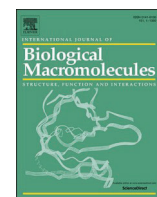




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journal homepage: www.elsevier.com/locate/ijbiomacHeat-killed *Lactacaseibacillus paracasei* GMNL-346 exerts anti-oral cancer effect by suppressing cancer stem cell activity and rebalancing gut microbiota dysbiosisYu-Fan Chen^{a,b}, Chi-Shuan Fan^c, Yu-Chieh Hung^d, Peng-Ju Chien^{d,e}, Wan-Hua Tsai^f, Yao-Tsung Yeh^g, Jhih-Hua Jhong^h, Yu-Ning Hsieh^d, Yu-Hao Huang^d, Ming-Shiou Janⁱ, Chin-Fang Chang^{j,k,l,*}, Chih-Yu Yang^{a,m,n,o,**}, Wen-Wei Chang^{d,p,***}^a Institute of Clinical Medicine, School of Medicine, National Yang Ming Chiao Tung University, Taipei City, 112304, Taiwan^b Division of Plastic and Reconstructive Surgery, Department of Surgery, Mackay Memorial Hospital, Taipei City, 104217, Taiwan^c National Institute of Cancer Research, National Health Research Institutes, Miaoli County, 35053, Taiwan^d Department of Biomedical Sciences, Chung Shan Medical University, Taichung City, 402306, Taiwan^e Division of Thoracic Surgery, Department of Surgery, Changhua Christian Hospital, Changhua, Taiwan^f Research and Development Department, GenMont Biotech Incorporation, Tainan City, 741014, Taiwan^g Aging and Disease Prevention Research Center, Fooyin University, Kaohsiung City, 831301, Taiwan^h Department of Computer Science and Engineering, Yuan Ze University, Taoyuan City, 320315, Taiwanⁱ Department of Microbiology and Immunology, School of Medicine, Chung Shan Medical University, Taichung City, 402306, Taiwan^j Rayon Clinic, Taichung City, 412018, Taiwan^k Department of Otorhinolaryngology, Head and Neck Surgery, Taichung Hospital Ministry of Health and Welfare, Taichung City, 403301, Taiwan^l Rong Hsing Research Center For Translational Medicine, National Chung Hsing University, Taichung City, 402202, Taiwan^m Division of Nephrology, Department of Medicine, Taipei Veterans General Hospital, Taipei City, 112201, Taiwanⁿ Center for Intelligent Drug Systems and Smart Bio-devices, National Yang Ming Chiao Tung University, Hsinchu 300193, Taiwan^o Stem Cell Research Center, National Yang Ming Chiao Tung University, Taipei 112304, Taiwan^p Department of Medical Research, Chung Shan Medical University Hospital, Taichung City, 402306, Taiwan

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ABSTRACT

Oral squamous cell carcinoma (OSCC) presents a major therapeutic challenge, necessitating novel treatments. This study investigated heat-killed *Lactacaseibacillus 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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