A Comparative Analysis of Stem Cell Proliferation Dynamics in Ethyl Gallate-Functionalized Versus Non-Functionalized Hydrogels: Advantages and Limitations

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**Abstract:** Stem cells, capable of differentiating into various cell types, offer significant potential for tissue regeneration. 3-D porous scaffolds serve as spatial guides for cell positioning and demonstrate substantial promise in the field. Ethyl gallate, known for its non-toxic effects on cell lines of diverse tissue origins, also provides nutritional benefits and has been scientifically substantiated. This study explores the intriguing potential of ethyl gallate-functionalized hydrogels, focusing on their effects on stem cell proliferation, viability, and differentiation. We focus on unraveling their influence on cellular behavior and regenerative potential, a topic that has piqued the interest of many in the field. A mixture comprising 20 mL of gelatin solution and 20 mg of Gallic acid (ethyl gallate) was prepared and transferred into a 90 mm Petri dish. To create a thin membrane, the liquid was frozen on a 24-liter culture plate at four degrees Celsius for twelve hours. The manufactured membrane was then characterized utilizing scanning electronic microscopy (SEM) and tested for anti-inflammatory properties. The use of gallic acid (Ethyl gallate) modified gelatin membranes in this study demonstrates a significant potential for enhancing stem cell growth. The potential of diethyl gallate in critical regeneration tactics is highlighted by this discovery, which also offers a useful avenue for further regenerative medicine research.

