Skin Regeneration Potential of Mesenchymal Stem Cells Preconditioned with Quercetin in Burn Wound

Fatima Irfan*, Fatima Jameel, Asmat Salim
International Center for Chemical and Biological Sciences (ICCBS), Pakistan
*E-mail: famughal1@gmail.com

ABSTRACT

Burn injury is reported as a growing challenge in healthcare due to the failure of its management in a systematic and timely manner. 1.2 million cases of burn wounds are reported each year, amongst which 100,000 people require medical attention [1]. Wound healing is an intricate process that requires the regulation of cytokines, growth regulators, fibroblasts, keratinocytes, endothelial, and other blood-borne cells. The wound healing process involves four overlapping physiological processes; hemostasis, inflammation, maturation, and proliferation. Wound healing becomes complicated due to various medical ailments such as diabetes, obesity, hypoxia, and other inflammatory diseases. Delayed treatment of the wound or its management results in the loss of skin integrity which even leads to death in extreme cases. Available treatment options include only management of the wound to prevent infectionand restore adequate blood flow. Advancement in the field of regenerative medicine and tissue engineering has provided a basic management system for skin wounds caused by burn injury. Stem cell therapy is considered a promising approach to treat burn wounds due to their immense regenerative potential [2]. Among different stem cell types, mesenchymal stem cells (MSCs) have the capability to differentiate into skin cells. MSCs have regenerative potential and differential ability into multiple lineages such as bone, skin, kidney, and heart. Chemical compounds extracted from plants have long been used for skin diseases and wound treatment. They possess anti-inflammatory, anti-bacterial, and antioxidant activities. *Melia azedarach* is used for medicinal purposes as it contains many bioactive compounds [3]. Among various active components of *Melia azedarach*, the flavonoids have anti-inflammatory, anti-bacterial, and antioxidant activity which are potent for wound healing. Having many biological effects of medicinal importance, quercetin is thought to play a significant role in the wound healing process.

Objectives: The proposed study plans to elucidate the role of quercetin in enhancing the wound healing potential of MSCs. Our study aimed that local transplantation of preconditioned MSCs would aid in the process of healing due to the anti-inflammatory and antioxidantproperties of the compound.

Methodology: The study is divided into two parts, *in vivo* and *in vitro*. In *in vitro* part includes umbilical cord processing and culturing. Characterization of MScs using immunocytochemical staining by determining cells surface-specific markers. MTT assay was used to assess the cytotoxicity profile of quercetin. Scratch assay was performed to check the efficiency of quercetin in enhancing MSCs potential by creating a cell-free gap. In the *in vivo* part of the study cold burn wound model was developed using liquid nitrogen and MSCs transplanted after 24 hours of wound induction. The macroscopic analysis, histology and gene expression profile was analyzed at different interval of wound healing phases.

Results: The MSCs were isolated from the umbilical cord and subculture into different passages. MSCs were identified based on their fibroblast-like morphology and characterized using immunocytochemistry. The surface antigens were found to be positive i.e., CD90, CD117, Vimentin, and hematopoietic marker CD45 were negative. The cytotoxicity of the quercetin was analyzed through an MTT assay. Scratch assays were performed which showed a reduction of wound area in preconditioned MSCs group as compared to the untreated group.*In-vivo* results comprise macroscopic, histological, and gene expression profiles.The macroscopic evaluation was performed by capturing images of cold burn wounds at different time intervals according to wound healing phases. Macroscopic examination showed a decrease in wound healing time in preconditioned MSCs group. Histology examination ofthe burn wound, MSCs treated, Quercetin treated MSCs were analyzed. The results showed enhances skin regeneration based on reformation of skin adnexa, fibroblast connectivity, and overall tissue integrity.Gene expression profile showing decrease inflammatory

cytokine IL 1β, IL-6, and increase anti-inflammatory cytokine IL-4, IL-5. The oxidative stress also gets reduced as the expression of GPX7, PRDX, and TXNRD2. This study concluded that transplantation of treated MSCs had provided an environment for skin cell attachment, proliferation, and migration by inducing the release of growth factors and cytokines. The quercetin enhances the MSC's potential of healing based on its properties of anti-inflammation, oxidative stress reduction, increase cell migration. This study is expected to lead to an improvement in the cell-based treatment of acute or chronic wounds.

Keywords: burn wound, inflammation, quercetin, stem cells, wound healing

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