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Heat-killed *Lacticaseibacillus paracasei* GMNL-346 exerts anti-oral cancer effect by suppressing cancer stem cell activity and rebalancing gut microbiota dysbiosis

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ABSTRACT

Oral squamous cell carcinoma (OSCC) presents a major therapeutic challenge, necessitating novel treatments. This study investigated heat-killed *Lacticaseibacillus paracasei* GMNL-346 as a potential therapeutic agent for OSCC, targeting tumor progression and gut microbiota dysbiosis. In OSCC cell lines, GMNL-346 selectively inhibited proliferation by disrupting the cell cycle and suppressing cancer stemness proteins, while sparing normal gingival epithelial cells. In OSCC xenograft mouse models, the treatment enhanced survival rates and reversed tumor-induced gut microbiota dysbiosis, increasing beneficial metabolites such as propionic and isobutyric acids, which are associated with reduced OSCC progression. Whole-genome sequencing identified a heat-stable antimicrobial peptide that replicated GMNL-346's ability to suppress OSCC cell proliferation and cancer stemness protein expression. These findings suggest that heat-killed L. *paracasei* GMNL-346 may represent a promising and safe therapeutic candidate for OSCC, potentially acting through direct tumor suppression and microbiota modulation, which supports further exploration of its role in microbiome-based cancer therapy.

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