

Response to reviewer No. 02451558

Dear Mr./Mrs. Reviewer,

Thank you very much for your hard, attentive and thorough work conducted on our manuscript. Your comments and recommendations are very useful and make our paper much better. We tried to take all suggestions/corrections into consideration.

Comment

Abstract The emphasis is not obvious. Please revise it.

Response

We revised the abstract of our manuscript and added a sentence which emphasizes the main point of the work: “This article is aimed at summarizing and analyzing the literature data and basic achievements concerning diabetes mellitus type 1 treatment using medicinal mushrooms and showing the results obtained in our research.”

Comment

INTRODUCTION It is too verbose and can be reduced.

Response

We consider that the “INTRODUCTION” cannot be reduced due to an insufficient explanation of the reported problem, its treatment and scientific achievements in this case.

Comment

CONCLUSIONS They are too much and should be simplified.

Response

We revised our “CONCLUSIONS” and tried to make them shorter and simpler.

Response to reviewer No 00227633

Dear Mr./Mrs. Reviewer,

Thank you very much for your hard, attentive and thorough work conducted on this manuscript. Your comments and recommendations are very useful and make our paper much better. We tried to take all suggestions/corrections into consideration.

Comment

The title should be short and concise. According to recent studies that would favor future citations to the paper. What is really new in the review paper? The mushrooms on blood cells? The mushrooms on diabetes type I or type II or both? The mode of action of the mushrooms?

Response

Nowadays, according to trends in choosing the title for manuscript, you are completely right about that. But we, as authors, consider that the proposed title fully reflects the main theme of the article, and we decided not to change it based on the understanding of all associated risks. The review articles (in general) propose different views of different authors on the same problem to the readers (meaning that the authors focused on some very specific parts of the problem). In our case, we focused on the use of medicinal mushrooms, *Agaricus brasiliensis* and *Ganoderma lucidum*, on diabetes mellitus type 1 treatment. In order to be more precise, we tried to show what effects these mushrooms have on blood cells under the abovementioned disease. It should be noted that this kind of research and data are currently limited. Therefore, we can claim that it is new in this field. Also, the way these mushrooms are used is new. Most researchers use different extracts (e.g. water, ethanol extracts, etc.) in investigations, while we use the whole powder of submerged cultured mycelium.

Comment

Abstract should be also quantitative as possible for rapid comparison with others studies, referring also to amounts used or concentration and the effects quantified as possible. Although the abs should be the mirror of the paper, after reading the paper it that some data is missing. Some methodological specifications are not needed at this stage.

Response

In our opinion, it is not appropriate to give quantitative data in the abstract because it is an abstract to a review and not to an original article. Moreover, numerous meanings of all results will make the abstract bulky, too verbose, and less focused. All quantitative data you can find in relevant sections of the manuscript. The same is true with describing amounts or concentrations used in the research: if we add this information, the abstract will become too large (exceeding the number of words permitted). We think that we concisely described the main problem, provided solutions to the problem, and the obtained results in the abstract.

Comment

The paper includes about 10% (13) of recent references from the last 5 years (since 2012, but it should be clearly higher). Besides, references from 2016 are absent!

Response

We revised the manuscript and added new references from the last year.

Comment

The introduction should clearly state why these review is interesting and timely, and what is the wider relevance or impact of this work? All the points 1 to 4 would in the paper even more sound and solid.

Response

We looked through the introduction section and wrote a summarizing sentence about importance and relevance of our review.

Comment

Please avoid the sentence like “Obtained results showed significant growth of body weight of control rats to the end of the experiment while body weight of diabetic animals significantly decreased”. But how much?? two-fold? 2%.? If it is no significant, statistically no need to be mention, but if it increases the information about how much was the increase is relevant for comparison with others studies. In that case, the mode of administrations, time upon exposition and the amount/concentration and the model should, among others methodological aspects, should be indicate for instance in a Table or Tables. The description of several studies in random and such as phenomenological type of written induces a diffusion of the final message of the paper. Therefore, tables are needed to summarize the studies so far performed.

