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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 22551
Title: Synergistic anticancer properties of docosahexaenoic acid and 5-fluorouracil through interference in energy metabolism and cell cycle arrest in AGS cells
Reviewer's code: 02472104
Reviewer's country: United States
Science editor: Jing Yu
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[Y] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

This is generally a well-written manuscript evaluating mechanisms by which the fatty acid DHA can sensitize gastric cancer cells to the chemotherapeutic drug 5-FU. The results present cytotoxicity data, cell-cycle data and protein expression of mitochondrial electron transfer chain complex in gastric cancer cells. The major issue to clarify is whether or not there is in fact synergism of the two agents. Introduction: The text: "This subsequently allowed lower dosages of 5-FU to be administered in combination with DHA in colorectal cancer[6, 7]. The results showed DHA supplementation had a powerful adjuvant activity and ….." is worded as if it refers to clinical trials and yet the studies quoted are from experimental models. Please re-word this. The text: "The primary mechanisms by which DHA exert this apoptotic effect are believed to be the generation of reactive oxygen species and interaction with cellular signaling pathways though the detailed mechanisms remain to be investigated." is confusing. The primary mechanism is x but the detailed mechanism is not known? This needs to be re-worded. Perhaps using wording that leads in to the next paragraph could be used? If the intent of the paper is to evaluate mitochondrial toxicity, this should be stated here.

Previous literature on DHA plus 5-FU effects in gastric cancer would be better given in the introduction with an explanation of how the present work differs (eg. Refs. 28 & 29). Last paragraph- use past tense (aimed not aims) Methods: "Cell specimens "should be "cells"? Abbreviations should be defined such as PBST and mito-cyto. Results: Are IC50 values precise to 0.01 ug/ml? Discussion: The phrase: "agent 5-FU is the first-line chemical intervention" this needs to be worded in terms of "first-line chemotherapy". Instead of "more novel ", the term "new" would work better It is difficult to follow the discussion when literature results are given in uM DHA and the present results are given in ug/ml DHA. Please put the corresponding ug/ml in parenthesis for literature results. "to 12.9μg/mL, 34.17μg/mL" should be "to 12.9 μg/mL and 34.17μg/mL". Again, it is doubtful that the assays are precise to two decimal points, and be consistent in using the same number of decimal points. Same applies for "be 30 μg/mL, 12.5 μg/mL". Decimal point issues also exist in Figure 1 legend. Are the DHA and 5-FU concentrations used in this work something that could be achieved in vivo? "This decrease was also found to be synergistic in a statistically significant manner." A decrease cannot be synergistic but the combination of two compounds can be. The paragraphs in the discussion need to be tied together better instead of jumping from topic to topic without any pre-amble. Is there any mechanistic connection between the cell cycle effects and the mitochondrial toxicity observed? "a marked reduce" should be "a marked reduction" Is a decrease in mitochondrial activity a good thing in light of the fact that cancer cells display the Warburg effect? This is confusing on page 11. It would be useful to comment on the cell line used and its relevance to human gastric cancer. Table 1: Does a CI less than 1 indicate negative synergism? In methods, can the difference between negative and positive synergism be defined to facilitate interpretation of the results? Figure 1: It is not given which compounds were used to treat the cells in panels A-C. In panel D, it appears that there is an additive effect after 48 hours (not synergistic) and no benefit of the combination at 24 hours. How do the results support synergism? The blue line, representing 5-FU alone at 24 hours is the lowest line, indicating lowest inhibition. Please remove "could" from "could notably increased" and from "could markedly suppressed". The decimal points used are excessive again. The text in the Figure 1 legend is too detailed, making it hard to read.