

Efek *Lactococcus Lactis* subspecies *Lactis* Strain Y-PDH terhadap Keparahan Lesi dan Modulasi Mikrobiota pada Tikus Sprague-Dawley dengan Mukositis Rongga Mulut yang Diinduksi 5-Fluorourasil = The Effect of *Lactococcus lactis* subsp. *lactis* strain Y-PDH on the Lesion Severity and Microbiota Modulation of the 5-Fluorouracil-Induced Oral Mucositis

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Abstrak

Latar Belakang: Mukositis rongga mulut merupakan efek samping pada anti kanker 5-fluorourasil (5-FU). Kemoterapi memicu disbiosis yang berkorelasi dengan keparahan mukositis. Penggunaan probiotik merupakan pendekatan baru untuk mengurangi keparahan mukositis. Tujuan: mengetahui efek *Lactococcus lactis* subsp. *lactis* strain Y-PDH terhadap keparahan lesi dan modulasi mikrobiota terkait mukositis rongga mulut. Metode: Sebanyak 48 tikus Sprague Dawley dibagi menjadi enam kelompok: normal (N), normal dan *L. lactis* subsp. *lactis* strain Y-PDH dosis tinggi (N + LL HD), kelompok induksi 5-FU (5FU), induksi 5-FU dan diberikan LL LD (5FU + LL LD), induksi 5-FU dan diberikan LL HD (5FU + LL HD), serta induksi 5-FU dan diberikan *L. reuteri* DSM 17983 (5FU + LR). Pada hari ke sepuluh dilakukan penilaian keparahan klinis, biopsi mukosa bukal tikus untuk penilaian histopatologi, penilaian mediator inflamasi TNF, IL-6, dan IL-10 dengan ELISA, penanda FGF7 dan MMP2 dengan imunohistokimia, dan swab mukosa mulut untuk analisis metagenomik. Hasil: Pemberian LL LD menurunkan keparahan klinis dan histopatologis pada kelompok yang diinduksi 5-FU. Terjadi penurunan TNF, IL-6, dan IL-10, penurunan ekspresi FGF7 dan peningkatan ekspresi MMP2. Pemberian LL LD menurunkan kelimpahan genus *Fusobacterium*, meningkatkan kelimpahan *Rothia*, serta meningkatkan richness dan evenness pada kelompok 5-FU. Namun, pemberian LL HD meningkatkan keparahan klinis dan mengubah komposisi bakteri secara signifikan. Kesimpulan: Pemberian LL LD mengurangi keparahan lesi mukositis rongga mulut yang diinduksi 5-FU secara klinis dan histopatologis. Perbaikan oleh LL LD disertai penurunan kadar sitokin inflamasi, modulasi penanda penyembuhan serta restorasi disbiosis.

.....Background: Oral mucositis is one of the most common side effects in anti-cancer 5-fluorouracil (5-FU). Mucositis disrupts nutrition intake and interrupts anti-cancer regimens. The severity of oral mucositis correlates with dysbiosis. The use of probiotics becomes a novel potential therapy to reduce mucositis severity by restoring dysbiosis. Objective: To evaluate the effect of *L. lactis* subsp. *lactis* strain Y-PDH on lesion severity and microbiota modulation in oral mucositis. Methods: We randomly divided 48 Sprague-Dawley into six groups: normal (N), normal and high dose *L. lactis* subsp. *lactis* strain Y-PDH (N + LL HD), 5-FU-induced mucositis i.p. (5FU), 5-FU induced and LL LD (5FU + LL LD), 5-FU induced and LL HD (5FU + LL HD), and *L. reuteri* DSM 17983 (5FU + LR). On the tenth day, we observed clinical severity, and took buccal mucosa biopsy for histopathology analysis, TNF, IL-6, and IL-10 quantifications, wound healing markers (FGF7 and MMP2) evaluation with immunohistochemistry and oral mucosal swab for metagenomic analysis. Result: LL LD reduces clinical and histopathological severity in 5-FU-induced groups. There was a decrease in TNF, IL-6, and IL-10. The expression of FGF7 was diminished and the expression of MMP2 was increased. LL LD lowered the abundance of *Fusobacterium*, increased the abundance

of *Rothia*, and increase the richness and evenness of 5-FU groups. In contrast, LL HD increased clinical severity and significantly changed the bacterial composition Conclusion: Administration of LL LD can reduce clinical and histopathological severity in 5-FU induced oral mucositis. The improvement was concurrent with the decrease of inflammatory level, modulation of wound healing marker and restoration of dysbiosis.