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RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ

Bioactive Hydrofiber Dressings with Quince (*Cydonia oblonga)* Seed Mucilage for Cutaneous Tissue Repair

Merve ERGİNER [1,2]

[1] *Istanbul University-Cerrahpaşa Institute of Nanotechnology and Biotechnology, Department of Biotechnology, 34500, Istanbul, Türkiye*

[2] *Health Biotechnology Joint Research and Application Center of Excellence, 34220, Esenler, Istanbul, Türkiye*

Öz

Cilt, vücudumuzun en dışında bulunan ve en geniş yüzey alanına sahip organ olduğu için, bu dokuda meydana gelen herhangi bir bozulma veya hasar insan yaşamını önemli ölçüde etkileyebilmektedir. Bu tür yaralanmalar genellikle hastaneye yatış, ağrı, travma, yara izi riski ve enfeksiyonlarla sonuçlanabilmekte ve bu nedenle acil tedavi gerektirmektedir. Hidrofiber sistemler ve yara örtüleri, cilt yenilenmesini destekleyen, enfeksiyonları önleyen ve daha az ağrıyla hızlı iyileşmeyi teşvik eden yenilikçi yaklaşımlar olarak kapsamlı şekilde araştırılmaktadır. Biyolojik olarak aktif bileşenler, biyolojik ve hücresel yolları düzenlemede önemli rol oynamakta ve yara iyileşmesi ile cilt yenilenmesi stratejilerinde yaygın olarak kullanılmaktadır. Doğal polimerler, biyolojik kökenleri, doğal biyoaktif özellikleri ve büyüme faktörlerini taklit etme yetenekleri nedeniyle yara iyileştirme uygulamaları için umut verici adaylar olarak değerlendirilmektedir. Doğa, biyopolimerler açısından zengin bir kaynak olup, bitki özleri tarih boyunca tedavi amaçlı kullanılmıştır. Ayva olarak bilinen *Cydonia oblonga*, yara iyileşmesini ve cilt hastalıklarının tedavisini destekleyen çeşitli biyolojik aktiviteleri ile tanınmaktadır. Bu çalışmada, ticari olarak temin edilen bir hidrofiber yara örtüsünün, ayva çekirdeği müsilajı (QSM) ile zenginleştirilmiş halinin biyolojik aktivitesi incelenmiştir. QSM ile zenginleştirilen örneklerin, kontrol ve yalnızca hidrofiber ile karşılaştırıldığında İnsan Keratinosit Hücre Hatlarında (HaCaT) hücre canlılığı ve çoğalmasını artırdığı gösterilmiştir.

Anahtar Kelimeler: Yara iyileşmesi, Doğal Polimerler, Hidrofiber, Ayva Çekirdeği Müsilajı

Abstract

Since the skin is the outermost organ with the largest surface area, any disruption to this tissue can significantly affect human life. Such injuries often lead to hospitalization, pain, trauma, risk of scarring, and infections, and therefore require immediate treatment. Hydrofiber systems and wound dressings are extensively investigated and represent innovative fields that support skin regeneration, prevent infections, and promote rapid recovery with reduced pain. Biologically active ingredients play a crucial role in modulating biological and cellular pathways and are widely applied in wound healing and skin regeneration strategies. Natural polymers, due to their biological origin, inherent bioactivity, and their ability to mimic naturally occurring growth factors, are considered promising candidates for wound healing applications. Nature serves as a rich source of biopolymers, and plant extracts have been used since time immemorial for therapeutic purposes. *Cydonia oblonga*, commonly known as quince, is recognized for its diverse bioactivities that support wound healing and the treatment of skin ailments. In this study, a commercially available hydrofiber dressing enriched with quince seed mucilage (QSM) was evaluated. The QSM enrichment demonstrated improved cellular viability in Human Keratinocyte Cell Lines (HaCaT) when compared to control and hydrofibers.