**Keywords:** scaffold, ethyl gallate, gallic acid, and stem cell.

# INTRODUCTION

Stem cells, which are unspecialized cells found throughout the human body, have the unique ability to self-renew and differentiate into any cell inside the organism. They exist in both embryonic and adult tissues, exhibiting varying degrees of specialization. With each level of specialization, a stem cell's capacity to develop diminishes. On the other hand, pluripotent stem cells can differentiate into a variety of cell types, but an unipotent stem cell will only differentiate into one type of cell. Furthermore, stem cells are essential since they are the body's natural repair system, constantly renewing and creating new cells throughout an organism's life. The activity of stem cells is organ-specific, with variations observed in their division rates—while stem cells in the bone marrow undergo constant division, those in organs like the pancreas only divide under specific physiological conditions[(Zakrzewski et al., 2019)](https://paperpile.com/c/qpKMBG/bYPh)[(Ajay et al., 2023; Chokkattu et al., 2023; Padarthi et al., 2023)](https://paperpile.com/c/qpKMBG/xpYfM+Z7mp7+JbyCC)[(Dharman et al., 2023; S. Sindhu et al., 2023; Sreenivasagan et al., 2023)](https://paperpile.com/c/qpKMBG/vOs8j+JqfEE+zBn0D)[(Ramakrishnan et al., 2023; Shenoy & Maiti, 2023; J. S. Sindhu et al., 2023)](https://paperpile.com/c/qpKMBG/TKJy9+l3Mek+t6se2)Regenerative therapies are a fast-growing area of medical study that focuses on replacing damaged or non-functioning cells and repairing or regenerating organs and tissues to restore normal organ functions. Its goal is to transform healthcare completely. Regenerative therapy uses a variety of techniques, including stem cell transplantation, tissue engineering, genetic therapy, soluble biomolecules, and cell reprogramming directed at particular tissue types. Over the past few decades, transplantation of stem cells and tissue regeneration techniques have become increasingly popular as prospective treatments for a range of illnesses. These innovative medicinal techniques employ a variety of cell types, including mesenchymal, hematopoietic, testicular, mammary, intestinal, endothelial, neural, olfactory, embryonic, neural crest, & induced pluripotent stem cells [(Şahin et al., 2016)](https://paperpile.com/c/qpKMBG/4FOq). Tissue engineering is a vital subject of study that has attracted a lot of attention lately. It is strongly tied to regenerative medicine. From being a simple cell transporter, biomaterials technology has developed into a tool that can actively affect cellular development. These developments have made it possible to precisely mold biomaterials into 3D (three-dimensional) scaffolds that encourage cell proliferation & differentiation, which in turn aids in tissue regeneration (3)[(Kasabwala et al., 2021; Rajeshkumar & Lakshmi, 2021; Varghese et al., 2023)](https://paperpile.com/c/qpKMBG/BaBT+sBEK+Adyt)[(Keerthana & Ramesh, 2021; Murugesan, 2021; Tiwari & Jain, 2021)](https://paperpile.com/c/qpKMBG/WwOPy+jP4pF+90gA4)[(Keerthana & Ramesh, 2021; Murugesan, 2021; Subramanian et al., 2021; Tiwari & Jain, 2021)](https://paperpile.com/c/qpKMBG/WwOPy+jP4pF+90gA4+eJcRa)[(*Evaluation Composite Restoration Posterior Teeth Proanthocyanidin Pretreatment Liner Using Fédération Dentaire Internationale Criteria: Split-Mouth Randomized Controlled Trial*, n.d.; Pranati et al., 2021; Sakthi 2021)](https://paperpile.com/c/qpKMBG/cmouG+VRABp+CPmEi)[(G. & Ganapathy, 2022; I. L. Kumar & Ramesh, 2021)](https://paperpile.com/c/qpKMBG/PNTQm+YkogJ)).The intricate nature of scaffolds lies in their three-dimensional porous solid structure, which accurately spatially positions cells, thereby holding vast potential for tissue regeneration. It is essential to consider various mechanical parameters, including matrix stiffness, matrix nano topography, micro geometry, and extracellular stresses, as these factors significantly influence stem cell activity. Depending on where they come from, biomaterials can be classified as either natural or synthetic polymers. Collagen, alginate, chitosan, silk fibroin, keratin, & decellularized tissues like the de-epithelialized human amniotic membrane are a few examples of natural scaffolds that are frequently used in tissue engineering [(Krishna et al., 2019)](https://paperpile.com/c/qpKMBG/YDp2). The primary goal of manufacturing scaffolds for tissue regeneration is to replicate extracellular matrix (ECM) functions in a temporally and geographically organized framework[(Abdul et al., 2024)](https://paperpile.com/c/qpKMBG/TCOl). One of the central challenges involves encoding essential biological cues within the scaffold, thereby enabling comprehensive governance of various cellular responses, (Almatrafi et al., 2024) encompassing adhesion and migration, proliferation, and phenotypic selection[(Dorozhkin & Taylor & Francis Group, 2021)](https://paperpile.com/c/qpKMBG/mkxi)[(‘Development of a Modular Reinforced Bone Tissue Engineering Scaffold with Enhanced Mechanical Properties’, 2022)](https://paperpile.com/c/qpKMBG/4ZGm). Ethyl gallate demonstrates remarkable nontoxicity across cell lines derived from diverse tissue origins and serves as a valuable source of nutrition[(Prasad et al., 2024)](https://paperpile.com/c/qpKMBG/lT6t). Its pharmacological potency surpasses other catechins, demonstrating antibacterial, anticarcinogenic, antioxidative stress, and anti-inflammatory attributes (Saadh et al., 2024). Moreover, its safety profile and cost-effectiveness underscore its potential for broad medicinal utility[(Honda et al., 2018; Seetharaman et al., n.d.)](https://paperpile.com/c/qpKMBG/vpLi+gtHM).Our comprehensive research incorporating ethyl gallate could potentially impact stem cell growth, viability, and differentiation within hydrogels through various mechanisms that are yet to be fully understood. This study aims to provide a thorough insight into how ethyl gallate influences cellular behavior and overall regenerative potential within modified hydrogels, instilling confidence in the rigor of our research. The results of this study have the potential to have a major influence on the creation of sophisticated biomaterials for use in tissue engineering & regenerative medicine. These implications could include refining hydrogel compositions to optimize stem cell proliferation and differentiation and developing novel strategies for enhancing regenerative potential in biomaterial-based approaches, underscoring the importance of our study. Therefore, this study intends to assess the kinetics of stem cell proliferation within ethyl gallate-functionalized hydrogels. This involves assessing the impact of ethyl gallate incorporation on stem cell growth, viability, and differentiation, focusing on understanding how these modified hydrogels influence cellular behavior and overall regenerative potential.

