

Dear Jin-Zhou Tang, Science Editor, Baishideng Publishing Group Inc,

Thank you for your mail dated 2020-02-12,

We revised our manuscript NO: 53226 titled "Gut microbiota and Nutrients interactions with skin in psoriasis: A comprehensive review of animal and human studies", submitted to World Journal of Gastroenterology that you offered acceptance for publication in the World Journal of Clinical Cases. According to the reviewer comments we provided a point to point response. We also highlighted the change in yellow according to the comments.

Thank you very much for your efforts in expediting the processing of our manuscript.

Sincerely,

Marco Fiore, MD

2020-02-16

ANSWERS TO REVIEWER COMMENTS

Reviewer 1

Major:

1. There are many grammatical and contextual errors. Initially, I felt the entire review should be rejected because it is difficult to understand. However, I have re-written most of it (attached) because I think there is value to what is being reported.

A: We are really grateful for the efforts that both Reviewer 1 put in re-writing the manuscript and we have addressed all his suggestions

2. This might be a good place to discuss exposome (shown in the figure). What environmental factors are there besides obesity and oxidant stress? Drugs, toxins, pollutants? Lifestyle, alcohol, psychological factors?

A: We thank the Reviewer for the suggestion, and we add a paragraph discussing the exposome and its effect on disease evolution and management.

3. Sentence beginning with Although

Authors need to strongly defend why they think the microbiota are important despite these 2 systematic reviews. Do these reviews refute reduced microbial diversity?

A: We agree with Reviewers concern and we further analyze our reference restating the whole paragraph as follows:

"Recently a systematic review, including 933 psoriatic arthritis (PsA) patient and 1611 controls, aimed to global evaluate the link between infections (viral and bacterial ones) and the risk of psoriatic arthritis finding a controversial results but evidencing a certain trend that fails to achieve a statistically significance[51]. However, differences exist between infection, colonization and dysbiosis, as suggested by several studies highlighting a different myco- and microbiome in psoriasis, psoriatic arthritis and controls [52]. In fact, a dysregulation in the ratio Firmicutes/Bacteroidetes was highlighted in gut microbiome of psoriatic patients, furthermore Actinobacteria was less present in the gut of psoriatic patients. The gut dysbiosis was found also related to a skin dysbiosis; since a decreased beta-diversity in psoriatic skin microbiome is related to an increased risk to develop psoriatic arthritis, skin flora starts to be regarded as a possible sensitive and specific biomarker to predict comorbidities in psoriatic patients."

Consequently, we do not refuse the hypothesis of reduced microbial diversity in psoriasis.

4. The last paragraph is redundant with the last sentence in section 6. There is limited, evolving information suggesting some benefit from fecal microbiota transplantation, not probiotics, although durability of response is a concern and under investigation.

A: We are really grateful for the suggestion; we have included references of the ongoing trial that try to address the issue.

5. Sentence: "Moreover, various antimicrobial peptides which regulate the cutaneous microbiome have been identified as autoantigens in psoriasis" is important. This should be mentioned early in this review.

A: We moved the sentence early in the introduction

Minor:

6. I do not understand the statement: "a very high correlation of dietary regimens or selected food components recommendation on the protection against cancer was documented among the general population."

A: We agree with Reviewer 1 and we rephrase the sentence as follows: Interestingly psoriatic patients displayed a higher risk of cancer compared to the general

population; furthermore, this increase is not fully explained by anti-psoriatic immunosuppressants therapies so several real-life or ecological studies have suggested an intimate relation with diet. This theory is supported by the evidence that different foods modify microRNA expression in psoriatic patients.

7. Last sentence Section 4: solenopsin analogs: What are these?

A: Solenopsin is a compound of fire ant venom, that chemically is similar to ceramides; his analogs, synthesized in laboratory demonstrated an anti-psoriatic effect by decreasing thickening and inflammation in a murine psoriatic model.

8. Table 1: there are several questions. Psoriasis risk factor (without s). Reduced vitamin D level. Reference 46: Increase of Akkermansia (or decrease)?

Many thanks for the suggestions: We deleted the s. We apologize but as we stated “reduced relative abundance” of Akkermansia in the text is correct, an error was reported in table 1.

9. reference 47. Which probiotic(s)? Two studies on probiotics are in Table. These should be discussed.

We completely agree with the reviewer, the name of the probiotic is now specified in the table and discussed in the text

10. I do not understand the sentence: The absence in the anamnesis of an infection could be attributed to the fact that even silent infections can act as triggers for autoimmune diseases.

A: We thank for the opportunity to further develop this important concept. We change the sentence as follow:

"Despite the medical history play a crucial role in the psoriasis management, it has some limitations such as recall bias. In particular, is already demonstrated that not all infections or even dysbiosis may be clinically evident but are still capable to trigger an immune/autoimmune response. "

11. First sentence, section 7. Authors should mention that the microbiome has been previously reviewed in 58.

A: We agree, and we insert the remind in the text.

12. Candia levels in gut microbiome? Levels? I don't understand. Candida is in the mycobiome.

A: We apologize for this mistake, we meant that the deep inter-relation between myco- and microbiome seem to act as a disease-modifier in psoriatic patients. Although it is well known that gut and skin microbiome deeply interact, scattering information are present for gut and skin mycobiome. Thus, we enlarged and explain the current promising evidence on the topic.

We changed the title of the paragraph adding also the myco-biome.

13. Last sentence: The transition from immune-targeted therapy to precision therapy will be based on the mix between biological signature, the endotype, and the specific interaction with the exposome. No additional sentence is needed

A: we completely agree and we canceled the sentence that was not necessary

Reviewer 2:

Minor comments:

1. There is no short (running) Title

A: Many thanks for the suggestion, we inserted the running Title

2. In "Introduction", the authors wrote "In addiction", instead of "In addition". Please correct.

A: We apologize for the error we have corrected properly

3. "Psoriasis, diet and circadian rhythm". There is nothing about circadian rhythm in this paragraph. There are mentions about vitamin D, but nothing about the rhythm

A: We thank the Reviewer for the suggestion, and we enrich the circadian rhythm with several studies real-life based and wet lab based.