

Abstract

Diabetic wounds are severe diabetes complications characterized by delayed healing through chronic inflammation, impaired angiogenesis, decreased collagen production, and increased infection risk. Hyperglycemia interferes with normal processes of wound healing to produce chronic wounds. Conventional therapeutic approaches frequently cannot handle the complexity, leading to the utilization of innovative, biocompatible therapies. Plant-based hydrogels have been proven to be effective in keeping the wound moist, delivering bioactive substances, and facilitating tissue repair. This research focuses on formulating a mucilage-based smart hydrogel with *Bergenia ciliata*, a herb found to have antioxidant, anti-inflammatory, and antimicrobial activities in order to improve the healing of diabetic wounds. The current research explored the therapeutic ability of *Bergenia ciliata*-loaded mucilage-based smart hydrogels towards the promotion of diabetic wound healing. Mice were made diabetic by a single intraperitoneal administration of streptozotocin (STZ) at a dose of 150 mg/kg, which is a widely used model for mimicking diabetic conditions. After hyperglycemia confirmation, the mice were divided into seven (treatment) groups: Diabetic Negative Control (DNC), Positive Control (PC or Beta C), Hydrogel only, Hydrogel + *B. ciliata* 2% (Hg+BC 2%), Hydrogel + *B. ciliata* 4% (Hg+BC 4%), Hydrogel + *B. ciliata* 8% (Hg+BC 8%), and Hydrogel with *B. ciliata* nanoparticles (Hg+BC NPs). Each group was topically treated after inducing the wound, and the process of healing was followed over time.

Hydrogel formulations were made to create a moist wound bed along with the controlled delivery of *B. ciliata* phytoconstituents like bergenin and arbutin, which are anti-inflammatory, antioxidant, and antimicrobial in nature. Interestingly, the hydrogel group treated with Hg+BC nanoparticles (Hg+BC NPs) exhibited the fastest healing, finishing healing in only 10 days, followed by the Hg+BC 4% and 8% groups, which also exhibited significantly increased healing relative to the DNC and PC groups. Histological analysis corroborated the findings, showing increased granulation tissue, collagen deposition, and re-epithelialization in the treated groups. These findings emphasize the synergistic value of blending natural mucilage with bioactive plant extracts and nanotechnology to create an effective, biocompatible, and environment-

friendly treatment for diabetic wounds. In the diabetic negative control, there was no recovery of inflammatory, antioxidant, and tissue remodeling biomarkers. Pro-inflammatory cytokines TNF- α (15.2 \pm 0.4), IL-6 (15.0 \pm 0.7), IL-8 (15.6 \pm 1.2), and IL-1 β (153.0 \pm 3.1) were lowered significantly, reflecting anti-inflammatory action possibly through NF- κ B suppression. IL-10 (50.5 \pm 1.8) level increased while antioxidant enzymes glutathione (GSH) (16.1 \pm 1.2), superoxide dismutase (SOD) (178.0 \pm 3.4), catalase (CAT) (3.9 \pm 0.1), and glutathione peroxidase (GPx) (207.6 \pm 4.3) were significantly increased, lowering deleterious reactive oxygen species which are generally found in diabetic ulcers. Matrix metalloproteinases MMP-2 (216.0 \pm 11.6), MMP-7 (251.4 \pm 9.9), and MMP-9 (159.8 \pm 12.2) level significantly reduced, Tissue inhibitors of metalloproteinases (TIMPs) (173.0 \pm 8.0) level increased. Bergenia ciliata-incorporated mucilage-based hydrogels facilitate the accelerated wound healing and showing extensive potential towards clinical translation. Hydrogel with Bergenia ciliata nanoparticles has great potential as a treatment for diabetic wounds.