

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 38588

**Title:** mitochondrial pathway mediated by reactive oxygen species involvement in  $\alpha$ -Hederin-induced apoptosis in hepatocellular carcinoma cells

**Reviewer's code:** 00607640

**Reviewer's country:** Taiwan

**Science editor:** Xue-Jiao Wang

**Date sent for review:** 2018-03-12

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**Review time:** 23 Hours

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

## COMMENTS TO AUTHORS

$\alpha$ -Hederin, a secondary saponin isolated from *Hedera* or *Nigella* species, is one of the major active component of various traditional medicinal herbs which has been reported to possess many biological activities such as antioxidant activity, anti-inflammatory activity, etc. This study examined whether  $\alpha$ -Hederin could have inhibitory effect on hepatocellular carcinoma. The authors further demonstrated that  $\alpha$ -Hederin can induce apoptosis of HCC cells via the mitochondrial pathway mediated by increased intracellular ROS and imply the therapeutically potential of  $\alpha$ -Hederin for human HCC. I have some minor concerns: 1). How's the cytotoxicity of  $\alpha$ -Hederin on normal hepatic cells. Please discuss it. 2). What's the possible mechanism for  $\alpha$ -Hederin in inducing ROS production in HCC cells. Please discuss it. 3) Is  $\alpha$ -Hederin inducing apoptosis of HCC cells a direct or indirect effect? Please discuss it.

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**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 38588

**Title:** mitochondrial pathway mediated by reactive oxygen species involvement in  $\alpha$ -Hederin-induced apoptosis in hepatocellular carcinoma cells

**Reviewer's code:** 02878348

**Reviewer's country:** Taiwan

**Science editor:** Xue-Jiao Wang

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
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<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> Plagiarism	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

## COMMENTS TO AUTHORS

Summary and general comments Using in vitro (i.e., human SMMC-7721, HepG-2, and Huh-7 HCC cell lines) and in vivo (i.e., subcutaneous implantation of human hepatocellular carcinoma cells into nude mice), the present study attempted to investigate the effects of  $\alpha$ -hederin on HCC cells by performing cell proliferation and apoptosis assays as well as detecting ROS, GSH, and ATP levels and mitochondrial membrane potential. Western blotting analysis was conducted to examine related proteins. Their results showed that  $\alpha$ -hederin induced the apoptosis of HCC cells in vitro and in vivo in their experimental settings and the authors concluded that the mechanism involves the mitochondrial pathway mediated by increased intracellular ROS. Although the effects of alpha-hederin on several human cancer cell lines have been reported 10 years ago, its effect on human hepatocellular carcinoma cells has not been reported. As a



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whole, the manuscript is detailed and well-prepared. On the other hand, there are some major concerns that need to be addressed. Major comments 1. Figure 1A: What is the unit of the x-axis in Fig. 1A ( $\alpha$ -hederin 0 – 60)? The authors stated that  $\alpha$ -hederin significantly reduced HCC cell viability in a dose- and time-dependent manner but there is no statistical comparison among the three time periods to support their statement. A “trend” does not mean statistical significance. The authors may use t-test, ANOVA, or other applicable statistical tool to verify their findings. 2. Figure 1B: In the Results, the authors stated that “ $\alpha$ -hederin induced the apoptosis of HCC cells in a dose-dependent manner”. However, the figure merely showed that the degree of apoptosis of each dosage of  $\alpha$ -Hederin (i.e., 5, 10, and 20  $\mu$ M) was significantly different from that of the control (marked by “a” above each bar). Despite a seemingly progressive increase with increasing dosage, it seems that there was no statistically significant difference among the three dosages. Therefore, the authors’ claiming of a “dose-dependent manner” is incorrect unless proved otherwise. The authors may use “p for trend” to validate the dose-dependent relationship. The same argument also applies to Fig. 1C, D, and E. and Figure 4. Minor comments Please state the full term in figure captions as it first appeared (e.g., AIF) because each figure is stand-alone.