

## Modulation of the ROCK/Akt/eNOS pathway by simvastatin protects against 5-fluorouracil cardiotoxicity

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### Abstract

**Background:** 5-Fluorouracil (5-FU) is a highly effective anticancer drug, widely incorporated in the management of different solid tumours, and is a cornerstone therapy in colorectal cancer. Its use is associated with a wide range of different toxicities, including several reports of fatal cardiotoxicity which was first reported four decades ago. Since then, only some efforts were done to understand the pathophysiology and molecular mechanisms associated with this type of toxicity, moreover; there is no effective preventive measure against this toxic effect. Until now, myocardial ischemia due to coronary vasospasm is the most accepted theory.

**Aim:** 5-FU cardiotoxicity is still controversial, the involvement of ROCK/Akt/eNOS and ET-1/ERK signalling in this toxic effect has not yet been reported. In addition, simvastatin was tested for its ability to ameliorate this toxicity through modulation of such molecular pathways.

**Methods:** Adult Male Albino Wistar rats were used and allocated into four groups, where 5-FU (50 mg/kg/ week; i.p, 6 weeks) and simvastatin (15 mg/kg/day; p.o, 8 weeks) were either administered alone or combined except for the normal control group. Markers of cardiomyocyte injury and stress, inflammation, oxidative stress, apoptosis as well as histopathology were assessed. Additionally, the role of ROCK/Akt/eNOS and ET-1/ERK downstream from 5-FU activity to increase the vasoconstrictor response and endothelial dysfunction were tested. Finally, ECG monitoring was carried out to test for the perturbed myocardial electrical activity.

**Results:** 5-FU boosted serum level of NT-proBNP, aortic contents of ET-1 and TXA<sub>2</sub>, cardiac contents of Nox, COX-2, MDA, p-Akt, p-ERK1/2 and the protein expression of ROCK and caspase-3. On the other hand, it suppressed cardiac GSH and p-eNOS. Antagonistically, simvastatin overcame these disturbed events, particularly modulated ROCK/Akt/eNOS signalling axis and abrogated the overactive ET-1/ERK cue.

**Conclusions:** The present study highlights the following important findings; coronary artery spasm cannot solely account for 5-FU cardiotoxicity and it appears that NT-proBNP is a potential early marker for this toxicity, but more studies are needed. The present study shows a significant role of ROCK/Akt/eNOS and ET-1/ERK pathways in the protective effects of simvastatin, a drug with potent antioxidant and pleiotropic properties, on the cardiotoxicity induced by 5-FU in rats. These signalling axes contribute via different means to cause an upset in the vasoconstriction/vasodilatation equilibrium, endothelial cell function, and finally promoting cardiomyocyte stress and death.



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