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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 5462
Title: Oleanolic acid and ursolic acid inhibit proliferation in malignantly rat hepatic oval cells
Reviewer code: 00364584
Science editor: Ma, Ya-Juan
Date sent for review: 2013-09-11 16:57
Date reviewed: 2013-09-24 21:38

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	[ ] 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:	[ ] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[Y] Major revision
		[ ] No records	

COMMENTS TO AUTHORS
The authors induced malignant transformation into rat hepatic oval cells WB-F344 by low dose H2O2 treatment and evaluated the effects of OA and UA. Overall the data is convincing. Addressing a few issues will improve the paper. 1. In addition to cell cycle data results from cell proliferation assays (MTT or BrdU incorporation) should be included in Fig. 1. 2. In page 9 it was mentioned 'an increasing nucleus to cytoplasm ration was observed, as were many mitotic cells, polykaryocytes and even tumor giant cells'. These findings need to be shown in Fig. 2. 3. The methodology for measuring aneuploidy is not clear and needs to be described in detail. 4. In addition to BRL cells proliferation assay needs to be performed in non-transformed WB-F344 cells upon treatment with OA and UA. This data will strengthen the paper. 5. The paper needs changes in some terminology, e.g., i. In the title: 'malignantly' should be replaced by 'transformed' ii. What is meant by 'premalignant and malignant lesion'?

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
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[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[Y] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[Y] Major revision

COMMENTS TO AUTHORS

The manuscript by Han et al. describes the effect of the phytochemicals oleanolic acid (OA) and ursolic acid (UA) on the malignant phenotype of tumor cells. They used H2O2 to induce proliferation and malignant transformation in the rat liver oval cell line WB-F344. The authors analyzed cell morphology and colony formation rates. Although the data presented in this manuscript is with great interest, several points should be addressed in order to improve the manuscript. My major concern is that all the conclusions obtained in this study are based on one cell line (cell line WB-F344). It will be appreciated if the obtained data were confirmed with at least with another cell line. Fug.2A. a global view of the figure is necessary in order to appreciate the difference between Con and H2O2 figures. In Fig 2B. The cell line WB-F344 doesn't make colonies at all? Fig 3A, 3b, error bars are missing.

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[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[Y] Major revision

The manuscript by Huan et al attempts to show that the OA and UA inhibit transformed cell growth in culture using WBF344 cells that have been subjected to extended H2O2 exposure.

Overall the manuscript and data do not really add any degree of novel or significant findings to the field as a whole and, if anything, distract from advancing it. The data and manuscript are further weakened by poor experimental design and use and interpretation of the data as it is presented. Overall this is a disappointing manuscript on many levels starting with a poor grasp of the current data and literature available, the rudimentary nature of the study design, and the limited (if not negative) impact this will have on the field. As such my comments are limited to those that are "major" in nature rather than going through the manuscript line-by-line with additional minor corrections.

1. Both the title and running head are inaccurate; "…proliferation in malignantly rat hepatic oval cells" makes no sense and "OA and UA inhibit hepatocarcinogenesis" is simply not what this study addresses. This study addresses the effect of OA and UA on proliferation following (alleged) transformation of WB cells. Indeed the manuscript would be of considerably more interest if it studied whetherthese compounds affected transformation as opposed to progression.

2. The abstract uses terms such as "a low dose of H2O2" and "over a long period" these make no sense when not referenced to specific dose or time periods.

3. Reporting H2O2 causes cell transformation is not novel at any level. Indeed there are several

studies available using proven transformed derivatives of the WB cell line published by the originator of the line (WB Coleman, UNC Chapel Hill, NC, USA). Since the authors make no effort to study the effects of OA or UA on the transformation process it is unclear as to why they would bother going through the transformation process at all when transformed WB cells are available. For that matter they could have used numerous other hepatoma cell lines available that would likely be relevant/important if they were human. Out of interest, the authors state these cells were a gift from a Dr. Liu at the China UnionMedical University; I would be interested to know if Dr. Coleman is aware of this and has granted appropriate permissions? To my knowledge these cells are not commercially available or held in any public access repositories such as ATTC?)

4. 4. Using UA and OA to show inhibition ofproliferation in cells, whether transformed or not, is not novel at all. Numerous studies have already looked at UA and OA and cell proliferation and/or survival, many of which have gone on to look at potential mechanisms by which these effects occur. There is no attempt at any mechanistic analysis in thecurrent paper. Simply taking transformed cells and putting these agents on them and showing they inhibit growth has almost no value to the field other thanshowing they inhibit proliferation in (yet another) cell line.

5. It is uncertain why the authors are using 5-FU as a "control" when they propose that OA and UA inhibit proliferation. 5FU is a thymidylate synthase inhibitor that inhibits thymidine production, DNA synthesis and so induces cell death. To my knowledge neither OA or UA act in this way so using 5-FU as a control seems, at a minimum, a strange choice.

6. These studies would have a degree of relevance if they were able to correlate the doses of OA and UA relative to those that are found in traditional Chinese medicines. That is, there appears to be a research ethos that is currently in vogue that if a chemical exists in TCM then by simply putting it on cancer cells and measuring inhibition of growth (ormore often cell death) then this is de facto proof that this is an active constituent of the TCM and the root of the alleged anticancer properties. Surely the authors of this, and numerousother papers using the same approach, must realize that this applies to a huge range of chemical compounds whether taken off the shelf or derived from an herb or plant. Indeed, many of these poorly designed studies act to detract frompotentially important, rigorously designed studies to sort the important data from the "scientific noise" that surrounds potentially important TCMs.

7. The discussion is completely unfocused and reflects the unfocused nature of the experimental design.