



**SDI Review Form 1.6**

Journal Name:	<a href="#">British Journal of Medicine and Medical Research</a>
Manuscript Number:	2013_BJMMR_6088
Title of the Manuscript:	<b>Doxorubicin Cardiotoxicity in Acute Lymphoblastic Leukemia: Possible Protective Role of Grape Seed Extract Proanthocyanidins</b>
Type of the Article	<b>Research article</b>

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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)
<b>Compulsory</b> REVISION comments		
<b>Minor</b> REVISION comments		
<b>Optional/General</b> comments	<p>5</p> <p>I am reading manuscript 2013_BJMMR_6088 entitled " Doxorubicin Cardiotoxicity in Acute Lymphoblastic Leukemia: Possible Protective Role of Grape Seed Extract Proanthocyanidins" which you submitted to the British Journal of Medicine and Medical Research</p> <p>This manuscript describes Grape Seed Extract Proanthocyanidins play protective role in Doxorubicin Cardiotoxicity in Acute Lymphoblastic Leukemia.</p> <p>The English is not clear and concise. There are many instances of badly worded/constructed sentences. E.g.,</p> <p>Page 1, in Abstract Aim:To evaluate early DOX cardiotoxicity in asymptomatic leukemic patients and to explore whether GSE proanthocyanidins would prevent the DOX-induced cardiotoxicity. DOX should be doxorubicin</p> <p>GSE should be Grape Seed Extract</p>	<p>Abstract &amp; the whole MS have been modified &amp; revised and most of your comments were considered. Modifications &amp; corrections were highlighted in yellow.</p> <p>This was corrected in the abstract aim, lines 8 &amp; 9, page no 1.</p>



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	<p>In Abxtract Place and Duration of study: Mansoura University Hospital, between January 2011 and May 2013 forty two newly diagnosed ALL patients were enrolled in this study. asymptomatic leukemic patients and newly diagnosed ALL patients, this two part is not comprehensible.</p> <p>Page3 2.2 Drugs Doxorubicin hydrochloride was provided in the form of Adriamycin vials (25mg/m<sup>2</sup> ) according to BFM protocol . Grape seed proanthocyanidin extract was administered in the form of Gervital capsules (GSE; 150mg). It was provided by Arab Company for Pharm. and Medicinal plants (Mepaco, Egypt) and stored at 4°C until used.</p> <p>There were all sorts of names of doxorubicin: such as adriamycin and doxorubicin Other drugs should also be listed .</p> <p>In introduction, I don't follow the logic of your part, I would advice you to describe knowledge of and treatment of cardiac toxicity of Doxorubicin in acute lymphoblastic leukemia patients, in addtion, you should describe the advantages of proanthocyanidins.</p>	<p>Corrected in <u>abstract</u>, place and duration, lines 12- 15, page no 1.</p> <p>"I don't get the point here. Apart from DOX in BFM protocol and GSE, no other drugs were administered. " we don't understand that you mean other drugs in the BFM protocol, of course we did not mean that our ALL children received only DOX for the treatment, we did not say group I received DOX only and when we discussed drugs, we mentioned "Adriamycin vials (25mg/m<sup>2</sup> ) according to BFM protocol" .However we tried to clarify this point in:</p> <p><u>Abstract</u>, place &amp; duration, lines15&amp;16, page no1.</p> <p><u>Materials &amp; methods</u> section, subsection2.2, lines 113&amp; 114, page 3 "<b>Group I received chemotherapy containing cardiotoxic DOX, and Group II received chemotherapy containing cardiotoxic DOX plus proanthocyanidin GSE"</b> . Subsection2.3, lines 121-124, page 3 "<b>Doxorubicin hydrochloride was provided as Adriamycin vials (25mg/m<sup>2</sup> per dose for 4 doses weekly), in combination with other</b></p>
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	<p>Table 4 no line</p> <p>In discussion, I suggest that you focus on the protective effect and possible mechanism of proanthocyanidins in ALL, moreover, you should read literature more.</p> <p>Please do not revise only the examples indicated in the comments, but check your entire manuscript thoroughly and carefully to refine the language. You are encouraged to have the manuscript critically edited by a colleague in your field who is a skilled writer in English.</p>	<p><b>chemotherapeutics according to modified BFM protocol ( prednisone 60 mg/m<sup>2</sup>, vincristine 1.5 mg/m<sup>2</sup>, L- asparaginase 6000u/m<sup>2</sup>, cyclophosphamide 1000 mg/ m<sup>2</sup>, 6- mercaptopurine 60 mg/ m<sup>2</sup>, arabinosyl cytosine 75mg/ m<sup>2</sup> and age dependent dose of methotrexate) "</b></p> <p>Introduction was revised according to your valuable comments to include the following items : cardiotoxicity as a serious complication of ANT antibiotics including Dox; Types of cardiotoxicity ; <u>Possible mechanisms involved in DOX-induced cardiotoxicity ( lines 54-58, page 2)</u> ;Methods for early detection of cardiotoxicity especially conventional echocardiography and biochemical cardiac markers; <u>Several attempts that minimize the DOX-induced cardiotoxicity including Dexrazoxane, the most commonly used cardioprotective agent( lines 80-89, page 2)</u> &amp; finally GSE proanthocyanidins,the antioxidant of interest. Regarding GSE, we mentioned structur and mechanism of action as a cardioprotective agent ( <u>lines 90-98, page 2 &amp; 3</u>). The advantages or the beneficial health of GSE were mentioned in short in <u>lines 94-95, page 3</u>. "The anti-inflammatory and anticancer effects of GSE". It was also mentioned in <u>discussion: cardioprotective effect after ischaemia/reperfusion injury (lines294-296, page 8), improved plasma antioxidant capacity in high cholesterol subjects (lines 299-300, page 8) ,protective effects on vascular endothelial cells through inhibition of endothelial NADPH oxidase activity (lines 323-</u></p>
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		<p>324, page 9) and of course the cardioprotective effect against cytotoxic drugs as DOX .</p> <p>Lines were added to table 4 page 6.</p> <p>Discussion was revised regarding the knowledge, language, references. Six references were deleted (Lipshultz et al., 2004, Schiller et al., 1989, Lipshultz et al., 2012, Sherief et al.,2012, Andreadou et al.,2007, Hou et al.,2007) &amp; eight were added ( no. 9- Al-Biltagi et al.,2012 ,no. 10- Migrino et al.,2008, no.12- Kinova &amp; Goudev 2012, no.17- Bryant et al.,2007,no.18- Choi et al.,2010, no. 43- Kar et al.,2009, no. 44- Hollis et al.,2009, no. 45- Zhou &amp; Raffoul2012 ). The protective effect and possible mechanism of proanthocyanidins is one of the discussed items in our MS ( lines 314-324). New paragraph on previous in vivo studies of antioxidant activities of grape phenolic compounds were added. In addition, limitations of study were listed (lines 334-338 page no 9).</p>
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