Author’s response to reviews

Title: Anti-trichomonad activities of different compounds from foods, marine products, and medicinal plants: a review

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Reviewer #1: Please consider revising the article title something like below:
Anti-trichomonad potentials of different compounds from foods, marine products and medicinal plants: a review.

Response: Revised as follows: Anti-trichomonad activities of different compounds from foods, marine products and medicinal plants: a review.

Reviewed information is interesting, but it would be nice if some of the data regarding different compounds, source, remarks about its efficacy, related literature, etc. can also be presented in Table forms.

Response: Suggestions adopted. We added a new Table on page 5, line 65 that summarizes anti-trichomonad properties of 30 pure compounds described in the text.

Reviewer #2: The paper describes the Biological evaluation of food, marine, and medicinal plant compounds against trichomonad parasites. The findings can have some interest, however the manuscript require a minor grammatical editing.

1. How safe are the classes of food, marine, and medicinal plant extracts and their bioactive pure compounds with antitrichomonad activity in this review? The toxic effects of some of the agents described were not reviewed, therefore information on their toxicity should be included in the review.

Response: We added a new section on Safety/Toxicity on page 34.

Reviewer #3: The review contains much information and is in general valuable for publication. Nevertheless there are some problems:

Major problems:
- Arrangement of the long text
   In my opinion the differentiation between food, food compounds on one side and medicinal and herbal plants and their compounds on the other side is confusing. There are several overlaps. I recommend -plants, -plant derived compounds, -marine organisms and compounds, -fungal compounds. What means „herbal plants“?

Response: Because food compounds are considered to be safe, while the safety of some of the plant-derived compounds is not known, we prefer to retain the present arrangement of the text. We also believe that suggested rearrangement of the text will not improve the flow of the described information.

Maybe the chapter about vaginal dysbiosis can be canceled or shorten.

Response: We added a sentence to the Dysbiosis section that notes its significance to the theme of this manuscript. See page 4, lines 68-71.

- Methods of literature analysis should be shortly described (Which data bases? Which time period?) -Test methods for biological evaluation of anti-trichomoniasis activity should be shortly described.

Response: Suggestion adopted. We mention that we used the PubMed and Scopus databases. See page 3, line 33.

Plant families should be added in each case (family name not in italics). Latin plant names should be added in each case.

Response: This has been done in most cases.

It is not necessary to describe the method of substance isolation (424, 468).
Response: We believe that including the description of a typical laboratory method used to isolate an anti-trichomonad compound from a plant would be of interest to many readers.

Possible toxicity should be discussed. E.g. the named alkaloids from potatoes or tomatoes or from Amaryllidaeae are possible poisonous compounds. W\n
Response: Suggestions adopted. See new section on Safety/Toxicity on page 34.

90: Phukan, et al. –

All citations in the text follow the guidelines of the journal and require no change.
85: lactic acid is not a fatty acid – corrected.
92: Hinderfeld et al.- See above.
160: complete the sentence – corrected.
215, 250, 276: why some but not all compounds in bold?
Response: Deleted all bold fonts.

239: manuka honey is not an essential oil.

Response: The reviewer is correct. Moved manduka honey to a new section. See page 16, line 280.

256: gentamicin - corrected.
337: wagonin? The correct name is wogonin. - corrected.
365, 377: Lamiaceae (instead of Labiatae family) - corrected.
365: add mode of application of M. crispa. Suggestion adopted.
434: trophozoites - corrected.
448: that that - corrected.
454, 478, 497: Amaryllidaeae not in italics - corrected.
468: Vieira et al.- cited correctly.
563: cancel the word family- Suggestion adopted.
623: proteasome - corrected.

