Faculty of Science
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# Ameliorative effect of rosemary (*Rosmarinus officinalis* L.) against oxidative stress induced by docetaxel in male mice.

**By**

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## Summary

Chemotherapy is a fundamental component of cancer treatment. In recent decades, there has been significant progress in the development of anticancer agents, which have shown promising potential for the chemical management of cancer. Regrettably, multiple reports have shown the genotoxic and carcinogenic potential of certain anticancer agents, which may result in the development of secondary cancer. Most anticancer medications lack target specificity and are unable to differentiate between tumor cells and normal non-cancerous cells, especially those that are proliferating. Hence, it is noteworthy that the most efficacious anticancer medications may elicit adverse reactions. The majority of efficacious drugs utilized in the treatment of cancer are classified as toxic agents. Considerable research has been conducted to formulate efficacious and less hazardous anticancer agents or to utilize natural antioxidants that could potentially mitigate the adverse effects of current medications.

Docetaxel (DTX) is a chemotherapeutic drug belongs to taxane class, used mostly for treatment a wide range of cancer. Docetaxel acts as an antineoplastic drug that works by reducing the amount of free tubulin by encouraging its assembly into stable microtubules and blocking its disintegration. Like all chemotherapeutic drugs, side effects are collective, and many varying side-effects have been known. DTX is cytotoxic to all dividing cells in the body because it is a cell cycle specific agent. This includes tumor cells as well as hair follicles, bone marrow and other germ cells.

Rosemary is an evergreen plant whose leaves has the shape of a needle. It is a well-known spices herb that belongs to the Labiatae family and used in traditional medicine. Rosemary's leaves have many beneficial effects, such as antitumor, antidiabetic, antioxidant, anti-inflammatory, and antibacterial activities.

Rosemary's antioxidant properties led to its initial investigation as a potential anticancer drug. Carnosic acid, carnosol, and methyl carnosate are phenolic diterpenes found in this plant, and these, together with rosmarinic and caffeic acids, are thought to be responsible for its therapeutic effects.

Solid lipid nanoparticles (SLNs) have been extensively studied during the last decade owing to their increased efficacy, biodegradability, stability, and ease of preparation. They are submicron colloidal drug delivery have a vital role in controlled bio-distribution of drug molecules with enhanced efficacy and decreased side effects.

As Solid lipid Nanocarriers are cheap, non-toxic, biocompatible, and release drugs with proper control, so this study loads rosemary leaves extract onto Solid lipid Nanocarriers to raise its therapeutic efficacy.

The aim of the present study is to evaluate the ameliorative effect of Rosemary loaded solid lipid nanoparticle against oxidative stress induced by (DTX) anticancer drug in Ehrlich Ascites Carcinoma bearing mice.

Tumor-bearing mice were prepared by injecting the left flank of mice with 2 x $10^6$ viable Ehrlich Ascites Carcinoma (EAC) cells / mouse in a volume of 0.2 ml. The tumor was allowed to grow for approximately 15 days then mice were haphazardly distributed to 7 different groups (10 animals / group) plus normal control group.

- **The 1st group,** control group "Normal control".
- **The 2nd group,** Positive control injected with Ehrlich ascites carcinoma (EAC).
- **The 3rd group,** (EAC) treated with Solid lipid nano (SLN).
- **The 4th group,** (EAC) treated with Docetaxel alone (DTX).
- **The 5th group,** (EAC) treated with rosemary loaded SLN (200mg /kg).
- **The 6th group,** (EAC) treated with rosemary loaded SLN (400mg /kg).
- **The 7th group,** (EAC) treated with (DTX) + (ROS)200.
- **The 8th group** (EAC) treated with (DTX) + (ROS)400.

The ameliorative effect of rosemary loaded SLN against oxidative stress induced by the tested anticancer drug (Docetaxel) was assessed by determining malondialdehyde (MDA), Glutathione disulfide (GSSG), Nitric oxide (NO) and reduced glutathione (GSH) levels in liver tissues. In addition, Mortality rate, Tumor size, Tumor Necrosis Factor-alpha (TNF-α), haematological parameters, liver (ALT & AST).

Results showed that the treatment with rosemary alone or with combination with docetaxel showed significant reduction in the elevated level of (MDA), (GSSG) and (NO), While (GSH) level showed significant ($P<0.05$) elevation in rosemary treated groups relative to docetaxel treated group alone.

Rosemary extract had a significant effect of decreasing mortality rate and tumor size and stopping its growth. Combined treatment with docetaxel and rosemary low and high doses showed significant elevation ($p<0.05$) in hemoglobin content, RBCs count and platelets count as compared to docetaxel treated group alone, despite the rosemary combined treatment in high dose showed more pronounced effect. Rosemary treated group with high dose showed normal values of WBCs count as control group. Our data indicated that the treatment with rosemary alone or with combination with docetaxel showed significant reduction in the elevated levels of the hepatic enzyme activities (ALT & AST) and Tumor Necrosis Factor Alpha (TNF-α). Rosemary treated group with high dose alone or with combination with docetaxel showed a significant ($P < 0.05$) increase in percentage value of the G0/G1-cells (cell cycle arrest at G0/G1 phase) and showed a significant ($P < 0.05$) decrease in percentage value of the G2/M-cells (stops cell cycling during G2/M) as compared to docetaxel treated group alone. Histopathological observations of Liver showed improvement in hepatic tissue in rosemary treated groups.

In conclusions, the results of the present study reflect clearly that rosemary leaves extract-loaded Solid lipid nanoparticles caused a significant reduction in oxidative stress induced by docetaxel and raised its therapeutic efficacy due to its direct Reactive Oxygen Species (ROS) scavenging activity.