# Materials and methods

To investigate the effect of ethyl gallate (gallic acid) on tissue regeneration and its cytotoxicity, a series of experiments were conducted using gelatin, a natural polymer rich in collagen (70-85%), as the scaffold material. The process began with the preparation of a gelatin solution. This study incorporated 20 mg of ethyl gallate into 20 ml of the gelatin solution. The mixture was poured into 90 mm Petri dishes and frozen at 4°C for 12 hours in a 24-well culture plate, forming a thin membrane. After freezing, the membrane was carefully extracted for further analysis. The structural characterization of the gelatin-ethyl gallate membrane was performed using a Field Emission Scanning Electron Microscope (FESEM). To prepare the samples for SEM, the membranes were placed on glass coverslips and dehydrated with 70% ethyl alcohol for 10 seconds. Once dried, the samples were coated with a thin layer of platinum for 30 seconds to enhance conductivity. Imaging was conducted at a magnification of 5 μl and an acceleration voltage of 3000 Kμ, allowing detailed visualization of the surface morphology of the gelatin-ethyl gallate membranes. In addition to the morphological characterization, anti-inflammatory and cytotoxicity tests were carried out to assess the biocompatibility of the ethyl gallate-loaded gelatin hydrogel. Colorectal spheroid cell lines were used for these tests to determine the effects of ethyl gallate on cell viability and inflammatory response. The results from these assays provided crucial insights into the safety and potential therapeutic benefits of using ethyl gallate-functionalized gelatin hydrogels for tissue regeneration applications.

# RESULT

## Scanning Electron Microscopy

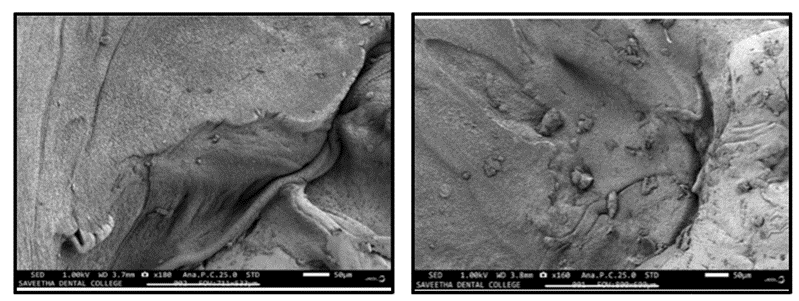


Figure. 1 SEM Image of Ethyl Gallate-Functionalized Hydrogel Showing Porosity and Stem Cell Interaction

**Surface Morphology:** The SEM analysis of the ethyl gallate-functionalized hydrogels reveals a porous surface morphology characterized by a network of interconnected pores. This porosity is essential for facilitating cell attachment and enabling effective nutrient diffusion throughout the hydrogel matrix.

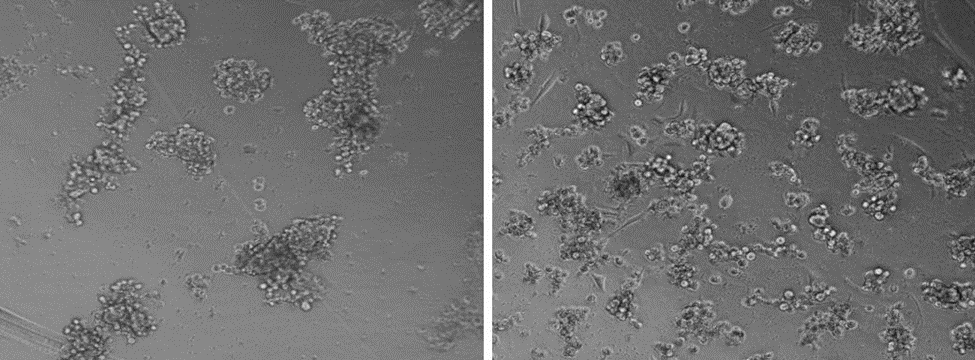
**Porosity and Texture:** The image demonstrates high porosity within the hydrogel structure. The well-defined pore architecture indicates a scaffold that supports stem cell proliferation by allowing cells to migrate and expand within the matrix.

