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CMES Risk Assessment Tool for Restrictions Imposed on Ingredients in the Therapeutic Goods (Permissible Ingredients) Determination

Instructions

The tool is intended for use only to assess the risk of revised restrictions imposed on an ingredient in the 26BB determination to determine whether education and implementing a timeframe for sponsors to action the required changes or whether immediate action is required.
This tool is to be applied to updates to the 26BB determination that impose a restriction on the use of an ingredient (i.e. decreasing the maximum recommended daily dose (MRDD)). Any update that expandes the use of an ingredient does not require an implementation period (i.e. expanding the use of an ingredient from an excipient to active).
It is expected that an evaluation of a substance or a TGA-initiated safety review has already been conducted and has provided a recommendation of the safety of the substance/ingredient.
In addition to considering the likelihood and consequences of the risk to consumers if a restriction is not imposed immediately, the evaluator should also give regard to the inherent low risk nature of the ingredient (i.e. to be eligible for inclusion in the 26BB determination, an ingredient must be considered low risk). Another consideration is that the ingredient is likely to already be available in products, as such information regarding the history of supply/compliance should be considered.
The assessment of a risk occurring (likelihood) or the impact of an event (consequence) can be a subject to personal biases. For this reason, risk management best practice requires assessments should be undertaken as a collaborative exercise.

It is intended that this risk assessment tool is completed in conjunction with the SOP [Title] - [Live TRIM link]

Risk Assessment Matrix

The use of a **Risk Assessment Matrix** (see tab 'Risk assessment Tool and Matrix) ensures that the level of the risks is objectively determined and comparable across the department. A current risk rating reflects the risk level at the time of the risk assessment, with controls in
The Risk Assessment Matrix has a scale for consequence levels to assist in determining how significant a risk event could be. Similarly, the likelihood scale, which is the probability of an event or activity occurring is a scale of probability based on historical fact.

Considerations for assessing the likelihood of risk

Likelihood of a safety issue or AE that may affect the public.
Consideration of previous frequencies/trends in AE reported (if available), evidence of causation (RUCAM) and the proportional use of products that may include this ingredient.
If available, the number needed to harm (NNH) may be help define the likelihood of risk, a high NNH value (e.g.. 100) may help provide confidence that the potential likelihood is low. It is likely that this value won't be available for the ingredients but if they are the value should be scrutinised to ensure the value is meaningful and that there is no bias and there are reliable confidence intervals for the estimated value.

Qualitative measures of likelihood

Likelihood Rating	Description
Almost certain	Occurs in almost all circumstances
Likely	Occurs in most circumstances
Possible	Occurs in some circumstances, but not most circumstances
Unlikely	Occurs in exceptional circumstances
Rare	Occurs in rare circumstances only

Considerations in assessing the consequences of risk

Consequences to the consumer should include consideration of the kind and severity of a potential safety issue AE, reversibility of the injury, the requirement of a medical professional or hospitalisation, uncertainty involved.
The consequence to consumers should also take into consideration how the ingredient is used in a product in combination with other ingredients.
Consideration should also be given the reputational risk to TGA.
Consideration of the impact on sponsors may also be relevant.

Qualitative measures of consequence or impact if the restriction is not implemented immediately

Descriptor	Description (related to the safety of our people)	Example(s)	Description (external scrutiny related)
Insignificant	Incident but no injury or illness Injury, illness, condition or ailment not requiring first aid or medical assessment	Transient superficial skin irritation Mild diarrhoea	Low impact on a small number of citizens.
Minor	Injury, illness, condition or ailment which doesn't usually require medical intervention, but may require minor first aid treatment	Minor first degree chemical burn Mild eye irritation	Medium impact on moderate number of citizens.
Moderate	Non-life threatening injury, illness, condition or ailment which requires medical intervention	Reversible liver injury Vertigo Prolonged and or moderate diarrhoea Nausea and vomiting Heart palpitations	Medium impact on moderate number of citizens and scrutiny required by external committees or ANAO Media scrutiny.
Major	Life threatening injury; Serious injuries causing hospitalisation; or serious irreversible impairment	Organ failure Irreversible liver injury Cancer Infertility	Intense public, political and media scrutiny evidenced by front page headlines and/or television coverage.
Catastrophic	Death; Permanent disability; Multiple life threatening injuries	Organ transplantation required Teratogenic effect Permanent blindness	Royal Commissions/ Parliamentary Enquiries. A lack of confidence in regulatory decisions demonstrated by the community.

Note: the consequence in relation to 'safety of our people' and 'external scrutinty' may be rated differently, in the instance where consequence ratings differ, the conservative approach is to select the highest rating. For example, if the consequence to 'safety of our people' is minor but the consequence to 'external scrutinty' is major, the overall consequence is rated major.

Workflow Process for completing this risk assessment

Ensure the excel file is saved within the application trim folder - using the naming convention - [insert substance name] - CMES Permissible Ingredient Safety-Review Risk Assessment Tool s22

Evaluator completes the document and refers for review by CMES team
Document is reviewed
Once the review is completed, the Evaluator removes all guidance information and ensures the font is formatted to black.
The Evaluator and Reviewer(s) sign the document
electronically using TRIM workflow
The document is then 'Finalised' using TRIM workflow
Add the assessed restrictions to the 'History - Examples' tab in the template

CMES Risk Assessment Tool for Restrictions Imposed on Ingredients in the Therapeutic Goods (Permissible Ingredients) Determination

The information in RED is for guidance only. It should be deleted and all font should be formatted to black before completing the assessment.
Please ensure you refer to the 'Instructions' tab before completing this assessment and the 'History - Examples' tab for consideration of whether the risk of a similar restriction for a similar ingredient has been assessed before.

It is intended that this risk assessment tool is completed in conjunction with the SOP for 'Enact a high-moderate risk changes to the Permissible Ingredients Determination (D25-4289063).

Ingredient Name	Andrographis paniculata	**TRIM ref**	D26-553953
Date of Risk Assessment	4/02/2026	**Safety Review TRIM Ref**	D25-3983815
		Note regarding Update TRIM Ref	
Background	Allergic-type ADR attributed to Andrographis paniculata prompted a review by Pharmacovigilance and Special Access Branch 2015 which was followed up with measures intended to mitigate the risk of anaphylaxis. Despite implementation of mitigation measures in 2020 following a high moderate risk change, serious adverse events, including a fatality in 2024 and two additional serious likely cases currently under investigation, have continued to increase. A follow-up safety review in 2025 concluded that the risk cannot be adequately mitigated through warnings, formulation restrictions, or educational measures, and that A. paniculata is not appropriate for inclusion in the listed medicines framework. To 31 December 2024, the TGA has received 254 reports of anaphylaxis associated with Andrographis. The updated safety review (2025) reports that the true rate of occurrence of anaphylaxis from Andrographis could be estimated to occur rarely (1/1,000 [0.1%) to 1/10,000 [0.01%]) or very rarely (<1/10,000 [<0.01%]).		

Amended restriction(s)	Potential impact(s) of delayed implementation	Consequence	Likelihood	Risk	Comments
Removal of the medicine from use within the low-risk medicine framework.	Potential for cases of anaphylaxis, a serious adverse event, including sudden, unpredictable and severe reactions (i.e., life-threatening).	Catastrophic	Rare	H-M	Anaphylaxis is reasonably assumed to occur during any compliance transition period.

Recommendation	There is a fatality in 2024. Two serious cases are currently under investigation, including seizure sequelae to anaphylaxis, and a report of induced coma suspected, and together indicate that the consequence is catastrophic. The ADR data indicates that the likelihood of continued reporting of anaphylactic reactions related to andrographis is rare or very rare As such, the risk categorisation of high is appropriate.

Completed by	s22	**Reviewed by**	s22

RISK ASSESSMENT MATRIX

Likelihood	Consequences: Insignificant	Minor	Moderate	Major	Catastrophic	*cannot be determined
Almost certain	H-M	H-M	H-M	H-M	H-M	
Likely	L-N	H-M	H-M	H-M	H-M	
Possible	L-N	L-N	H-M	H-M	H-M	
Unlikely	L-N	L-N	L-N	H-M	H-M	
Rare	L-N	L-N	L-N	L-N	H-M	
*cannot be determined						*Requires further review

L-N	Low-negligible risk
H-M	High-moderate risk

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ANDROGRAPHIS PANICULATA AND ANAPHYLAXIS – UPDATED SAFETY REVIEW 2025

SUMMARY

- The TGA has received an increasing number of reports of anaphylaxis involving Andrographis-containing medicines since 2019 – a fatal case was reported in June 2024.
- Anaphylaxis from Andrographis cannot be predicted with reports describing allergic reactions after prior sensitisation or on first exposure. Expert advice from a clinical immunologist supports this observation.
- Expert advice has also confirmed that known risk factors for allergic reactions include concurrent infection, use of non-steroidal anti-inflammatories, exercise and alcohol.
- It is possible that the risk of allergic reactions associated with Andrographis-containing medicines is increased because these products are mainly used for symptomatic treatment of viral infections, which often also involves concurrent use of non-steroidal anti -inflammatory medications.
- To 31 December 2024, the TGA has received 254 reports of anaphylaxis associated with Andrographis. Of these, a higher proportion were for products also containing Echinacea compared to products without Echinacea (81% vs 19%). This appears to reflect a higher supply volume of Echinacea-containing Andrographis products on the market. During the same period, the TGA has only received 13 reports of anaphylaxis related to products containing Echinacea without Andrographis.
- During the Covid-19 pandemic, there was an increase in supply of Andrographis-containing products. This was associated with an increase in the number of anaphylaxis reports to the TGA.
- There was also a notable increase in reports in 2024 after a fatal anaphylaxis case. This likely reflected increased public awareness of this safety risk following increased public communication and media.
- The true rate of anaphylaxis relating to Andrographis cannot be determined from spontaneous (voluntary) adverse event reporting. Based on incomplete supply data from medicine sponsors, we tentatively estimate anaphylaxis from Andrographis occurs at a rate of 0.1-0.01% of people who take these products.
- Analyses of reporting data for the top 20 Andrographis products supplied in Australia did not identify any ingredient preparation types or extracts that were not associated with anaphylaxis adverse events.
- A qualitative case review of reports that included sufficient data elements for further analysis revealed that:
    - most reports occurred either on first exposure to the suspected medicine or after previous use without any reaction, highlighting the unpredictable nature of anaphylaxis to Andrographis.
    - most had a rapid onset of symptoms (within 30 minutes).
    - most were treated with adrenaline, and most presented to hospital (emergency and/or admission).
    - more than half of the cases had no history of allergy, and most (77%) had no history asthma.
- Risk mitigation options that were considered as part of this review included strengthened label warnings, restrictions on ingredient preparation (such as extract concentration ratios, extract solvents, plant parts or dose), and public education. Analyses of cases, supply data and medicine formulation data found no compelling evidence that any of these risk mitigation options would reduce the occurrence of anaphylaxis or the risk of serious outcomes (see Data analysis of preparation type and Risk mitigation options).

- s47G
- There is currently no concerning safety signal for other ingredients known to trigger anaphylaxis that are permitted for use in listed medicines.
- The number of anaphylaxis adverse events for Andrographis is alarmingly high when compared with other oral registered medicine ingredients known to trigger anaphylaxis. Also concerningly, global data showed disproportionately high reporting for Andrographis and anaphylactic reactions, that was greater than for any of these registered medicine ingredients and anaphylactic reactions (see Other medicines at risk of anaphylaxis).
- A review of medical literature published since November 2011 found only a small number of reports of anaphylaxis in clinical studies however most had methodological limitations for detecting rare adverse events. A small number of published case reports of anaphylaxis or severe allergic reactions were also found in the literature.
- Non-clinical studies provide some evidence that some of the active constituents in Andrographis could evoke allergenic mediators and potentially result in anaphylactoid reactions, while one study found anti-inflammatory actions using a mouse model.
- Many international authorities do not authorise medicines containing Andrographis or do not regulate Andrographis-containing products as medicines. Some have received adverse event reports of anaphylaxis and hypersensitivity reactions associated with Andrographis, mostly in multi-ingredient preparations. Some have related label warning requirements, and one has published a safety communication on the topic (see Table 8: International Regulation and Appendix E).
- For an ingredient to remain appropriate for use in listed medicines, which can be supplied for purchase by consumers from retail outlets, it should be safe for self-administration without the need for medical advice or supervision. With only limited benefits permitted for listed medicines, the risk must also remain sufficiently low.
- As the risk of life-threatening anaphylaxis cannot be predicted or reliably mitigated, and with an increasing number of reports involving Andrographis-containing listed medicines, this ingredient cannot be considered low risk.
- The evidence considered in this updated safety review does not support stronger label warnings, formulation restrictions or further education as effective options to reduce the risk of anaphylaxis from Andrographis when used in listed medicines.
- It does not appear that Andrographis remains appropriately positioned within the regulatory framework of listed medicines.

