

# Acemannan/alginate composite hydrogels promote STO cell spreading and metabolic activity

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## *Abstract*

Alginate-based hydrogels are widely used as biocompatible scaffolds. However, their limited cell-adhesive properties restrict their application in tissue engineering. This study aimed to fabricate acemannan/alginate (ACE/ALG) composite hydrogels and evaluate their cytocompatibility and ability to support STO cell spreading and metabolic activity. Composite hydrogels were prepared by blending different concentrations of ACE with alginate, followed by Ca<sup>2+</sup>-mediated ionic crosslinking. Rheological analysis showed that ACE incorporation increased both the storage modulus (G') and loss modulus (G'') of the hydrogels. Cell viability and morphology were evaluated using Live/Dead staining on day 7, and cellular growth was assessed using an MTT assay on days 1, 4, and 7. Live/Dead staining showed high cell viability in all groups, with few dead cells observed. STO cells on pure alginate hydrogels remained mostly spherical, whereas those on ACE/ALG composite hydrogels exhibited enhanced spreading and formed spindle-shaped cellular networks. Quantitative analysis showed that ACE incorporation significantly increased cell viability compared with the pure alginate group (1ALG, 90.1 ± 1.8%), with the 0.25ACE/2ALG and 0.5ACE/2ALG groups showing the highest viability ( $P < 0.05$ ). MTT analysis showed that the 0.5ACE/2ALG group exhibited significantly higher metabolic activity than the 1ALG group on day 4. The highest metabolic activity was observed on day 7 ( $P < 0.05$ ). These results suggest that ACE improves the cytocompatibility and cell-supportive properties of ALG hydrogels, with 0.5ACE/2ALG providing the most favorable formulation for STO cell spreading and growth. Therefore, ACE/ALG composite hydrogels may serve as promising naturally derived and biocompatible scaffold platforms for tissue engineering, with potential application in future cultured meat production.

**Keywords:** acemannan, alginate, cell spreading, hydrogel, metabolic activity, STO cells

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## Introduction

Alginates (ALG) are primary structural polysaccharides sourced from brown seaweeds (Phaeophyceae). Commercially, they are isolated from various genera, including *Laminaria*, *Macrocystis*, *Sargassum*, *Ascophyllum*, *Lessonia*, *Ecklonia*, and *Durvillaea* (Martinsen *et al.*, 1992). In terms of global abundance, ALG represents one of the most prevalent biopolymers in marine environments and is second only to cellulose on a global scale (Kanasan *et al.*, 2017; Dey *et al.*, 2019). As a critical biomaterial, it is predominantly utilized for wound healing, wound dressing, and cell culture. ALG salts exhibit strong gelling capacity through ionic cross-linking with divalent cations (notably Ca<sup>2+</sup> and Ba<sup>2+</sup>). Coupled with its inherent biocompatibility, low toxicity, and biodegradability (Ulery *et al.*, 2011), these properties make ALG an ideal candidate for scaffolding in biomedicine and tissue engineering. However, ALG lacks cell-binding motifs and carries a negative charge (Sahoo and Biswal, 2021), which often leads to poor cell adhesion and limited biological signaling. This biological inertness significantly restricts its application in scenarios where active cell interaction and tissue integration are paramount. To address these limitations, various strategies have been explored to functionalize ALG, including the coupling of RGD peptides or blending with other bioactive natural polymers. Beyond biochemical functionalization, current scaffold-engineering strategies also emphasize the regulation of pore architecture, surface wettability, stiffness, viscoelasticity, and mass transport through composite formulation and advanced fabrication techniques. These approaches aim to balance cell-material interactions with scaffold stability, processability, scalability, and compatibility with the intended application (Drury and Mooney, 2003; Lee and Mooney, 2012). While effective, there is an ongoing search for naturally derived, cost-effective additives that can simultaneously enhance biological performance and maintain the structural integrity of the scaffold.

Acemannan (ACE), a bioactive  $\beta$ -(1,4)-acetylated mannan extracted from *Aloe vera* (AV), has emerged as a promising candidate. Previous studies have demonstrated that ACE possesses remarkable immunomodulatory, anti-inflammatory, and wound-healing properties (Jithendra *et al.*, 2013; Agnes Mary and Giri Dev, 2015). More importantly, it has been reported to stimulate the secretion of growth factors and promote the proliferation of various cell types, such as fibroblasts and osteoblasts (Jettanacheawchankit *et al.*, 2009; Xing *et al.*, 2015; Liu *et al.*, 2019). These properties provide a rationale for combining ACE with ALG. As a plant-derived polysaccharide, ACE can be incorporated into ALG through direct aqueous blending without additional peptide-conjugation steps. Its incorporation was expected to retain the ionically cross-linked ALG network while modifying the structural and viscoelastic properties of the hydrogel and its cell-material interface. Unlike collagen and gelatin, ACE also avoids the use of animal-derived components.

