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Title :
Effects of Ellagic Acid On Extracted Tooth Socket Healing in Nicotinic Diabetic Rats

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The resorption of alveolar bone that occurs after tooth extraction leads to many esthetic and functional problems. Ellagic acid (EA) is a member of the flavonoid family that regulates various processes of bone function. Statins are speculated to increase bone formation. This study was designed to evaluate the healing of extracted tooth sockets in diabetic and non-diabetic rats administered with EA orally and treated with rousavastatin (RSV) locally in nicotinic and non-nicotinic rats. Sixty-four male *Sprague–Dawley* rats weighing 250-300 g were selected to conduct the tooth extraction experimental study. The rats were divided into two main groups. The first main group was considered as the non-diabetic group and divided into four sub-groups; (A) The tooth rat socket filled with RSV+ The rats treated with NaCl orally (RSV+NaCl). (B) The tooth rat socket filled with RSV + the rats treated with EA orally (RSV+EA). (C) The tooth rat socket filled with RSV + The rats injected with Ni (RSV+Ni). (D) The tooth rat socket filled with RSV + the rats injected with Ni + treated with EA (RSV+Ni+EA). The second main group was considered as the diabetic group and divided into four sub-groups: (A) The tooth rat socket filled with RSV+ the rats treated with NaCl orally (RSV+NaCl). (B) The tooth rat socket filled with RSV + the rats treated with EA orally (RSV+EA). (C) The tooth rat socket filled with RSV + The rats injected with Ni (RSV+Ni). (D) The tooth rat socket filled with RSV + the rats injected with Ni + treated with EA (RSV+Ni+EA). Both main groups were intraperitoneally anesthetized with 0.08 ml of xylazine and 0.17 ml of ketamine, and the upper left central incisor was then extracted. Subsequently, the whole sockets were filled with 10 mg/kg RSV and closed with a dental resorbable suture. Immunohistochemical technique (IHC) was performed on the serial sections to assess the healing process using several biomarkers. These biomarkers include anti-transforming growth factor beta 1, anti-vascular endothelial growth factor (VEGF), anti-proliferating cell nuclear antigen (PCNA), anti-fibroblast growth factor 2, anti-alkaline phosphatase (ALP), anti-osteocalcin, and anti-bone sialoprotein antibodies (BSP). Serum tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) were measured using the ELISA kit before and after the experiment. Malondialdehyde (MDA) levels as well as superoxide dismutase (SOD) and catalase (CAT) activities were determined in the homogenized gingival tissue of rats at the end of the experiment using a commercial kit. Results showed that the expression levels of TGF-β, VEGF, PCNA, FGF-2, ALP, OCN and BSP significantly increased following the EA administration in diabetic (RSV+EA) and diabetic nicotinic rats (RSV+Ni+EA) compared with those of untreated diabetic (RSV+NaCl) and diabetic nicotinic rats (RSV+Ni) at day 14 ($P<0.05$). A decrease in MDA levels and a significant increase in the CAT and SOD activities of nicotinic and diabetic rats were observed following the EA treatment when compared with untreated nicotinic and diabetic rats ($P<0.05$). Pro-inflammatory factors TNF-α and IL-6 significantly elevated in nicotinic and diabetic rats and then decreased after EA treatment ($P<0.05$). We conclude that oral administration of EA adjunct with RSV exerted a positive effect on bone formation and bone remodeling biomarkers. EA with RSV may provide a promising line of treatment for nicotinic and diabetic patients after tooth extraction.

*** (MS) = Main Supervisor (CS) = Co Supervisor**