RECOMMENDATIONS

Action	Comments
Referral to ACCM for advice	AEMDS recommends that advice is sought from ACCM on whether the committee agrees that, based on the available evidence, when Andrographis is used in listed medicines: • there is increased risk posed to the consumer because the presence of viral illness can increase the likelihood or severity of an allergic reaction, and these products are mainly used for symptomatic treatment of viral illnesses. • anaphylaxis adverse events have been sudden and unpredictable and therefore the risk of anaphylaxis is difficult to mitigate. • further risk minimisation measures to strengthen label warnings, restrict formulations or publish further education are unlikely to mitigate the risk of anaphylaxis.

AEMDS also recommends the committee be asked to advise whether there is:

- any additional evidence that has not been considered by the TGA, or in the recent published literature that provides compelling evidence as to whether a specific preparation, use, dose, source of herbal material, or herbal constituent, is responsible for anaphylaxis observed with Andrographis.
- any other evidence pertaining to Andrographis and anaphylaxis that has not been considered by the TGA in this safety review.

UPDATED SAFETY REVIEW

Background

The Adverse Event & Medicine Defect Section (AEMDS) within the Pharmacovigilance Branch of the Therapeutic Goods Administration (TGA) is re-examining the safety of the herbal ingredient *Andrographis paniculata* (Andrographis) in listed medicines due to its association with anaphylaxis and other severe allergic reactions. Anaphylaxis is a serious, rapid onset allergic reaction that can result in death and is characterised by life-threatening upper airway obstruction, bronchospasm and/or hypotension[1].

The TGA previously reviewed this issue, sought advice from the Advisory Committee on the Safety of Medicines (ACSOM) in 2014 and published a safety advisory and a safety review on the TGA website in 2015[i]. Subsequently, in 2019 new requirements were implemented requiring listed medicines that contain Andrographis to display the following label statement:

> '*Andrographis may cause allergic reactions in some people. If you have a severe reaction (such as anaphylaxis), stop use and seek immediate medical attention'*, (or words to this effect).

This requirement was implemented as a high-moderate risk change to permissible ingredients determination in December 2019. From 2 May 2020, all listed medicines containing Andrographis released for supply from that date were required to display the above label warning.

Since then, the AEMDS has undertaken ongoing post-market monitoring activities related to the effectiveness of the risk mitigation. This has identified an ongoing and increasing pattern of reporting of adverse event reports of anaphylaxis related to Andrographis-containing medicines. Of particular concern are adverse event reports that describe that the ingredient has been used by the consumer without incident in the past, sometimes many times. Additionally, the unexpected, unpredictable, and serious nature of these reactions for consumers is of significant concern when associated with a listed medicine.

In June 2024, the TGA received a report of fatal anaphylaxis associated with the use of a product containing Andrographis. Subsequently the TGA published an updated safety advisory to raise awareness of this safety concern with consumers and health professionals. s47 s47

This updated safety review considers whether there is compelling evidence that strengthened risk mitigation sufficiently addresses the risk of anaphylaxis in association with Andrographis in order for it to remain appropriate for use in listed medicines which are available to consumers without medical consultation and monitoring. Information considered includes expert advice from a clinical immunology and allergy specialist, adverse events in Australia and internationally, the risk profile for Andrographis-containing medicines including the formulations of medicines involved in Australian adverse events, available published literature since November 2011, a toxicological review of non-clinical studies, and international regulation of Andrographis. Risk mitigation options considered after evaluating the available evidence were:

- Strengthened label warnings, including contraindications in subgroups

[i] The full version of the safety review including summary of ACSOM advice can be found in TRIM: R15/746298.

- Providing sufficient information at the point of purchase for the consumer to make an informed decision about risk
- Restrictions on certain preparations
- Education

Key points – background

- The TGA previously reviewed this safety concern and published a safety advisory in 2015 and introduced a label warning requirement in 2019 for Andrographis-containing listed medicines to warn about allergic reactions and anaphylaxis.
- Since then, there has been an increasing number of anaphylactic reaction reports for Andrographis-containing listed medicines
- A fatal case was reported to the TGA in June 2024. An updated safety advisory was published in July 2024 s47 s47
- This review considers available evidence to determine whether strengthened risk mitigation strategies would sufficiently address the risk of anaphylaxis in association with Andrographis-containing medicines in order for them to remain positioned as low risk listed medicines.

Expert advice

AEMDS sought expert advice from an independent specialist advisor, Professor s22 , a clinical immunology and allergy specialist. Specific advice was sought on the following:

1. Whether the link between Andrographis and hypersensitivity reactions, including anaphylaxis, is a recognised risk among clinical immunologists, allergists, or other health professionals.
2. Whether the pattern observed in adverse events reported to the TGA (particularly the onset and severity) is consistent with other known allergens commonly found in foods or other medicines.
3. Whether there are risk factors for onset of hypersensitivity/anaphylactic reactions in the context of the use of Andrographis, including, but not limited to, the common indications of relief of cold and flu symptoms, or immune support.
4. Whether the presence of Echinacea, another herbal ingredient with reported allergenic properties, could potentiate or exacerbate reactions to Andrographis.
5. Whether there are any clinical investigations that can be used to confirm whether or not a patient has an allergy to Andrographis and/or Echinacea.

The advice provided is summarised below, and reproduced in full in Appendix A.

1. Recognised link between Andrographis and hypersensitivity by health professionals

Adverse reactions to Andrographis have not been widely appreciated despite earlier publications by the TGA, the New Zealand regulator and in the literature. More attention was focused on the issue after the recent TGA alert in July 2024 and media reports in June 2024 of a fatality likely due to anaphylaxis caused by Andrographis.

Cases reported to date may be a significant underestimate as milder reactions may not come to the attention of the medical community and go un-reported. It is well established there is under-reporting of adverse reactions to drugs and even more so for herbal products due to the public perception of safety, and also because they can be obtained independent from medically qualified practitioners.

2. Patterns in adverse reports / consistency with allergic reactions seen to other agents

Where details are available, reported reactions are entirely consistent with allergic reactions regardless of the mechanism.

Reactions that occur after many previous uses is consistent with any allergic reaction regardless of cause. IgE-mediated reactions require prior sensitisation before a reaction occurs, as seen with many drug reactions where patients take repeated courses before they demonstrate an allergic reaction, for example with antibiotics.

The expert advice also stated:

> Factors causing a reaction at a particular time when the substance has been tolerated previously are not entirely clear but modifying factors such as presence of infection, other medications, concomitant exercise or alcohol ingestion may all act as modulating factors.
>
> A reaction occurring on the first ever use suggests either that sensitisation has occurred by prior exposure to the allergen in another form, or that the reaction has been caused by non-IgE-mediated hypersensitivity. Non IgE-mediated pathways can induce symptoms indistinguishable from classic anaphylaxis and may do so via mast cell or basophil activation, via other antibodies, generation of anaphylatoxins, or via other receptors such as G-coupled receptors.

The expert advice also commented that judgement of severity based on whether a patient presented to hospital or was administered adrenalin is not a reliable measure, as often adrenalin is not administered when it should have been or is sometime administered when it is not necessary. In addition, some people choose not to go to hospital where medical advice would suggest they should.

3. Risk factors in the context of typical Andrographis use

The expert advice stated:

> In general terms, there are known risk factors that can potentiate an allergic reaction or act as co factors to make a reaction more likely. These include ingestion/exposure to the allergen in close proximity to vigorous exercise, ingestion of alcohol or non-steroidal anti - inflammatory medications and in the context of viral infections. The full history of those who have had reactions and have been reported is not known but as this “supplement” is used as a treatment for upper respiratory infection, it is highly likely that most had a viral illness at the time and it is also possible that some anti-inflammatory medication may have been used as well.

4. Role of Echinacea in allergic reactions

Considering the known association between Echinacea and allergic reactions, it is possible that some of the present reports represent adverse reactions to the Echinacea component or are a result of synergy between the two components. However as there are reports to Andrographis alone, both are implicated in reactions.

The expert advice stated:

> Furthermore, from the reports available, positive skin tests were achieved with Echinacea but none of the patients seen in our unit with convincing histories of allergic reactions to Andrographis or Armaforce had positive skin tests which suggests that perhaps this compound causes reactions by an IgE-independent mechanism. Further investigations will be required to elucidate the culprits and the mechanism(s) underpinning the observed adverse reactions such as direct mast cell histamine release or mechanisms via stimulation of other pathways or receptors.

5. Clinical investigations for diagnosis

The expert advice stated that all investigations in allergy practice begin with a detailed patient history. Further investigations include:

> Skin testing with extracts of all implicated ingredients will assist in identifying whether the reaction might be IgE-mediated; some research laboratories offer BAT (basophil activation testing) and this could be set up and conducted on blood samples; measurement of serum tryptase within hours of the reaction if anaphylaxis has occurred can be very useful in determining whether there is mast cell activation. Ultimately a supervised challenge can be conducted as the "ultimate proof" of causation, however most specialists and patients would be reluctant to undertake this particularly for such a dispensable compound that is easily avoided!

The expert advice also made comment on the limited knowledge of traditional preparations of Andrographis and the chemical composition of the final product used medicinally, and similarly that little is known about the manufacture and other relevant details of unregulated products available for use in our society. The expert advice also commented on the need for risk-benefit analysis noting that evidence of benefit is equivocal s47G s47G s47G . The advice also suggested that data collection regarding harm is needed so that a risk-benefit assessment can be undertaken.

Key points – expert advice

- This safety concern was not widely known until the TGA safety alert and media coverage of the fatal case in 2024.
- Reactions seen for Andrographis are consistent with allergic reactions observed for other agents.
- Allergic reactions can occur after prior sensitisation or on first exposure.
- Non IgE-mediated pathways that occur without prior sensitisation can induce symptoms indistinguishable from classic anaphylaxis.
- It is not entirely clear why reactions occur when a substance has been tolerated previously. Possible modifying factors that can potentiate an allergic reaction or act as co factors to make a reaction more likely include presence of infection, other medications, concomitant exercise or alcohol ingestion.
- As Andrographis is used a treatment for upper respiratory infection, it is highly likely that most who reacted had a viral illness at the time and possibly used concurrent anti-inflammatory medication.
- It is possible that some reports relate to the Echinacea component, or to a synergy between components, however as there have been reactions to Andrographis alone, both are implicated.
- Negative skin tests observed for Andrographis in some case reports suggest a non-IgE mechanism.

Adverse events

Australian adverse events

Australian adverse event reports

To 31 December 2024, the TGA has received 1217 adverse event (AE) reports related to medicines containing Andrographis[ii]. The top three reaction terms were ageusia (300), anaphylactic reaction (248) and dysgeusia (232)[iii]. There were 254 cases with reported reaction terms specific to anaphylaxis: anaphylactic reaction (248), anaphylactic shock (7) and anaphylactoid reaction (1), noting that some cases included more than one anaphylaxis-specific reaction term.

Reporting pattern

Since 2019, there has been an increase in the number of case reports of anaphylaxis related to Andrographis-containing medicines (Figure 1), with 184 reports received between 2019 and 2024[iv]. It is recognised that there may have been increased use of complementary medicines by consumers to support the immune system, during and following the COVID-19 pandemic. We have considered medicine supply data from sponsors to account for this. There may also have been increased reporting and issue awareness due to the communications about, and introduction of, the label warning requirement for anaphylaxis related to Andrographis from late 2019. This supports that AEs

[ii] Adverse events reported to the TGA are entered into the Adverse Event Management System (AEMS) and reaction terms are coded using the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA is a highly specific standardised medical terminology to facilitate sharing of regulatory information internationally for medical products used by humans. It was developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).
[iii] Products containing Andrographis are also required to include a label warning about taste disturbance (see Regulatory status).
[iv] See D25-691898 for raw data.

are under-reported as the association between Andrographis and anaphylaxis has not been well known, as discussed in the expert advice above and in the section below on supply data and rate.

There were 47 products associated with the 254 cases of anaphylaxis[v]. Five products, supplied by one sponsor and with the same ingredient formulation and tradename s47G accounted for 159 (63%) cases of anaphylaxis.

s47G

As shown in Figure 1 below, the majority (205/254 [81%]) of the 254 anaphylaxis adverse event cases related to Andrographis are associated with medicines that also contain *Echinacea* species (Echinacea), including s47G Therefore, the higher supply volume may explain the higher number of reports. Notwithstanding, the total number of cases (49/254 [19%]) that involved medicines without Echinacea further confirms a signal for the ingredient Andrographis.

This is also supported by the far smaller number of anaphylaxis cases related to medicines containing Echinacea without Andrographis present in the medicine, with only 13 reports received by the TGA since 2005.

