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Journal Name:	British Journal of Medicine and Medical Research
Manuscript Number:	2013_BJMMR_6088
Title of the Manuscript:	Doxorubicin Cardiotoxicity in Acute Lymphoblastic Leukemia: Possible Protective Role of Grape Seed Extract Proanthocyanidins
Type of the Article	Research article

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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.

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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	<p>The study aimed to evaluate early DOX cardiotoxicity in asymptomatic leukemic children and to explore whether grape seed extract (GSE) proanthocyanidins would prevent the DOX-induced cardiotoxicity. The authors demonstrate that that cardiotoxicity markers could be valuable beside echocardiographic evaluation in the early detection of DOX-induced subclinical cardiotoxicity and GSE has a potential application as a cardioprotective agent against DOX induced cardiotoxicity.</p> <p>The study is of clinical interest.</p> <p>Concerns</p> <p>1 It is not clear whether this study is a prospective double-blind study or an open study. Please, specify this and also the eventual retrospective nature of the study.</p> <p>2 The use of endocardial fractional shortening by M-mode echocardiography should be an obsolete index even in children with cancer because it is based on the motion of only two walls while it is well recognized that the abnormalities of wall motion can involve other walls. In this view, the calculation of ejection fraction by two-dimensional echocardiography shall be recommended. This is also very well specified in the ref # 30 cited by the authors. Indeed, also leukemic children can develop segmental wall motion abnormalities during anthracycline therapy.</p> <p>3 The authors present only ejection fraction value pre and post-therapy while it is well known that other</p>	<p>Thanks for your valuable comments.</p> <p>1-Regarding study design, it is <u>prospective</u> (in which the method for analyzing data has been specified in the protocol before the study has begun) <u>randomized</u>(as the patients have been randomly assigned to receive either DOX or DOX & GSE) <u>double blind</u> study (in which neither the patient nor the physician conducting the study know which treatment is being given to the patient). <u>This has been changed in study design within abstract, line 11, page no. 1 and a new subsection 2.1 was added in materials & methods section, lines 100-106, page 3.</u> Research methodology expert was consulted to carryout randomization and blinding of the current work. The method researcher and data analyst were not involved by any mean in assessing outcome or treatment of cases.</p> <p>2a -According to the study design, cardiologist was unaware of the participants' condition. So the adopted <u>routine</u> echocardiographic approach depended mainly on the estimation of left ventricle ejection fraction (LVEF) and left ventricle fractional shortening (LVFS) using M-mode. On the basis of dimensional changes and volume calculations, FS and EF were calculated. Lack of use of Simpson method for calculation of EF& FS is one of our limitations</p>



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	<p>parameters such as Doppler-derived diastolic indices and left atrial volume index can be impaired by chemotherapy. Can the authors add the analyses of these parameters. Alternatively, they should add this lacking as a limitation of the present study. This is important also in view the demonstration that BNP values are better correlated with diastolic indices than with ejection fraction in patients with heart failure.</p>	<p>(discussion section, lines 336 & 337, page 9). Modifications were performed in <u>materials & methods section</u>, subsection 2.7, lines 154 & 159, page 4. Reference no 30 (Schiller et al., 1989) were deleted and the numbering were revised.</p> <p>2b-Regarding development of segmental wall motion abnormalities during anthracycline therapy, Kinova & Goudev (2012) argued about the importance of regional dysfunction, diagnosed by strain echocardiography. They stated "It is not clear enough if regional dysfunction, diagnosed by strain, is clinically essential. If it is important - what are the cut-off values of these parameters for prediction of cardiotoxicity". They further suggested larger studies with long-term follow-up of children and adults after chemotherapy, with multivariable approach to clarify these issues.</p> <p>3- Lack of Doppler evaluation of left ventricular diastolic indices & left atrial volume index is another limitation (lines 337 & 338 page no 9 in discussion section) as it isn't assigned in our protocol from the start. Most studies have investigated separately echocardiographic variables and biomarkers to identify patients at risk for early detection of subclinical cardiotoxicity. But the current study evaluated both modalities in the same cohort of patients to detect cardiotoxicity then to prove improvement after administration of GSE along with DOX.</p> <p>NB: we also rephrase the fourth paragraph in <u>introduction section</u> to clarify our point of view, lines 60-68, page 2.</p>
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<u>Minor</u> REVISION comments		
<u>Optional/General</u> comments		