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The probiotic *Lactiplantibacillus plantarum* attenuates ovariectomy-induced osteoporosis through osteoimmunological signaling†

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Osteoporosis is characterized by low bone mass and bone tissue microarchitectural deterioration with increased fracture risk in numerous populations. Probiotics are reported to be a potential biotherapeutic for the prevention and treatment of osteoporosis. In this study, the IL-10 secretion properties of probiotics were simulated *in vitro* and the potential applications of the novel strain *Lactiplantibacillus plantarum* 622 were investigated in an *in vivo* osteoporosis model. Female Sprague–Dawley rats were ovariectomized (OVX) and orally administered *Lp. plantarum* GMNL-662 or alendronate for 14 weeks. The *Lp. plantarum* treatment group exhibited an increase in the level of fecal *Lp. plantarum*, *Lactobacillus*, and Lachnospiraceae. Bone marker analysis indicated improvements in the levels of osteocalcin and N-terminal telopeptides in the *Lp. plantarum* treatment group. Compared with the OVX control group, the *Lp. plantarum* treatment group exhibited marked improvements in femur bone mineral density, trabecular bone volume, trabecular number, and lumbar vertebrae. Moreover, biomechanical three-point bending testing indicated considerably higher improvements in femur maximum load, stiffness, and energy to maximum load in the *Lp. plantarum* treatment group than in the OVX control group. Quantitative polymerase chain reaction analysis indicated reduced expression levels of OVX-induced IL-1, IL-6, TNFα, and RANKL and increased expression levels of IL-10, TGF-β, and osteoprotegerin in the *Lp. Plantarum* treatment group. In summary, *Lp. plantarum* GMNL-662 exhibits high probiotic potential and potentially influences osteoimmunity through the modulation of proinflammatory cytokines and bone metabolism-related markers.

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1. Introduction

As defined by the World Health Organization, osteoporosis is a condition in which the bone mineral density (BMD) lies 2.5 standard deviations or more below the average value. The prevalence of osteoporosis increases with age, and both older women and men are at a higher risk of fractures associated with both osteopenia and osteoporosis.[1] The population group most at risk from osteoporosis is postmenopausal women due to decreased levels of estrogen, a hormone that protects the bone in reproductive age from bone turnover regulation.[2,3] Patients diagnosed with osteoporosis exhibit low BMD along with a compromised bone microarchitecture, resulting in a higher risk of fractures. Among the global population, osteoporosis is especially prevalent in postmenopausal women because of lower estrogen levels. Various Food and Drug Administration–approved drugs and monoclonal antibodies are used in the treatment of osteoporosis, but all of these compounds, in addition to providing relief, also cause various side effects. The identification of safer and more cost-effective interventions, both preventative and therapeutic, for the management of osteoporosis is crucial.

The gut–bone axis has received tremendous scholarly attention.[4] Dysbiosis in the intestinal microbiota is reported to contribute to the pathogenesis of various diseases; this can then lead to bone loss and to the development of secondary osteoporosis. Furthermore, numerous animal and small scale human studies have reported that the intake of probiotics is a potential therapy for osteoporosis.[5] The mechanism of probiotics in bone protection may involve bacterial metabolites, such as short chain fatty acids, or the effects of probiotics on osteoimmunity.

Lactiplantibacillus is a genus of lactic acid bacteria, and *Lactiplantibacillus plantarum* is regarded as a nomad and ideal

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