



SDI Review Form 1.6

Journal Name:	Cardiology and Angiology: An International Journal
Manuscript Number:	Ms_CA_19092
Title of the Manuscript:	Antioxidant and radical scavenging properties of β-carotene on Cisplatin induced cardiotoxicity.
Type of the Article	Original Research Article

General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound.

To know the complete guideline for Peer Review process, reviewers are requested to visit this link:

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SDI Review Form 1.6

PART 1: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Compulsory REVISION comments	The paper reports that it is free radical induced oxidative stress (OS) by cisplatin for which LpX (MDA content), GSH, Catalase parameters and Creatine kinase-MB, Lactate dehydrogenase (LDH), Alkaline phosphatase (ALP), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Triglycerides (TG) and Total cholesterol (TC) are studied by authors. The free radicals or ROS formation can also be detected by staining cisplatin treated heart tissue/HL1 cardiomyocytes with dihydroethidium (DHE), 6-carboxy-2, 7-dichlorodihydrofluorescein diacetate bis (acetomethyl) ester (DCDHF-DA) that can give more clear picture of OS by free radicals. EPR can also be carried out to detect the O₂·, OH· radicals. However, biomarkers GST, GGT activity and western blot can be done to detect drug induced effect. One more important biomarker of heart Atrial natriuretic peptide (ANP) can be detected to confirm cardiotoxicity. The authors can also explain the role of these enzymes in drug metabolism. Authors did not explain mechanism of action of cisplatin in cardiac tissue, that is whether it is cisplatin-GSH conjugates/aquated species responsible for OS. Literature till date have reported that the conjugates are responsible for nephrotoxicity/hepatotoxicity therefore it is important to know that cardiac tissue metabolize the drug in same way as liver/kidney or there are other metabolites of cisplatin formed by heart that causes cardiotoxicity. All other parameters definitely gives us clue that there is OS	Cisplatin overdose mainly causes nephrotoxicity and also causes cardiotoxicity which were reported. The present study is a continuation for the study of BC against CP induced nephrotoxicity. Based on the laboratory equipments available at our college we were able to the study this far as mentioned in the paper. We look forward to extend it though in future, I'm sure your review helped me explore to a far extent. We have done GGT, which we presented it in another/nephrotoxicity paper. The occurrence of cardiotoxicity is comparatively less in contrast with nephrotoxicity and hepatotoxicity. Though there are evidences/literatures that prove Cisplatin inducing cardiotoxicity. The pathways by which Cisplatin causes cardiotoxicity yet to be explored completely in detailed.



SDI Review Form 1.6

	and also histopathology studies explains the necrotic tissue in cisplatin which can be prevented by treatment with betacarotene(BC). Also further including BC in anticancer therapy should not interfere in treatment because BC might decrease the potency of anticancer drug therapy. There is also a possibility that when multiple anticancer drugs/salvage therapy(cisplatin,bleomycin,doxorubicin) is given along with BC the cancer tissue might develop multidrug resistance(MDR) due to antioxidants and it is possible that it might increase intracellular GSH content thereby increasing drug efflux and make cancer tissue more resistant to drugs. The authors need to explain that BC should not develop MDR or induce metallothionein enzyme as cisplatin is platinum-coordinated complex in cancer tissue. Cisplatin in its parent form is inactive it has to undergo bioactivation reaction to form hydroxylated/aquated species to induce drug effect. Therefore cancer therapy with antioxidant might inhibit the reactions.	The rationale behind this is to study the cessation of adverse effects caused by ROS generated by the overdose of CP by using a natural antioxidant-carotenoid, β-carotene. Laboratory and observational studies have produced a plausible hypothesis that specific combinations of antioxidant micronutrients, at doses greater than the RDA, may improve tumour control and reduce toxicity when administered with some conventional anti-cancer therapies Moreover, BC reacts with the lipid peroxidation compounds(ROS generated) but there are no evidences showing BC could produce MDR with Cisplatin. Infact, further work beyond this could draw the conclusion.
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<u>Minor</u> REVISION comments	No revision for grammer,language all sections are clear.	
<u>Optional/General</u> comments	The study is informative but thinking beyond these common parameters and including drug metabolism/mechanism of action of cisplatin and cisplatin with betacarotene(BC) in cardiac tissue (explanation) can give more detailed view and make studies more challenging. It is not compulsory that authors carryout all the suggessted experiments but if literature is avaliable they can quote the references or provide explanation for the comments.	