

Reviewer #1: The manuscript written by Yang W-N et al. describes the SNP analysis of HLA for the understanding of genetic predisposition of Polygonum multiflorum-induced liver injury. The study is well performed and the manuscript is well written. Since prediction of susceptibility to a drug that could cause liver injury for each people is important, this kind of analysis is valuable. In addition, this kind of approach could be available for other drugs that are reported to be a cause of liver injury.

Answer: We are grateful for your kindly review.

Reviewer #2: This is a generally competent study. I have the following major and minor comments for the authors to consider. Specific comments: 1. Please change "herbal-induced liver injury" to "herb-induced liver injury (HILI)". 2. In the introduction, authors should also mention some salient clinical aspects of DILI, e.g. the diagnosis of DILI can be difficult to make as it relies largely on the exclusion of other potential causes and it requires a high index of suspicion as patients are often asymptomatic (citation: ncbi.nlm.nih.gov/pubmed/31749902). 3. Please change "To promote the clinical application of PM" to "To improve the safe use of PM". 4. Please provide the actual institutional review board (IRB) study/approval number. 5. Was the study protocol prospectively registered? 6. How was sample size determined? There is currently no evidence of power calculation. 7. Scientific names such as "Radix Bupleuri" and "Malaytea Scurfpea" should be italicized and written according to binomial nomenclature. 8. Please define the abbreviations "ALT, AST and Tbil" in the first instance of their use. 9. "Few studies have compared clinical differences between PM-DILI and other-DILI." In general, it is thought that the clinical manifestations of herb-induced liver injury (HILI) are identical to those of drug-induced liver injury (DILI) (citation: ncbi.nlm.nih.gov/pmc/articles/PMC6027193). 10. Please change "Limitation occurs that the sample size is small" to "Limitations include the small sample size". There are also other limitations the authors have failed to mention.

Answer: Thanks very much for your kindly suggestions. We have made some revisions to our manuscript according to your suggestion.

1. We have changed "herbal-induced liver injury" to "herb-induced liver injury (HILI)".
2. We have mentioned the provided clinical aspects of DILI in the introduction in the revised manuscript.
3. We have changed "To promote the clinical application of PM" to "To improve the safe use of PM".
4. The approval number is 2015[892], which is provided in the revised manuscript.
5. The study protocol was not prospectively registered.
6. We didn't calculate the sample size. Because at the time we began the study, none the incidence of PM-DILI or the rs1055348 associated PM-DILI was reported, which is essential for sample size calculation.
7. "Radix Bupleuri" and "Malaytea Scurfpea" have been be italicized and written according to binomial nomenclature.
8. Abbreviations "ALT, AST and Tbil" have been defined in the first instance of their use.

9. Thank you for the recommendation. We have made revision in the manuscript.

10. We have changed "Limitation occurs that the sample size is small" to "Limitations include the small sample size" and mentioned another limitation.

Reviewer #3: To investigate the association between single-nucleotide polymorphisms (SNPs) and polygonum multiflorum-induced liver injury (PM-DILI), the authors studied SNPs in 73 PM-DILI patients, 118 other drug-induced liver injury (other-DILI) patients and 191 healthy controls and concluded that rs1055348, which could be a tag for HLA-B*35:01, was specific for PM-DILI. The authors' conclusion is not novel because it is same as the previous paper (ref. 15). Furthermore their study did not include validation cohort. However, this study is interesting in that they showed that rs1055348 SNP could be a tag for HLA-B*35:01. I have several questions to the authors. 1. How did the authors recruit DILI patients? Please describe more details on the recruitment criteria. 2. Please describe the background of DILI patients. How long were the patients taking PM? Did they take other medicine? 3. When analysis is limit to the patients taking single PM, how is the association with rs1055348? 4. Are there any differences in background variables including ALT and TBil between PM-DILI patients with rs1055348 major and those with rs1055348 minor?

Answer: Thanks very much for your kindly suggestions. We have made some revisions to our manuscript according to your suggestion

1. The recruitment criteria were supplemented in the "Participants" section of the revised manuscript.

2. The medication time of PM and other drugs were provided in Table 2. In the PM-DILI group, patients didn't take other medicines. Patients who took both other drugs and single PM or PM preparation were excluded. And this was declared in the "Participants" section of the revised manuscript.

3. As almost all herbs are used as preparation, it is difficult to recruit patients taking single PM. The previous paper (ref. 15) has well clarified the association between *HLA-B*35:01* and PM-DILI, however not all patients in this study took single PM. In the current study, to ensure the correct diagnosis of PM-DILI, patients taking other drugs were excluded and the causality of PM were evaluated by a panel of two hepatologists. 10 of 11 (90.91%) PM-DILI patients who were caused by single PM and 4 of 4 (100%) PM-DILI patients who were rechallenged by PM preparations carried rs1055348, the results could strengthen the association with rs1055348. The results were provided in the "Association between SNPs and PM-DILI" section of the revised manuscript. Yet, the analysis is limit to the patients taking single PM, we have mentioned this limitation in the revised manuscript.

4. We compared the background biochemical characters between patients with rs1055348 and those without rs1055348 and some differences were found. The results were provided in Table 5 and related discussion were provided in the revised manuscript.

Reviewer #4: Authors are kindly requested to clearly state that not only Polygonum multiflorum is one of the leading causes of herbal-induced liver injury, but also another natural substance

is a major cause of DILI, as clearly demonstrated by previous research, such asDrug-induced liver injury due to "natural products" used for weight loss: A case report. ... WJG, 2009.

Answer: Thanks very much for your kindly suggestion. We have mentioned this opinion in the introduction section of the revised manuscript.

According to editor's work and kindly suggestions. We have made the following revision to the manuscript.

1. Decomposable figure of all the figures is provided and named as "Manuscript No.53091-image files.ppt".
2. The manuscript have been prepared with Word-processing Software, using 12 pt Book Antiqua font and 1.5 line spacing with ample margins except Table 3 and Table 5 which are too big for one page.
3. We think the running title "SNPs and Polygonum multiflorum-induced liver injury" is more suitable for the manuscript but have too many words. Finally, we chose "Polygonum multiflorum-induced liver injury" as the running title.
4. Author contributions have been revised according to the provided format.
5. The grant application form(s) or certificate of funding agency for each grant have been provided and named as "Manuscript No.53091-grant".
6. Abbreviations and acronyms are defined the first time they are used within the abstract, core tip, main text, and the figure/table legends.
7. Spaces before cited references number have been deleted.
8. References have been revised according to your suggestion.
9. ARTICLE HIGHLIGHTS have been supplemented.
10. Because of the order of occurrence, we interchange the order of tables 4 and 5.

Sincerely,

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