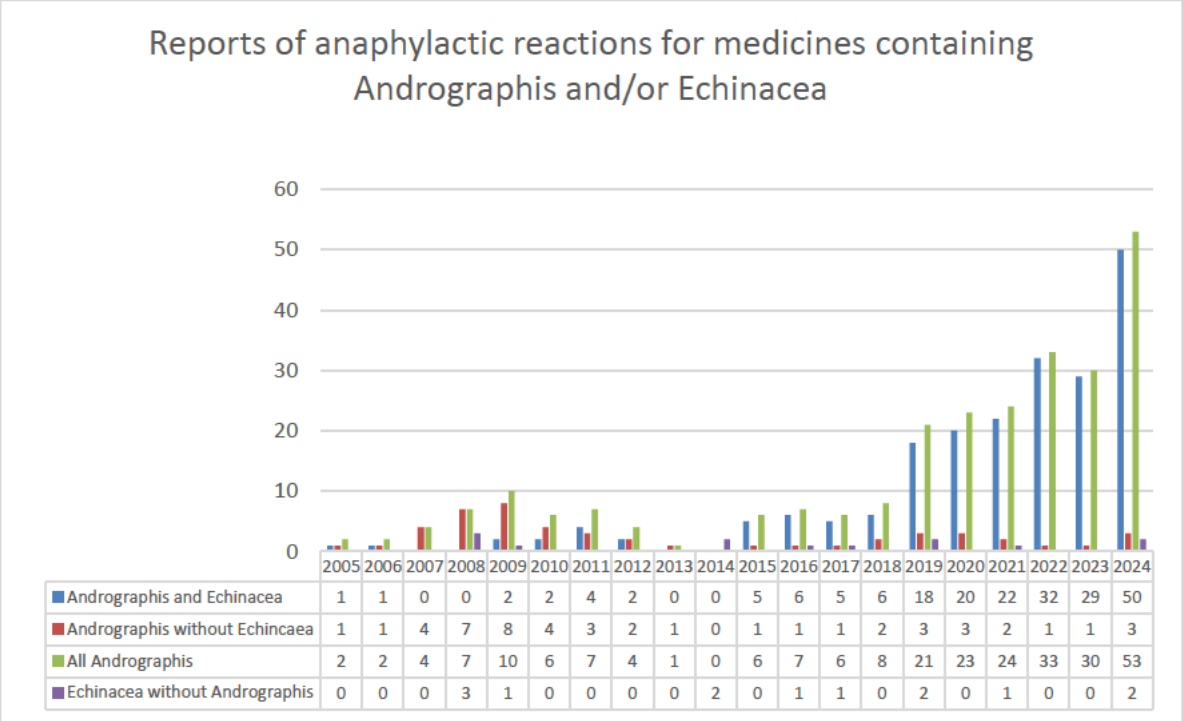
Of the 205 reports for medicines which contain both Andrographis and Echinacea, 159 (78%) reports were for s47G products, and 46 (22%) reports were for twenty-seven other medicines.

Therefore, of the total 254 anaphylaxis reports for Andrographis, 63% (159/254) involved s47G 18% (46/254) involved other medicines that contained both Andrographis and Echinacea, and 19% (49/254) involved Andrographis-containing medicines that did not contain Echinacea.

Figure 1. Reports of anaphylactic reactions for medicines containing Andrographis and/or Echinacea

[v] See D25-691898 for data

s47



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Andrographis and Echinacea	1	1	0	0	2	2	4	2	0	0	5	6	5	6	18	20	22	32	29	50
Andrographis without Echincaea	1	1	4	7	8	4	3	2	1	0	1	1	1	2	3	3	2	1	1	3
All Andrographis	2	2	4	7	10	6	7	4	1	0	6	7	6	8	21	23	24	33	30	53
Echinacea without Andrographis	0	0	0	3	1	0	0	0	0	2	0	1	1	0	2	0	1	0	0	2

Supply data and estimated rate

In late June and early July of 2024, the TGA issued Notices under section 31 of the *Therapeutic Goods Act 1989* for all Andrographis-containing medicines listed on the Australian Register of Therapeutic Goods (ARTG). The Notices required the sponsors of these medicines to provide the TGA with:

- medicine supply data to the Australian market,
- anaphylactic reaction and hypersensitivity adverse event report details and
- information about the Andrographis extract that was used in their medicine(s) including andrographolide content and dosage information.

Sponsors of current Andrographis- containing medicines were also required to provide this information about any of their non-current Andrographis-containing medicines that had been on the ARTG within the previous 5 years (from July 2019 onwards)[vii]. The supply data provided by sponsors was analysed against TGA's AEMS data to identify adverse event trends in the context of volume supplied to market.

However, it is important to note that the true rate of occurrence of an adverse event cannot be determined from spontaneous adverse event reporting systems, due to both under-reporting and lack of usage data. Although sponsors provided data on the number of units (bottles/containers) supplied, using this supply data to determine a rate of anaphylaxis has multiple limitations and cannot be used to determine a conclusive rate of anaphylaxis. These limitations are further discussed below.

[vii] The 5-year time frame was selected as sponsors of listed medicines are required to keep information about their medicine for 5 years following cancellation from the ARTG.

Under-reporting

Under-reporting is well documented in spontaneous reporting systems[2] (ref: Hazell L, Shakir SA. 2006).

The TGA receives reports from sponsors, health professionals and consumers. Under-reporting is an issue for each of these groups, for various reasons.

Sponsors are required to report serious adverse events to the TGA. The collection and reporting of adverse events is dependent on the sponsor's pharmacovigilance system. Pharmacovigilance inspections have shown that the pharmacovigilance system implemented by some listed medicine sponsors are not always effective. Deficiencies have been identified in adverse event collection and records management, seriousness and causality assessment and adverse event follow up processes, all of which may contribute to under-reporting. Deficiencies have also been identified in ongoing safety evaluation for listed medicine sponsors which could result in delays to risk mitigation for any significant safety issues.

Reporting adverse events by health professionals is optional. Uncertainty around the potential causal relationship between a medicine and an adverse event can contribute to under-reporting by health professionals[3]. Therefore, many cases associated with lesser-known medicines, such as complementary medicines, may go unreported due to lack of awareness of an association and/or lack of readily available information of a possible causal association. Other contributing factors to under-reporting by health professionals include lack of time to complete a report, the belief that a single case may not contribute to medical knowledge, or that very serious adverse events are already well documented by the time a medicine is marketed[3].

Reporting adverse events by consumers is optional. It is dependent on establishing suspicion for a consumed medicine, as well as the motivation and ability to report. There is a general consumer perception that complementary medicines are safe[4], which can lead to a failure to identify a causal association with a listed complementary medicine.

Some case narratives for adverse event reports associated with Andrographis, describe that the causative role of the Andrographis-containing medicine was only discovered after a second anaphylactic reaction on subsequent exposure. Some consumer reports also describe that an allergen was not identified by treating health professionals and the patients have been advised to carry adrenaline auto-injector for life as the cause was unknown. These cases demonstrate that under-reporting due to a lack of awareness by both consumers and health professionals is highly likely.

Therefore, it is important to note that the true occurrence of Andrographis-related anaphylaxis is higher than the number of reports in the TGA AEMS.

Supply data limitations

The use of supply data provided by sponsors presented multiple limitations, including:

- it cannot be confirmed that all units supplied were consumed.
- there was no supply data for all non-current Andrographis medicines for which adverse event reports have been received, rather data was only required for any non-current medicines from sponsors of current Andrographis-containing medicines.
- analyses are reliant on the completeness of sponsor records. Supply data was not able to be provided for some medicines, including for medicines with a transfer of sponsorship.

Limitations for using combined supply data from multiple products to estimate a rate of anaphylaxis or identify trends include:

- Supply data was not fully reflective of the total amount of product supplied to the market in the time period as supply data was not collected for all cancelled products that contained Andrographis.
- Supply data for each year cannot be directly correlated with all adverse events for the same year. Following market supply, product could remain in the market at consumer level until the end of shelf life, typically 2-3 years. For instance, adverse events with an onset in 2019 may be related to product supplied to the market in 2017, 2018 or 2019. Similarly, product supplied in 2023 or 2024 may correlate to adverse events that could occur up until 2027.
- At least 12 anaphylaxis adverse events could not be linked to supply data as a distinct AUST L number could not be determined from the adverse event report.

An analysis was performed on 135 anaphylaxis adverse event cases that could be linked to supply data provided by sponsors[viii]. Notwithstanding the above limitations, and in the context of under-reporting, the true rate of occurrence of anaphylaxis from Andrographis could be estimated to occur rarely (1/1,000 [0.1%) to 1/10,000 [0.01%]) or very rarely (<1/10,000 [<0.01%]) (see Table 1).

Therefore, it is not surprising that anaphylaxis adverse events were often not reported for products supplied in low volumes. Indeed, supply data for individual medicines confirmed that a higher volume of supply correlated with a higher number of anaphylaxis adverse event reports.

Table 1. Estimated rates based on anaphylaxis adverse events and sponsor supply data

Medicine Name	AUST L	Anaphylaxis to Dec 24[ix]	Units supplied	Estimated rates
s47G			s47	s47G

[viii] See spreadsheet in TRIM D25-1386479

[ix] Adverse events that occurred prior to supply dates were not included. While medicine supply data was provided up to June 2024, adverse events that occurred up to December 2024 were included as it is plausible that the adverse events that occurred during this time were related to product supplied up to June 2024.

s47G s47 s47G

s47

Figure 2. Supply data by year

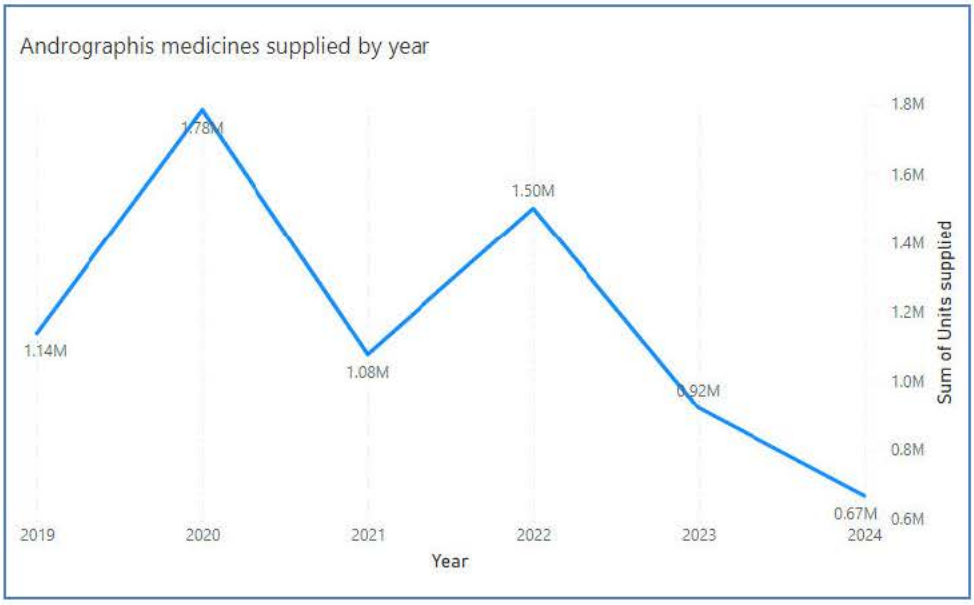


Figure 2 is derived from the sponsor supply data obtained from responses to the s31 Notices. It reflects the total supply volume of the medicines for each year as reported to the TGA by the sponsors.

Increased use of complementary medicines to support the immune system during and following the COVID-19 pandemic may account for the apparent peaks in supply in 2020 and 2022. The significantly lower supply in 2024 reflects that supply data was only provided for the first five months of the year as required in the s31 Notice.

Figure 3 below shows the overall number of anaphylactic adverse reaction reports included in the analysis for each year from 2019 to 2024. The lower numbers of adverse events in 2019 and 2020 may relate to the exclusion of a number of adverse events for the purposes of the analysis to ensure that adverse events could be plausibly linked to the obtained supply data.[x]

Figure 3. Anaphylaxis adverse events related to supply data

[x] 17 adverse events in 2019, 11 in 2020, and 16 across the remaining years were excluded from this analysis as they did not have a definite AUST L associated with them (for example s47G with no AUST L number reported), or the adverse event was likely associated with different supply data not obtained for this analysis (D24-4058590).

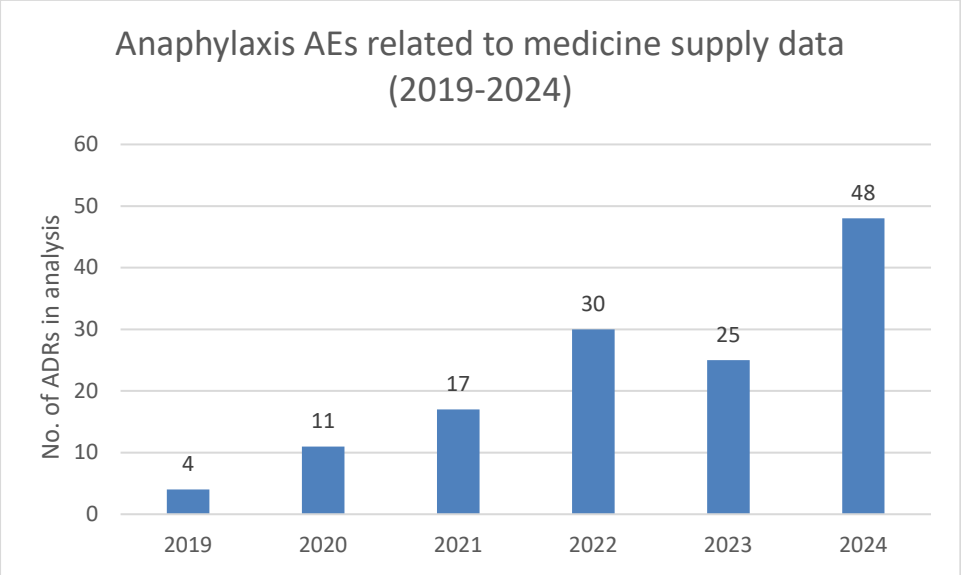
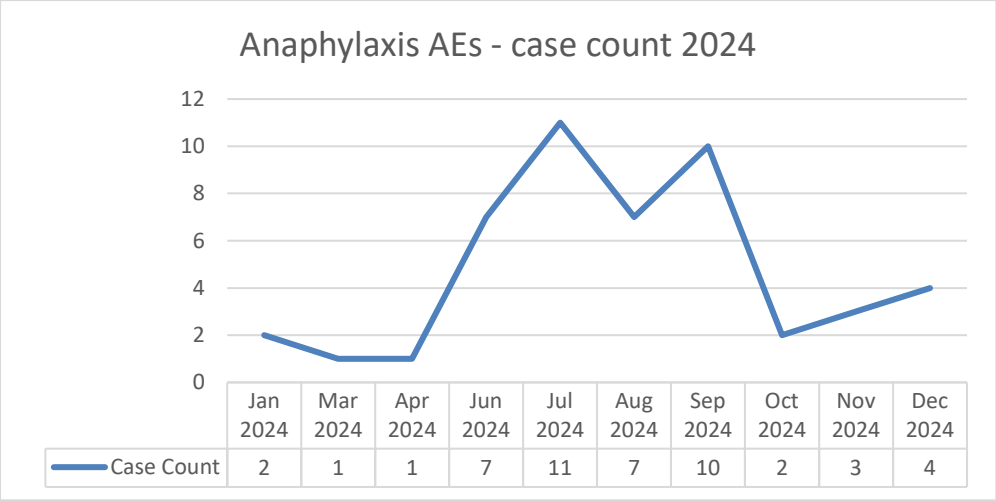


Figure 3 indicates that there may be a slight correlation between the increase in adverse events in the years following increase in supply (2021, 2022 and 2023) however, the largest spike in adverse events occurred in 2024. Figure 4 shows an increased number of reports were received between July and September 2024. A TGA safety alert for medicines containing Andrographis was published on 2 July 2024 which may have promoted increased awareness of the issue and increased reporting.

Figure 4. Anaphylaxis adverse events related to supply data - 2024



Broader search results using a Standardised MedDRA Query (SMQ)

The TGA AEMS was also searched using standardised MedDRA queries (SMQs) for anaphylactic reactions and anaphylactic /anaphylactoid shock conditions for cases up to 31 December 2024 associated with Andrographis. SMQs are tools developed by MedDRA/ICH to facilitate retrieval of cases coded with reaction terms that could be considered consistent with a reaction or condition under investigation. 619 cases were identified using the 2 anaphylaxis-related SMQs. Amongst these cases, the top 4 reaction terms were anaphylactic reaction (248), pruritis (195), urticaria (150) and rash (138). See Appendix B(1) for an expanded list of reaction terms and case counts identified with these SMQs.

Similarly, TGA AEMS was searched using the SMQ hypersensitivity for cases reported during the same period for medicines containing Andrographis. 641 cases were identified. Amongst these cases, the top 4 reaction terms were anaphylactic reaction (248), pruritis (195), hypersensitivity (152) and urticaria (150) (see Appendix B(2) for all reaction terms and case counts).

While all cases identified using SMQs have not been further analysed in detail, these results suggest the number of cases with reaction terms related to anaphylaxis and hypersensitivity that may have in fact been cases of anaphylaxis or other serious allergic reactions are far greater than only those coded with the specific reaction terms anaphylactic reaction, anaphylactic shock and anaphylactoid reaction.

Qualitative case review

The case narratives of adverse event reports often contain data that is not captured in the structured data fields of AEMS. These narratives, not available publicly in the Database of Adverse Event Notifications (DAEN), may provide additional information on:

- history of previous use of a medicine with or without reactions,
- information on detail of medical interventions to treat the reaction,
- time to onset of reaction,
- any reported medical history of allergies or asthma.

A subset of case reports of anaphylactic reactions related to medicines containing Andrographis reported from 1 January 2016 to 31 December 2024 were reviewed for further information contained in the narratives[xi]. Case review was limited to those cases coded with a reaction term of 'anaphylactic reaction' or 'anaphylactic shock' and with sufficient information in the narrative to provide some or all of the additional information above. This identified 171 cases for further review where the Andrographis-containing medicine was the sole suspected medicine in the reaction.

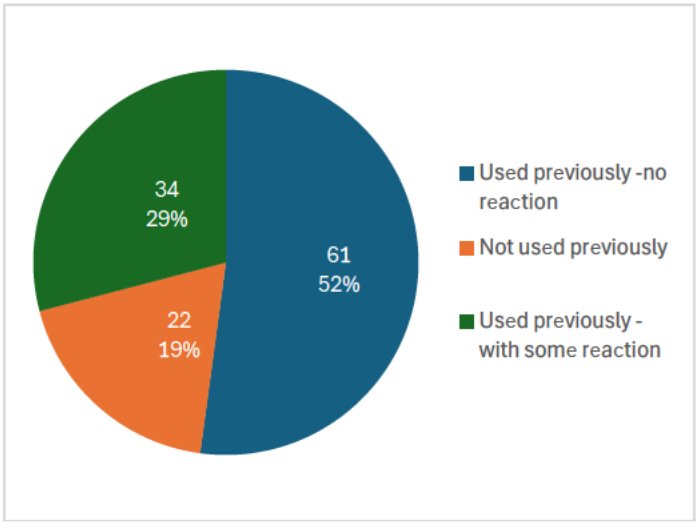
Prior use of suspected medicine

Of the 171 reviewed cases, 117 cases reported on prior use of the suspected medicine. Of these 117 cases:

- 22 (19%) cases reported the patient had never used the suspect medicine before.
- 61 (52%) cases reported the patient had used the suspect medicine with no previous reaction.
- 34 (29%) cases reported the patient had used the product before with a previous reaction (symptoms of reaction varies).

Figure 5. Pie chart showing anaphylaxis cases with history of use of the suspected medicine containing Andrographis

[xi] See spreadsheet in TRIM D25-658144



As can be seen, of the 117 cases that reported on prior use, most (83/117 [71%]) reported that the reactions occurred either on first exposure or after previous use with no reaction.

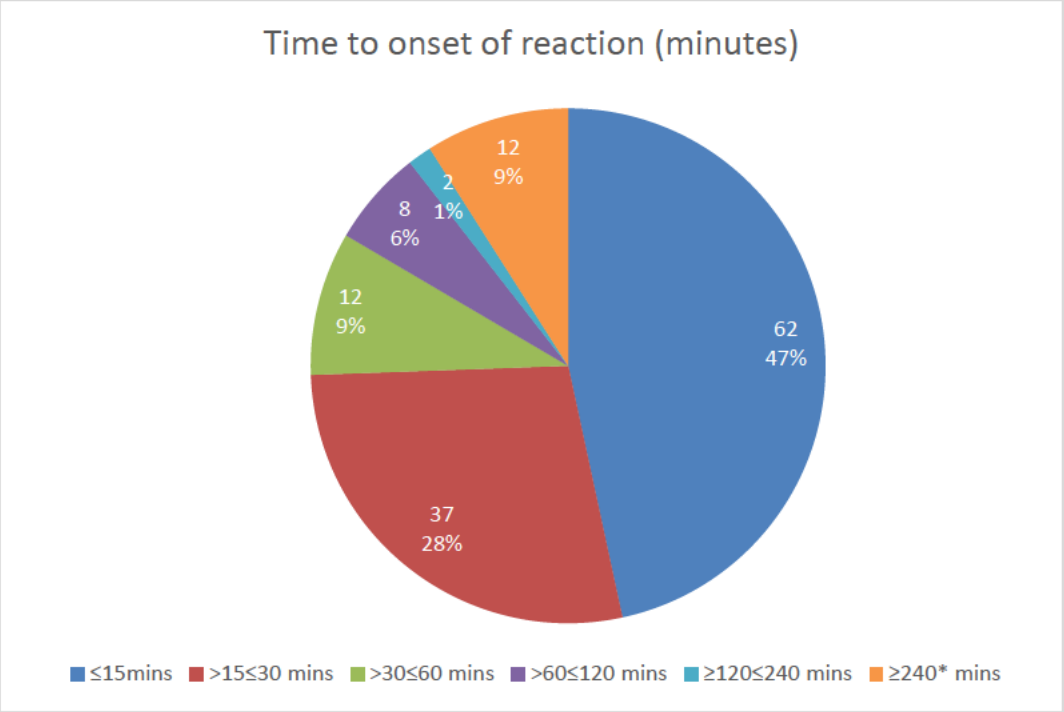
Time to reaction onset

Of the 171 reports, 133 included reaction onset time[xii] after exposure to the medicine. Of these:

- 62 (47%) cases reported symptoms started within 15 minutes or less of taking product.
- 37 (28%) cases reported symptoms started between 15 and 30 minutes after taking product.
- 20 (15%) cases reported symptoms stated between 30 and 120 minutes after taking product.
- 14 (10.5%) cases reported symptom onset after 2 hours.

Figure 6. Reaction onset time

[xii] Reaction onset time was taken as the time from taking the medicine to when the first symptoms of the reaction occurred, as reported.



*including same day or longer

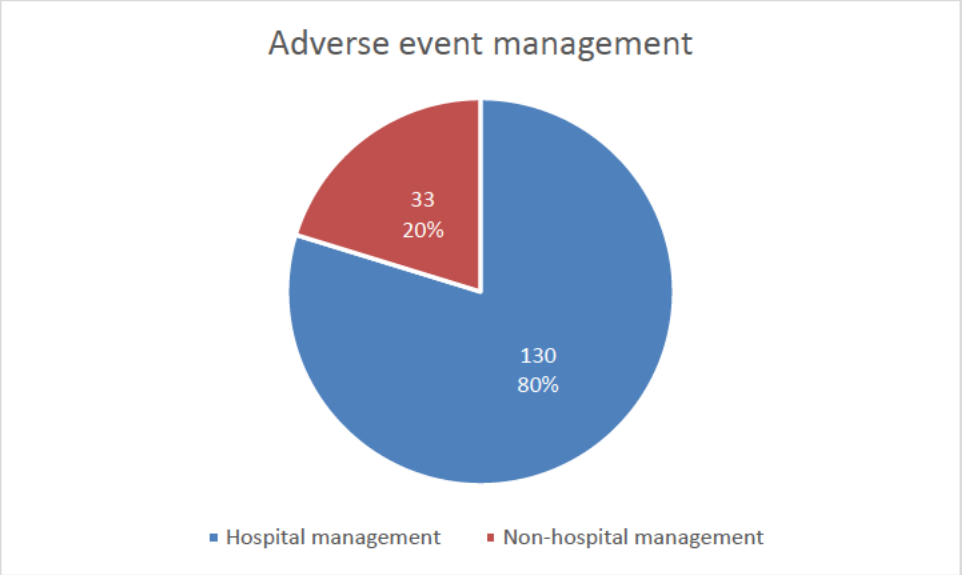
Of the cases that reported time to onset, it is concerning that the time to onset occurred in 30 minutes or less in most cases (99/133 [74%]). This may not provide sufficient time to access treatment, nor to look for the possible cause and instructions on a label warning once a reaction has commenced, with rapid progression a key feature of anaphylactic reactions.

Adverse event management

Of the 171 reviewed cases, 163 reported on management of the adverse event. Of these:

- 130/163 (80%) cases reported hospitalisation which may have included presentation at an emergency department or hospital admission and/or treatment.
- 33/163 (20%) cases reported non-hospital management which may have been through a GP, pharmacist, nurse, ambulance or self-treatment.
- 68 (42%) cases reported ambulance attendance with 64 of these cases also reporting hospital attendance.