**Cell Interaction:** The SEM image highlights the interaction between stem cells and the hydrogel surface. Observations indicate the presence of stem cells adhering to the hydrogel and spreading within the pores. The cells exhibit both elongated and round shapes, suggesting successful cell adhesion and initial stages of proliferation.

**Material Integration**: The uniformity and texture of the hydrogel surface suggest successful functionalization with ethyl gallate. The homogeneous surface texture observed in the SEM image indicates enhanced biocompatibility of the hydrogel, which is conducive to promoting stem cell proliferation.

The SEM image (Figure 1) provides evidence of a porous, well-structured ethyl gallate-functionalized hydrogel that supports stem cell adhesion and proliferation. The hydrogel's structural integrity and surface characteristics highlight its potential as a scaffold for tissue engineering applications.

## Cytotoxicity Effects of Gallic Acid Gallic-loaded Alginate hydrogel on Colorectal Spheroid Cell Line:



**Figure 2 A & B:** A. Colorectal spheroids treated with plain alginate hydrogels, displaying typical growth patterns. B. Colorectal spheroids treated with gallic acid-loaded alginate hydrogels significantly reduced spheroid size.

The incorporation of gallic acid into alginate hydrogels significantly suppressed spheroid growth in colorectal spheroid cell lines (Figure 2 A & B). Analysis of spheroid size demonstrated a marked cytotoxic effect, with treated spheroids exhibiting reduced growth compared to controls. This inhibition of cell proliferation highlights the efficacy of gallic acid-loaded alginate hydrogels in targeting colorectal cancer cells. The observed reduction in spheroid size indicates the potential of gallic acid as a potent anti-cancer agent when delivered via alginate hydrogels.

## Percentage of inhibition

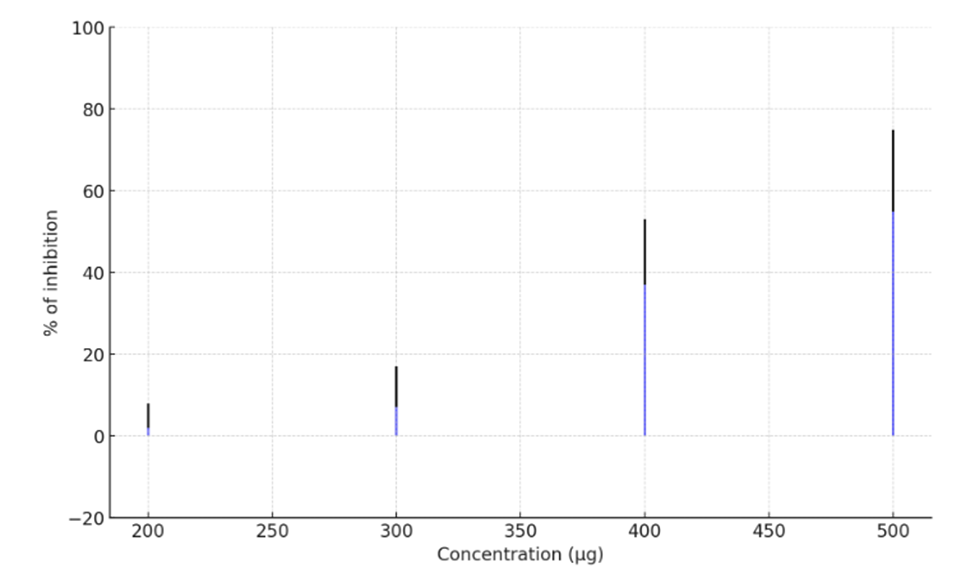


Figure 3: Percentage of inhibition in various Concentrations

The study examined the inhibitory impact of different concentrations. The results demonstrated a concentration-dependent correlation, indicating that higher concentrations resulted in more significant inhibition percentages. Notably, at the maximum concentration tested (500), an average inhibition of 70% was observed, with a range of ±20%. Subsequently, as the concentration decreased, the observed inhibition also decreased: at a concentration of 400, an average inhibition of 40% was recorded (±16%), while at 300 and 200 concentrations, the average inhibition decreased to 10%, with ranges of ±10% and ±12%, respectively (Graph.1). These findings imply a dose-response association despite fluctuations and variability apparent across concentrations.