Keywords: Wound Healing, Natural Polymers, Hyrofiber, Quince Seed Mucilage

I. INTRODUCTION

The skin has evolved to protect the body from pathogens, toxins and other potential damage from the external environment and has neural, perceptual, cosmetic and regulatory effects. It maintains the body's moisture and electrolyte balance. It has the ability to "self-renew", resulting in the formation of a new layer of skin every two to three weeks. It consists of 3 layers called epidermis, dermis and hypodermis. The epidermis consists of squamous epithelium, melanocytes (which contain pigment), Langerhans cells, Merkel cells (which sense pressure), and

Corresponding Author: MERVE ERGİNER, **Tel:** 128663790 dahili-51548, **E-mail:** merve.haskoylu@iuc.edu.tr

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keratinocytes, which act as a protective layer. The epidermis consists of 5 sub-layers (stratum corneum, stratum spinosum, stratum lucidum, stratum gronulosum and stratum corneum) and interacts with textiles, pathogens, toxins, cosmetics and many other surfaces and prevents skin dehydration. The dermis is responsible for the mechanical properties of the skin and is composed of fibroblasts, fibronectin, ECM, proteoglycans, elastin, collagen, blood vessels, lymphatic system and nervous network and is separated from the epidermis by a basal layer. Collagen and elastin are structural proteins that support tissues, bind cells together, and are responsible for the shape and function of the body. The hypodermis is a layer of fatty tissue beneath the epidermis that separates the dermis from the muscle layer [1-4].

Although the skin is defined as the largest and outermost organ and it is exposed to many damaging factors, any wounds or damage to this layer adversely affect the quality of life and it is vitally important to heal these wounds promptly with minimal scarring and scar tissue formation. Acute injuries and traumas (cut, surgery, accident), burns (physical, chemical), ulcers, infections are known to affect the function of tissues, cells, and organs and effect host life and well-being several. The number of health problems related to chronic wounds is increasing rapidly due to the growth of the aging population worldwide. In particular, the money spent on healing chronic wounds threatens not only our country but also the whole world by causing direct and indirect economic losses.) [5,6]. Wound can be classified into three main titles by rank (tidy, untidy), type (clean, lacerating, hematoma, bruising and abrasion) and thickness (epidermal loss only, superficial, deep, and full). Wounds only epidermal loss is known to heal with basic dressings and expected full re-epithelization with minimal scar tissue formation is observed in 5-7 days in epidermal loss and superficial wounds which have partial thickness where epidermis and some papillary dermises are lost and heal 2-4 weeks. Epidermis, papillary dermis and deep into reticular dermis wounds are named as superficial wounds and heal approx. 3-5 weeks with scar formation. Deep and Full thickness wounds require months to heal with no complete tissue regeneration and scar formation where epidermis, dermis and subdermal tissues are damaged [5-8].

Wound healing is a response of body to injury and tissue disruption and known to consist of four main stages namely, hemostasis, inflammation, proliferation, and remodeling. Keratinocytes response to violation and start hemostasis followed by vasoconstriction and clotting. Secretion of growth factors, proinflammatory cytokines. In the second step, inflammation, is known to start with fibroblast related growth secretion and neutrophil reaction to wound area where monocyte cell transformation to macrophages and result in inflammatory response and angiogenesis. Proliferation stage is named also granulation tissue formation, and several growth factors (VEGF, FGF) start proliferation stage where endothelial cell reproduction and angiogenesis occur together with production of ECM components to support skin. Final stage, remodeling, is the replacement of type III collagen by Type I collagen and degraded in control to correct tissue form [5,6,9,10].