Figure 9. Adverse event management

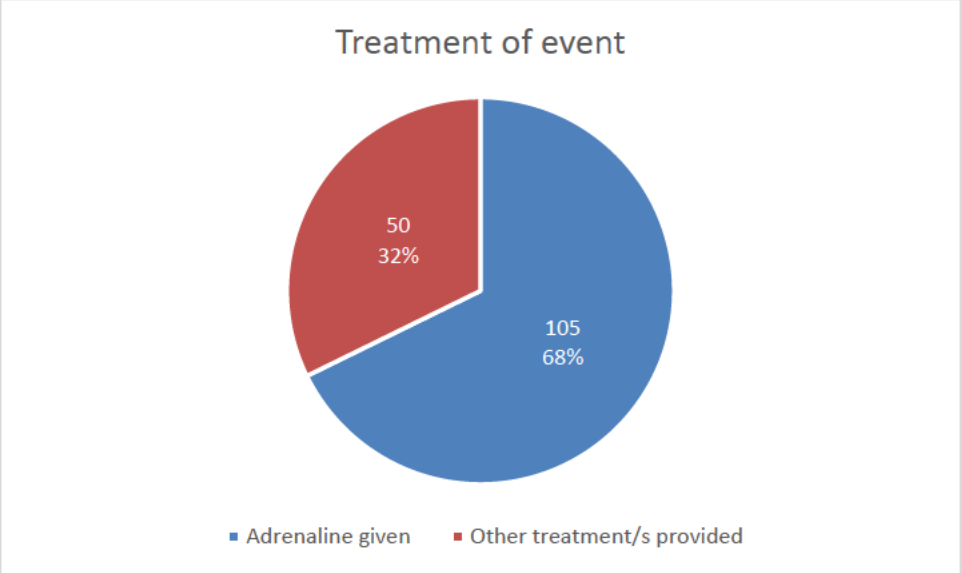


Treatment of event

Of the 171 cases, 155 reported on the type of treatment administered. Of these:

- 105 cases (68 %) reported use of adrenaline for treatment
- 50 cases (32%) reported treatment other than adrenaline

Figure 7. Treatment of event

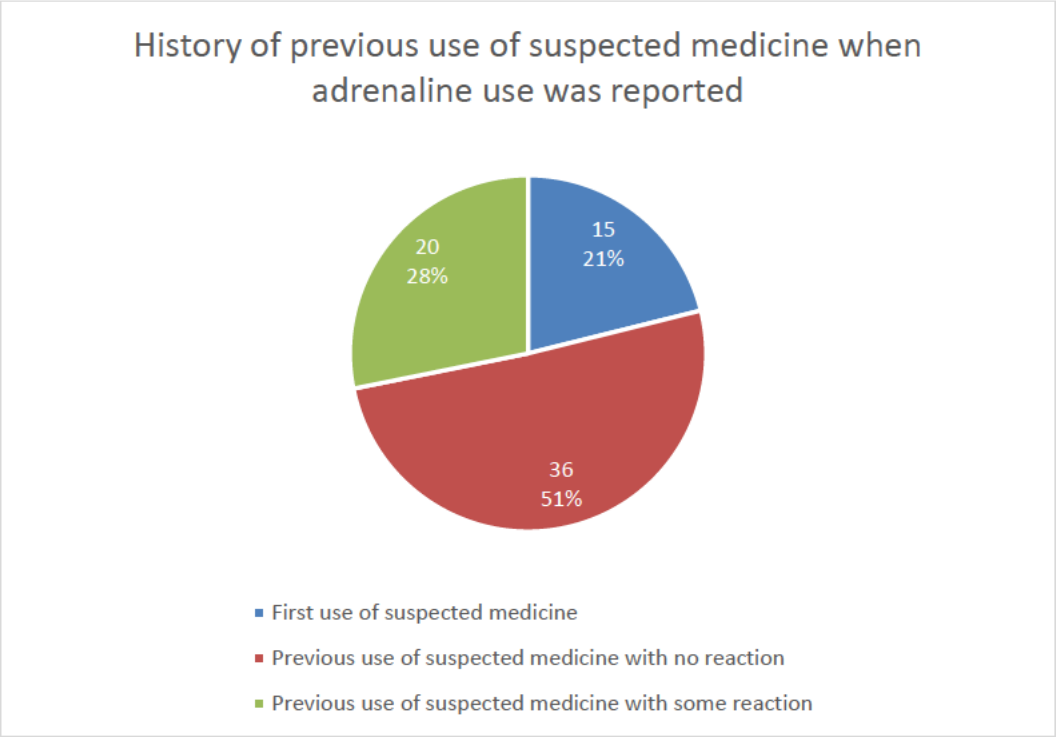


- Of the 50 cases where treatment other than adrenaline was reported, treatments included antihistamines, corticosteroids, IV fluids or hospital observation. Of these:

- 24 cases reported attendance at hospital with 8 of these also reporting ambulance attendance.

- Of the 105 cases that reported use of adrenaline for treatment, 71 also reported on previous exposure to the suspected medicine. Of these:
  - 15 patients had experienced a reaction with their first use of the product.
  - 36 patients had previously used the product without a reaction.
  - 20 patients had experienced a previous reaction (symptoms of reaction varies).

Figure 8. Adrenaline administration relative to history of use of suspected medicine.



These cases show that of those that reported on the type of treatment administered, most (73%) patients were given adrenaline, however of those not given adrenaline, 44% (17/39) still attended hospital. Concerningly, of the 71 cases that reported that adrenaline was administered and that also reported on previous exposure to the suspected medicine, in 72% (51/71) the reaction occurred either on first exposure or after previous use with no reaction (Figure 8). This indicates that a precautionary approach of carrying an adrenalin auto-injector for individuals who have previously experienced a reaction would potentially only help in 28% of cases. Notwithstanding, the need to carry an adrenalin auto-injector as risk mitigation is not consistent with the listed medicines low risk framework.

Although the expert advice noted that hospital presentation or administration of adrenaline are not reliable measures of severity, the figures reported above illustrate that most reactions in this subset of cases were serious enough to result in hospital presentation and/or adrenaline administration. This indicates these reactions likely had a significant impact on the consumer and on health services, even if reaction management was conservative, which appears appropriate for management of allergic reactions as they can rapidly progress to anaphylaxis even where previous reactions have not been as severe[5].

History of asthma and allergy

Of the 171 reviewed cases, 88 cases reported on the presence or absence of a history of allergy, and 64 cases reported on the presence or absence of a history of asthma. Of these:

- 41/88 (47%) reported a history of allergy
- 15/64 (23%) reported a history of asthma
- 6 of these cases reported a history of both allergy and asthma.
- History of allergy was reported to a wide range of substances, noting that many cases reported more than one allergen:
    - medicines in 17 cases (amoxicillin/penicillin/flucloxacillin/codeine/augmentin/antihistamines/adrenalin/ACE inhibitors/other Andrographis medicines/sulfur antibiotics/topical cream/ suxamethonium/Friar's balsam)
    - other allergens in 15 cases (cats/bees/latex/ants/dust/dust mites/grass seeds/certain trees/corn/soy/eggs/crustaceans/flowers/pet dander/ryegrass/Bermuda grass/Jack jumpers/cold/pollen)

The information obtained about allergy and asthma history suggests that if the advice was followed, a label warning to contraindicate use in individuals with a history of allergy would only have prevented less than half of cases, while a contraindication for those with asthma would have only prevented 23% cases.

The use of adverse event data by the TGA

Collecting reports of adverse events is a critical part of the pharmacovigilance system to monitor medicine safety.

While reporting of an adverse reaction to the TGA does not necessarily mean that a causal link with the medicine is established, a close temporal relationship between the exposure and clinically acute adverse events (such as anaphylaxis) is considered to increase the strength of evidence supporting a causal link.

The TGA uses adverse event data, together with other information sources, to determine whether the weight of evidence is sufficient to demonstrate a causal relationship between a medicine and/or ingredient and an adverse event. Identified safety concerns are then addressed through risk mitigation to ensure that medicines retain a positive benefit to risk balance and/or appropriately positioned within Australia's regulatory framework.

The causal link between anaphylaxis and Andrographis-containing medicines is well established and supported by the high number of adverse event reports received by the TGA, most with a close temporal association with the medicine. Label warning requirements are currently in place for listed medicines in Australia.

Summary of Australian adverse events

There has been an increasing number of Andrographis-associated anaphylaxis cases reported to the TGA, with most (184/254 [72%]) received since 2019. s47G

s47G

s47G was one of 27 medicines for which anaphylaxis cases were reported that also contained an Echinacea ingredient. Echinacea is also associated with allergic reactions. Although the majority of cases related to medicines with both Andrographis and Echinacea, supply of these medicines was far higher. Notwithstanding, 19% (49/254) of Andrographis-related anaphylaxis cases involved medicines that did not contain Echinacea. Since 2005 there have only been 13 anaphylaxis cases reported to the TGA involving medicines that contain Echinacea without Andrographis. This indicates that Echinacea was not the primary causative factor in the anaphylaxis adverse events observed for Andrographis-containing medicines.

Supply data provided by medicine sponsors suggests that anaphylaxis to Andrographis is possibly rare or very rare, however a true rate of occurrence cannot be estimated due to under-reporting and limitations with the use of supply data. Nevertheless, supply data for individual medicines confirmed that there were a higher number of anaphylaxis adverse event reports for medicines supplied in higher volumes while reports of anaphylaxis were often not reported for products supplied in low volumes.

Although there is a slight correlation between the increased number of reports and an increase in supply during the Covid-19 pandemic, a high number of reports in 2024 suggests that a greater awareness of anaphylaxis from Andrographis through safety alerts and media may also have contributed to increased reporting. This supports that under-reporting due to lack of awareness is likely.

A detailed review of anaphylaxis case narratives revealed that of the cases where certain data elements were able to be obtained from the report:

- Most (83/117 [71%]) occurred in patients who had either use the suspected medicine for the first time, or who had previously used without a reaction, therefore anaphylaxis cannot be predicted in the majority of cases.
- Most (99/133 [74%]) had a rapid onset of symptoms within 30 minutes of exposure to the suspected medicine.
- Most (105/155 [68%]) were treated with adrenaline
- Most (130/163 [80%]) presented to hospital (emergency and/or admission).
- Less than half (41/88 [47%]) had history of allergy while only (15/64 [23%]) reported a history of asthma.

The adverse event data did not identify any consumer subgroups at greater risk of anaphylaxis associated with Andrographis.

International adverse events

World Health Organization (WHO) VigiBase

A review of the World Health Organization's (WHO) VigiBase[xiii] data up to 16 March 2025 identified 52 cases of anaphylactic reaction, anaphylactic shock, anaphylactoid reaction or anaphylactoid shock

[xiii] VigiBase is the WHO global database of reported potential side effects of medicinal products, developed and maintained by Uppsala Monitoring Centre (UMC). Information in VigiBase comes from a variety of sources, and

that involved oral[xiv] Andrographis as the sole suspected single ingredient, excluding Australian cases. s33 .

Although the number of anaphylaxis cases for sole suspected oral Andrographis appears quite low, VigiBase data up to 16 March 2025 showed positive disproportionality scores for Andrographis and the reactions anaphylactic reactions (3.5) and anaphylactic shock (2.1) using the information component model and its lower limit of a 95% credibility interval (IC^{025}) [xvi, xvii]. This reveals a higher-than-expected number of reports compared with all reported reactions for Andrographis and all reports of anaphylactic reaction and anaphylactic shock for all active ingredients. It should be noted that these disproportionality scores were based on all routes of administration and were not limited to the oral route.

A search of VigiBase data up to 18 March 2025 was also performed for oral[xiv]**Error! Bookmark not defined.** (cross ref to footnote re oral use) use of *Echinacea* species (*Echinacea angustifolia*, *Echinacea purpurea*, *Echinacea pallida*, *Echinacea* spp.) which identified 4 cases of anaphylactic reaction, anaphylactic shock, anaphylactoid reaction or anaphylactoid shock where Echinacea was the single suspected ingredient.s33
s33 .

The only positive IC^{025} disproportionality score for any *Echinacea* spp. and reaction terms specific to anaphylaxis was *Echinacea purpurea* and anaphylactic shock (1.1)[xix]. There was no disproportionate reporting for other *Echinacea* species and reaction terms specific to anaphylaxis.

Therefore, international adverse event data reveals that disproportionate reporting for anaphylactic reactions (3.5) and anaphylactic shock (2.1) for single ingredient Andrographis products is greater than for Echinacea, which showed disproportionately high reporting for anaphylactic shock with *Echinacea purpurea* (1.1) only, with a lower IC^{025} disproportionality score than for Andrographis.

