

Reply to reviewers

REVIEWER 1 Number ID 02860897

Aloe vera is a food ingredient that has been used all over the world for a long time. Aloe vera is an attractive substance and many researchers have already paid attention to the action of Aloe vera. Result of your study is interesting, however, further study is needed.

1. Aloe vera contains many ingredients. First, it is necessary to clarify which ingredient is effective. In previous report, Japanese group reported that aloe derived phytosterols could reduce visceral fat accumulation and would be useful for the improvement of hyperlipidemia and hyperglycemia.

Answer: We used aloe vera crude extract in this study. As a result, we could not pinpoint the actual active ingredient of aloe vera that might have therapeutic effects against NASH. However, previous studies suggested that phytosterols might be the substances of interest. We have added this information and references in the Discussion, page 13, line 10-20.

2. It is necessary to clarify the cause of weight loss. Did the rats in the weight loss group have sufficient food intake?

Answer: We did not measure the total caloric intake of rats in each group; therefore, we could not say with absolute certainty that rats in HFHFD diet received the equal amount of calories compared to control rats.

This was added in the Discussion, page 16, line 14-16

3. Also, it is necessary to compare blood lipoproteins in each group.

Answer: We acknowledged our limitations. Unfortunately, we did not have spare samples to perform further analyses and would keep this in mind for future studies.

REVIEWER 2 Number ID 03475479

Authors evaluated the therapeutic effect of aloe vera using NASH rat model. This report was interesting, but several issues should be addressed.

1. In present model, liver fibrosis was not found. Furthermore body weight decrease was found, inconsistent with human NASH. Thus present model was quite different from that of human. Authors should aware these situation and discuss about it.

Answer: We have added the following statement in the Discussion, page 16, line 18-21

“Rats with NASH in our model were slim, which differed from the usual NASH phenotype in human. Our findings might be useful in the understanding of “lean” NASH in human but translating our results to the “obese” NASH should be done with caution.”

2. In aloe vera treatment group, fat deposition was not found. Authors should consider the amount of food intake.

Answer: we did not measure the total caloric intake of rats in each group; therefore, we could not say with absolute certainty that rats in HFHFD diet received the equal amount of calories compared to control rats.

This was added in the Discussion, page 16, line 14-16

3. In present experiment, authors administered aloe vera along with HFHFD. Authors should evaluate the therapeutic effect of aloe vera after NASH development.

Answer: We have added the following statement in the Discussion, page 16, line 21-23

“Aloe vera and HFHFD were administered simultaneously making our study represent more of a prevention model than treatment model. Further studies are warranted to confirm the therapeutic effects of aloe vera.”

4. The target or action of aloe vera was unclear. Authors should evaluate the effect of aloe vera also in vitro models using hepatocytes or macrophages cell lines.

Answer: We have added the following statement in the Discussion, page 17, line 1-3

“We evaluated the gross effects of aloe vera on NASH development in this study. Additional in vitro studies would be needed to determine cellular and subcellular targets of aloe vera.”

REVIEWER 3 Number ID 02861303

The article makes a good impression. First of all, the high methodological level, which allows to obtain modern and original results, draws attention. There is a small comment on the discussion section. The article, in its essence, is an original study. In this regard, in the "discussion" section it is advisable to justify the novelty of the study. The lecture character of the discussion is acceptable for reviews, but not for original articles. In the list of references, it is desirable to increase the share of works published over the past 5 years. In general, after a small adjustment, the article deserves publication in the World Journal of Hepatology.

Answers: Thank you for your comments. We have added the following statements in our revised manuscript.

To justify the novelty of this study, we added “To the best of our knowledge, this was a first study to evaluate the effects of aloe vera on NASH development in an animal model.” in the Introduction, page 6, line 7-9

According to Pubmed search, the latest study we found on aloe vera treatment in fatty liver was from 2012. We could not find any more recent studies specifically on aloe vera and NASH. We have added this as reference number 15.