Healing skin wounds fast without any mark on skin surface after trauma, diabetes related conditions or surgery is important because of not only aesthetic reasons but also reducing hospitalization, scarring, pain and life threating infection problems. Providing microenvironment for cells, non-toxic, antimicrobial, antiallergic, anti- scar tissue former and non-sticky wound dressings are required for skin wound healing while maintaining moisture and hydration of wounded area is known to enhance the quality of the newly formed tissue Keratinocyte proliferation and migration to wounded area is an important process for tissue regeneration and intra and extracellular interactions play role in it. After acute cutaneous injuries cells close to wound bed and start to migrate through wound area and this process play vital role in wound closure. Epidermal cellular migration is known to be much more dynamic and higher than leukocyte migration [11-12]. Tissue engineering and regenerative medicine seek alternative ways to repair injured or dysfunctional tissues in the human body in the light of biology, materials science, medicine, engineering and mechanics. Tissue engineering has become increasingly important over the past three decades [11,13]. This field seeks to develop biocompatible tissue constructs that contact existing cells or tissues to regenerate damaged tissue and provide a three-dimensional matrix at the implanted site, as well as support cell-cell signaling, growth factor production, extracellular matrix (ECM), cell proliferation and differentiation. Natural or synthetic-based scaffolds such as hydrogels, micro/nanofibrous scaffolds, porous matrices, fibers, sponges, and foams are increasingly being used to provide a natural-like ECM environment and support cell growth, proliferation, and differentiation to replace damaged tissue function [14]. Various strategies have been developed to produce scaffolds that can be cellular/cell-free, synthetic, biosynthetic or natural and support the regions where they are placed. Nanofibers, sponges, 3D printed

scaffolds, foams, cryogels, decellularized matrices are widely used in tissue engineering applications [5].

The biological activities of cells and tissues can be regulated by biochemical factors such as hormones and growth factors, and thanks to the concept of "Materiobiology", it is known that the biophysical properties of the designed scaffold have significant effects on the biological response. This concept takes into account the properties of biomaterials that affect the biological response and functionality, and attempts to improve the biological behavior of these materials with a multidisciplinary approach Cell proliferation, differentiation, migration, and other functions are influenced by pore size, mechanical properties such as Young's modulus (stiffness), elasticity, topography (2D), geometry (3D), chemical and temporal properties such as degradation rate, and biocompatibility of scaffolds [15,16].

Nano- and microfibers produced by solution blowing or electrospinning have been widely applied in biomedical fields such as wound dressing, tissue engineering, immobilized enzymes and artificial blood vessels. Biodegradable polymers such as polylactic acid (PLA) have been converted into PLA nanofibers and applied to drug delivery, bone remodeling, and tissue engineering. The use of existing nanofiber products in the market is still limited due to the lack of sufficient research on the effectiveness of wound treatment, easy availability, and high cost to the patient and the national economy. Therefore, in the treatment of chronic wounds that are difficult to heal, the emergence of qualified health products because of scientific research and development of wound care products that will support healing, which can be an alternative to ordinary dressing materials that are commercially sold and currently used, will make a serious contribution to reducing costs in the field of health expenditure of our country [17,18].

Natural and synthetic polymers are used widely to correct, restore or maintain skin tissue dysfunction. Synthetic polymers are non-biological components with the advantage of stability and controlled production, but they can sometimes be bioinert or lack bioactivity. It is desirable that these polymers do not cause toxic effects when broken down into their components in the living body. Because of their low cost and availability, they are often preferred in tissue engineering applications. Synthetic polymers such as polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), polyethylene glycol (PEG), and polyethylene oxide (PEO) are examples of synthetic materials often preferred in tissue engineering applications. Synthetic polymers are often used in combination with biopolymers to design combined scaffolds that take advantage of the matrix strength of synthetic materials and the bioactivity of natural polymers [5]. Natural polymers are frequently used in stem cell culture and regenerative medicine applications because they are compatible with the human body. Different types of polysaccharides such as β-glucans, dextran, cellulose (neutral), alginic acid, hyaluronic acid (acidic), chitin, chitosan (basic), heparin, chondroitin, dermatan sulfate and keratan sulfate are frequently preferred in tissue engineering applications [19-21]. Microbial and plant-based polysaccharides are superior to animal-oriented ones with extraction easiness, low risk of contamination and ethical Concerns.