A broader search of VigiBase data up to 18 February 2025 using SMQs Anaphylactic reaction (Broad) or Anaphylactic/anaphylactoid shock conditions (Broad) identified 368 case reports involving oral[xiv] (cross ref to oral footnote) use of Andrographis, excluding Australian cases[xx]. This shows there were far more global cases that were possibly related to anaphylaxis than those with anaphylaxis-specific reaction terms alone.

Of the 368 cases, 335 involved Andrographis as the sole suspected single ingredient. None involved andrographolide. Of the 335 cases:

- 49 were characterised as serious:

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the probability that the suspected adverse effect is drug-related is not the same in all cases. The information does not represent the opinion of the UMC or the WHO.

[xiv] It should be noted many cases did not include a route of administration, therefore limiting case numbers to those that reported 'oral' is likely an understatement of actual case numbers associated with oral use.

[xv] D25-1090179. Filters: Country of primary source: Australia unchecked, Route of admin: oral checked.

[xvi] D25-1090179

[xvii] It should be noted that the IC does not imply causality, but an IC value that increases over time and a positive IC025 value suggests a connection between the drug and adverse reaction based on reporting to VigiBase. Alternative explanations for the positive IC need to be considered and clinical assessment remains essential (Uppsala Monitoring Centre, 2016).

[xviii] D25-1189996. Filters: Country of primary source: Australia unchecked, Route of admin: oral checked, Role: suspect only or suspect/concomitant combinations only.

[xix] D25-1189996

[xx] D25-778388. Filters: Country of primary source: Australia unchecked, Route of admin: oral checked.

  - 4 of these were reported as life threatening,
  - 40 caused / prolonged hospitalisation,
  - 5 were reported as other medically important condition,
- 138 cases reported 'no' to serious (in response to a yes/no field on the reporting form),
- 148 cases did not report on the seriousness,
- no cases reported a fatal outcome,
- s33

s33

In the literature, one retrospective study that assessed a subset of WHO VigiBase data for acute hypersensitivity reactions to herbal medicines in children between 1968 to August 2014 identified Andrographis as attributing to 4.7% of reported cases[6]. Interestingly, another study using WHO VigiBase data from the same time period found that Andrographis was the 3rd most frequently reported herbal medicine associated with immediate allergic-like reactions, when strict inclusion criteria was applied, with 5% of immediate allergy-like reactions attributed to this ingredient. However a disproportionality analysis did not reveal a disproportionate number of reports for Andrographis at that time[7].

Thailand

s33

[xxi] D25-1190013

[xxii] Prior to 2018 ingredients were not coded in the TGA adverse event database, therefore reports provided to VigiBase prior to 2018 may not have included ingredient data. However, our analysis showed that there were Australian cases both prior to 2018 and post 2018 that were not in the customised VigiBase data.

s33

According to earlier published reviews of pharmacovigilance data for Thailand, several cases of anaphylactic shock and anaphylactic reactions associated with oral Andrographis have been reported to Thai authorities[8, 9].

A retrospective post-market study of AE data held in Thailand's adverse event database (Thai Vigibase) between 2001 and 2012 located 106 hypersensitivity cases involving Andrographis as the sole suspected medicine. Of these, 88% cases were reported with no previous history of a drug allergy. Additionally, 18 cases were serious, 16 required hospitalisation, with 13 cases considered critical according to WHO criteria: 5 cases of anaphylactic shock, 4 cases of anaphylactic reaction and 4 cases of angioedema. Of the 13 critical cases, the onset time ranged from 5 minutes to 1 day, with doses varying from 352mg to 1750mg, all being Andrographis dry powder. Of the 106 reports, reactions developed during the first day of administration in 57.6% of cases, and during the second day of administration in 22.6% of cases, although reactions still developed on or after 4 days of use in 4.7% of cases. In total, 2 cases were considered life threatening[8].

In another post-market study using a subset of data in the Thai Vigibase from 2002 to 2013, adverse event reports for Thai traditional medicines (TTMs) were analysed to quantify their contribution to all adverse event reports and to determine how many were serious. The paper reported that the number of reports for single herbal medicines was highest for Andrographis (179 reports), which also had the highest number of serious reports (44 [24.6%])[9]. Six reports for Andrographis were of anaphylactic shock. A disproportionality analysis using reporting odds ratio (ROR) was applied to these cases. Authors commented that a high ROR suggests public health importance. Andrographis and anaphylactic shock was found to have a significant crude ROR (2.32 [95% CI: 1.03, 5.21]) and adjusted ROR (2.68 [95% CI: 1.19, 6.04]). ROR). However, authors further commented that the reported population attributable risk (RPAR), which 'indicates the proportion of a specific ADR in the whole dataset that could be avoided if the medicine is removed from use', was very low (0.05%) compared to Western medicine due to the low number of reports for Andrographis and anaphylactic shock in the dataset. Authors also provided ROR and RPAR values for reports of anaphylactic shock for the three most reported conventional medicines and also for Penicillin G. The adjusted ROR for Andrographis was higher than for all except for Penicillin G, whereas the RPAR was lower than for all four conventional medicines reported in the paper. Nevertheless, the authors concluded that the association between Andrographis and anaphylactic shock was weak but significant.

Key points – adverse events

- Andrographis-related anaphylaxis reports to the TGA have notably increased since 2019, with 184 received between 2019 and 31 December 2024 of a total of 254 reports.
- Although most reports are for medicines that also contain Echinacea, supply data shows these medicines were supplied in far higher numbers. Notwithstanding, 49 (19%) cases involved medicines with no Echinacea. The number of anaphylaxis cases for Echinacea-containing medicines without Andrographis is low, with only 13 reports received since 2005.
- The increasing number of anaphylaxis cases since 2019 may relate to an increase in supply since the Covid-19 pandemic. However, the increase in reports in 2024 suggests that heightened awareness through safety alerts and media has led to increased reporting, which indicates that under-reporting due to lack of awareness is likely.
- Of the Andrographis-related anaphylaxis cases that reported on certain details in the case narratives:
    - most occurred in patients who had either used the suspected medicine for the first time, or who had previously used without a reaction, therefore anaphylaxis cannot be predicted in most cases.
    - most had a rapid onset of symptoms within 30 minutes of exposure to the suspected medicine.
    - most were treated with adrenaline
    - most presented to hospital
    - less than half (41/88 [47%]) reported a history of allergy while (15/64 [23%]) reported a history of asthma.
- The adverse event data did not identify any consumer subgroups at greater risk of anaphylaxis associated with Andrographis.
- International reporting reveals disproportionately high reporting for Andrographis that is greater than that for Echinacea.
- Several cases of anaphylactic shock and anaphylactic reactions associated with oral Andrographis have been reported to the FDA Thailand and described in literature.

Risk profile

Data analysis of preparation type

The TGA's adverse event data for anaphylaxis reports for Andrographis-containing medicines and data provided by sponsors was analysed for trends[xxiii] related to:

- Andrographis extract ingredient and manufacturer;
- extract concentration ratios;
- extract solvents;
- plant part; and
- andrographolide content per dose.

Considering that anaphylaxis from Andrographis is possibly rare or very rare, an absence of adverse event reports for products supplied in low volumes is not unexpected and analyses of these products

[xxiii] See spreadsheet in TRIM D25-1386479

for trends is not reliable. Therefore, analyses were conducted on the 'top 20' products by supply volume, s47

Andrographis extract ingredient manufacturer

There were eight different manufacturers of Andrographis extract ingredients for the 20 medicines supplied in highest volumes. Adverse events were noted for products with extracts from five of these manufacturers (63%). Although there were no adverse events reported for medicines that contained extracts from 3 manufacturers, only 4 medicines used extracts made by these manufacturers. When considered together with further data analysis of extract types, this was not considered compelling evidence that extracts from these manufacturers were in some way different to other extracts and less likely to cause adverse events. Therefore, no clear trends could be identified for anaphylactic adverse events associated with any particular extract ingredient manufacturers (see Table 2).

Table 2. Proportion of products with anaphylaxis adverse events using Andrographis extract ingredients by manufacturer

Andrographis ingredient manufacturer	Count of products using manufacturer	No of products with adverse events	% of products using manufacturer associated with adverse events
s47			

Andrographis extract ingredients, extract concentration ratios and extract solvents

There were 11 different Andrographis extract ingredients for the 20 medicines supplied in highest volumes. Adverse events were identified for seven of these (64%). Adverse events have occurred in products with concentration ratios from 14:1 to 200:1 (see Table 3). While no adverse events have been received for the product that contained a 10:1 extract, adverse events had also not been received for products with a 16:1 extract and a 28:1 extract. The extract solvents were a mixture of ethanol, methanol and water (see Table 4). No clear trends could be identified for anaphylactic adverse events associated with particular extract ingredients, extract solvents or extract concentration ratios.

Table 3. Proportion of products with anaphylaxis adverse events using Andrographis extract ingredients / extract concentration ratios

Manufacturer	Name of Andrographis extract ingredient	Count of products using extract ingredient	No of products with adverse events	% of products using extract ingredient associated with adverse events
s47				

Table 4. Proportion of products with anaphylaxis adverse events using extracts made with certain solvents

Solvent	Count of products using solvent	No of products with adverse events	% of products using solvent associated with adverse events
Ethanol, or Ethanol/H_20	7	4	4/7 (57%)
Methanol, or Methanol/H_20	10	7	7/10 (70%)
H_20	3	2	2/3 (67%)

Plant part

Typically, the dried stems and leaves of Andrographis are used in medicinal preparations[10]. ARTG entries and information provided by sponsors in response to s31 Notices refer to plant parts herbs, herb top, leaf and whole plant.

Of the 20 medicines supplied in highest volumes, adverse events were reported for products that used each of these plant parts. While herb top and leaf had a slightly lower proportion of products with adverse events reported, this was not considered compelling evidence of a trend as there is considerable overlap in plant part definitions[xxiv] (see relevant definitions below). Further, while the definition of whole plant includes underground parts, Andrographis roots or rhizomes are not known for medicinal use.

Herb

- all the aerial parts present at harvesting when only vegetative parts are present—that is, the reproductive structures of flowers and fruits are not present.
- stems with attached leaves where there is little flower or fruit material in the harvest (not with root or rhizome).

Herb top

- terminal ends of stems/branches with attached leaves where there is little flower or fruit material in the harvest (not with root or rhizome)

Leaf

- where true leaf, including leaf blade and stalk of simple leaf, or leaflets and stalks in compound leaf, with any stipules and axillary buds
- where broad portion of leaf (lamina) with leaf stalk (petiole)

Whole plant

- where entire plant body, including any underground parts, holdfasts and reproductive structures.
- where only aerial parts, refer herb and herb top

Table 5. Proportion of products with anaphylaxis adverse events using different plant parts

[xxiv] TGA approved terminology for therapeutic goods

Plant part	Count of products using plant part	Number of products adverse events	% of products using plant part associated with adverse events
Herb	2	2	2/2 (100%)
Herb top	2	1	1/2 (50%)
Leaf	14	8	8/14 (57%)
Whole plant	2	2	2/2 (100%)

Andrographolide content per dose

The quantity of the constituent andrographolide was requested from sponsors, however not all sponsors provided this information. It is not a requirement to declare the andrographolide content in ARTG entries when using Andrographis in listed medicines.

The products' recommended dose as per the label provided by the sponsor was used for this analysis i.e. andrographolide content per dosage unit multiplied by the recommended single dose on the label. The recommended single dose was used rather than the maximum recommended daily dose as the qualitative case review indicated that most anaphylactic adverse event reactions occurred following a single dose of the medicine rather than after cumulative exposure.

No clear trends could be identified for anaphylactic adverse events associated with certain andrographolide doses.

Table 6. Proportion of products with anaphylaxis adverse events for certain andrographolide doses

Andrographolide content per single dose (to nearest whole number)(mg)	Count of number of products with andrographolide content in each range.	No of products with adverse events	% of products for each andrographolide range associated with adverse events
≤20	1	1	1/1 (100%)
21-40	2	0	0/2 (0%)
41-60	2	2	2/2 (100%)
61-80	7	6	6/7 (86%)
81-100	1	1	1/1 (100%)
101-120	1	0	0/1 (0%)
120-140	3	3	3/3 (100%)

Comments on dose from the literature and sponsor risk assessment

A systematic review and meta-analysis on the safety of Andrographis reported no significant difference in incidence of serious AEs between low dose and high dose oral andrographolide (≤120 mg/day vs >120 mg/day), however only 5 serious AE reports were included in the analysis. Notwithstanding, the authors concluded that this was consistent with existing evidence, that serious adverse events are usually immunological-allergic responses and unlikely to be dose related[11].

In contrast, an earlier reported dose escalation study involving oral Andrographolide reported one anaphylactic reaction in a HIV+ patient in week 4 of the study after the dose was increased from 5mg/kg to 10mg/kg[12]. While the impact of HIV on any immunological reaction is not clear, the occurrence of anaphylaxis after the dose was increased could suggest a dose-response relationship. However, considering reactions can occur after many previous uses as provided in the expert advice, and that this study identified one case only, the occurrence of anaphylaxis after the dosage increase may be due to other factors and/or unrelated to dose.

