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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 94441

Title: Digesting gluten with oral endopeptidases to improve the management of celiac disease

Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 00503448
Position: Peer Reviewer
Academic degree: MD
Professional title: Associate Professor, Research Assistant Professor
Reviewer's Country/Territory: Italy
Author's Country/Territory: United States

Manuscript submission date: 2024-03-18

Reviewer chosen by: Ming Fan

Reviewer accepted review: 2024-05-07 08:56

Reviewer performed review: 2024-05-23 09:10

Review time: 16 Days

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

In this editorial, the authors aimed to comment on the recently published clinical study by Stefanolo et al. assessing the "Effect of Aspergillus niger prolyl endopeptidase in patients with celiac disease on a long-term gluten-free diet". They critique the study findings and also summarize endopeptidase-based as well as other strategies and how they can complement gluten-free diet in the management of celiac disease. In my opinion, the authors can improve their editorial by adding the critical role of markers allowing to explore the mucosal recovery, ideally, in a non-invasive way. When they stated that ".One limitation of development of new therapeutics is lack of animal models that reflect various aspects of human disease. Another limitation is the lack of standardization of randomized controlled clinical trials..." they should recall previous studies trying to investigate the potential use in clinical practice of serological markers of mucosal damage and villous atrophy. In this regard, they should recall and underline that anti-tissue transglutaminase and anti-endomysial antibodies, unfortunately, do not correlate with severity of mucosal damage in adult celiac patients as previously demonstrated (World J Gastroenterol. Oct 14, 2009; 15(38): 4775-4780; doi:

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10.3748/wjg.15.4775), while anti-actin IgA antibodies that are significantly correlated with villous atrophy, are not detectable in 100% of patients but only in nearly 50% of celiacs with severe villous atrophy. This support the urgent need of non invasive markers of mucosal damage to better follow celiac patients after gluten free diet initiation and check potential exposure to gluten due to unintentionally ingest gluten from food contaminations. -A further clinically relevant point to recall is the current recommendation of the most recent international guidelines on the managment of celiac disease. In fact, all guidelines (European Society Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) 2020; European Society for the Study of Coeliac Disease (ECD) 2019; World Gastroenterology Organization (WGO) 2017; Central Research Institute of Gastroenterology, Russia, 2016; National Institute for Health and Care Excellence (NICE), 2015;British Society of Gastroenterology (BSG), 2014; and (7) America College of Gastroenterology (ACG), 2013), also provide information about the essential information that should be collected during follow-up evaluations to ascertain gluten-free diet response and accuracy.