Quince namely, *Cydonia oblonga* Miller belongs to Rosaceae family and various components used for medicinal effects like sedative, antipyretic, anti-diarrheal. This leafy tree usually grows in the Middle East, South Africa and Central Europe. Quince is known to be rich in bioactive materials such as tannins, carotenoids, flavonoids, phenolic acids, total polyphenol, vitamins (retinol, thiamine, riboflavin, ascorbic acid), minerals (potassium, sodium, calcium, iron, magnesium) [22-24] Seeds are known to include polyphenols (C-glucosyl flavones, lucenin-2, vicenin-2, stellarin-2, isoschaftosyde, schaftosyde, 6-C-pentosyl-8-C- Glucosyl chrysoeriol and 6 6-C-glucosyl-8-C-pentosyl chrysoeriol, and kaempferol-3-Orutinoside), fat soluble compounds(tocopherols, phytosterols and phenolic acids), and organic acids (citric, ascorbic, malic, quinic, shikimic, fumaric acids, ursolic acid, tormentic acid, and β-daucosterol) [24-26]. Quince seed mucilage consist of water-soluble polysaccharides and cellulose and acidic hydrolysis (reverse reaction of esterification) is form the sugar presence in quince seeds (D-xylose, 4-Omethyl glucose, and D-glucose) [27]. Quince seed mucilage is reported to have complete healing when applied to wound area of rabbit full thickness model for 13 days reported by Tamri et al., [28]. Wounds infected with Staphylococcus aureus is reported to be healed by quince seed extracts [29]. Antifungal activity of quince seed mucilage nano hydrogel decorated with essential oils against *C. albicans* and *M. furfur* reported [30] . QSM is known to have high medicinal properties but cannot be applied to exudative wounds directly due to its high-water content and non-absorption of infection of open wounds [31]. Thus, here in this study quince mucilage (QSM) is combined with hydrofiber wound dressings to observe cell proliferating abilities of mucilage to improve bioactivity of hydrofiber and enlighten their bioactivities to be used in skin tissue

engineering and wound dressing applications when combined with fiber/matrix systems.

II. MATERIALS and METHODS

2.1. Preparation of Quince Seed Mucilage

Quince fruits (*Cydonia oblonga*) are purchased from a local market in city of Istanbul (early fall). Quince seed mucilage (QSM) is prepared after removing seeds from pulp, washed with ethanol and 5 grams of seeds are mixed with 10 mL of dH_2O for 24 hours. Seeds are filtered and mucilage is precipitated with ethanol washed, centrifuged and freeze-dried for further usage [27,32].

2.2. Preparation of QSM- Wound Dressings

Aquacell hydrofiber wound dressings (Convatec) is fortified with QSM. Briefly wound dressings coated with QSM mucilage with different concentrations prepared in PBS (4mg/ml, 2 mg/ml and 1 mg/ml) via dropwise on to precut surfaces (0.5x 0.5 cm) in 400 µl for each concentration and freeze dried and further used for cellular proliferation and attachment studies.

2.3. Characterization of QSM-Wound Dressings

The structural integrity of the wound dressing, QSM and QSM fortified dressings were analyzed using Fourier Transform Infrared Spectroscopy via Thermo Fisher Scientific NICOLET 6700 FTIR spectrometer (Waltham, MA, USA) over a range of 400–4000 cm^{-1} and attenuated total reflectance (ATR) capability operating in 600–4000 cm^{-1}.