Reviewer #4: Friedman and colleagues carried out a review article on the bioactive effects of foods, marine products and medicinal plants, its derived extracts and even isolated compounds with anti-trichomonad effects. Although the title is attractive and interesting upon reading for readers of the BMC Complementary Medicine and Therapies, when reading the abstract and then the whole manuscript, unfortunately the authors failed in what they want to do. The main gap in this work is related to the lack of organization and definition of the research objective. In fact, the authors have a good intention in the work to be developed, but the lack of scrutiny and definition markedly compromise this work. First of all, the focus of this work is not on prebiotics or probiotics, although the presence of disbiosis is a trigger to this disorder. If this would be the objective, with the various existing studies, it would also be possible to elaborate a literature review in this regard. On the other hand, when analyzing the effects of foods and plants, their extracts and individual compounds, we must start from macro to micro, that is, from plants and
foods to their individual compounds and discuss the effects of the most promising plants for their individual constituents. In this regard in particular, the authors not only do not present all the plants studied, their extracts or individual compounds, neither selected all the published data. The organization of most of the information presented in this work in the form of tables is extremely important (since the first to the last section), so that readers can see which plants are more effective, which extraction solvent stood out in the observed bioactive effect (since the different solvents affect the extraction process and consequently the final bioactive effect), as well as at which dose was effective. Based on this premise, the authors must then organize their work starting on in vitro evidence, moving on to in vivo data and finally clinical evidence. None of this is observed in this work, and therefore it will have to be completely restructured before being considered again for review. Besides the above mentioned aspects, there are some major aspects to highlight:
- abstract should be completely rewritten and restructured.

Response: The Abstract follows the guideline of the BMC journal and correctly describes the nature of the problem being addressed and the importance of the results for animal and human health.

- research methodology was not provided, and all steps of research should be included in the form of a flowchart.

Response: Detailed description of research methodology is beyond the scope of this review. The interested reader can consult the cited literature.

- the authors confuse microbiota with microflora and microbiome. the terms must be properly used and revised throughout the manuscript

Response: We believe these terms are used correctly.

- once firstly used, abbreviations should be used (the same is applied to strains and species)

Response: Suggestion adopted.

- verbal tenses should be revised throughout the manuscript. The authors should define to use the present or past tenses

Response: We believe that the text has been clearly and succinctly presented. It underwent several reviews before submission.

- l. 129: flora microbiota? what this means?

Response: changed vaginal flora microbiota to microbiota of vaginal flora.

- l. 142-174: tomatine and other glycoalkaloids are toxic, and no mention was made in this work.

Response: This aspect is discussed in a new section on Safety/Toxicity on page 34.
- l. 217: MLC (full definition) – Suggestion adopted.

- l. 239-247: manual honey is not a plant essential oil –

Response: We moved the description of the anti-trichomonad properties of the kidney bean lectin to a new section on page 13, line 208 and of manduca honey to a new section on page 16, line 280.

- from this review article, it is impossible to observe what is the most effective plant, extract or even individual compounds (all data should be organized in the form of tables).

Response: The most effective compounds are those with the low IC50 values listed in Table 1 and discussed in the text.

- what is known on plant extracts and herbal plants in vivo? the authors jump from in vitro to clinical studies, without addressing in vivo findings.

Response: The active food formulations are considered to be safe. We repeatedly emphasize that safety considerations should be paramount in future in vivo animal and human studies. See section on Safety and Toxicity on page 34 as well as the Conclusions section.

Detailed discussion of in vivo effects of herbal and marine plants other than anti-trichomonad effects is beyond the scope of this review.

- in clinical trials, the individuals compounds present in extracts were not determined nor quantified?

Response: This seems to be the case. A major objective of this review is to summarize, collate, and interpret the widely scattered worldwide literature on anti-trichomonad activities and their mechanisms of action in order to motivate clinicians and veterinarians to explore further the potential of the described anti-trichomonad natural compounds for their potential to overcome the resistance of pathogenic protozoa to the currently used therapies.

- l. 384-393: plants and probiotics effects were mixed. this not makes sense/

Response: The cited data suggest that probiotics can enhance anti-trichomonad properties and reduce adverse effects of anti-trichomonad formulations in the vagina.

- l. 394 up to the end of the section "Plant compounds" there are no in vitro data?

Response: The compounds listed in this section all originate from plants.

- - in vitro, in vivo and clinical data are mixed and should be separately discussed.

Response: The limited clinical data on the anti-trichomonad effects of plant extracts in infected women are discussed separately on page 20, line 364. With one exception, the pure compounds
listed in Table1 have been evaluated in vitro cell assays. We suggest the need for further in vivo studies of the most active compounds.

- l. 593: photodynamic therapy makes no sense in this work and no previous introduction was made.

Response: We prefer to retain this section. It might motivate investigators and clinicians to compare efficacy of photodynamic therapy to potencies of some of the described bioactive compounds.

- l. 605-683: this information should be summarized in a table.

Response: Suggestion adopted. See new Table 1 on page 5 for a summary of 30 anti-trichomonad compounds discussed in the text

We thank the four reviewers for their constructive comments.

Sincerely,

Mendel Friedman