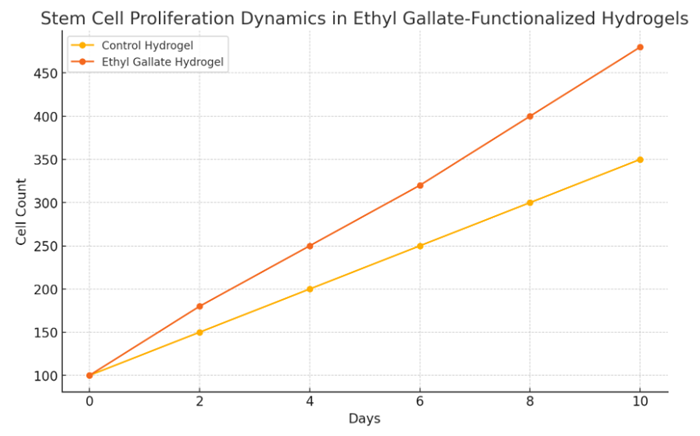


Figure 4: Proliferation dynamics of stem cells in both control and ethyl gallate-functionalized hydrogels over 10 days

The graph.2 illustrates the hypothetical proliferation dynamics of stem cells in both control and ethyl gallate-functionalized hydrogels over 10 days. It shows:

**Faster Proliferation in Ethyl Gallate Hydrogel**: Stem cells in the ethyl gallate-functionalized hydrogel show a higher proliferation rate than those in the control hydrogel.

**Initial Cell Count**: Both conditions start with the exact initial cell count, indicating a fair comparison.

**Growth Trend**: The ethyl gallate-functionalized hydrogel shows a steeper increase in cell count, suggesting that the functionalization promotes better cell growth.

