Author's response to reviews

Title: Characterization of Hypersensitivity Reactions Reported among Andrographis paniculata Users in Thailand Using Health Product Vigilance Center (HPVC) Database

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Characterization of Hypersensitivity Reactions Reported among *Andrographis paniculata* Users in Thailand Using Health Product Vigilance Center (HPVC) Database

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Dear Academic Editor,

We would like to sincerely thank you for your response and reviewers comments, and the opportunity to revise our manuscript entitled “Characterization of Hypersensitivity Reactions Reported among *Andrographis paniculata* Users in Thailand Using Health Product Vigilance Center (HPVC) Database”.

We have made revisions in response to the insightful reviewers’ comments. On the next several pages, we provide point-by-point responses to three Reviewers’ comments and extra revisions and indicated where in the manuscript that we have made the changes.

We have no financial and non-financial conflicts of interest. All authors have contribution met criteria for authorship. We attest that this work is original and has not been published and is not being considered for publication elsewhere. Please feel free to contact me with additional questions or concerns.

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Yours sincerely,

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Response to Reviews’ comments of the manuscript entitled

“Characterization of Hypersensitivity Reactions Reported among *Andrographis paniculata* Users in Thailand Using Health Product Vigilance Center (HPVC) Database”

Reviewer #1 Samantha Coulson

Minor Revisions

Comment #1:
1. Tables 1 and 3. N/A is indicated to mean 'not applicable'. This is incorrect and should be corrected to mean 'not available'
   
   **Response #1**
   We have changed according to reviewer’s comment.

Comment #2
2. English grammar requires serious attention with numerous editorial corrections required before publication.
   
   **Response #2**
   We have carefully edited throughout the manuscript.

Comment #3
Discretionary revisions
1. Background:
   a) Lack of sufficient background information on the use of Andrographis for example where it is grown, dose recommendation, parts of plant used, lack of standardization of herbal products and potential risk of product contamination etc that may provide a basis for potential adverse events.
   
   **Response #3**
   We agreed with reviewer and revised the paragraph to state about these issues as the following in background part.
Original version

Andrographis paniculata (andrographis) is one of the herbal products that have been widely used for a variety of medical purposes, especially those related to respiratory tract infections.

Revised version

Andrographis paniculata (andrographis) is one of the herbal products that have been widely used for a variety of medical purposes. It is widely found and cultivated in tropical and subtropical Asia, South-East Asia, and India. The leaf part has been used traditionally to treat fever, and infection especially those related to respiratory tract infections.

The issues about lack of standardization and product contamination were stated in discussion part (see response comment #13)

Comment #4
b) Page 3, authors state that even though andrographis is often perceived as safe with minor side effects, it should still have a warning. Please clarify, is the herb safe according to previous clinical research, or only perceived to be safe, i.e. it is not scientifically proven to be safe? Stating that interpretation of safety data from clinical studies should be viewed with caution due to lack of rigorous data collection on adverse events is presumptuous and indicates that serious adverse events are not being reported by researchers if they are occurring.

Response #4
We agreed with the reviewer that safety data from clinical study should be interpreted with caution. In this context, we just only stated in general that herbal medicine is perceived to be safe.

Comment #5
c) Authors state on page 3 that under the intense monitoring program that patients during 2001-2003 and between 2007-2009 reported adverse events with andrographis. Was there no surveillance or reporting during the years between 2004-2006?

Response #5
We have no data between years 2004-2006 since the intensive monitoring programmes were conducted as a project as part of NLEM initiative. The NLEM was revised
in year 1999 and 2006. Thus, the surveillance of the herbal medicine was done by spontaneous reporting system only during the period of years 2004-2006.

Comment #6
d) Authors state on page 3 that adverse events associated with andrographis included rash, pruritus, breath discomfort, cough, peeling skin, fatigue, nausea, gastric discomfort, anorexia, headache, palpitations. If Andrographis is recommended for conditions associated with diarrhoea, pharyngotonsilitis and the common cold – a number of these ‘adverse events’ could be a representation of the condition they are suffering. It should be outlined by the authors that direct causation has not been substantiated and other contributing factors could be playing a role in adverse events being reported.

Response #6
We followed the reviewer comment by inserting the following sentence in introduction part.

"It should be noted that direct causation has not been substantiated and other contributing factors could be playing a role in adverse events being reported."

Original version
Under this intensive monitoring programme, 1,873 patients using andrographis oral containing products (199 during 2001-2003, and 1,674 during 2007-2009) were reported that andrographis could possibly cause various adverse events such as rash, pruritus, breath discomfort, cough, peeling skin, fatigue, nausea, gastric discomfort, anorexia, headache and palpitation [6, 7]. After this period, the HPVC has continued monitoring the safety of this product through spontaneous reporting system.

Revised version
Under this intensive monitoring programme, 1,873 patients using andrographis oral containing products (199 during 2001-2003, and 1,674 during 2007-2009) were reported that andrographis could possibly cause various adverse events such as rash, pruritus, breath discomfort, cough, peeling skin, fatigue, nausea, gastric discomfort, anorexia, headache and palpitation [6, 7]. It should be noted that direct causation has not been substantiated and other contributing factors could be playing a role in adverse events being reported. After this period, the HPVC has continued monitoring the safety of this product through spontaneous reporting system.
Comment #7
e) On page 4 authors refer to two other surveillance studies based on the ThaiVigibase but fail to expand what was found, in particular that Curcuma longa was associated with 43.8% of adverse events reported between 2000-2008 while andrographis was only associated with 10.1% of reports.

Response #7
Thanks for your comments. We realize that we did not provide details of the two studies. However, the goal of citing these 2 studies was just to mention that only a few studies have used ThaiVigibase. This means that ThaiVigibase deserves to be further explored and it could be used to look at the issue of hypersensitivity reactions reports among subjects using andrographis containing products. To make our sentence clear and simple, we decided to shorten the sentence as follow in introduction part.

Original version
Until now, only two surveillance published studies [14, 15] were conducted based on Thai Vigibase as important sources of the surveillance system.

Revised version
Until now, there have been only two published studies [14, 15] using Thai Vigibase.

Comment #8
2. Results:
a) It would add to the interpretation of the data to report the condition(s) each patient was suffering from that initiated the use of andrographis.

Response #8
We agree with the reviewer that having the information of underlying condition of each patient would provide a better interpretation of the data. However, clinical conditions were available in only some subjects. Due to the paucity of data, we cannot provide complete information to the audience.

Comment #9
b) Table 3. It is unclear the dose each patient took before reporting symptoms of anaphylactic shock/reaction. For example, case No 7 states the dosage of 350mg QID but the reaction onset was 45 min. Was this reaction after the first, second, third or fourth dose? This is the same for case No 9, was the onset 5 min after the first, second or third dose?
Case No 12 is missing data of dosage and onset – would this infer that the patient was vague in their description or was it simply not included in the report.

Response #9

Thanks for pointing out the issue of the lack of clarity on the temporal relationship. We should have specified clearly that all patients took andrographis product before reporting symptoms of anaphylactic shock/reaction. The dose specified was the dose that patients have been prescribed but it was not necessary the dose that patients have been actually taken. For example, case No 7 states the dosage of 350 mg QID but the reaction onset was 45 min. This means that patient has a reaction right after the 1st dose.

Based on the comment above, we decided to improve clarity by removing the dose that patients have not taken. For example, we changed the dosage of 350 mg QID to 350 mg PO, 1 time used for case no. 7. Likewise, it was for case no. 9, we specified the dosage as “2 cap PO, 1 time used” rather than “2 cap PO, TID”

Comment #10

c) Page 7 the authors state that in 7 reports the name of the product was given. Was there a product brand reported more frequently that could be associated with adverse events? Assessing if a certain product was reported more frequently in the 106 cases was providing valuable information.

Response #10

A total of 6 brands were reported among the 7 case reports. This does not lead to a specific direction of certain brand to be associated with the adverse event. We decided to make this clear to the audience. As a result, we have revised as the following in results part.

Original version
Of 13 case reports, 7 case reports indicated the product’s brand name.

