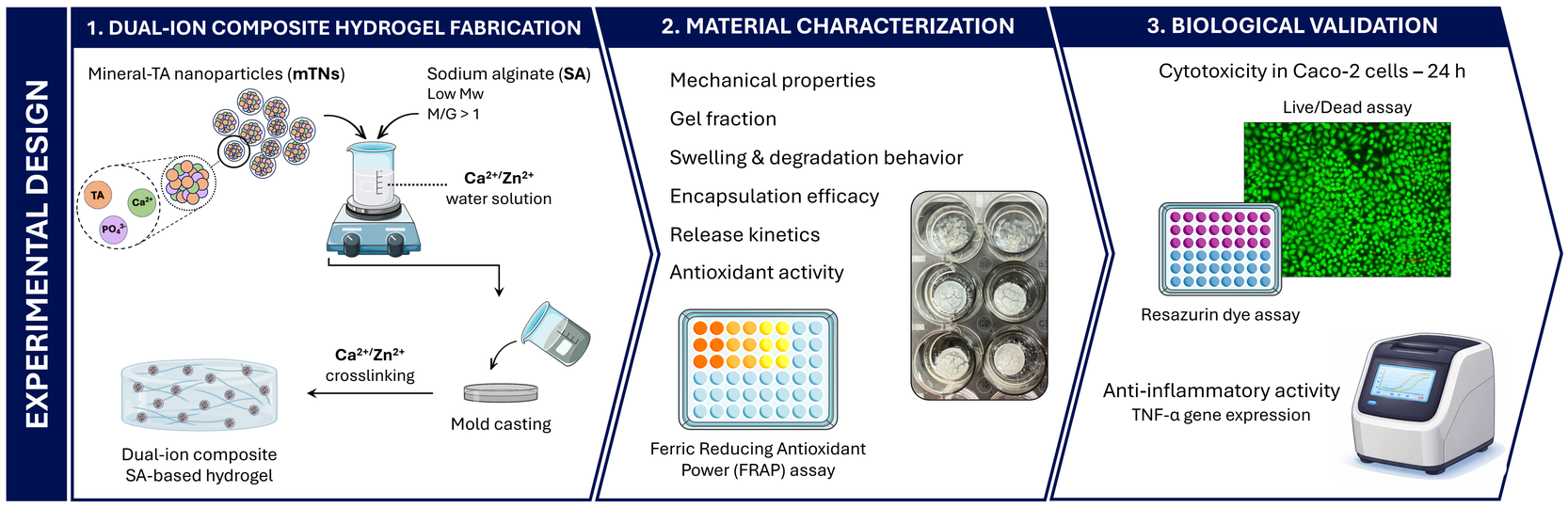
