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ESPS Peer-review Report
Name of Journal: World Journal of Hepatology
ESPS Manuscript NO: 6653
Title: Melatonin attenuated cisplatin induced hepatoma (HepG2) cell death via regulation of mTOR and ERCC 1 expression
Reviewer code: 00724585
Science editor: Ma, Ya-Juan
Date sent for review: 2013-10-27 12:16
Date reviewed: 2013-11-28 18:00

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[Y] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[Y] 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	[ ] Existed	[ ] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS
Overall - good structure, easy-to-read despite lots of abbreviations, even for inexperienced readers in this field - very important and up-to-date subject, but the clinical applicability should be elucidated a little more concrete in the introduction and discussion (how exactly will these findings help physicians and patients in the future?) - nice, clear, relevant pictures, and Figure 11 (an overview of the major findings mentioned) is a welcome and supporting addition to your article. You could refer to them in the results section and the legends should contain more information about what we see (eg Western Blotting, Flow Cytometry, fluorescent microscopic image) - language: revision of English grammar and spelling is necessary before publication Minor point - motivation for choice of doses 1mM/20mM melatonin/cisplatin, respectively, remains unclear until we arrive at the results, maybe mention it earlier, already in the methods

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ESPS Peer-review Report
Name of Journal: World Journal of Hepatology
ESPS Manuscript NO: 6653
Title: Melatonin attenuated cisplatin induced hepatoma (HepG2) cell death via regulation of mTOR and ERCC 1 expression
Reviewer code: 01215835
Science editor: Ma, Ya-Juan
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[Y] Grade A: Priority Publishing	Google Search:	[ ] Accept
[Y] Grade B (Very good)	[ ] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[Y] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[ ] Major revision
		[ ] No records	

COMMENTS TO AUTHORS
In this article the authors study whether adjuvant therapy with melatonin could mediate a protective effect against cisplatin-induced apoptosis in human hepatoma (HepG2) cells. They conclude that the association of melatonin with cisplatin ameliorates the adverse effects of this anticancer drug. In words of the authors, these findings might open new insights in the treatment of patients with hepatocarcinomas. The work is interesting, technically correct and well written Specific comments 1. My only concern is the dose of melatonin used in the experiment. Milimolar melatonin is a concentration 106 times higher than nocturnal concentration in human serum. Consequently, the described effects of melatonin cannot be explained by its interaction with MT1 or MT2 melatonin receptors (Kd in pM range). Of course, melatonin actions independent of receptors (particularly antioxidant properties) could explain the effects of these pharmacological doses. By accepting that mM concentration of melatonin at the level of the target cell to be effective to improve the effects of cisplatin, what should be the dose of melatonin administered to patients with hepatocarcinoma to obtain the same positive effects? 2. The authors use frequently in the text the expression "concentration dependent". They must specify in all cases the range of concentrations in which the effect is "concentration dependent" (i.e. melatonin effects on HepG2 viability are concentration dependent only between 1 to 5 mM). 3. Results. Effect of melatonin and cisplatin on viability of HepG2 cells. Please, include the results of the two-way ANOVA demonstrating that the effects are time and dose dependent. Minor questions 1. Page 5 line 6. "…melatonin also posses antiproliferative effects". Please, indicate in which kind of cells. 2. Reference 27 is incomplete.

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ESPS Peer-review Report
Name of Journal: World Journal of Hepatology
ESPS Manuscript NO: 6653
Title: Melatonin attenuated cisplatin induced hepatoma (HepG2) cell death via regulation of mTOR and ERCC 1 expression
Reviewer code: 00605951
Science editor: Ma, Ya-Juan
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[Y] Grade B (Very good)	[ ] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[Y] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[Y] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[ ] Major revision
		[ ] No records	

COMMENTS TO AUTHORS

The study by Bennukul et al describes an important role for melatonin as an adjuvant to cisplatin, a therapy known to cause severe toxicity in the body. The studies were well-designed, clearly presented, were highly mechanistic and demonstrated novel pathways regulated by melatonin to improve health outcomes associated with hepatic cancer and cisplatin-induced hepatotoxicity. This study will open up new research areas in this field. The authors used myriad techniques and approaches to tackle this deadly disease. This reviewer's comments are minor but need to be addressed before this paper is acceptable for publication. Please see my comments below: (1) Please provide the rationale for the concentrations of melatonin used in this study. For many not in the melatonin field, these would seem VERY high. The authors need to stress that they are looking at the anti-oxidant and free-radical scavenging effects of melatonin which require these concentrations of melatonin and cite relevant papers. A good paper to cite is: Liu L, Xu Y, Reiter RJ. Melatonin inhibits the proliferation of human osteosarcoma cell line MG-63. Bone. 2013 Aug;55(2):432-8 because these authors explain why they are looking at these higher concentrations of melatonin on a bone cancer. This needs to go into the Introduction (2) Please provide the range of concentrations of melatonin and cisplatin used under Methods-Cell viability assay (3) Under Discussion, the authors need to tone down their conclusions because most of their results are correlative and not causative. By use of inhibitors to each of the kinases along the signaling cascade, could the authors really show that activation of one kinase by melatonin leads to the activation of the other. For example in this sentence, "Therefore, melatonin induced cisplatin induced DNA damage resulting in the decrease activation of DNA repair capacity. This finding was the first time to report that

melatonin can activate ERCC1 in a dose-dependent manner via mTOR pathway." the authors can only show causation by use of specific inhibitors. Also, cells are given concentrations of drugs-not doses. Animals are given doses. (4) Please change abcissa of Fig 1 to read "Concentration of melatonin..." or Concentration of cisplatin..." (Fig. 1) since animals are given doses of drugs-not cells. (5) Please remove tracking notes on Figs 4 and 8. (6) For all figure legends, please put the number of observations "n" for each point or bar graph and state whether or not these were done in duplicate, triplicate, etc. Statistical analysis is missing in Fig. 1. For Figs 4, 7, even though these were representative photos, please state how many times these experiments were repeated. Also, please change the title to Fig. 11-this is not an outline but a schematic. (7) The grammar needs to be revised extensively throughout this manuscript (e.g., under Introduction, second paragraph, first and second sentences, please change "have been clinical" to "have been used clinically." and change "wildly" to "widely". Also, please rephrase the last sentence to read something like ".....searching for agents that can enhance the potency of cisplatin so that lower doses of cisplatin can be used to protect against hepatotoxicity....."