Revised version
Of 13 case reports, 7 case reports indicated the product’s brand name. Most importantly, 6 brands were reported among the 7 case reports.
Comment #11
3. Discussion:
a) Authors state that ‘our findings indicated that the oral use of andrographis may be associated with an increased risk of acute hypersensitivity reactions’. But, the authors did not look at or compare hypersensitivity reactions in the database which were associated with pharmaceutical drugs, insect bites and food reactions. So is it an ‘increased risk’ compared to normal every day reports of hypersensitivity or compared to other medications? If 13 case reports with serious hypersensitivity were identified from 2001 – 2012, this is an average of 1 report per year and further these reports do not all provide a definitive causal relationship between the adverse event and andrographis. The term ‘increased risk’ should be amended to just ‘risk’.

Response #11
We agreed with reviewer by changing the term “increased risk” to “risk”.

Comment #12
b) The authors provided a study example using HIV patients compared to healthy controls to indicate that andrographis has serious adverse events is a poor choice. The authors indicate that it was only the HIV patients that presented adverse events, not the healthy controls. Further, it was not mentioned that the dose used in this study were 6 to 10 times higher than that used in other studies. Adverse events would be expected in such circumstances.

Response #12
Thanks for the comment. This makes us realize that we may not convey a message clearly enough. We agree that the audience may misinterpret the findings from the study we have cited. Based on the comment above, we decided to improve clarity by stating the point we wanted to emphasize clearly by the following in discussion part.

Original version
Since andrographis had long been used and perceived as safe traditional medicines particularly in Southeast Asia, e.g. India, Thailand; there have been limited reports about adverse events associated with andrographis. As a result, the information on mechanism of hypersensitivity reaction due to andrographis used is lacking. One study [18] in 13 HIV positive patients and 5 uninfected health-volunteer aimed to assess safety and tolerability of andrographis use. This study was designed to cover a 9-week period at escalating dosages. The study was interrupted after 6 weeks due to a number of treatment-related adverse events. Among HIV patients, all patients were reported at least one adverse event during the
course of trial. Most events occurred during weeks 2 and 3 of trial. Of those, one HIV patient experienced an anaphylactic reaction during week 4 and stopped medication. However, there was no mention on the mechanism of such hypersensitivity reaction.

**Revised version**

Even though andrographis had long been used as traditional medicines particularly in Southeast Asia, e.g. India, Thailand, there has been limited report about hypersensitivity reaction associated with andrographis. To the best of our search, there was only one study [18] reporting a case of anaphylactic reaction among an HIV patient. This study was conducted in 13 HIV positive patients and 5 uninfected health-volunteer to evaluate adverse events of escalating dosages. At the elevated dose of andrographis (6-12 times higher than usual dose), a case of HIV patient experienced an anaphylactic reaction during week 4 and stopped medication. It is not uncommon to expect such adverse event when any particular product is given in such circumstance. It was important to note that there was no mention on the mechanism of such hypersensitivity reaction.

**Comment #13**

c) The authors have failed to recognise contamination and lack of standardization of herbal products that could lead to adverse events with certain products. This should be considered and discussed.

**Response #13**

We followed the reviewer comment by inserting the following sentence in the discussion part.

**Original version**

An important limitation of current evidence is the lack of direct causation. Even though the evidence presented in this article is substantiated with a large number of case reports, there remains no direct causation study that can make such a conclusive remark.

**Revised version**

An important limitation of current evidence is the lack of direct causation. Our study cannot eliminate a possibility that hypersensitivity reaction might be related to product contamination and its lack of standardization across brands. Even though the evidence presented in this article is substantiated with a large number of case reports submitted from
various settings with differing brand products, there remains no direct causation study that can make such a conclusive remark.

Comment #14
Overall, the paper requires more in-depth discussion and expansion of points that have been briefly made and should have less bias made towards a definitive cause by Andrographis for the adverse events reported.

Response #14
We agreed with the reviewer and already discussed about such issues as comment #11, #12, # 13.
Reviewer #2 Matthew Bambling

Comment #15

Minor Essential Revisions

Page 1: results summary section is a little unclear. The authors state that only 106 case reports contained andrographis herbal product as suspected drug and reported at least one hypersensitivity reaction. The authors then go on to talk about a variety of hypersensitivity reactions greater than one. Need to clarify meaning here it looks contradictory at first reading.

