Reviewer’s report

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

Version: 4
Date: 31 March 2014

Reviewer: Samantha Coulson

Reviewer’s report:

Minor Revisions
1. Tables 1 and 3. N/A is indicated to mean 'not applicable'. This is incorrect and should be corrected to mean 'not available'
2. English grammar requires serious attention with numerous editorial corrections required before publication.

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.
   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.
   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?
   d) Authors state on page 3 that adverse events associated with andrographis included rash, puritis, 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.
   e) On page 4 authors refer to two other surveillance studies based on the Thai
Vigibase 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.

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.

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 350 mg 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.

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 provide valuable information.

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 data base 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’.

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.

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

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.
**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests