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ESPS PEER REVIEW REPORT

Name of journal: World Journal of Cardiology
ESPS manuscript NO: 11325
Title: Mitochondria-targeted antioxidants: Future perspectives of mitochondrial pharmaceutics in cardiovascular diseases
Reviewer code: 00504653
Science editor: Ling-Ling Wen
Date sent for review: 2014-05-15 23:03
Date reviewed: 2014-05-17 03:44

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] Existing	[ ] High priority for publication
[ ] Grade C: Good	[Y] Grade C: A great deal of language polishing	[ ] No records	
[ ] Grade D: Fair		BPG Search:	[ ] Rejection
[Y] Grade E: Poor	[ ] Grade D: Rejected	[ ] Existing	[ ] Minor revision
		[ ] No records	[Y] Major revision

COMMENTS TO AUTHORS

In their manuscript, Ajith and Jayakumar review a controversial field of mitochondrial antioxidant therapies for CVDs. While authors provide in their review some useful information, some statements are inaccurate or outdated, and therefore are misleading to the reader. Specifically: 1. On p.4 statement that "Energy for the cardiomyocytes as well as endothelial cells (EC), even though relatively little dependence, is solely met from the mitochondrial OXPHOS". This statement is inaccurate, since endothelial cells derive about 50% of their ATP from glycolysis and are among cell types with the LOWEST reliance on OXPHOS (reviewed in [1]). 2. P.5, contains a statement "where as, 1-5 % of O2 can give rise to potentially cytotoxic ROS such as superoxide anion radical (O2-.), hydroxyl radical (.OH) and hydrogen peroxide (H2O2), indicating that mitochondria itself is the source of ROS". This statement is not sourced (no reference provided) and contains two factual inaccuracies: a) less than 0.2% of oxygen is converted to ROS by the ETC under physiological conditions in vitro [2,3], and this percentage in vivo remains to be determined b) actively respiring mitochondria can CONSUME extramitochondrial ROS [4], and therefore it is unclear whether mitochondria in vivo are net producers or net consumers of ROS. 3. P.5 "The O2– is a primary radical that could produce other ROS, such as H2O2 and O2–?" This statement makes no sense. 4. P.5 "The .OH is generated by the reduction of H2O2 in the presence of endogenous iron by means of the Fenton reaction." Fenton reaction can also be catalyzed by other transition metals such as copper. 5.

P.5 “Further, the declined antioxidant status in the mitochondria, during ageing, can provoke the generation of ROS especially in cardiomyocytes as well [6]”. Declined antioxidant status can not change ROS generation (it can only affect ROS detoxification), but can induce oxidative stress. 6. P.6 “Among the damage induced by generated ROS at the cellular level, mtDNA remains the major target”. Whether mtDNA can be damaged by physiologically produced ROS is highly controversial [3,5]. 7. P.6 “Since 1988, when the first mutation in mtDNA has described”. This is not accurate. In 1988 a link between mtDNA mutations and human disease was established for the first time. mtDNA mutations were known before that. 8. P.6 “The mutations described are either being typically 50 to 60 % for single, large-scale deletions or 80 to 90 % for point mutations”. What authors apparently mean, are thresholds for phenotypic manifestation of mtDNA mutations, not typical mutation loads. 9. P.7 “Further more, it is believed that a mammalian DNA recombinase is involved in repairing recombination processes”. The statement is not sourced. Most experts in the field agree that mammalian mitochondria lack homologous recombination system Questions: P.5 Is it possible that the effect of the isoproterenol on ROS production is direct, and not mediated by increased cardiac output? It would be useful to provide references for the following statements found in the manuscript: 1. Around 2% of the adults suffer from HF; the prevalence is found to be increased up to approximately 6–10% over the age of 65. 2. HF from IHD is found to be ~62%. [1] X.L. Zu, M. Guppy, Cancer metabolism: facts, fantasy, and fiction, Biochem Biophys Res Commun 313 (2004) 459-465. [2] M.P. Murphy, How mitochondria produce reactive oxygen species, Biochem J 417 (2009) 1-13. [3] M.F. Alexeyev, Is there more to aging than mitochondrial DNA and reactive oxygen species?, FEBS J 276 (2009) 5768-5787. [4] D.A. Drechsel, M. Patel, Respiration-dependent H2O2 removal in brain mitochondria via the thioredoxin/peroxiredoxin system, J Biol Chem 285 (2010) 27850-27858. [5] S.R. Kennedy, J.J. Salk, M.W. Schmitt, L.A. Loeb, Ultra-sensitive sequencing reveals an age-related increase in somatic mitochondrial mutations that are inconsistent with oxidative damage, PLoS Ge