However, because the present study did not directly compare ACE with RGD-, collagen-, or gelatin-based materials, ACE is proposed as a complementary strategy rather than a demonstrably superior biomaterial. Its potential advantage lies in combining straightforward hydrogel fabrication with the reported biological activity of ACE. Therefore, incorporating ACE into ALG may provide a more supportive microenvironment for cellular responses.

In this study, we hypothesized that incorporating ACE into alginate hydrogels would modify their structural and viscoelastic properties and provide an environment supportive of STO cell attachment, viability, and metabolic activity compared with alginate alone. The primary objective of this study was to fabricate ACE/ALG composite hydrogels and characterize their structural and rheological properties. The secondary objective was to evaluate cellular responses to these hydrogels by examining cell morphology, viability, and MTT-derived metabolic activity. Collectively, this study aimed to assess the potential of ACE/ALG hydrogels as a preliminary scaffold platform for future cell-culture applications.

## Materials and Methods

**Materials and reagents:** High-glucose Dulbecco's Modified Eagle Medium (DMEM; Gibco™, Thermo Fisher Scientific Inc., Waltham, MA, USA; Cat. No. 12800-058), fetal bovine serum (FBS; HyClone™, Cytiva, Marlborough, MA, USA; Cat. No. SV30160.03), and ALG (Krungthep Chemi Company Limited, Bangkok, Thailand; Cat# F040SA) were used as the primary cell culture and scaffolding materials. Cell viability reagents, including Calcein-AM (Calbiochem®, EMD Millipore Corp., Burlington, MA, USA; Cat. No. 206700-1MG) and ethidium homodimer-1 (EthD-1; Sigma-Aldrich, St. Louis, MO, USA; Cat. No. 46043-1MG-F), were obtained from their respective manufacturers.

**Cell culture:** STO cells (mouse embryonic fibroblasts; ATCC CRL-1503) were maintained in fresh medium consisting of DMEM supplemented with 10% (v/v) FBS and 1% (v/v) antibiotic-antimycotic. The cells were cultured in a humidified incubator at 37°C with 5% CO<sub>2</sub>. The culture medium was refreshed every other day.

**ACE extraction:** Fresh AV leaves were sourced from a private farm in Phetchaburi Province 76160, Thailand. ACE was extracted following a previously established protocol (Lee *et al.*, 2001). Briefly, the leaves were peeled, and the transparent inner pulp was thoroughly rinsed to remove the yellow latex. The purified gel was cut into 2–3 cm pieces and homogenized. The homogenate was centrifuged at 4,000 rpm for 20 min at 4°C to separate the soluble fraction from the insoluble fibers. The resulting clear supernatant was mixed with three volumes of absolute ethanol and maintained overnight to precipitate ACE. The resulting white precipitate was collected by centrifugation under the same conditions (4,000 rpm for 20 min at 4°C) and subsequently lyophilized to obtain ACE powder.

**Hydrogel fabrication:** To investigate the effects of different compositions, four groups of hydrogels were prepared. A 1% (w/v) ALG solution was used to fabricate the control group, designated as 1ALG. For the composite groups, a 2% (w/v) ALG solution was blended with varying concentrations of ACE solution (0.25%, 0.5%, and 1%) at a 1:1 volume ratio. The resulting composite hydrogels were labeled as 0.25ACE/2ALG, 0.5ACE/2ALG, and 1ACE/2ALG, respectively. These labels refer to the concentrations of the precursor solutions. After 1:1 (v/v) mixing, all composite hydrogels contained a final ALG concentration of 1% (w/v), while the final ACE concentrations were 0.125%, 0.25%, and 0.5% (w/v), respectively. The CaCl<sub>2</sub> solution was sterilized by filtration through a 0.22- $\mu$ m membrane filter before use. All precursor solutions were mixed thoroughly and cross-linked with a 10% (w/v) CaCl<sub>2</sub> (Sigma, Cat# C7902) solution for 10 min. The formed hydrogels were then rinsed with deionized water three times (10 s each) to remove excess Ca<sup>2+</sup>. Subsequently, the hydrogels were exposed to UV light for 30 min in a biosafety cabinet before cell seeding.