Response

We revised the abovementioned sentence and added quantitative data.

Comment

Also avoided sentences that are paragraphs such as “To quantify the content of apoptotic cells, the apoptotic index was calculated, i.e., the ratio between cells with morphological apoptotic features and the general quantity of cells”. Please add figures at several parts of the review in order to illustrates the message of the paper, if these results ad figures are worthy for the authors and include in the legend of the figures the relevant methodology information.

Response

We checked and rewrote that paragraph. It was just a misprint. We took into consideration your advice and added figures to visualize the obtained results and to illustrate the message of the manuscript.

Comment

7) Several sections must be divided in sub-section and with a message for each to avoid misunderstandings', such sentences like: "Besides the abovementioned glucans, *A. brasiliensis* also contains low-molecular weight compounds such as tocopherol, ergosterol, phenols, etc.[114] and metal ions (e.g., copper, zinc, etc.)[89,115] that can inhibit formation of free radicals and the development of oxidative stress due to their scavenger properties". First, what are the amounts of the metals in these samples, micro, nano g per g? The amounts are important once "sola dosis facit venenum", according to Paracelsus, there is nothing without poison. That should be discussed and referred in the paper, once we are talking about mushrooms and metals. Secondly, would not be better to separate and discussed in this section organic from inorganic compounds? Besides, phenols could also be toxic and the references from 2016 should be including about these topics.

8) But Zn is different from Cu. Is it not copper inducing Fenton reactions? It is not a contradiction that "can inhibit formation of free radicals and the development of oxidative stress due to their scavenger properties"? It is known that although they are both transition metals, Zn as an non-redox chemistry, and they have different metallomics. Please insert a recent reference about the biochemistry and medicinal applications and diseases associated with these metals.

Response

Comments "7" and "8" are related and that is why we give one response for both comments. First of all, we want to thank you one more time for such amazing and thorough work concerning our manuscript. Now, we will answer your questions. First, concerning the amounts of metal ions, the amounts were presented in mg per kg of dry weight. To avoid contradicting statements in our paper, we rewrote the abovementioned sentence ("Besides the abovementioned glucans, *A. brasiliensis* also contains low-molecular weight compounds such as tocopherol, ergosterol, phenols, etc.[114] and metal ions (e.g., copper, zinc, etc.)[89,115] that can inhibit the formation of free radicals and the development of oxidative stress due to their scavenger properties") and deleted information about which exact metal ions were detected in the studied mushroom. We did this because your revision and comments presented us with a new idea. In this paper, we wanted to show the effects of medicinal mushroom treatment on blood cells under condition of diabetes in general. We wanted to show what had already done and what we did. Our manuscript is already big. If we include what you suggest in the paper, it will make it even longer and too verbose. So, we

made a decision to write another paper where in details will describe the effects of mushrooms caused by their organic and inorganic compounds. And a separate section in a future paper will be devoted to metal ions and their impact on living systems, medical applications, etc.

Comment

What was the dosis of STZ used?

Response

In our research diabetes mellitus was induced by a single intraperitoneal injection of streptozotocin in a dosage of 50 mg/kg of body weight dissolved in 10 mM citrate buffer (pH 5.5). Blood glucose concentrations were measured within 72 hours and for 14 days after the induction of diabetes. The animals used in the experiment had glucose levels exceeding 14 mM.

Responses to reviewer No 00227350

Dear Mr./Mrs. Reviewer,

Thank you very much for your hard, attentive and thorough work on our manuscript. Your comments and recommendations are very useful and helped make our paper much better. We tried to take all suggestions/corrections into consideration.

Comment

It is a good work and authors would have discussed with some results Unnecessary references can be deleted.

Response

We revised the manuscript and deleted unnecessary references.