2.4. *In-vitro* Cytotoxicity and Cellular Adhesion Evaluation of the Hydrofibers

2.4.1. Assessment of cytotoxicity

In-vitro cytotoxicity evaluation of the wound dressings fortified with QSM were determined using method of in-direct toxicity assessment according to ISO-10993-5: Biological evaluation of biomedical devices-*in-vitro* cytotoxicity test [33]. Human epidermal keratinocyte cell line (HaCaT) used for *in-vitro* cytotoxicity and adhesion studies. HaCaT cells cultured in 3Dulbecco's Modified Eagle Medium (DMEM (Biosera/France) fortified with 10% FBS (Biosera/France) and 1% penicillin-streptomycin (Pan Biotech/Germany) and cells were maintained at 37 °C in a 5% CO2, 95% humidity environment. Cell viability is analyzed via MTT, a tetrazolium salt, metabolized by live cell mitochondria to form insoluble purple formazan to inspect cellular viability through optical density [34]. Cells seeded to 96 well cell culture plates at the density of 1X 10^4 cells/well and incubated for attachment overnight. Hydrofiber wound dressing itself, and fortified with "QSM (4mg/ml, 2mg/ml and 1 mg/ml) containing samples were extracted according to ISO-10993-12 [35] extraction protocol after UV sterilization for 1 hour both sides and submerged in DMEM (Dulbecco's Modified Eagle Medium) at 37 °C in a 5% CO2, 95% humidity environment for 24 hours and used as 100% extract and diluted with DMEM (Dulbecco's Modified Eagle Medium) and applied on to cells and cells incubated in DMEM only used as control (0%) and cells incubated with those extracts for 72 hours. After incubation period media in wells replaced by 110 µL MTT reagent prepared in PBS and mixed with DMEM and incubated for 4 h incubation, after which 100 µL of DMSO added on to wells to dissolve formazan crystals and absorbance was measured at 570 nm with a 630 nm reference.

2.4.2. Investigation of cellular adhesion on hydrofibers

Investigation of cellular adhesion on hydrofibers (both QSM fortified and commercial) examined through visualization of cellular attachment via fluorescence microscopy DM:4000B with a DFC7000T camera (Leica, Germany) and SEM investigations (Thermo Fisher Quattro S). Cells at the density of $5X10^5$ cell/well seeded onto presterilized and media saturated hydrofibers and incubated for 72 hours. After incubation period media removed and hydrofibers washed with PBS and fixed with 2.5% glutaraldehyde in PBS for 20 minutes. Hydrofibers examined with Fluorescence microscopy is dyed with DAPI (Sigma-Aldrich) to mark nuclei of the cells for 30 minutes in dark and washed with PBS and further dehydrated via washes with increasing ethanol concentrations (70%, 80% 90% and 100%). Samples used in SEM investigation is washed with PBS and dehydrated as described for fluoresce microscopy investigation samples.

2.5. Statistical Analysis

The experiments were performed at least in triplicate, and Statistical significance between the experimental groups for cell culture experiments was assessed using a one-way ANOVA followed by Kruskal Wallis multiple comparison test. A p-value below 0.05 was considered as statistically significant.

III. RESULTS and DISCUSSION

3.1. Characterization

FTIR analyses of hydrofiber, QSM enriched hydrofibers (1, 2 and 4 mg/ml) and QSM were performed by measuring absorbance values in the frequency range of 400–4000 cm^{-1}. Results shared in figure 1.

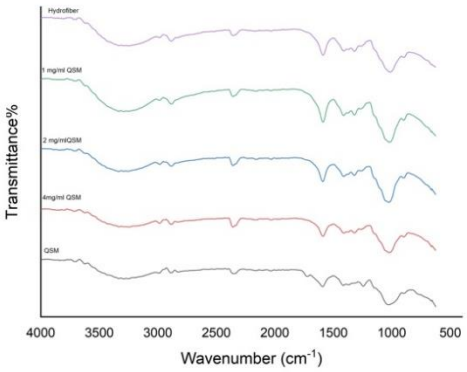

Figure 1. FTIR image of hydrofiber, QSM and QSM enriched hydrofibers (1 mg/ml, 2 mg/ml, 4 mg/ml)

Figure 1 Shows the FTIR spectra of QSM, hdyrofiber and QSM absorbed hydrofibers with different concentrations (1mg/ml, 2 mg/ml and 4 mg/ml). QSM is known to contain large fraction of hemicelluloses that consist of charged uronic acids. At the 3323 cm^{-1}, which corresponds to stretching of –OH groups of QSM while the band observed between 1633 and 1784 cm^{-1} is symmetric COOH and asymmetric C=O vibrations. Peaks around 1518-1530 cm^{-1} could be resonance of COOH functional groups in COO^{-} ions. Peaks around 610, 1283, 1200, 1620 and 1730 cm^{-1} ascribed to the C-(O)-O stretching and β-D-glycosidic linkages of uronic acid in the polysaccharide structures in Mucilages previously mentioned by researchers while QSM is known to contain large fraction of hemicelluloses that consist of charged uronic acids [36-38].