**Rheology:** Rheological properties of the hydrogels were measured using an ARES G2 rheometer (TA Instruments, USA) equipped with a 25 mm stainless-steel parallel plate. All measurements were performed at 25°C. Frequency sweep tests were performed over an angular frequency range of 0.1–100 rad/s at a fixed strain of 0.5%. The storage modulus ( $G'$ ) and loss modulus ( $G''$ ) were recorded to evaluate the viscoelastic properties of the hydrogels, and the corresponding frequency sweep curves were obtained. For quantitative comparison,  $G'$  and  $G''$  values were extracted at 1 rad/s from the frequency sweep data. For each formulation, three independent hydrogel samples were measured, with each hydrogel treated as an independent experimental replicate ( $n = 3$ ).

**Live/Dead fluorescence assay:** Cell viability on the hydrogels was evaluated via 2  $\mu$ m Calcein-AM and 2  $\mu$ m EthD-1 staining on day 7. After a 20-min dark incubation in the dye working solution, fluorescence images were acquired using an Olympus BX51 microscope equipped with DP2-BSW software (Olympus, Shinjuku, Japan). One fluorescence image was acquired and analyzed from each independently prepared hydrogel sample. A total of 3 independent hydrogels and 3 images were analyzed per group, with each hydrogel treated as the experimental unit.

**MTT assay:** Cellular metabolic activity was assessed using the MTT assay. At each designated time point (days 1, 4, and 7), the culture medium was substituted with fresh medium containing MTT solution (Invitrogen, Cat# M6494) and incubated for 3 hours at 37°C. Following incubation, the supernatant was aspirated, and the accumulated formazan crystals were solubilized in dimethyl sulfoxide (Sigma, Cat# D4540). The optical density (OD) was then quantified at 570 nm using a microplate reader. For each formulation, three independent cell-seeded hydrogel samples were

analyzed at each time point, with each hydrogel treated as an independent experimental replicate ( $n = 3$ ).

**Assessment of cell viability:** Quantitative cell viability was determined by processing the fluorescence micrographs through ImageJ software (NIH, Bethesda, MD, USA). After setting a uniform threshold, the integrated density of green and red signals was measured. The ratio of live cells to the sum of live and dead cells was calculated to yield the final viability percentage.

**Statistical analyses:** Statistical analyses were performed using GraphPad Prism 11.0.1 (GraphPad Software, San Diego, CA, USA). Data are presented as mean  $\pm$  standard deviation (SD), with three independent hydrogel samples per group ( $n = 3$ ). Rheological parameters and Live/Dead-derived viability percentages were analyzed using ordinary one-way analysis of variance (ANOVA), followed by Tukey's multiple-comparisons test. MTT-derived metabolic activity was analyzed using ordinary two-way ANOVA, with hydrogel formulation and culture time as the two factors, followed by Tukey's multiple-comparisons test.  $P < 0.05$  was considered statistically significant.

## Results

The composite hydrogels were successfully fabricated by blending varying concentrations of ACE with ALG, followed by Ca<sup>2+</sup>-mediated cross-linking (Fig. 1A). As shown in the macroscopic images (Fig. 1B), the control group (1ALG) exhibited a high degree of transparency. Notably, a gradual transition from transparent to translucent was observed as the precursor ACE concentration increased across the 0.25ACE/2ALG, 0.5ACE/2ALG, and 1ACE/2ALG groups.