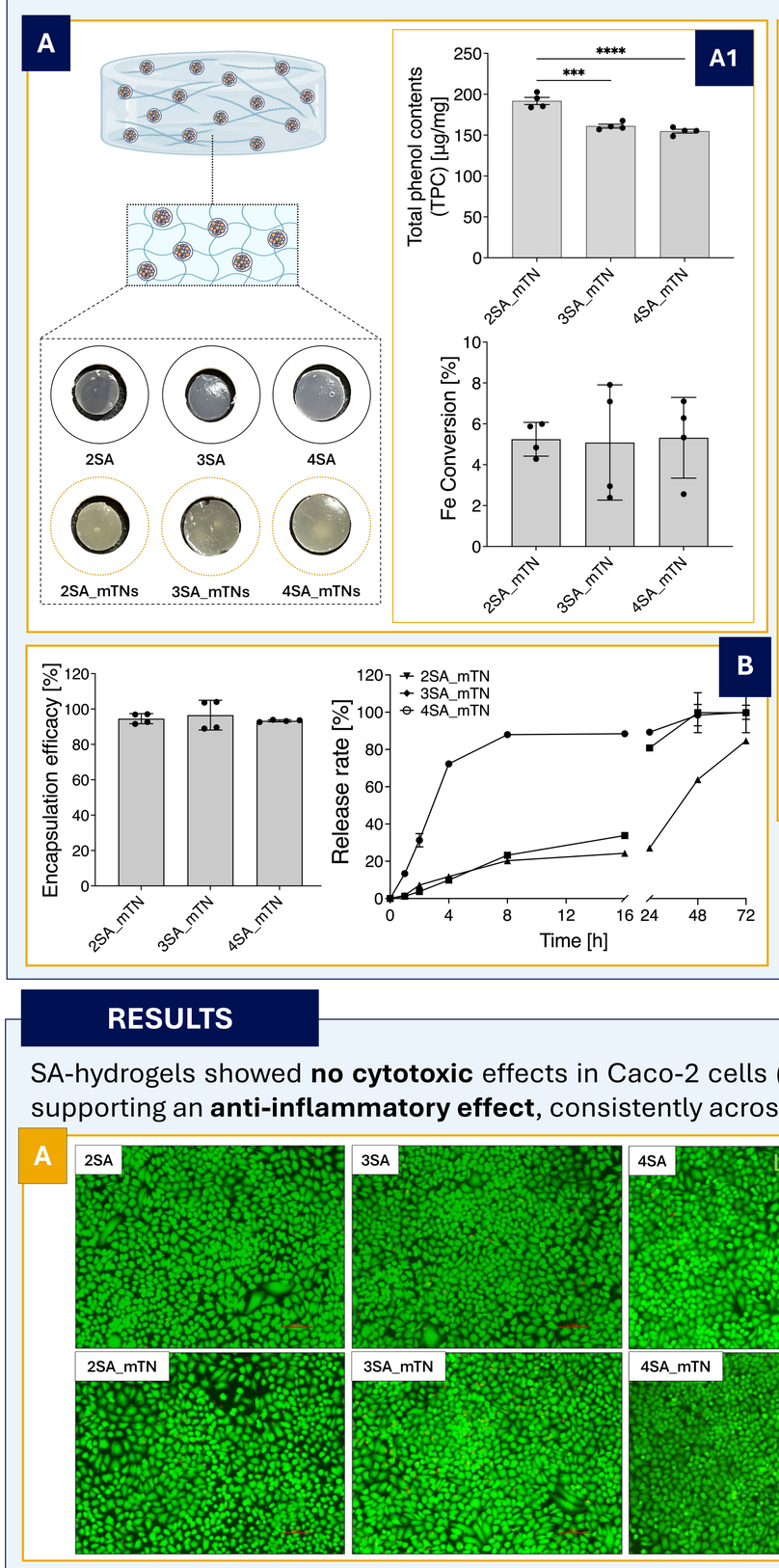