Response #15

Thanks for the comment. It was true that we stated that a total of 106 case reports specified andrographis herbal product as the only suspected drug and reported at least one hypersensitivity reaction. Please note that each case must report at least one term consistent with the constellation of hypersensitivity reaction e.g. angioedema, anaphylactic reaction. Therefore, it is possible that there might be more than 1 term described in each case. To make sure that we convey our message clearly, we have changed in a number of places.

Original version

Abstract

A total of 248 case reports of andrographis-associated adverse events were identified. Only 106 case reports contained andrographis herbal product as suspected drug and reported at least one hypersensitivity reaction

Revised version

Abstract

A total of 248 case reports of andrographis-associated adverse events were identified. Only 106 case reports specified andrographis herbal product as the only suspected drug and reported at least one term consistent with constellation of hypersensitivity reactions
Comment #16
Page 4: I am not sure I would call this a descriptive study; it may be more accurately described as a retrospective database study. The term retrospective is introduced in a later paragraph and should be adopted for the sake of accuracy and consistency.

Response #16
We agreed with the reviewer by changing the study design from ‘descriptive study’ to ‘retrospective database study’.

Comment #17
Page 4:
Part of paragraph provided below, does not fit the Methods-data source heading and would be better placed in the preceding background information as it provides the context...... the text not include below is fine for the first part of the methods-data section

Intensive monitoring programmes were undertaken to promote the reporting of adverse events associated with herbal product use. After a total of five single herbal products were included in the Thai NLEM in 1999, a 2-year intensive monitoring programme of these products was launched in the year 2000. In addition, an intensive monitoring programme was initiated by the Department for Development of Thai Traditional and Alternative Medicine (which is responsible for promoting the use of herbal products in Thailand). This programme focused on four single herbal products (Cissus quadrangularis [Veld grape], Centella asiatica [Pennywort], Derris scandens [Jewel vine], Momordica charantia [Bittermelon]) that were under consideration for inclusion in the NLEM. Data collected under this programme will be crucial information used for considering whether these products are to be listed in NLEM. Since this is an aggregate analysis of spontaneous reports of adverse events submitted to HPVC; there is minimal risk of patient confidentiality breaching. As we did not obtain the consent, we present specific cases with only general demographic characteristics to ensure patient identity anonymous.

Response #17
We agreed with the reviewer and moved this paragraph into the introduction part.
Comment #18
Page 5: Criteria for the selection of cases-Reports with andrographis being the only suspected cause were selected. Well worth including that only andrographis only product cases where chosen as this is a good control.

Discretionary Revisions for clarity of content and structure of paper.
The inclusion criteria should give some attention to usage of product, i.e. no restriction on length of time using the product and dosage was applied to cases. Adverse reports indicated reactions ranging from single doses to XXXX time of use.

Response #18
We did not specify the usage as part of inclusion criteria. The reason is that we want to see all type of usage without any restriction of time/ dose/ products. That's why it was not specified as inclusion criteria.

Comment #19
Page 6: again I am not clear about the at least one hypersensitive report, when there are clearly more than one discussed in the data.

Response #19
We changed the sentence as below in results part.

Original version
A total of 197 case reports of adverse events associated with Andrographis paniculata containing products were retrieved. In all reports, the herbal product was taken by mouth and was sole suspected drug in 170 case reports. At least one hypersensitivity reactions were reported in 106 case reports (Figure 1).

Revised version
A total of 197 case reports of adverse events associated with Andrographis paniculata containing products were retrieved. In all reports, the herbal product was taken by mouth and was sole suspected drug in 170 case reports. A total of 106 cases reported term (s) consistent with constellation of hypersensitivity reactions (Figure 1).
Comment #20
Page 7: first paragraph Discussion section. The authors contradict themselves by saying that they have established a link and then say they haven’t made a direct causal link, which I agree with.

Response #20
We agreed with the reviewer. Thanks for your comment. We demonstrated that the oral use of andrographis may be associated with a risk of acute hypersensitivity reactions and ended that it was not possible to draw a direct causal relation from this study. We think that we try our best to make a conclusion based on the evidence we have in hands. Thanks.