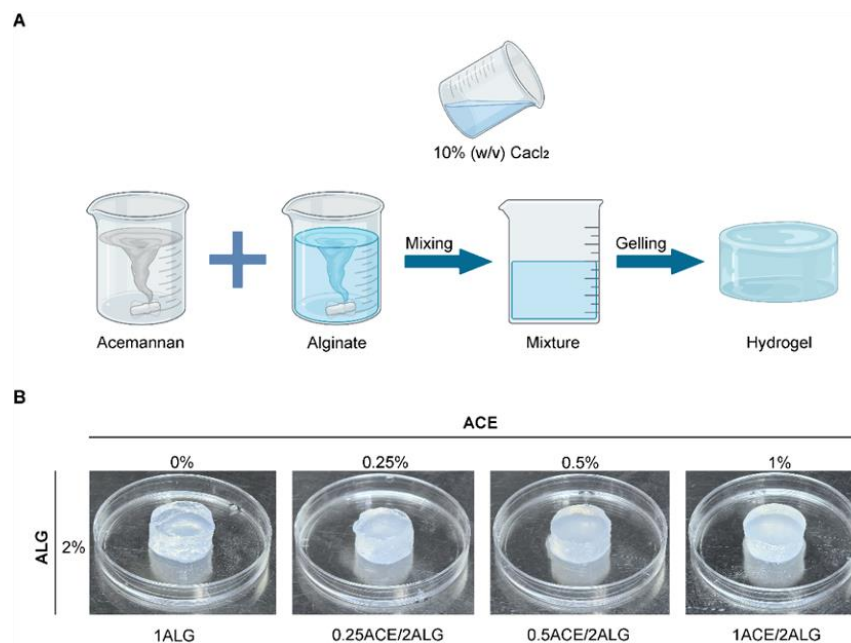
Rheological analysis showed that ACE incorporation altered the viscoelastic properties of the alginate-based hydrogels (Fig. 2). The storage modulus ( $G'$ ) was  $8,039.69 \pm 301.15$  Pa,  $8,451.77 \pm 765.92$  Pa,  $9,031.98 \pm 532.87$  Pa, and  $9,644.54 \pm 537.99$  Pa for the 1ALG, 0.25ACE/2ALG, 0.5ACE/2ALG, and 1ACE/2ALG groups, respectively (Fig. 2A). The corresponding loss modulus ( $G''$ ) values were  $1,278.22 \pm 44.16$  Pa,  $1,201.86 \pm 34.66$  Pa,  $1,403.16 \pm 69.31$  Pa, and  $1,624.09 \pm 71.99$  Pa, respectively (Fig. 2B). Compared with the 1ALG group, the 1ACE/2ALG group exhibited significantly higher  $G'$  ( $P = 0.0214$ ) and  $G''$  ( $P = 0.0468$ ).

To assess the cytocompatibility of the scaffolds, a Live/Dead assay was performed on day 7 (Fig. 3). Fluorescence micrographs revealed a high density of viable cells (green) across all formulations, with a negligible presence of dead cells (red). Qualitative differences in cell morphology were observed among the groups. STO cells on the 1ALG scaffolds remained largely spherical and failed to spread fully. In contrast, cells on the composite scaffolds exhibited a more spread, spindle-shaped morphology, with cytoplasmic extensions and interconnected cellular networks.

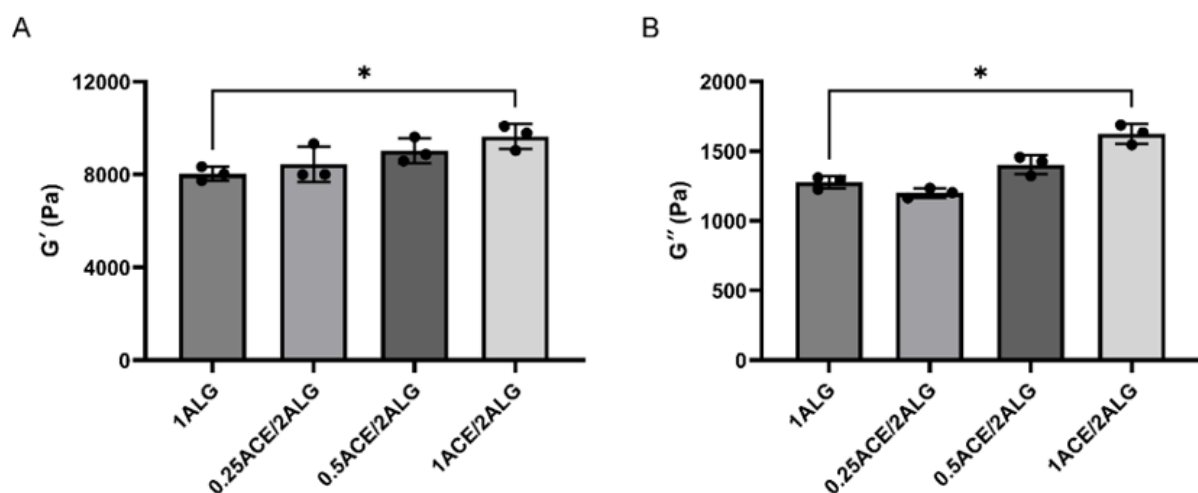
However, cells in the 1ACE/2ALG group appeared less extensively spread than those in the other composite groups.