Figure 1. Schematic of stress-induced intestinal inflammation via gut–brain axis.

RESULTS

SA-based hydrogels (2-4% w/v) incorporating mTNs (1% w/v) showed high **shape fidelity** after molding and **effective nanoparticle incorporation**, with preserved **antioxidant activity** (Fig. 2A, A1). Mechanical analysis confirmed **elastic-dominant behavior (G' > G")** with **tunable stiffness** increasing with SA concentration (Fig. 2C, C1). Higher polymer content enhanced **network stability** (gel fraction >85%) (Fig. 2D), and reduced **swelling and degradation rates** (Fig. 2E). **Encapsulation efficiency (>90%)** and **controlled release kinetics in simulated colonic fluid (SCF)** (up to ~90% at 72 h) demonstrated SA-dependent modulation of mTN delivery (Fig. 2B). Notably, 3-4% SA formulations provided the most balanced performance in terms of stability and sustained release.



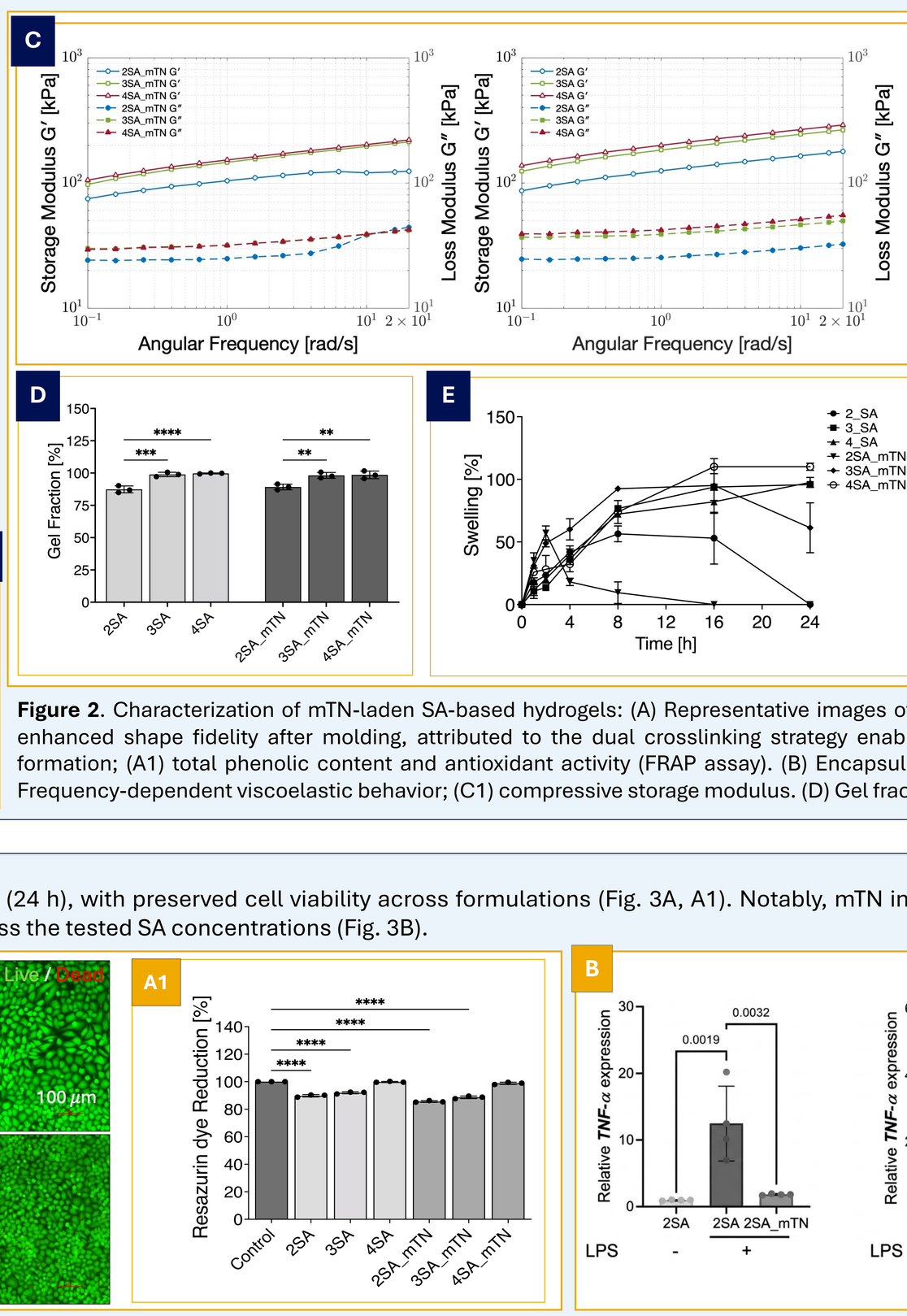


Figure 2. Characterization of mTN-laden SA-based hydrogels: (A) Representative images of SA hydrogels with and without mTNs, showing enhanced shape fidelity after molding, attributed to the dual crosslinking strategy enabling homogeneous ion distribution and network formation; (A1) total phenolic content and antioxidant activity (FRAP assay). (B) Encapsulation efficiency, and release kinetics in SCF. (C) Frequency-dependent viscoelastic behavior; (C1) compressive storage modulus. (D) Gel fraction. (E) Swelling and degradation profiles in SCF.

RESULTS

SA-hydrogels showed **no cytotoxic** effects in Caco-2 cells (24 h), with preserved cell viability across formulations (Fig. 3A, A1). Notably, mTN incorporation reduced TNF-α gene expression, supporting an **anti-inflammatory effect**, consistently across the tested SA concentrations (Fig. 3B).

Figure 3. Biological evaluation of mTN-loaded SA hydrogels: (A) Live/Dead staining of Caco-2 cells after 24 h showing absence of cytotoxic effects; (A1) cell viability quantified by resazurin dye reduction assay. (B) Relative TNF-α gene expression in LPS-stimulated macrophages, showing reduced expression upon mTN incorporation.

CONCLUSIONS

Dual-crosslinked SA hydrogels provide a tunable platform for sustained mTN delivery, combining structural stability and biological activity, with optimal performance observed in the 3-4% SA range. These systems hold strong potential for colon-targeted antioxidant and anti-inflammatory therapies.

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