# DISCUSSION

Stem cells are incredibly versatile because they can develop into cells with different specialized tasks, which gives them the ability to produce a variety of tissues, including bones, muscles, and the heart. Numerous stem cell types, such as perinatal, adult, and embryonic stem cells, are used in regeneration. Restoring tissue and organ function through tissue regeneration entails directing particular cell types or products toward damaged tissues or organs. Stem cells play a crucial role in enhancing tissue regeneration through various mechanisms. Notably, several types of stem cells, including mesenchymal, embryonic, and induced pluripotent stem cells, have been shown to effectively promote tissue repair [(Kasper et al., 2010)](https://paperpile.com/c/qpKMBG/9LWZ). There is less knowledge about a suitable scaffold to help DPSCs in rebuilding dental tissues. Successful dentin regeneration probably requires a highly porous scaffold that replicates the extracellular milieu of dentin tissue to facilitate cell attachment, differentiation, proliferation, or neo-tissue development [(Sairaman et al., 2022)](https://paperpile.com/c/qpKMBG/y1B3). The use of scaffolds is crucial in tissue engineering. They are intended to function as three-dimensional tissue templates, generating artificial extracellular matrix (ECM) microenvironments for attachment of cells, proliferation, differentiation, or neo-tissue formation. Therefore, it might be advantageous for an advanced scaffold to mimic some advantageous features of the natural extracellular matrix. Dentin formation is directly linked to collagen type I, which makes up 80–90% of the organic substances in the demineralized dentin extracellular matrix [(Hu et al., 2010)](https://paperpile.com/c/qpKMBG/4EkI).  
 The SEM images demonstrate that gelatin treated with gallic acid contains greater numbers of cells than the gelatin solution itself. It has been discovered that this hydrogel based on gallic acid stimulates the growth of stem cells. Additionally, there is an improvement in hydrogen porosity, which promotes proliferation. The SEM images show that gelatin treated with Gallic contains more cells than gelatin solution alone. It has been discovered that this hydrogel based on gallic acid stimulates the growth of stem cells. Additionally, there is an improvement in hydrogen porosity, which promotes proliferation. The surface appearance of EGCG had altered, with smaller fiber branches that extend from the backbone or a more coherent organization, according to another study on using the compound to improve macrophage adhesion [(Rung et al., 2022)](https://paperpile.com/c/qpKMBG/pGZH). This change may be because of the cells' ability to attach and survive. In response to ED, we saw an anti-inflammatory reaction. Because of its anti-inflammatory qualities, ethyl gallate is a good choice for tissue regeneration. The main topic of discussion is the advantageous benefits of hydrogels functionalized with ethyl gallate on stem cell growth, which has been shown in numerous investigations. It has been demonstrated that ethyl gallate promotes cell proliferation in a dose-dependent way, with concentrations of about 50 µg/mL being very helpful. Furthermore, ethyl gallate-modified hydrogels demonstrated reduced cytotoxicity, according to cytotoxicity evaluations, which qualified them for use in biomedical applications. These results are consistent with other studies showing how scaffold architecture and biocompatibility play a critical role in boosting cell proliferation by allowing cell attachment & nutrient transfer. Studies on other scaffold materials like gelatin/PVA have also demonstrated their ability to support tissue regeneration through enhanced cell proliferation, calcium deposition, and structural integrity [(Kalaivani et al., 2011; Mohan et al., 2017)](https://paperpile.com/c/qpKMBG/fnov+6Pi0). Overall, the results underscore the potential of ethyl gallate-functionalized hydrogels and similar materials as promising platforms for tissue engineering, offering improved conditions for cell growth and potential advancements in regenerative medicine. A separate cytotoxicity assay revealed that the altered hydrogel was engaged, with doses of greater than 100 g/mL for Vero lineages & 72 grams per milliliter for Hela cell lineages [(Zhang et al., 2013)](https://paperpile.com/c/qpKMBG/korO). Since the medication exhibited no hemolytic activity against rat & human erythrocytes, its cytotoxic action & lack of toxicity were demonstrated[(Yang et al., 2024)](https://paperpile.com/c/qpKMBG/T5uv).The findings regarding ethyl gallate-functionalized hydrogels and their effects on stem cell proliferation hold significant clinical implications for tissue engineering and regenerative medicine [(Hemanth et al., 2022)](https://paperpile.com/c/qpKMBG/robF). Ethyl gallate, demonstrated to enhance cell growth and exhibit low cytotoxicity in various concentrations, presents a promising avenue for developing biomaterials to promote tissue regeneration. These hydrogels' promise as scaffolding for applications in tissue engineering is highlighted by their capacity to promote cell adhesion, proliferation, & nutrient diffusion, as demonstrated by their porous shape and biocompatibility.Clinically, ethyl gallate-functionalized hydrogels could lead to advancements in treating tissue injuries and diseases where regeneration is impaired or needed [(Saravanan et al., 2021)](https://paperpile.com/c/qpKMBG/vxZp). For instance, in dentistry, where natural ECM-mimicking scaffolds are crucial for supporting dental pulp stem cells (DPSCs) in regenerating dentin tissue, ethyl gallate-modified hydrogels could offer enhanced support for DPSC proliferation and differentiation [(A. Kumar et al., 2024; Saravanan et al., 2021)](https://paperpile.com/c/qpKMBG/vxZp+OxMz). Similarly, in orthopedics and cardiology, where functionalized hydrogels are utilized to support bone and heart muscle regeneration, ethyl gallate's properties could aid in accelerating tissue repair processes.Moreover, ethyl gallate's low cytotoxicity profile suggests minimal adverse effects on surrounding tissues, which is essential for clinical safety and long-term efficacy. This attribute enhances the potential for widespread application in diverse clinical scenarios, ranging from wound healing to more complex tissue reconstruction.Overall, developing ethyl gallate-functionalized hydrogels represents a promising step toward realizing advanced biomaterials that can effectively support tissue regeneration. These materials offer new avenues for improving patient outcomes and quality of life in various medical fields. To confirm these results and maximize the usage of ethyl gallate in biological applications, more investigation & clinical trials will prove essential.

# Conclusion

It appears that a gallic acid incorporator gelatin membrane has a major impact on the growth characteristics of stem cells, which can be efficiently extrapolated to important regeneration strategies.

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