MTT analysis showed a time-dependent increase in STO cell metabolic activity on all hydrogel scaffolds over the 7-day culture period (Fig. 4). Although the four groups displayed comparable cell metabolic activity at the early time point, ACE-containing hydrogels supported progressively greater cell metabolic activity from day 4 onwards. Among them, the 0.5ACE/2ALG scaffold produced the most pronounced metabolic activity, reaching the highest values by day 7, followed by 0.25ACE/2ALG and 1ACE/2ALG. In contrast, cells cultured on 1ALG showed the slowest increase over time. By day 7, both 0.5ACE/2ALG and 0.25ACE/2ALG exhibited significantly higher cell proliferative activity than the

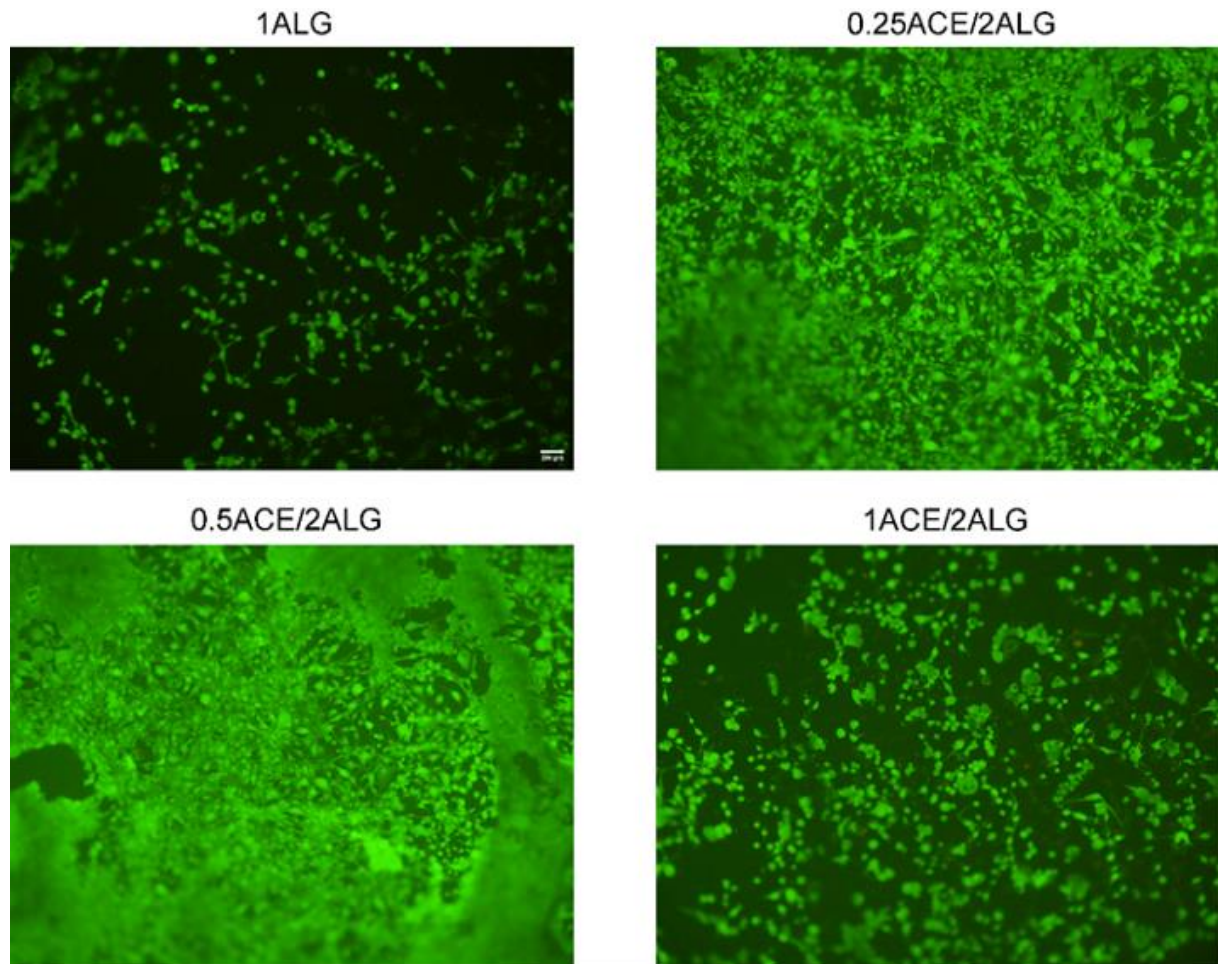
1ALG group ( $P < 0.05$ ). Quantitative analysis of Live/Dead staining on day 7 showed cell viabilities of  $90.13 \pm 1.65\%$ ,  $100.00 \pm 0.00\%$ ,  $100.00 \pm 0.00\%$ , and  $94.30 \pm 0.70\%$  for the 1ALG, 0.25ACE/2ALG, 0.5ACE/2ALG, and 1ACE/2ALG groups, respectively (Fig. 5). Compared with the 1ALG group, cell viability was significantly higher in both the 0.25ACE/2ALG and 0.5ACE/2ALG groups ( $P = 0.0230$  for both comparisons), whereas the difference between the 1ALG and 1ACE/2ALG groups was not significant ( $P = 0.0899$ ). Cell viability in the 1ACE/2ALG group was significantly lower than that in both the 0.25ACE/2ALG and 0.5ACE/2ALG groups ( $P = 0.0126$  for both comparisons). No difference was detected between the 0.25ACE/2ALG and 0.5ACE/2ALG groups, as both groups exhibited 100.00% viability.



