

Erlangen, 12-20-2017

Dear Prof. Strom, Prof. Garcia-Olmo, Prof. Tarnawski,
Editors-in-chief, *World Journal of Gastroenterology*

We thank you for the opportunity to improve our minireview manuscript “Regulation of the intestinal immune system by flavonoids and its utility in chronic inflammatory bowel disease” for the journal *World Journal of Gastroenterology* (Manuscript: NO: 36829-revision1).

We have carefully read the comments of the three reviewers and corrected the remarks concerning the missing references in the introduction part. Furthermore we added now more references to give the manuscript a more comprehensible character. Then, we explained more terms and tried to link different aspects in the hope that the reader will now be able to understand the link e.g. flavonoids and the PERM hypothesis.

We would be honored if the improved minireview manuscript for the journal *World Journal of Gastroenterology* is now in a more acceptable status for publication.

We thank you very much for your consideration in advance,
With kind regards,

PD Dr. Benno Weigmann

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Point –to-point reply

Reviewer 1 (**Reviewer's code:** 02741591):

Abstract: The abstract is truncated (141 words). It could better be expanded.

We thank the reviewer for the comment. We have now expanded the abstract and tried to explain more.

The word 'dysbalance' should be (imbalance). English language needs polishing and revision by a native speaker.

We agree with the reviewer. We have changed the word and tried to improve the English language.

Ah receptor COMMENT: Fully expand the abbreviation at its first appearance in the abstract (aryl hydrocarbon) receptor.

We regret this mistake and thank the reviewer. We have now added the full written term together with the abbreviation in the text.

Introduction: The first 20 lines (2 paragraphs) should include references.

We have now added more references.

The strucutre should be improved so that an introductory paragraph is presented before the subsequent subheadings. The review lacks in-depth of the presented literature. The references are overused for lenghty paragraphs. The subheading 'Flavonoids regulate the Ah-receptors', includes 12 lines cited by one reference. The literature presented in the last paragraph of the review does not comply with the preceeding subheading and does not confer evidence of inhibition of intestinal inflammation by flavonoids. The references are few for a review article. As mentioned at the end of the conclusion, an orginal article clinical study design would be more appealing than a shortly presented incompletely informative review

We agree with the reviewer and have now increased the reference number from 21 to 38. We hope that we will able to give the readership a more qualitatively and informative minireview to this interesting theme. We think that in the future more therapeutic studies will appreat to demonstrate that phytochemicals are able to regulate immune responses during chronic inflammation.

Reviewer 2 (**Reviewer's code:02822560**):

The main cause of IBDs is not fully understood, but an immune system disturbance as well as genetic disposition and environmental factors are associated with their pathogenesis. Significant antioxidant and free radical scavenging properties of flavonoids are well known and additionally, accumulating evidence in animal models or cell cultures suggest that flavonoids can inhibit inflammatory pathway via nuclear transcription factor, including NF- κ B, ameliorating the intensity of inflammation in the digestive tract. In this mini-review, the authors briefly explain the Ah-receptor regulated by flavonoids as their main inhibitory effects against intestinal inflammation, but it seems difficult for the readers of this journal to understand the following two items: cytochrome, including CYP1A1, and PERM system, at each section of "FLAVONOIDS AND MICROSOMAL ENZYMES" and "FLAVONOIDS AND PERM", because they had written them too concisely. Their abnormality in patients with IBD and therapeutic benefits from some flavonoids should be explained in parallel.

We thank the reviewer for his expertise and his vision that in the future more and more impact will be given to nutritional therapies for IBD patients. We have tried to explain more terms e.g. PERM concept and Flavonoids. We have added much more references to allow the readership to find appropriate literature.

Reviewer 3 (**Reviewer's code: 02998194**):

Abstract: The abstract is truncated (141 words). It could better be expanded. The word 'dysbalance' should be (imbalance). English language needs polishing and revision by a native speaker. Ah receptor COMMENT: Fully expand the abbreviation at its first appearance in the abstract (aryl hydrocarbon) receptor. Introduction: The first 20 lines (2 paragraphs) should include references. The strucutre should be improved so that an introductory paragraph is presented before the subsequent subheadings. The review lacks in-depth of the presented literature. The references are overused for lenghty paragraphs. The subheading 'Flavonoids regulate the Ah-receptors', includes 12 lines cited by one reference. The literature presented in the last paragraph of the review does not comply with the preceeding subheading and does not confer evidence of inhibition of intestinal inflammation by flavonoids. The references are few for a review article. As mentioned at the end of

the conclusion, an original article clinical study design would be more appealing than a shortly presented incompletely informative review.

We thank the reviewer for his important comments and his expertise for the importance of nutritional therapies for IBD patients. We have now increased the text of the introduction and lined more references. Overall, we added more references as recommended by the reviewer. We deleted the last paragraph and tried to limit the use of references to a realistic state. We thank the reviewer for his valuable work.