

Grape Skin Extract Hydrogel Restores Systemic Redox Balance in Diabetic Rats

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Abstract: Chronic diabetic wounds are difficult to heal due to prolonged inflammation and oxidative stress, often leading to severe complications. This study aimed to evaluate the systemic redox status in diabetic rats treated with grape skin extract (GSE)-loaded alginate-gelatin hydrogels. Hydrogels were prepared with 8 mg/mL GSE and applied topically to full-thickness skin wounds in streptozotocin-induced diabetic Wistar rats. Redox biomarkers including TBARS, H₂O₂, O₂⁻, SOD, CAT and GSH were analyzed in blood samples on days 3, 7, and 15 post-treatment. Results showed that untreated diabetic rats exhibited significantly elevated prooxidative markers and reduced antioxidant enzyme activities. In contrast, rats treated with GSE-loaded hydrogels showed progressive normalization of all redox parameters, particularly by day 15, suggesting both early and sustained antioxidant effects. These findings indicate that GSE, which is rich in polyphenols, contributes to systemic redox balance restoration, making these hydrogels a promising therapeutic agents for diabetic wound management.

Keywords: hydrogel, diabetic wound, oxidative stress

1. Introduction

Chronic diabetic wounds, such as diabetic foot ulcers, are still a major clinical challenge mainly due to persistent inflammation, impaired angiogenesis, and delayed re-epithelialization [1].

Current treatment strategies remain insufficient, with high rates of complications like limb amputations in diabetic patients. Natural polymeric hydrogels offer a promising alternative due to their biocompatibility, moisture retention and ability to deliver therapeutic agents that enhance tissue regeneration [2].

Recent research has turned to plant-derived active compounds, especially polyphenol-rich grape skin extract (GSE), a byproduct of the wine industry as promising therapeutic agents. GSE exhibits strong antioxidant and anti-inflammatory properties. These compounds counteract oxidative stress and inflammation, which are key factors in delayed diabetic wound healing [3].

Despite these advancements in chronic wound treatment, their systemic impact has not been widely explored. Therefore, our aim was to evaluate the systemic redox status of diabetic rats whose wounds were treated with GSE-based hydrogels through biomarkers of oxidative stress and antioxidant defense to fully understand the therapeutic potential and safety profile of this novel approach to diabetic wound healing.

2. Methodology

2.1 Preparation of GSE-loaded hydrogels (HG+GSE)

Ultrasound-assisted extraction with ethyl acetate was used to obtain the grape skin extract (GSE) and kept refrigerated at 4 °C. A solution of GSE at 8 mg/mL was blended with alginate and gelatin in equal proportions (3% each), thoroughly mixed, poured into molds, frozen, and then cross-linked using calcium chloride (CaCl₂). Control hydrogels (HG) without GSE were prepared using the same method but with water instead of the extract [4].

2.2 Experimental Design and Treatment Groups

Adult male Wistar rats were used in this study. Diabetes was induced by a single intraperitoneal injection of streptozotocin dissolved in citrate buffer. After 72 hours and a 12-hour fast, rats with fasting blood glucose >11.1 mmol/L were considered diabetic and included in the study. They were then divided into three treatment groups (8 animals in each group): CTRL (untreated control), HG (hydrogel without extract) and HG + GSE (hydrogel containing grape skin extract).

Full-thickness excisional wounds were made under anesthesia, and the appropriate gel was applied topically once daily. Animals were sacrificed on days 3, 7 and 15 post-wounding, and blood samples were collected for further biochemical analysis.

2.3 Systemic redox state assessment

Collected blood samples were used to obtain plasma and red blood cell lysates used in the analysis of the systemic redox status. The analysis included markers such as lipid peroxidation (TBARS), hydrogen peroxide (H₂O₂) and superoxide anion (O₂⁻), along

with antioxidant indicators like superoxide dismutase (SOD), catalase (CAT) and glutathione (GSH). All parameters were measured using standard spectrophotometric assays [5].

3. Results and Discussion

Figure 1 shows the levels of prooxidative markers measured. The levels of all of the parameters were higher in CTRL and HG animals, especially H_2O_2 and O_2^- , indicating excessive ROS generation. These were significantly reduced in the HG + GSE group on day 15.

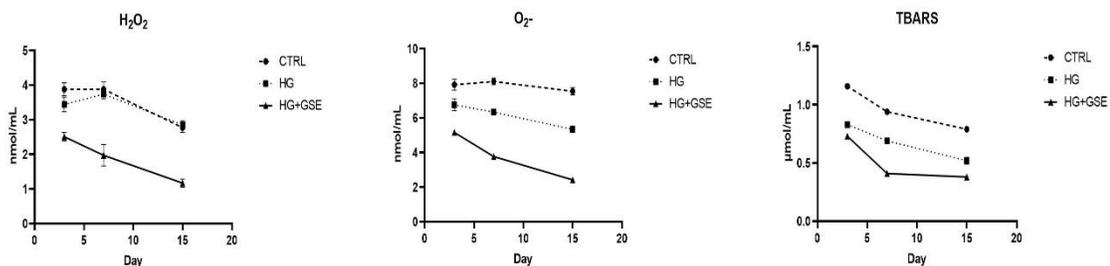


Figure 1. Levels of prooxidative markers (H_2O_2 , O_2^- and TBARS) measured in diabetic rats on days 3, 7, and 15 post-treatment

Figure 2 shows the levels of antioxidative markers measured. SOD and CAT activities were significantly reduced at all time points, indicating impaired antioxidant defense. Treatment with HG + GSE restored both enzyme activities, with the most notable effect observed by day 15.

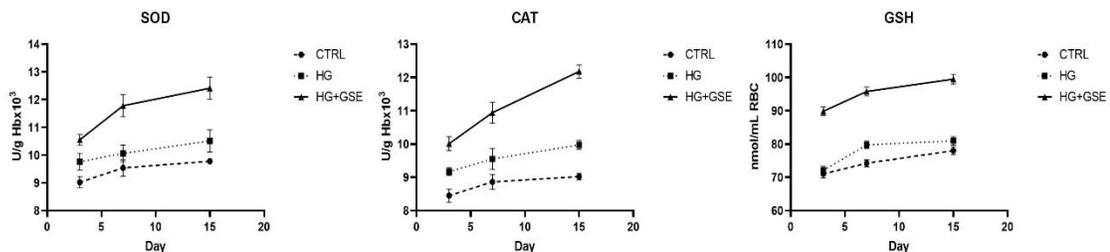


Figure 2. Levels of antioxidative markers (SOD, CAT and GSH) measured in diabetic rats on days 3, 7, and 15 post-treatment

GSE loaded hydrogels demonstrated a systemic antioxidant effect by normalizing redox markers and restoring oxidative balance. That effect can be attributed to the polyphenolic compounds found in GSE [6], making them a promising therapeutic option for managing oxidative stress in diabetic conditions.

4. Conclusions

GSE-loaded alginate-gelatin hydrogels demonstrated strong potential to restore systemic redox balance in diabetic rats, highlighting their use as antioxidant wound dressings for managing chronic diabetic wounds.

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