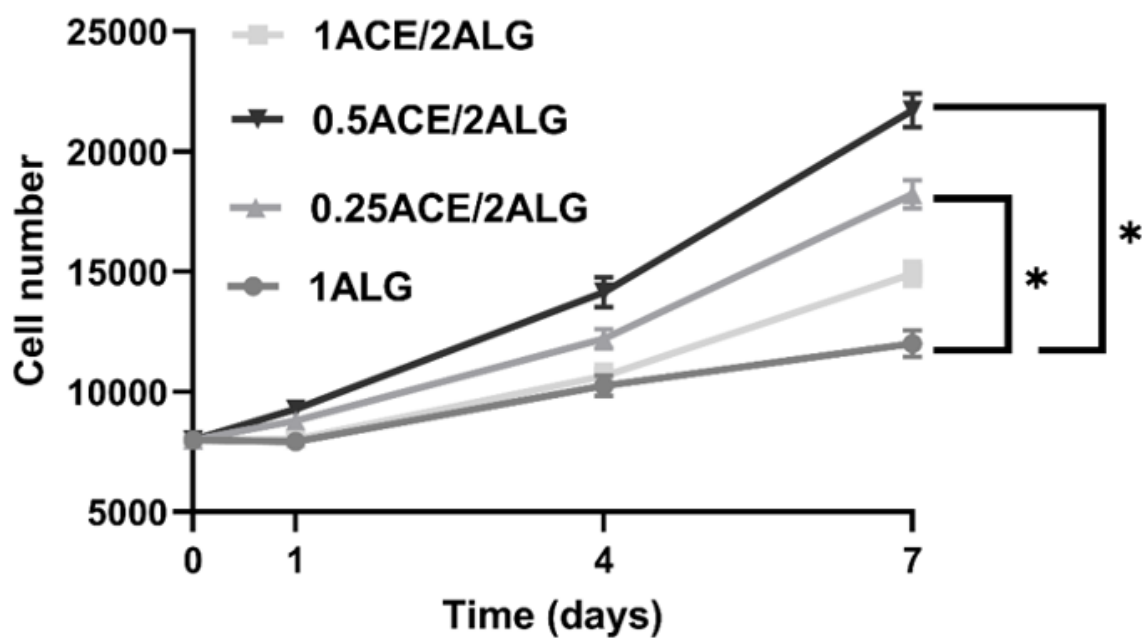
**Figure 1** Preparation and macroscopic appearance of ACE/ALG hydrogels. (A) Schematic illustration of the fabrication process of composite hydrogels. Created with BioRender.com. (B) Representative macroscopic images of the hydrogels in different experimental groups: 1ALG, 0.25ACE/2ALG, 0.5ACE/2ALG, and 1ACE/2ALG.