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Composition of Andrographis extracts

The ARTG does not capture the full constituent profile of Andrographis extracts nor the complexity of the extraction process. s47

s47

It is noted that the monograph for Powdered Andrographis Extract in the United Stated Pharmacopeia (USP) includes a limit of no more than (NMT) 15% for the constituent 14-deoxy-11,12-didehydroandrographolide[10].

This limit is not present in the USP monographs for Andrographis ('the dried stems and leaves of *Andrographis paniculata* (Burm. f.) Nees (Fam. Acanthaceae)'), or Powdered Andrographis ('Andrographis reduced to a fine or very fine powder').

The definition of Powdered Andrographis Extract in the USP monograph states:

> 'Powdered Andrographis Extract is prepared from Andrographis by extraction with methanol or alcohol. The ratio of plant material to extract is between 15:1 and 10:1. It contains NLT 90.0% and NMT 110.0% of the labeled amount of diterpene lactones, calculated on the dried basis as the sum of andrographolide, neoandrographolide, 14-deoxy-11,12-didehydroandrographolide, and andrograpanin. The content of 14-deoxy-11,12-didehydroandrographolide is NMT 15% of the total diterpene lactones. It may contain suitable added substances as carriers.'

It is not clear why the NMT limit is in place for 14-deoxy-11,12-didehydroandrographolide in the USP monograph for Powdered Andrographis Extract. A brief literature search for review articles could not locate compelling evidence that 14-deoxy-11,12-didehydroandrographolide is more likely than other constituents to cause anaphylaxis or other adverse events.

A systematic review and meta-analysis on andrographolide derivative medications included salts of 14-deoxy-11,12-didehydroandrographolide, which are used in injections in China as potassium sodium dehydroandrographolide succinate (PSDS) (Yanhuning injection), and potassium dehydroandrographolide succinate (PDS) (Chuanhuning injection). The article reported a similar rate of adverse events for PDS and Andrographolide sulfonate (AS) injections[13]. Authors identified adverse events from randomised controlled trials (RCTs), non-RCTs and case series, with 11 cases of anaphylaxis reported for AS and 17 unspecified anaphylactic reactions reported for PSDS. Authors also identified a further 97 cases of anaphylaxis identified in literature case reports (AS: 30 cases, PSDS: 21 cases, PDS: 45 cases, and andrographolide sodium bisulfite (ASB): 1 case). Of these, 55 were life-threatening anaphylactic shock (CTCAE grade 4[xxv]), and three patients died (CTCAE grade 5), one each using AS, PSDS and PDS (see Appendix C – Shang et al. 2022). Authors did not identify any derivative injection medication as associated with more adverse reactions nor as higher risk. Notwithstanding, the relevance of adverse event data for andrographolide-derivative injections to oral Andrographis extracts is limited.

Comments on risks inherent to typical Andrographis use

There are several factors inherent to the typical use of Andrographis that may increase risk. Andrographis is commonly indicated for symptomatic relief from viral infections such as common colds and flu and to support healthy immune system function. As stated in the expert advice, factors that increase the risk of occurrence or that increase the severity of allergic reactions include viral infection and use of other medicines such as Non-Steroidal Anti-inflammatory Drugs (NSAIDs). Both can be present when using Andrographis which is primarily used in the presence of viral infections for which concurrent use of NSAIDs is possible. While there is limited evidence from the analysed TGA cases that NSAIDs were commonly consumed as concomitant medications, it is possible that not all concomitant medicines were reported.

General allergy advice recommends that anaphylaxis treatment guidance should be followed for allergic reactions as they can rapidly worsen to a severe anaphylactic reaction, even where similar milder reactions have occurred in the past, as the next reaction may be more severe[5]. This pattern was observed in Andrographis cases that reported on reactions to previous use, where most were mild reactions followed by anaphylaxis on subsequent exposure. This further highlights the way typical use of Andrographis can increase risk where milder reactions such as rash or flushing could be mistaken for symptoms of a virus for which Andrographis is being consumed. Therefore, it is possible that consumers may not be aware of the increased risk of a severe reaction if they did not recognise a milder reaction after a previous use. This also indicates that strengthened label warnings to contraindicate use in people who have experienced allergic reactions in the past may not effectively mitigate risk (further discussed below).

Notwithstanding, a mild or moderate reaction does not always occur prior to developing anaphylaxis[5], again highlighting the unpredictable nature of anaphylaxis that can occur without warning and the limitations of a label contraindication.

Comments on consumer subgroups at greater risk

As noted above in the detailed analysis of narratives in a subset of anaphylaxis cases, consumer subgroups at greater risk could not be conclusively identified.

[xxv] CTCAE = Common Terminology Criteria for Adverse Events, G1 = mild, G2 = moderate, G3 = severe or medically significant, G4 = life-threatening, G5 = lethal.

Of the cases that reported on a history of allergy or asthma, 53% (47/88) reported no history of allergy while 77% (49/64) reported no history of asthma. This indicates that a contraindication for those with a history of allergy or asthma is not sufficient to reduce the risk of occurrence.

Of those who reported previous use of the suspected medicine, only 36% (34/95) reported they had experienced a reaction after previous use, with 64% (61/95) reporting no reaction after previous exposure. This indicates that a contraindication for those who experienced a previous anaphylactic reaction to the Andrographis-containing medicine is not sufficient to reduce the risk of occurrence.

The majority of anaphylaxis reports where age has been provided are for adults aged between 18 and 65 years (214/225 [95%]), while 11 (5%) anaphylaxis cases occurred in adolescents 12-17 years old. It is not a requirement for listed medicines containing Andrographis to be restricted to adult use only. However, even where instructions may state for adults only, adolescents 12 years and over can be considered by some consumers to be suitable for adult dosing. Adolescents may not have the capacity to manage unexpected and rapid anaphylaxis onset if they are not with caregivers, therefore this is a particularly vulnerable population group. While placing an age restriction on Andrographis when used in listed medicines may go some way towards addressing risks of anaphylaxis for younger consumers, it is not considered an adequate or appropriate option as risk mitigation is required for all age groups.

Other medicines at risk of anaphylaxis

The ingredient Royal Jelly is permitted for use in listed medicines and is associated with severe allergic reactions including anaphylaxis. Listed medicines that contain Royal jelly are required to display the following label warning statements:

> 'Not suitable for children'
> 'Not to be taken by asthma and allergy sufferers' in 3 mm type, prominent on front and
> 'This product contains royal jelly which has been reported to cause severe allergic reactions and in rare cases fatalities, especially in asthma and allergy sufferers'.

Although there have been 3 deaths reported for Royal Jelly products in Australia between 1993 – 1997 which led to strengthened label warnings, the TGA has not received any allergic-like reaction reports for Royal Jelly containing medicines since 2015. When this matter was considered by the TGA and the then Complementary Medicines Evaluation Committee (CMEC) in 1997 the available information suggested that royal jelly products could be contaminated or adulterated, and that the introduction of a standard would ensure royal jelly products on the market did not contain allergens such as pollen. A compositional guideline for Royal Jelly was subsequently developed. It is not known whether this or the strengthened label warnings or both led to a decrease in serious reports. Further consideration will be given to appropriate risk mitigation for this ingredient if any additional serious reports are received. A point of difference for Andrographis is that there have been no quality or preparation concerns identified for the Andrographis ingredients in listed medicines involved in reactions (discussed above in the section: Analysis of preparation type).

Other ingredients that require an allergy warning when used in listed medicines are propolis and pollen. There has been 1 report of an anaphylactoid reaction for a propolis containing medicine in 1998, and 3 reports of anaphylactic / anaphylactoid reactions for medicines containing pollen, with the most recent being in 2020. The risk of these medicines causing serious allergic reactions in Australia appears relatively low compared to Andrographis, based on recent AE reporting.

Other medicines known to commonly trigger anaphylaxis include NSAIDs such as ibuprofen, acetyl salicylic acid (aspirin), paracetamol and the antibiotics amoxicillin and moxifloxacin[14]. These medicines have undergone full evaluation for safety and efficacy prior to approval by the TGA to ensure risk-benefit remains favourable, unlike listed medicines (see below section on Regulatory status – Australia).

These medicines are very likely more widely used than Andrographis-containing medicines. The following table compares the number of cases of anaphylaxis for each of these medicines in the TGA adverse event management system (AEMS), in VigiBase, as well as VigiBase IC^{025} disproportionality scores. Alarmingly the relatively high number of Australian cases for Andrographis, the high disproportionality scores for Andrographis in global data compared with those for registered medicines known to cause anaphylaxis further supports that Andrographis may not be appropriately positioned within the regulatory framework for use in low risk listed medicines.

Table 7. Comparison with other medicines known to cause anaphylaxis

Drug name	No. sole suspect AE anaphylaxis[xxvi] reports in AEMS	No. sole suspect AE anaphylaxis[xxvii] reports in VigiBase[xxviii]	Disproportionality IC^{025} values from VigiBase
Andrographis	254	73	Anaphylactic reaction (PT): 3.5 Anaphylactic shock (PT): 2.1
Aspirin & acetylsalicylic acid	38	1793	Anaphylactic reaction (PT): 0.2
ibuprofen	102	3816	Anaphylactic reaction (PT): 1.6 Anaphylactic shock (PT): 0.4
paracetamol	66	1594	Anaphylactic reaction (PT): 0.3 Anaphylactic shock (PT): 0.1
Amoxicillin, amoxycillin, amoxicillin sodium, amoxicillin trihydrate, amoxycillin trihydrate.	425	6612	Anaphylactic reaction (PT): 2.2 Anaphylactic shock (PT): 2.0 Anaphylactoid reaction (PT): 0.6 Anaphylactoid shock (PT): 0.6
moxifloxacin	9	3382	Anaphylactic reaction (PT): 2.4 Anaphylactic shock (PT): 2.4 Anaphylactoid reaction (PT): 1.7

Key points – risk profile

[xxvi] Qlik AEMS search: data up to 16 March 2025, default bookmark on, sole suspect filter on, reaction terms anaphylactic shock, anaphylactic reaction, anaphylactoid shock, anaphylactoid reaction. Medicine ingredient names searched: [Andrographis paniculata], [aspirin and acetylsalicylic acid], [ibuprofen], [paracetamol], [amoxicillin, amoxycillin, amoxicillin sodium, amoxicillin trihydrate, amoxycillin trihydrate].

[xxvii] VigiBase search: Global data up to 16 March 2025, reaction terms: anaphylactic shock (preferred term [PT]), anaphylactic reaction (PT), anaphylactoid shock (PT), anaphylactoid reaction (PT), role: sole suspect or sole suspect with concomitant combinations only. Individual active ingredient names searched: Andrographis paniculata (D25-1090179), acetylsalicylic acid (D25-1090187), ibuprofen (D25-1090207), paracetamol (D25-1090214), amoxicillin (D25-1090197) and moxifloxacin (D25-1090222).

[xxviii] Reasons for the low number of reports globally for Andrographis include that VigiBase has limited functionality for multi-ingredient medicines. Additionally, herbal medicines are mostly not regulated as medicines in other jurisdictions, therefore AE data is not collected and reported to VigiBase. Where AEs are collected for herbal medicines, ingredient level data may not be collected, particularly for multi-ingredient medicines. s33 s33 .

- Analysis of adverse event data for the 20 products supplied in highest volumes did not identify any trends related to the Andrographis extract ingredient or manufacturer, extract concentration ratios, extract solvents, plant part or andrographolide content to support that restrictions on preparation type would mitigate risk.
- Factors inherent to the typical use of Andrographis that may increase risks of anaphylaxis and severe outcomes include:
    - use during viral infections
    - concurrent use of other medicines such as NSAIDs
    - milder reactions could be mistaken for symptoms of a virus, and lead to subsequent exposure
- Consumer subgroups at greater risk could not be identified
- The risk of anaphylaxis for other ingredients permitted in listed medicines that require allergy label warnings appears relatively low compared to Andrographis, based on recent adverse event reporting in Australia.
- Australian adverse event data and international disproportionality adverse event data suggest the risk of anaphylaxis from Andrographis is similar or greater than the risk for registered medicine ingredients known to commonly trigger anaphylaxis.

Risk mitigation options

Strengthened label warnings

The wording of the current label warning requirement is:

> 'Andrographis may cause allergic reactions in some people. If you have a severe reaction (such as anaphylaxis), stop use and seek immediate medical attention' (or words to that effect).

The inclusion of 'or words to that effect' to the requirement allows for variation to the wording of the warning if the meaning is retained.

