Combination of probiotics and resveratrol to target drug resistance in breast cancer: an *in vitro* and *in vivo* study

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Abstract

Background: Probiotics are beneficial microorganisms that positively affect the host by improving its microbial balance. Probiotics have a significant activity in the immune system by the activation of multiple immune mechanisms. Numerous studies have shown the anticancer and immunomodulatory activity of probiotics. Phytochemicals have a considerable impact on the process of developing new drugs. Resveratrol (3, 4′, 5 trihydroxystilbene) is a non-flavonoid polyphenol. It has various pharmacological effects, including antioxidative, anti-inflammatory, anti-proliferative, and anti-angiogenesis. Resveratrol has high efficiency as an anti-cancer via targeting multiple cancer hallmarks.
Aim: The present study investigates and evaluates the potential immunomodulatory and anti-tumor activity of the probiotics and resveratrol and their combination in sensitive and resistant breast cancer cell lines.

Methods: The study′s *in vivo* model included inoculation of Balb/C mice with EMT6/P and EMT6/CPR breast cancer cells, which were treated with $2.5*10_8$ CFU/ml probiotics, 50mg/kg resveratrol, and their combination for one month before tumor inoculation and one month after tumor inoculation. The changes in tumor size, along with cure and prevention rates, were measured. MTT assay was applied to measure the effect of probiotics and resveratrol alone and in combination on splenocytes proliferation. Lactate dehydrogenase (LDH) colorimetric assay kit was used to measure the effect of probiotics, resveratrol, and their combination on Natural killer cells activity. Nitro blue tetrazolium assay and neutral red method was used to evaluate macrophage function.

Results: The combination group significantly increased lymphocyte proliferation in both cell lines. LDH assay also showed a significant increase in NK cell activity of the combination group in both cell lines. The combination group in both cell lines achieved a remarkable increase in phagocytosis and pinocytosis activity. *In vivo* models showed a significant inhibition of cancer cell progression and development for probiotics, resveratrol, and their combination in both cell lines. Tumor size and weight were inhibited for all groups in both cell lines. The prevention percentages of EMT6/P were 50% for probiotics, 50% for resveratrol, and 60% for the combination group while the control group showed 30% prevention. The prevention percentages of EMT6/CPR were for probiotics 50%, resveratrol 60%, and the combination group 70% compared to the control group with 30%. The cure percentages of EMT6/P were for probiotics 60%, resveratrol 60%, and the combination group 50% compared with control 14.2 % and cisplatin groups 70%. The cure percentage of EMT6/CPR was for probiotics 20%, resveratrol 0%, and the combination group 33.3 % compared with control 14.2% and cisplatin groups 0%.

Conclusion: The results indicated that the combination treatment of probiotics and resveratrol had a valuable activity against sensitive and resistant breast cancer cells and

may act as a stimulator of the immune system. Therefore, the combination of probiotics and resveratrol deserves further analysis in order to be used in cancer prevention and treatment.