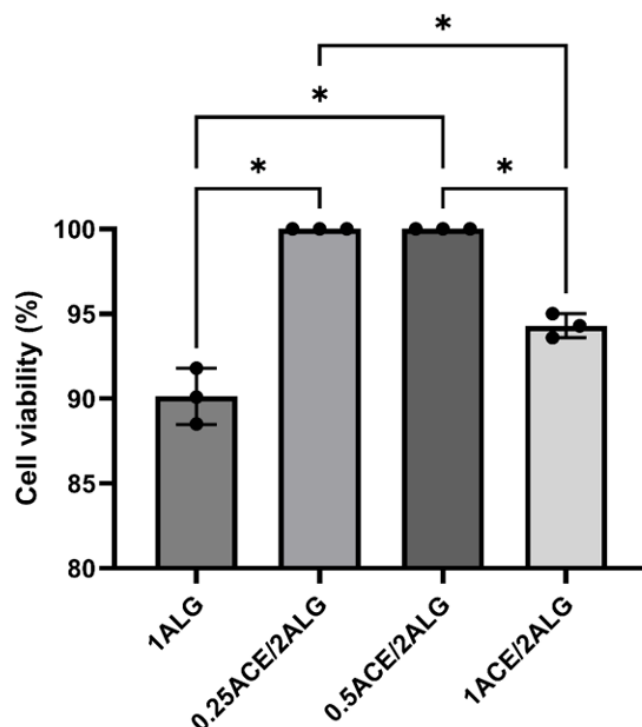
**Figure 2** Rheological properties of ACE/ALG hydrogels. (A) Storage modulus ( $G'$ ) and (B) loss modulus ( $G''$ ) values extracted at 1 rad/s from the frequency sweep data of ACE/ALG hydrogels. Data are presented as mean  $\pm$  standard deviation (SD) ( $n = 3$  independent hydrogel samples per group).



**Figure 3** Biocompatibility and cell viability on ACE/ALG hydrogels. Representative fluorescence images of Live/Dead stained STO cells cultured on 1ALG, 0.25ACE/2ALG, 0.5ACE/2ALG, and 1ACE/2ALG scaffolds on day 7. Green fluorescence (Calcein-AM) indicates live cells, while red fluorescence (EthD-1) indicates dead cells. Scale bar = 200 μm.



**Figure 4** Cellular metabolic activity on hydrogels assessed using the MTT assay. Metabolic activity of STO cells cultured on 1ALG, 0.25ACE/2ALG, 0.5ACE/2ALG, and 1ACE/2ALG scaffolds over a 7-day period. Data are presented as mean  $\pm$  SD (n = 3 independent hydrogel samples per group).



**Figure 5** Quantitative analysis of cell viability on day 7. Cell viability percentages of STO cells cultured on different hydrogel formulations were determined following Live/Dead staining. For each group, one fluorescence image was analyzed from each of three independent hydrogel samples ( $n = 3$  hydrogels; three images in total per group). Data is presented as mean  $\pm$  SD. An asterisk indicates a significant difference among groups ( $P < 0.05$ ).

### Discussion

The present study demonstrates that the incorporation of ACE into ALG hydrogels significantly enhances cellular responses, including spreading and metabolic activity, compared to pure ALG scaffolds. While ALG is widely recognized for its biocompatibility and ease of gelation, its intrinsic bioinertness often limits effective cell-material interactions. In this work, the introduction of ACE successfully mitigated these limitations, resulting in a more cell-supportive microenvironment. Notably, the 0.5ACE/2ALG formulation exhibited the most pronounced improvement in cell metabolic activity, suggesting that an optimal concentration of bioactive components is critical for maximizing scaffold performance.

The limited cell spreading observed in the pure ALG group is consistent with previous reports and can be attributed to the absence of intrinsic cell-binding motifs (Ahmad *et al.*, 2024) and the negatively charged nature of ALG (Seo *et al.*, 2023), which inhibits protein adsorption and subsequent focal adhesion formation. In addition to this biochemical inertness, the mechanical microenvironment of alginate hydrogels may also contribute to poor cell-material interactions. Hydrogels with insufficient stiffness may fail to provide adequate mechanical cues for cytoskeletal tension generation, cell spreading, and stable adhesion, all of which are closely associated with mechanotransduction-mediated cellular responses (Zhou *et al.*, 2019). It should be noted, however, that the stiffness of alginate hydrogels is not an inherent fixed

property, but is strongly governed by the extent of ionic crosslinking (Freeman and Kelly, 2017). In  $\text{Ca}^{2+}$ -crosslinked alginate systems, increasing the concentration of  $\text{CaCl}_2$  can promote the formation of a denser egg-box network, thereby improving the mechanical stability of the hydrogel. Consistently, Seo *et al.* reported that increasing  $\text{CaCl}_2$  concentration enhanced the compressive modulus of alginate-based hydrogels, with high  $\text{CaCl}_2$  concentrations also being associated with improved cell attachment area and cell viability. Importantly, this improvement was not explained by stiffness alone; the authors further suggested that high  $\text{CaCl}_2$  concentrations altered the surface architecture and zeta potential of alginate fibers, making the surface more favorable for initial cell attachment (Seo *et al.*, 2023).

