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Resveratrol influences platinum pharmacokinetics: A novel mechanism in protection against cisplatin- induced nephrotoxicity

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Abstract

Cisplatin (CP) is a widely used drug in treatment of solid tumors. However, the use of CP was hampered by its serious side effects especially nephrotoxicity. This study aims to investigate the effect of resveratrol (RES) on CP-induced nephrotoxicity, particularly, the effect of RES on CP pharmacokinetics (PKs). Male white albino rats were divided to four group's six rats each. The first group received (1%) tween 80 in normal saline and served as control. The second group received RES (30 mg kg^{-1}) per day for 14 consecutive day's i.p. The third and fourth groups were given a single i.p. injection of CP (6 mg kg^{-1}) with or without pre-treatment of RES (30 mg kg^{-1}per day for 14 consecutive days), respectively. Following administration of CP, plasma, urine and kidney platinum concentration were monitored to study PKs of CP. Five days after the CP injection, rats were killed; blood samples were collected; kidneys were dissected; and biochemical, immunohistochemical, and histological examinations were performed. Our results revealed that CP treatment significantly deteriorated kidney functions with subsequent alteration in redox balance of the kidney. On the other hand, RES successfully ameliorated CP-induced kidney injury and recovered normal kidney tissue redox status. Importantly, while RES pre-treatment did not significantly alter the plasma CP level, it dramatically decreased the urine concentration of CP and lowered its accumulation into the kidneys. Moreover, it increased CP plasma half-life ($t_{1/2}$) with subsequent decrease in its elimination rate constant, indicating an important role of PKs modulation in RES protection against CP-induced renal damage. Taken together, RES may protect the kidney tissue from the deleterious effects of CP through constringe of CP renal accumulation and enhancement of CP-induced oxidative stress.

Key words: Cisplatin, nephrotoxicity, resveratrol, cancer.

1- Introduction

Platinum-based chemotherapeutic drugs, like cisplatin (CP), are widely used worldwide for treatment of various human cancers, including lung, bladder, head and neck, ovarian, and testicular cancer**[1]**. Being one of the few metal-based cancer chemotherapeutics, CP has become one of the most widely used and successful anti-cancer drugs. However, like most anti-cancer drugs, treatment resistance and side effects in normal tissues are the two major drawbacks in the use of CP. In particular, nephrotoxicity associated with CP remains a major concern **[2,3]**. For years, efforts