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Dermal wound healing properties of redox-active grape seed proanthocyanidins.

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Angiogenesis plays a central role in wound healing. Among many known growth factors, vascular endothelial growth factor (VEGF) is believed to be the most prevalent, efficacious, and long-term signal that is known to stimulate angiogenesis in wounds. The wound site is rich in oxidants, such as hydrogen peroxide, mostly contributed by neutrophils and macrophages. We proposed that oxidants in the wound microenvironment support the repair process. Proanthocyanidins or condensed tannins are a group of biologically active polyphenolic bioflavonoids that are synthesized by many plants. Previously we have reported that a grape seed proanthycyanidin extract containing 5000 ppm resveratrol (GSPE) potently upregulates oxidant and tumor necrosis factor-alpha inducible VEGF expression in human keratinocytes (Free Radic. Biol. Med. 31:38-42, 2001). Our current objective was to follow up on that finding and test whether GSPE influences dermal wound healing in vivo. First, using a VEGF promoter-driven luciferase reporter construct we observed that the potentiating effect of GSPE on inducible VEGF expression is at the transcriptional level. The reporter assay showed that GSPE alone is able to drive VEGF transcription. Next, two dermal excisional wounds were inflicted on the back of mice and the wounds were left to heal by secondary intention. Topical application of GSPE accelerated wound contraction and closure. GSPE treatment was associated with a more well-defined hyperproliferative epithelial region, higher cell density, enhanced deposition of connective tissue, and improved histological architecture. GSPE treatment also increased VEGF and tenascin expression in the wound edge tissue. Tissue glutathione oxidation and 4-hydroxynonenal immunostaining results supported that GSPE application enhanced the oxidizing environment at the wound site. Oxidants are known to promote both VEGF as well as tenascin expression. In summary, our current study provides firm evidence to support that topical application of GSPE represents a feasible and productive approach to support dermal wound healing.