Inhibitory effects of luteolin on titanium particle-induced osteolysis in a mouse model

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ABSTRACT

Wear particles liberated from the surfaces of an implanted prosthesis are associated with peri-implant osteolysis and subsequent aseptic loosening. In the latter wear particle-induced inflammation and osteoclastogenesis have been identified as critical factors, and their inhibition as important steps in the treatment of affected patients, such as those undergoing total hip replacement. In this study the ability of luteolin to inhibit both titanium (Ti) particle-induced osteoclastogenesis in vitro and osteolysis in a murine calvarial model of osteolysis was examined. The results showed that luteolin, a highly potent and efficient inhibitor of tumor necrosis factor α (TNF-α) and interleukin-6 expression, inhibited Ti particle-induced inflammatory cytokine release, osteoclastogenesis, and bone resorption in bone marrow macrophages. Microcomputed tomography and histological analyses showed that the Ti particle-induced inflammatory response and increased osteoclastogenesis were significantly suppressed in the luteolin treatment group, in which osteolytic suppression was accompanied by a decrease in both TNF-α production and serum levels of osteoclast marker the C-terminal telopeptide fragment of type I collagen. These results support the use of luteolin as a natural compound in the prevention and treatment of aseptic loosening after total replacement arthroplasty.

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1. Introduction

Arthroplasty is an effective treatment for severe trauma and arthritic joint diseases. However, particle-induced periprosthetic osteolysis and subsequent aseptic loosening are a major cause of arthroplasty failure [1,2]. Wear particles released from the prosthesis are thought to play a central role in the initiation and development of osteolysis [3]. The pathophysiology of the ensuing aseptic loosening remains unclear, but considerable evidence suggests that periprosthetic osteolysis is initiated by activation of the receptor activator of nuclear factor κB (RANK) and RANK ligand (RANKL) signaling pathways [4,5]. Macrophages/phagocytes at the implant site are responsible for engulfing wear particles, with repeated phagocytosis leading to the secretion of high concentrations of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and IL-1. These factors directly and/or indirectly stimulate osteoclast formation and bone resorption [6–8]. Therefore, compounds that specifically target functional osteoclasts are candidates for the prevention and treatment of pathological bone loss.

To date the only established treatment for periprosthetic osteolysis is revision surgery, which is associated with greater morbidity and a poorer functional outcome. Recent approaches to limiting osteolysis have focused on understanding and manipulating osteolysis at the molecular level through pharmacological interventions [9,10]. Several studies have shown that nitrogen-containing bisphosphonates such as alendronate and zoledronate inhibit wear debris-induced osteolysis and increase peri-implant bone mineral density [11–14]. However, side-effects, such as fever, throat and stomach ulcers, and the low bioavailability of these drugs limit their use in systemic treatment. Consequently, in many countries there has been increasing interest in alternative strategies, including herbal medicines.

Flavonoids are a group of polyphenolic compounds widely found in plants. Their multiple beneficial biological effects are due to their anti-inflammatory, antioxidant, and estrogenic activities [15,16]. Luteolin (3,4,5,7-tetrahydroxyflavone), a flavone found in high concentrations in celery, green pepper, and camomile, is a

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