

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastrointestinal Pathophysiology

**Manuscript NO:** 33967

**Title:** Effects of Commercially Produced Almond By-products on Chemotherapy-induced Mucositis in Rats

**Reviewer's code:** 00035705

**Reviewer's country:** Scotland

**Science editor:** Yuan Qi

**Date sent for review:** 2017-03-20

**Date reviewed:** 2017-03-21

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input 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 type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input 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 type="checkbox"/> No	

### COMMENTS TO AUTHORS

This interesting study shows that the severity of mucositis caused by 5-fluorouracil (5FU) in rats was not ameliorated oral intake of almond extracts that contain phenolics and have anti-oxidant activity. A second aspect of the work is the use of burrowing behaviour by the rats as a monitor of animal well-being and severity of mucositis. Indeed, almost half of the discussion relates to this aspect of the work. The paper thus falls between two stools, and does not deal comprehensively with either aspect. The linkage between burrowing behaviour and animal well-being during chemotherapy was well established in Whittaker et al, 2015. It should thus just be a tool or marker in the present study. It is not part of the central question. As suggested by the title the emphasis should be on the effects of (or lack of) almond extracts on mucositis. The findings of rat study are intriguing, but also highlight the difficulties in dealing with ill-defined extracts in possible therapies. The extracts did contain phenolics and have anti-oxidant activity but these appear to account for only a small proportion of the



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material present. What was the rest? Could other components have interfered with action of the phenolics and anti-oxidant activity in vivo. Maximal gut disruption and damage due to 5FU occurs at around 2-3 days in rats. Crypt and villus regeneration and repair occurs thereafter. Some bioactive factors do not prevent this early damage to the gut but alter its nature, in particular the preservation of crypt stem cell microcolonies that facilitate rapid repair. This protective property would not be seen in the absence of longer study. However, more detailed analysis of crypt cell numbers / type and crypt organisation would be helpful in defining whether the extracts had any or no potential ameliorative effect. Pg. 5 para 3 What was the source of the almond hulls? Were they a certified stock? Was the blanched water extract from the same ones? Pg. 5 para 4 Phenolics and anti-oxidant appear to account for a small proportion of dry Pg. 10 para 1 weight. Any other analysis or indications what else could be present? Pg. 11 para 4 It would be useful to give additional detail of the individual histological Pg. 28-29 parameters that were evaluated, rather than just the global index. Pg. 12 para 2> See general comments on focus of discussion.

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**Reviewer's code:** 03471498

**Reviewer's country:** Brazil

**Science editor:** Yuan Qi

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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 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 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"/> 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

This study aimed to describe the effect of almond extracts on the severity of intestinal mucositis secondary to 5-FU administration. In addition, the authors purposed an investigation about the significance of burrowing behavior as a measuring tool for clinical outcomes after mucositis treatment. The study is well-written and the results are very interesting. However minor adjustments seem to be necessary. Introduction - "The severe nature of the symptoms often leads to a patient-requested reduction of chemotherapy dose" - The word "often" is not adequate; I suggest "can lead". In addition, it is important to add the information that intestinal mucositis can increase the frequency of peripheral parenteral nutrition prescription, which can predispose to high morbidity. Results - The histological sections were not explored sufficiently. For example, the authors quantified the myeloperoxidase activity, which signalizes, among other effects, neutrophils activation. What are the characteristics of the inflammatory infiltrate observed in the histological sections? What are the differences and similarities between



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the groups? A detailed description of the histological finding is necessary, showing the scores for each tissue element individually. This is very important considering the discrepancies about the effect of 5-FU on intestinal mucosa (as the authors commented in the Discussion) and the contributions that the current study can offer to the literature in this area. Caption - Figure 3 - C - I believe that it is "5FU/PBS ileum" not "jejunum". The resolution of the figures is not adequate, needing more sharpness. I suggest the replacement of the figures and the insertion of representative sections (two images) for almond groups. Discussion - it is necessary a commentary about the limitations of the study regarding the effect of gavage on animals, mainly regarding the low absorption episodes and alterations on the immune response that can be installed after repeated and chronic usage of this technique in rodents. Please insert the opinion of the authors about the influence of side effects of gavage on the results, mainly regarding the intestinal absorption and local effect of almond extracts.