Development and anticancer activity of resveratrol loaded polylactic – coglycolic acid (PLGA) implants against breast cancer implanted in mice

By: Eilaf Sabbar Al-Sa'adoon

Supervisor: Dr. Wamidh H.Talib Co-Suppervisor: Saleh AL-Lababidi

Abstract

Breast cancer is a solid tumor and the primary cause of cancer mortality in women . One of the main problems in treating solid tumors is the low penetration of anticancer drugs in tumor tissue. Thus, an increase in the concentration of the anticancer drug may increase the efficiency of the therapy, but the toxicity associated with the use of high drug concentration is a limiting factor. Local administration of a polymeric biodegradable implant containing an anticancer drug may be an effective method of increasing drug concentration near the tumor site.

The aim of our study was to develop and test resveratrol loaded polylactic – coglycolic acid (PLGA) implants as an anticancer therapy against breast cancer implanted in mice.

Melt casting method was used to prepare PLGA implants loaded with various concentrations of resveratrol. *In vitro* release of resveratrol of different formula was measured using UV spectrophotometer. *In vitro* release patterns of all implants were assessed in phosphate buffered saline and Lipofundin. Morphological characteristics of

the implants were examined using scanning electron microscopy (SEM). Balb/C mice were transplanted with EMT6/P cell line and *in vivo* antitumor activity was assessed for four groups: resveratrol injection treatment, treatment with PLGA implants loaded resveratrol, treatment with empty PLGA implants (vehicle), and untreated mic. Changes in tumor size were measured for each treatment. Histological examination of tumor sections was performed using standard hematoxylin/eosin staining protocol and TUNEL colorimetric assay was used to test the apoptosis induction ability for all treatments. ELISA was used to measure serum levels of interferon gamma (INF-γ), IL-4, IL-2, and IL-10. Serum levels of the liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were used as biomarkers of hepatotoxicity and serum creatinine was used to measure nephrotoxicity.

Poly lactide co-glycolic acid implants loaded with 40% resveratrol released ideal concentrations of resveratrol compared with other formula, Glycerol Mono Stearate was the best enhancer added to PLGA implant to reach the best release. Implants were fully degraded within 14 days. RES implant caused a significant decrease in tumor size with a percentage cure of 80%. This therapy induced extensive necrosis and increased apoptosis in tumor sections. Serum levels of INF-γ and IL-2 were increased in mice treated with resveratrol implants therapy. AST, ALT, and creatinine serum levels were close to their normal values.

In Conclusion, Our data indicate that PLGA implants loaded with resveratrol represent an active and safe option to treat breast cancer. The anticancer effect of

Resveratrol implants is mediated by induction of apoptosis, inhibition of cell division, andactivation of T helper 1 anticancer immune response.