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ESPS PEER REVIEW REPORT

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[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] Existing	[ ] High priority for publication
[ ] Grade C: Good	[Y] Grade C: A great deal of language polishing	[ ] No records	
[ ] Grade D: Fair		BPG Search:	[ ] Rejection
[ ] Grade E: Poor	[ ] Grade D: Rejected	[ ] Existing	[ ] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

This is an EXCELLENT paper but with HORRIBLE, ATROCIOUS grammar and typos. These MUST all be fixed and then this fine paper can be and should be published

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ESPS PEER REVIEW REPORT

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[Y] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[Y] Accept
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] Existing	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] No records	
[ ] Grade D: Fair		BPG Search:	[ ] Rejection
[ ] Grade E: Poor	[ ] Grade D: Rejected	[ ] Existing	[ ] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

The authors have thoroughly discussed the ROS production in mitochondria and its damaging effect on mtDNA, protein and lipid. The antioxidant and protection are also well documented. It is a well written review paper, which will give the readers of the journal good information on mitochondria ROS production and cardiovascular diseases.

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Existing	[Y] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] No records	
[ ] Grade D: Fair		BPG Search:	[ ] Rejection
[ ] Grade E: Poor	[ ] Grade D: Rejected	[ ] Existing	[ ] Minor revision
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COMMENTS TO AUTHORS

This article is a concise review illustrating mitochondrial dysfunction by reactive oxygen species associated with CVD and beneficial mitochondria-targeted antioxidants. However, this article should be corrected according to the following suggestions before publication. Page 2, line 7, line 1 up, Check the spelling. dialatation is dilation? Page 5, line 5, Check the follow sentence. The O2 – is a primary radical that could produce other ROS, such as H2O2 and O2–· in the failing myocardium. The .OH is generated…. I think that "such as H2O2 and OH" instead of "such as H2O2 and O2–·". Page 5, line 6, ETC; Give the full spelling. Page 6, line 9, Check the follow sentence. Further, the oxidized LDL abrogated the oxidative stress by binding to the lectin-like oxidized low-density lipoprotein scavenger receptor-1 (LOX-1) on the arterial wall. The oxidized LDL abrogated the oxidative stress, or the oxidized LDL is abrogated by LOX-1? Page 10, line 10, Check the follow sentence. Co-enzyme Q10 (CoQ10) and L-acetyl-carnitine can be considered to be a safe adjunct to standard therapies in CVD [18]. Although the authors mentioned L-acetyl-carnitine, there is no description about it. The authors should also refer to L-acetyl-carnitine. Page 10, line 1 up, Check the follow sentence. In another study, fifty consecutive new patients 11 discontinued 28 months of statin therapy due to side effects and began CoQ10 supplementation at an average of 240 mg/day [24]. The authors should describe the result of this study. Was the CoQ10 supplementation beneficial? Page 12, Table 1 The structures of mitochondria-targeted antioxidants listed in Table 1 should be

depicted for general readers.

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ESPS PEER REVIEW REPORT

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[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Existing	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] No records	
[ ] Grade D: Fair		BPG Search:	[ ] Rejection
[ ] Grade E: Poor	[ ] Grade D: Rejected	[ ] Existing	[Y] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

It is a very interesting topic. In this review, the authors discussed mtDNA point mutations. It would be helpful if the authors cover the review on the other effects of oxygen free radicals on mtDNA deletions, mutations or loss of large fragments. In this paper, the authors described mtDNA injury affected by the O2-, more discussions on the mechanisms are encouraged. Ca2+ overload occurs when the hearts are exposed to an excess amount of oxygen free radicals, and Ca2+ can increase the generation of oxygen free radicals in turn. The relationship between Ca2+ and oxygen free radicals is not entirely clear.