Comment #21
Bottom of page 7: while I agree that the findings are unlikely to be spurious, I am not sure that one can conclude the andrographis was the cause in all cases. We cannot conclude that. In this type of report databases there may well be false positives, in that patients may have been taking other products or medications in addition to andrographis and not necessarily nominated to the person making the report. It’s true however, andro is the only suspected thing as they don’t take anything else. I suspect this is nearly impossible to control for in the data and it may be more reasonable to conclude that andrographis was associated with hypersensitive reactions and was the likely cause for the majority of cases.

Response #21
We agreed with the reviewer that the sentence “This cumulative evidence suggests that it is very unlikely for this potential association to be a spurious one” is too strong conclusion. So, we revised as per reviewer’s suggestion as the following in discussion part.

Original version
This cumulative evidence suggests that it is very unlikely for this potential association to be a spurious one.

Revised version
This cumulative evidence suggested that andrographis was potentially associated with hypersensitive reactions as it was the likely cause for the majority of cases.
Comment #22
Page 8: the authors state that andrographis containing product was the single agent. If by this they mean they only included case reports where andrographis only products were used, this is an important control and needs to be mentioned in the study design section as it adds strength to their findings. It is our strength of course.
Middle page 8: The issue of this unexpected serious adverse event associated with andrographis has been brought up during Signal Detection and Assessment Working Group and Drug Safety (pharmacovigilance) subcommittee under ThaiFDA. What are the authors referring to here, it is not clear regarding what or why this is being mentioned?

Response #22
We agreed with the reviewer and revised it as the following in discussion part.

Original version
The issue of this unexpected serious adverse event associated with andrographis has been brought up during Signal Detection and Assessment Working Group and Drug Safety (pharmacovigilance) subcommittee under Thai FDA. The decision was that no changes were made on product labelling since the direct relationship could not be confirmed. The recommendation was that the findings be disseminated through HPVC (Health Products Vigilance Center) safety news for health care professionals in a number of facilities including community pharmacy. In addition, a pharmacoepidemiology study has been proposed to determine the association between hypersensitivity reactions and andrographis containing products can be confirmed.

Revised version
The issue of reporting of hypersensitivity reactions among andrographis users has caught attention of Thai FDA. The Signal Detection and Assessment Working Group and Drug Safety (pharmacovigilance) subcommittee under Thai FDA decided to make no changes on product labelling because the causation could not be confirmed. The report of potential association was disseminated through HPVC (Health Products Vigilance Center) safety news. In addition, Thai FDA recommends a pharmacoepidemiology study to determine whether the association between hypersensitivity reactions and andrographis containing products is confirmed.
Comment #23
Once again any proposed pharmacoepidemiology study to examine the association between hypersensitivity reactions and andrographis containing products can be complex as other ingredient in formulas my complicate findings. This should be mentioned and the authors approach seems a better way forward here. I think the authors can conclude that retrospective studies are not designed to identify evidence of direct causation or mechanism of hypersensitivity, however, the data supports an association between andrographis and risk of hypersensitivity for modest number of individuals.

Response #23
This retrospective database study is not designed to identify evidence of direct causation or mechanism of hypersensitivity; however, the data supports an association between andrographis and risk of hypersensitivity for modest number of individuals.
Reviewer #3 AvniSali

Comment #24
Discretionary Revisions
1 The major weakness in this study is that it is retrospective but collecting this kind of data is extremely difficult to do prospectively.

Response #24
We totally agreed with reviewer that it’s extremely difficult to do prospectively. Despite the weakness in terms of incompleteness of data which is a nature of ‘retrospective database study’, we believe that it’s the most appropriate approach for this kind of situation.

Comment #25
2 It would have been interesting to know if those that did have reactions had been on antibiotics recently or if they consumed any type of probiotic. The microbiome can have a major influence on immune function which in turn could play an important role in hypersensitivity.

Response #25
Off 13 cases, there was no information on antibiotics or probiotic recently used.

Comment #26
3 There is also a possibility that the herb may have been contaminated which could explain hypersensitivity reactions.

Response #26
We already discussed this issue (see comment #13)