Based on this rationale, a relatively high  $\text{CaCl}_2$  concentration was used in the present study to enhance ionic crosslinking and provide a mechanically more supportive ALG hydrogel network. Nevertheless, although this strategy may partially alleviate the unfavorable mechanical and surface properties of alginate, the pure ALG scaffold still lacks specific biological ligands required for cell adhesion. This may explain why cell attachment in the ALG group remained limited. In contrast, the addition of ACE markedly altered cell morphology and behavior. Cells cultured on ACE-containing hydrogels displayed a well-spread, spindle-shaped morphology with enhanced intercellular connectivity, consistent with more extensive cell spreading and cytoskeletal extension. All hydrogel formulations contained the same final ALG concentration of 1% (w/v); therefore,

the observed differences in cellular responses cannot be attributed to differences in ALG concentration. ACE does not provide canonical RGD motifs, and the present data therefore does not establish a specific receptor-mediated adhesion mechanism. ACE incorporation may have modified protein adsorption, wettability, microstructure, or viscoelasticity, thereby creating conditions more permissive to cell spreading. In particular, serum proteins from the culture medium may have adsorbed onto the hydrogel surface and facilitated subsequent cell attachment and spreading. However, these potential mechanisms remain hypothetical and require direct physicochemical and cell-adhesion assays.

Interestingly, a concentration-dependent effect of ACE was observed, with the 0.5ACE/2ALG formulation producing the most favorable cellular responses, whereas the 1ACE/2ALG formulation showed a slight decline. Rheological analysis further supported the effect of ACE on the mechanical behavior of ALG hydrogels. The increase in  $G'$  after ACE incorporation indicates an enhanced elastic response of the hydrogel network, while the increase in  $G''$  suggests greater viscous energy dissipation. These changes may be associated with stronger polymer chain interactions and a denser  $\text{Ca}^{2+}$ -crosslinked ALG network after ACE incorporation. However, the highest ACE concentration did not produce the best cellular response, although 1ACE/2ALG showed the highest rheological moduli. This suggests that excessive network reinforcement may not be optimal for cell spreading and metabolic activity. Instead, a balanced mechanical microenvironment may be more favorable, as reflected by the superior cell spreading and metabolic activity observed in the 0.5ACE/2ALG group. This phenomenon may also be attributed to the formation of a denser polymer network at higher ACE content, which could restrict nutrient diffusion and waste exchange, ultimately limiting cell activity. Additionally, excessive incorporation of polysaccharides may alter the mechanical properties of the hydrogel, potentially leading to suboptimal stiffness for cell metabolic activity. These findings highlight the importance of balancing bioactivity and structural properties when designing composite scaffolds and emphasize that higher concentrations of bioactive additives do not necessarily translate into better biological performance.

From an application perspective, the development of ACE/ALG composite hydrogels presents a promising strategy for fabricating edible and biocompatible scaffolds for cultured meat production. The use of naturally derived ACE may offer potential sustainability and cost advantages compared with synthetic modifications such as peptide conjugation. However, food safety cannot be inferred from the natural origin or in vitro cytocompatibility of the materials alone. Before application in cultured meat, food-grade sourcing and processing, residual-solvent and microbial safety, compositional consistency, digestibility, allergenicity, and relevant regulatory requirements must be evaluated. By improving cell

spreading and metabolic activity, this composite system may help address one of the key challenges in cultured meat engineering, namely the creation of a supportive three-dimensional microenvironment for efficient cell expansion.

Nevertheless, several limitations of this study should be acknowledged. First, the current work was conducted using fibroblast cells, which may not fully represent the behavior of muscle satellite cells that are directly relevant to cultured meat applications. Second, the underlying molecular mechanisms responsible for the observed improvements, such as the involvement of adhesion-related proteins or signaling pathways, were not investigated. Future studies should focus on validating these findings in muscle-derived cells and exploring the mechanistic basis of ACE-mediated bioactivity. Additionally, further optimization of scaffold properties, including mechanical strength and porosity, will be essential to fully realize the potential of this system in tissue engineering applications.

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**Declaration of artificial intelligence use:** The authors declare that no artificial intelligence tools were used in the preparation, writing, analysis, or production of this manuscript.

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