3.2. *In-vitro* Cytotoxicity and Cellular Adhesion Evaluation of the Hydrofibers

3.2.1. Assessment of cytotoxicity

Viability of QSM fortified hydrofibers and commercially available hydrofiber is incubated with keratinocytes for 72 hours and results shared in figure 2.

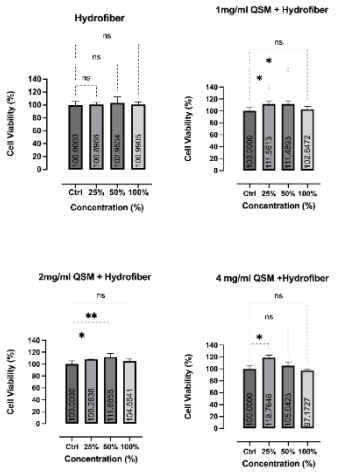

Figure 2. Cell Viability results of HaCaT cell line after being cultivated with hydrofiber and QSM fortified hydrofibers against control (ctrl) for 72h. (A P value below 0.05 considered as statistically significant).

Commercially available hydrofiber showed control similar biocompatibility. Enrichment of QSM increased cellular viability for 1mg/ml at the end of 72 hours for the doses of 25%, 50% and 100% as; 111.561%, 111.489%, 102.642% while control was 100%. Addition of 2 mg/ml QSM increased cellular viability to 108.283%, 111.885%, 104.664% for the doses of 25%, 50% and 100% after 72 hours. Viability recorded for 4 mg/ml QSM addition as 118.764%, 105.042%, 97.172 for 25%, 50% and 100% extracts. All QSM enriched hydrofibers showed greater viability than control and commercial hydrofiber resulting in addition of QSM improved cellular proliferation with the highest viability observed at 4 mg/ml enrichment extraction dose of 25%.

3.2.2. Investigation of cellular adhesion on hydrofibers

Cellular adhesion on the hydrofibers were visualized via fluorescent labelling of nuclei in cells with DAPI and analyzed with fluorescent microscopy and SEM. Results are shared below (Figure 3 and Figure 4).

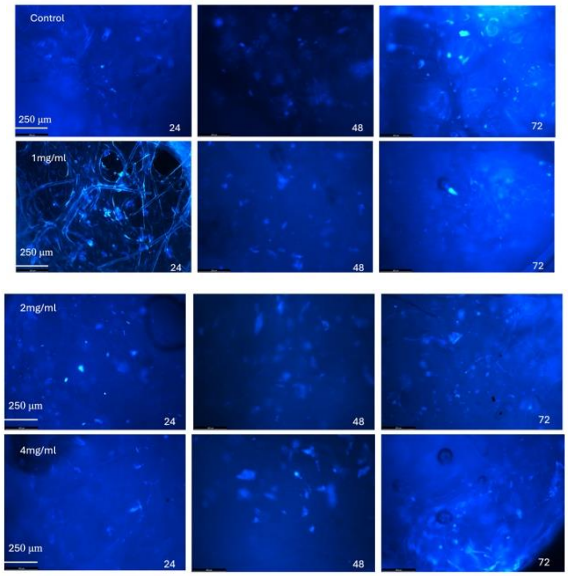

Figure 3 Fluorescent microscopy images of hydrofibers after being cultivated with HaCaT cells for 72 hours (A: Hyrdofiber, B: Hydrofiber with 1mg/ml QSM, C: Hydrofiber with 2 mg /ml QSM, F: Hydrofiber with 4 mg /ml QSM)

Cellular adhesion on hydrofibers were examined via fluorescent microscope marked via DAPI are shared in figure 3. Although cells observed inside the fibers due to swollen behavior and cellular adhesion inside the fibers clear images are struggled to be captured.

