



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 40888

Title: Mucosal adhesion and anti-inflammatory effects of Lactobacillus rhamnosus GG in the human colonic mucosa: A proof-of-concept study

Reviewer's code: 01434943

Reviewer's country: Australia

Science editor: Ruo-Yu Ma

Date sent for review: 2018-07-30

Date reviewed: 2018-07-30

Review time: 1 Hour

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input checked="" type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

English grammar requires serious attention throughout. For example, in the abstract the word 'assumed' is used instead of 'consumed'. **TITLE:** Suggest omit everything after the word 'mucosa' **ABSTRACT:** This is far too long. Reduce methods by at least 50%.



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7901 Stoneridge Drive, Suite 501,
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Telephone: +1-925-223-8242
Fax: +1-925-223-8243
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Include p-values to support claims of significance. INTRODUCTION: The correct term is 'proof-of-concept'. This section should be written around IBD more specifically. There are two grammatical errors in the first sentence. Also, the terms microflora and microbiota are used interchangeably. Which 'disease' is being referred to in the first sentence. The remainder of the introduction is logical but requires English correction. METHODS: Name the 'local ethics committee'. Remainder is appropriate scientifically. RESULTS: Well explained. Figures are clear and informative. DISCUSSION: The section on LGG and its 'postbiotic' products should be expanded somewhat. Please see: Probiotic factors partially prevent changes to caspases 3 and 7 activation and transepithelial electrical resistance in a model of 5-fluorouracil-induced epithelial cell damage. Prisciandaro LD et al. Support Care Cancer. 2012 Dec;20(12):3205-10 Lactobacillus fermentum BR11, a potential new probiotic, alleviates symptoms of colitis induced by dextran sulfate sodium (DSS) in rats. Geier MS et al. Int J Food Microbiol. 2007 Mar 20;114(3):267-74. also the importance of the growth medium should be discussed: Factors derived from Escherichia coli Nissle 1917, grown in different growth media, enhance cell death in a model of 5-fluorouracil-induced Caco-2 intestinal epithelial cell damage. Wang H et al. Nutr Cancer. 2015;67(2):316-26.

INITIAL REVIEW OF THE MANUSCRIPT

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Name of journal: World Journal of Gastroenterology

Manuscript NO: 40888

Title: Mucosal adhesion and anti-inflammatory effects of Lactobacillus rhamnosus GG in the human colonic mucosa: A proof-of-concept study

Reviewer's code: 04008386

Reviewer's country: Italy

Science editor: Ruo-Yu Ma

Date sent for review: 2018-08-09

Date reviewed: 2018-08-16

Review time: 7 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good		<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	(General priority)	Peer-reviewer's expertise on the topic of the manuscript:
<input type="checkbox"/> Grade E: Do not publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Minor revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Major revision	<input type="checkbox"/> General
		<input type="checkbox"/> Rejection	<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The Authors describe an interesting manuscript on the mucosal adhesion and anti-inflammatory effect of Lactobacillus rhamnosus GG in an in vivo ex vivo experimental model. Only minor comments need to be addressed in order to make it



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acceptable: 1. Please add also the possible risks of *L. rhamnosus* GG administration in both introduction and discussion sections. There is literature evidence of few cases of invasive infections by probiotics (and this strain in particular) following administration at therapeutical doses. 2. Please write all species names in italics. 3. Materials and methods: please specify the RPMI composition. 4. Please write numbers in proper scientific format (i.e. 12×10^6 should be 1.2×10^7). 5. Please change "did not assumed" in "did not assume" 6. Materials and Methods: please change "TNF α and" in "TNF α and" 7. Materials and Methods: are primers used for Real Time PCR specific for *L. rhamnosus* GG? How did you prove that other *Lactobacillus* spp. could be aspecifically detected? 8. Please check again statistical significance of 3.0 ± 0.3 vs. 3.7 ± 0.3 . 9. Discussion: please change "consistent reduction ad adherent mucosal " in "consistent reduction of adherent mucosal" 10. Discussion: please change "we observed in increase of mucosal adherent bacteria" in "we observed an increase of mucosal adherent bacteria" 11. Check the style of reference 23. 12. Remove repetitions in the following phrase in core tip section: "Further translational and clinical studies would confirm utility and better optimize the utilization of LGG administration in UC patients."

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Name of journal: World Journal of Gastroenterology

Manuscript NO: 40888

Title: Mucosal adhesion and anti-inflammatory effects of Lactobacillus rhamnosus GG in the human colonic mucosa: A proof-of-concept study

Reviewer's code: 00008160

Reviewer's country: Canada

Science editor: Ruo-Yu Ma

Date sent for review: 2018-08-09

Date reviewed: 2018-08-19

Review time: 10 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
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		<input type="checkbox"/> Major revision	<input type="checkbox"/> General
		<input type="checkbox"/> Rejection	<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input checked="" type="checkbox"/> Yes
			<input type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The manuscript submitted by Pagnini and colleagues describes experiments indicating comparable adhesion of Lactobacillus rhamnosus, strain GG (LGG) to colonic biopsies taken from patients with ulcerative colitis versus non-inflamed controls and then



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maintained in short-term organ culture. Conditioned medium from the same probiotic strain reduced mRNA levels of two pro-inflammatory cytokines. Comparable results were seen in patients with ulcerative colitis who consumed the probiotic for a week prior to colonoscopy and per-endoscopic biopsies. General Comments: 1. Novel findings arising should be highlighted both in the Abstract and Discussion sections of the manuscript. 2. The relative merits and limitations of employing short-term organ culture, instead of primary intestinal organoids and enteroids, must be considered in detail in the Discussion. 3. The rationale for testing only TNF-alpha and IL-17 must be provided. Levels of chemokines, anti-inflammatory cytokines, and Th2 predominant pro-inflammatory cytokines following exposure to both live LGG and conditioned medium derived from LGG also would be of considerable interest. 4. To confirm PCR studies of LGG colonization of the colon following oral ingestion of the probiotic, FISH and/or electron microscopy should be employed as complementary experimental approaches. Such studies also would serve to define whether the probiotic is directly adherent to the apical brush border of colonocytes or simply bound to the overlying mucus layer. Specific Comments: 1. Abstract, Conclusions: experimental findings included this report do not relate to potential efficacy of the probiotic tested. Accordingly, the final sentence in the Abstract should be deleted. 2. Methods: for comparative purposes, additional probiotic strains should be tested. Alternatively, the effects of a pilus-deficient, isogenic mutant of LGG on levels of pro-inflammatory cytokines and on bacterial colonization in vivo would add novel findings to this report. 3. Methods: the effects of incubating colon explants with LGG were tested at only a single point in time (2 hours). Both shorter and longer incubation periods could be evaluated. 4. Results: in addition to findings using conditioned medium, TNF-alpha and IL-17 mRNA levels in organ culture colonic explants after exposure to live LGG for 2 hours should be provided. 5. Results: levels of protein expression for the two pro-inflammatory



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cytokines after incubating LGG with colonic biopsies placed into organ culture also should be tested. 6. Results: “trends” reported are likely to simply reflect a type 2 statistical error. 7. Results: data “not shown” when testing normal colonic mucosa should be changed to include the findings as a third panel (panel C) in Figure 3.

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