

Is There a Role Of Resveratrol in Doxorubicin-Induced Hepatotoxicity?



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Abbreviations: DOX : Doxorubicin; RSV: Resveratrol; SOD: Superoxide Dismutase; CAT: Catalase; GSHPx: Glutathione Peroxidase

Introduction

Doxorubicin (DOX) has been used in the treatment of variety of cancers but its administration is limited by a dose-dependent toxicity. Its cytotoxic effects on malignant cells, have shown an increase in the risk of cardiotoxicity, hepatotoxicity, renal failure. Antioxydants have been explored for both their cancer preventive properties and chemodulatory of DOX toxicity. Resveratrol (RSV) is a polyphenolic constituent of several dietary mainly of grapes and wine origin recently its anti-cancer potential has been extensively explored, revealing its anti-proliferative effect on different cancer cell lines, both *in-vitro* and *in-vivo*. RSV is also known to have modulatory effects on cell apoptosis, migration and growth via various signaling pathways. Though, RSV have a great medicinal value, its applications as a therapeutics are limited.

Problems like low oral bioavailability and poor aqueous solubility make RSV an unreliable candidate for therapeutic purposes. Additionally, the rapid gastrointestinal degradation of RSV is also a major barrier for its clinical translation. Hence, to overcome these disadvantages RSV-based nanodelivery systems have been considered in recent times. Nanodelivery systems of RSV have shown promising results in its uptake by the epithelial system as well as enhanced delivery to the target site. Herein we have tried to bring new insights into the molecular mechanisms of DOX toxicity with respect to DNA damage, free radicals and whether RSV can be a playmaker as chemomodulatory of DOX [1].

Doxorubicin (DOX)

DOX has been used in the treatment of variety of cancers but its administration is limited by a dose-dependent toxicity. Its cytotoxic effects on malignant cells, have shown an increase in the risk of cardiotoxicity, hepatotoxicity, renal failure. Antioxidants have been explored for both their cancer preventive properties and chemodulatory of DOX toxicity.

Mechanisms of action and toxicity Doxorubicin (DOX)

Like other anthracyclines, is an intercalating agent which enters the space between the base pairs of the DNA agent. Furthermore these molecules are inhibitors of type II DNA topoisomerases, enzymes involved in the maintenance of the three dimensional structure of the DNA during transcription and of the phenomena of replication. Complex DNA/topoisomerase strands are stabilized thereby preventing DNA replication

Doxorubicin-induced hepatotoxicity

Oxygen-free radicals produced during the metabolic activation of DOX may have toxic effects on heart muscle [2], which is provided with poor mechanisms of detoxification of such species DOX is likely to have toxic effects on liver [3] by increasing levels of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSHPx) enzyme in liver tissue of guinea pigs [4]. Nevertheless, distribution of a unique dose of DOX decreases the content of cytochrome P450 and glutathione in rat liver [5] and high levels of glutathione have been found to protect isolated hepatocytes from DOX toxicity

Delivery systems for Doxorubicin

The pharmacokinetic studies of DOX have shown that doxorubicin is made up of several phases after intravenous injection, whereas intravenous infusion is often followed by three phases plasma clearance. The administration of DOX is 3 to 5 minutes, shows the rapid absorption of the drug by the cells. It is the terminal half-life of 24 to 36 h. This shows to remove the tissue from its absorption [6]. An equilibrium distribution of the drug is unavoidable to reduce the risk of toxicity. The range of constant distribution varies from 500 to 800 l/m², allowing body tissues to take a sufficient amount of doxorubicin. DOX binds to plasma proteins and most drugs, DOX enters the cell by passive diffusion, general accumulating at intracellular concentrations. DOX acts in a non-specific manner, acting on normal cells.

Which proves the side effects in the cancer patient due to DOX unpredictable cytotoxic properties. Several studies have been carried out to develop specific DOX distribution systems capable of reducing their toxicity to target its effects directly on tumor cells. The use of these drug delivery systems is constantly tested and improved to increase the efficacy, selectivity and total effect of anti-neoplastic drugs. Most promising DOX delivery systems include the entrapment of the chemotherapeutic drug into polymeric drug carriers, such as liposomes, and nanoparticles [7].

Resveratrol

Resveratrol (RSV) is a polyphenolic constituent of several dietary mainly of grapes and wine origin recently its anti-cancer potential has been extensively explored, revealing its anti-proliferative effect on different cancer cell lines, both in vitro and in vivo. RSV is also known to have modulatory effects on cell apoptosis, migration and growth via various signaling pathways [8,9].

RSV stands out as the molecule with the most potential for stifling the disease's consequent mortality rate and growing incidence. From studies using various liver cancer cell lines and chemically-induced tumors as well as implanted cancers in animal models as described in this review, it becomes apparent that RSV may play an important role not only in the prevention but also in the therapy of metastatic disease of the liver and reduces the toxic effect induced by chemotherapy [10,11]. All these studies largely establish that RSV has great promise for battling cancer and more exactly the liver cancer. From many studies, have indicated that RSV suppresses the growth of HCC cells and prevents hepato-carcinogenesis by mitigating oxidative stress. Future research should deal with further characterizing the exact mechanism by which RSV possesses its effects on the cell cycle, apoptosis and redox signaling. However, RSV scavenges modulates activities of antioxidant enzymes and ROS.

Future studies should explore these and other possible mechanisms of RSV action to understand the full potential of

this dietary agent in the prevention and treatment of HCC. RSV is currently investigated for the prevention and treatment of human colon cancer [12]. It is expected that additional research would lay the foundation for clinical trials with RSV in the prevention of HCC in high-risk patients predisposed with viral hepatitis, other liver diseases and environmental carcinogens. And RSV has effect against the toxicity induced by chemotherapy, several delivery systems described for RSV such as solution, suspension nanoparticles, nano emulsion RSV and compare it is the form more effective [13]. And see the influences ranging dose of RSV [14], all this research will be realized on different models: cell cultures, whole animal and isolated organ.

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