Cellular adhesion on to hydrofibers are further examined via SEM (Figure 4). Figure 4 A porous and fiber aligned surface structure of hydrofiber. Porous structure observed in figure 4B after being enriched with QSM prior to cell seed. Cells observed on surface figure 4C, D, E and F and enrichment of QSM showed dense cellular attachment on surface with the increase of QSM amount (Figure 4 D, E, F). Cell proliferation and cellular adhesion results evaluated together it can be concluded that QSM enrichment increased cellular viability and attachment on surface of the hydrofibers.

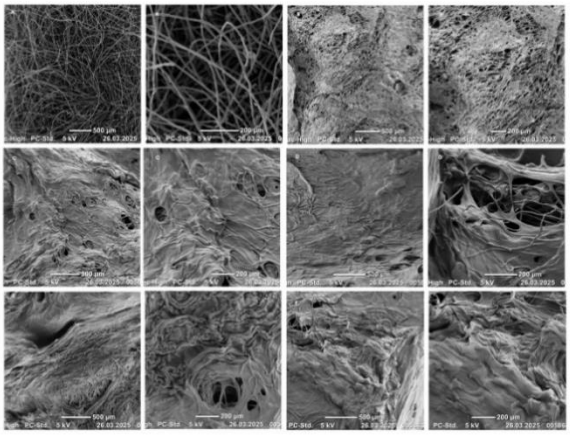

Figure 4: SEM images of hydrofibers after being cultivated with HaCaT cells for 72 hours. (A: hydrofiber without cells, B: Hydrofiber with 4mg/ml QSM without cells, C: Hyrdofiber with cells, D: Hydrofiber with 1mg/ml QSM with cells, E: Hydrofiber with 2 mg /ml QSM with cells, F: Hydrofiber with 4 mg /ml QSM with cells).

QSM containing (5%, 10% and 20%) in Eucerin base creams were applied to Iranian male rabbit full thickness model and increased wound contraction between QSM 10 and 20% and high hydroxyproline and growth factors in wound fluid is observed [28]. Aghmiuni et al. [31] examines QSM- based smart/stimuli-responsive PCL/Chitosan//PEG hybrid scaffolds on human adipocyte stem cells (h-ASCs), fibroblasts and keratinocytes and improved cellular adhesion, growth and wound healing and keratinocyte differentiation is observed. Crosslinked QSM porous scaffolds tested on human adipose-derived mesenchymal stem cells and improved cellular adhesion and migration observed [39]. In another study QSM applied to 45 primiparous women for 14 days and improved wound healing and reduced pain recorded [40]. A silicon-integrated QSM 3D cryogel is tested for osteobiologic capacity via human adipose derived mesenchymal stem cells (hAMSCs) and osteogenic differentiation is demonstrated via upregulation of osteogenesis related genes [41]. Hyaluronic acid/QSM injectable hydrogels synthesized for release of dissolved curcumin and hydrogels are proposed to be used in intra-articular drug delivery applications [42]. QSM is applied to mesenchymal stem cells isolated from newborn foreskin (hnFSSCs) and investigated for proliferative activities and dose of 100 µg/mL for 24 h concluded to be the best concentration foe cell proliferative activity when compared to control group. Higher immunoreactivity for Ki-67, c-Myc, OCT¾ QSM H-score: 266.5±12.6), OCT¾ (H-score: 239±8), and Sall4 (H-score: 243.8±7.5) [43]. Ex situ modification of QSM and bacterial cellulose (BC) are

designed as biocompatible scaffold for fibroblast proliferation and highlighted its great potential to be used as wound dressings in clinical applications with high swelling and good cell proliferation abilities [44]. Presence of positive result in literature for QSM when applied to wounded zones supported with current study data with improved epidermal keratinocyte proliferations.

IV. CONCLUSION

When literature and present data evaluated together it can be concluded that enrichment of QSM could be used to improve bioactivity of the scaffold with its cell proliferative, pain reducer, skin regenerating, wound healing abilities. Thus, QSM can be proposed as a strong candidate to be used together with PLA like biodegradable polymers to design wound dressings via electrospinning or solution blowing like technologies and further studies are in. need for mechanical, antimicrobial, wettability and biological activities both in histological and molecular level of QSM enriched fiber systems to support wound healing *in-vivo* and *in-vitro* are in need.

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