There are no requirements for where the warning must be positioned on the label, nor are there specific text requirements beyond the standard text requirements (i.e. that it must be clearly visible, in English, legible, in text size of not less than 1.5mm in a colour or colours that contrast with the background colour)[xxix].

One risk mitigation option is to strengthen existing label warnings. This could include:

- Increasing the prominence of the warning, such as a bolded warning on the front of label in a box, and/or with contrasting text colours.
- Contraindications for at risk subgroups, such as individuals with a history of allergic reactions or asthma.
- Providing a list of symptoms which require consumer to seek immediate medical assistance.

The success of this option in reducing risk is dependent on several factors:

[xxix] See subsection 7(2) General requirements, including label presentation, Therapeutic Goods Order No. 92 - Standard for labels of non-prescription medicines (TGO 92).

- That reactions are occurring because consumers do not read the current warning.
- That if read, the warning would lead to reduced occurrence of anaphylaxis.
- If read, that the prompt to seek urgent medical attention would reduce severe outcomes and death once symptoms appear.
- That there is clear evidence that a contraindication for certain subgroups will reduce the occurrence of serious reactions.

Reasons why this is not considered to be an effective option:

- Anaphylaxis from Andrographis is unpredictable and a label statement that warns of anaphylaxis is not expected to reduce the occurrence.
- s47G
- Evidence from the adverse event database shows most anaphylactic reactions are occurring within 30 minutes of consuming the medicine. Anaphylactic reactions typically progress rapidly and can include difficulty breathing and collapse. For consumers experiencing these symptoms, the label warning becomes irrelevant. A label warning is also not helpful for people who do not have quick access to emergency treatment including adrenaline. It is not appropriate for a listed medicine to require ready access to emergency facilities and/or adrenaline for safe use.
- There is no clear evidence that more cases of anaphylaxis have occurred in individuals with a history of allergy or asthma to support a contraindication in this subgroup.

Restrictions on preparation types

Consideration was given to applying restrictions on certain preparation types, such as those using a particular extract, solvent, extract ratio, andrographolide content or supplied by a particular raw ingredient manufacturer. As detailed in the Data analysis of preparation type section above, there was no evidence to support a restriction on any of these parameters based on adverse reaction reports and supply data.

Education as a risk mitigation option

Consideration has been given to additional education as a strategy to raise awareness about the risks of anaphylaxis associated with Andrographis.

It is apparent from expert advice and adverse event cases reported to the TGA that awareness of this issue by both consumers and health professionals remains low.

Awareness may have increased somewhat following TGA publications and media attention after the fatal case. Other Australian publications around this time included an information update for Andrographis by the Australasian society of clinical immunology and allergy on 4 July 2024, a medicine alert by Allergy & Anaphylaxis Australia on 3 July 2024, and a clinical safety notice by NSW Health on 5 July 2024.

Education strategies in the form of medicine safety updates or alerts can help to raise awareness of a safety concern, but their value is time limited, with repeated and continuous education required for sustained messaging with wide reach. The increased number of anaphylaxis reports in July 2024 to September 2024 following the TGA safety advisory and media publications suggests that communication at the time led to increased awareness, however it is not clear that this has had a sustained effect. Education can also be useful initially to communicate any changes to the risk of a

medicine or ingredient however ultimately the regulatory processes in place for a medicine/ingredient should be sufficient to maintain its safe use.

Education as a risk mitigation option for Andrographis-containing medicines, relies on consumer awareness that leads to either quicker treatment or avoidance in higher risk individuals for this to be effective. However as previously discussed, the rapid onset and occurrence in people with no history of allergy or of prior reactions means that education is unable to reduce risks of occurrence and may not always lead to quicker access to treatment and reduced risk of death.

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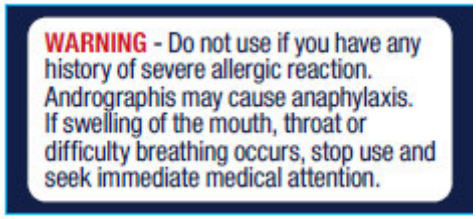

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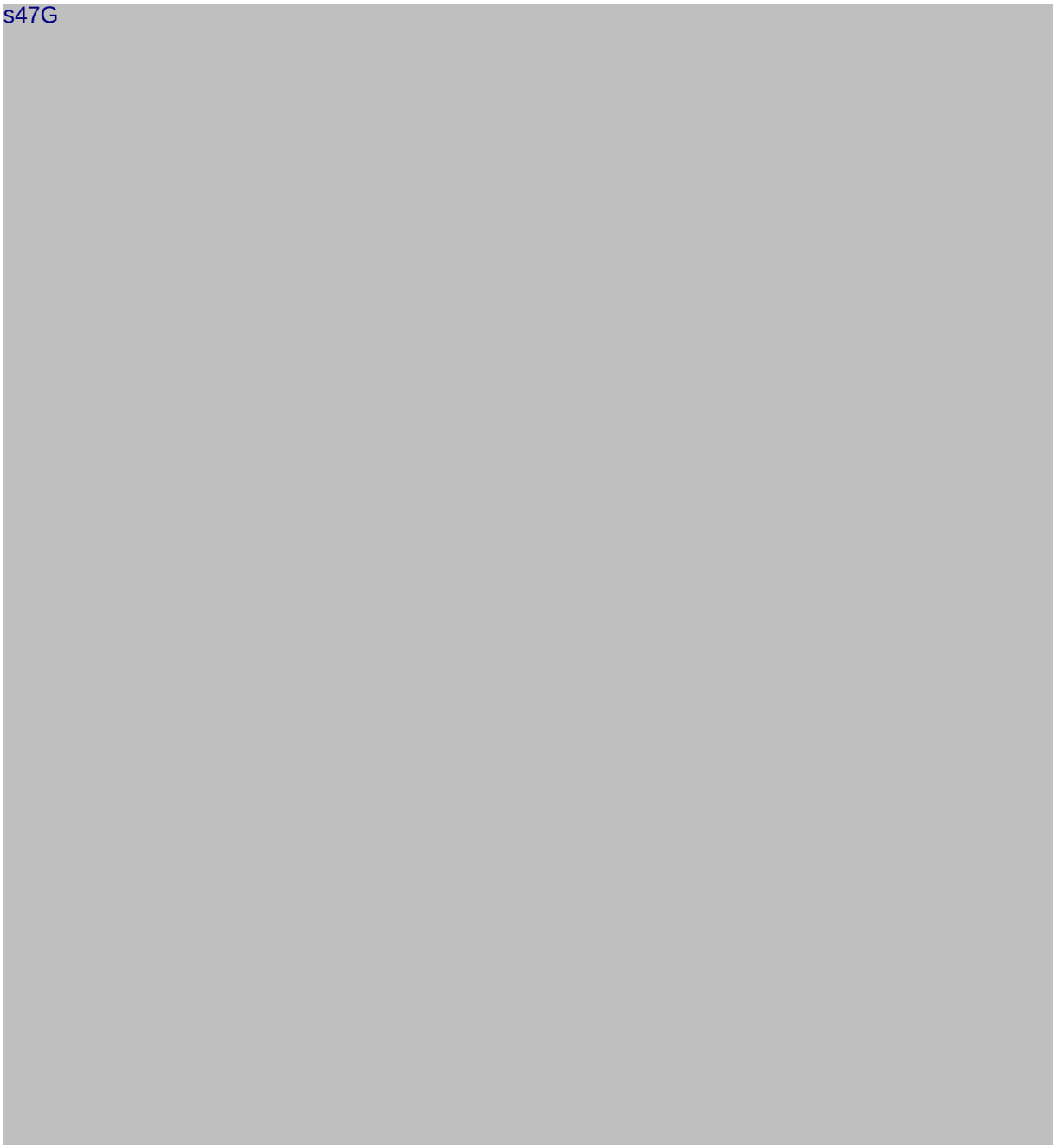

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s47G . We have not observed a decrease in the number of AE reports of anaphylaxis associated with this product since this time. This is unsurprising considering anaphylactic reactions from Andrographis are unpredictable and not limited to individuals with a history of severe allergic reactions. Therefore, stronger label warnings or prescribing practices (for practitioner supplied listed medicines) are not sufficient measures to reduce risk. If this ingredient continues to be consumed by individuals with no previous history of any allergic reaction, or indeed any individual if the ingredient label warning is ignored, serious and potentially life-threatening reactions can be expected to continue to occur.

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Information needed for informed consumer choice

Listed medicines are available without medical supervision. In addition to limiting these medicines to only use pre-approved low-risk ingredients and only have pre-approved low-risk indications, safe use is also managed through appropriate label warnings. The low-risk framework in which they are regulated likely adds to the perception by consumers that complementary medicines are safe. Therefore, when purchasing a medicine for use, an individual's own risk-benefit decision about the suitability of the medicine for them is likely weighted heavily towards the benefits and only towards the risks if the label warning is read by the consumer and it is considered applicable to their own individual circumstances. In some cases the label warning does not deter purchase but provides a guide on how to proceed if specific signs or symptoms of an adverse event are noticed or acts retrospectively to alert consumers to the cause of their symptoms.

While many over the counter medicines also have a risk of anaphylaxis they do not have the same consumer perception of safety, and they are regulated more rigorously as their safety and efficacy has been evaluated by the TGA and supply pathways to consumers have appropriate limitations or restrictions in place.

The adverse event data for anaphylactic reactions associated with Andrographis-containing medicines indicates that the number of anaphylactic reactions for this ingredient is higher than for other complementary medicines and indeed for most oral prescription medicines. It also indicates that the reaction can occur in consumers without any previous history of a reaction to the Andrographis-containing medicine. Therefore, the consumer perception of safety of the Andrographis-containing medicine needs to be adequately balanced by a description of the risk, given that anaphylaxis if not appropriately managed can be fatal. This allows a consumer to make an informed decision about whether the medicine is suitable for them in all circumstances.

Information about the Andrographis-containing medicine that would assist a consumer in making an informed decision about taking the medicine includes that:

- there is a risk of anaphylaxis associated with the ingredient Andrographis which can progress rapidly without treatment.
- anaphylactic reactions to the medicine can occur in people with or without any previous history of allergic reactions or asthma.
- anaphylactic reactions can occur in people who have previously used the medicine without any reactions even after many years of use.
- consumers should contact their doctor immediately or go the emergency department of their nearest hospital if they experience any of the following type of symptoms: shortness of breath, wheezing or difficulty in breathing; swelling of the face, lips, tongue, as they may need urgent medical attention or hospitalisation.
- Infections and other medications such as non-steroidal anti-inflammatory medicines (NSAIDs) may make anaphylaxis more likely to occur or increase the severity of the reaction and therefore the medicine should be used with caution under these circumstances.

This information is well beyond the scope of a label warning. In addition, it describes that a common indication and intended use for the medicine (for symptom relief during respiratory infections, colds and flu), has the potential to increase risk.

Key points – risk mitigation options

- Risk mitigation options that were considered included:
  - strengthened label warnings to:
    - Increase prominence
    - Contraindicate in subgroups
    - List symptoms that require consumers to seek immediate medical assistance.
  - restrictions on certain preparations
  - education to increase awareness.
- Available evidence indicates none of these options would reduce the risk of anaphylaxis occurrence or result in quicker access to treatment and reduced risk of death.

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- The information needed to accurately convey risks so that consumers can make an informed choice whether to use Andrographis-containing medicines goes beyond what could be included on a label. This information includes that a common indication for Andrographis-containing medicines (for symptom relief during respiratory infections, colds and flu), has the potential to increase the risk of occurrence and severity of allergic reactions and anaphylaxis.

Published literature

The previous TGA safety review of this issue considered literature published up to November 2011, therefore a targeted literature search was conducted for articles published after this date. The search was limited to articles that referred to *Andrographis paniculata*, adverse events and anaphylaxis / anaphylactic reactions / allergic reactions / hypersensitivity (see Appendix C for search strategy).

There were a small number of published clinical and non-clinical studies and case reports of relevance to this safety concern. Key points are summarised below with a more detailed summary of each article in Appendix C.

Clinical studies and case reports

Available clinical literature on the association between Andrographis and hypersensitivity / anaphylaxis is limited.

- Clinical trials involving oral Andrographis have mostly observed non-serious adverse events including gastrointestinal disorders (nausea, diarrhoea, vomiting, abdominal pain, dyspepsia, flatulence, constipation) and skin and subcutaneous tissue disorders (rash, pruritis, urticaria)[11, 13]. However most clinical trials involving oral use of Andrographis are of poor design, some with confounders, and have methodological limitations for the detection of rare adverse events, and many do not clearly report serious adverse events.[11,13, 15, 16]

- While one meta-analysis of RCTs involving oral Andrographis reported that serious AEs were very rare (<1/10000) or 0.02 per 1,000 patients, authors noted that the study methodology and design of the reviewed RCTs may have limited the identification of serious AEs and anaphylaxis in particular[11]. The authors reported that the pooled incidence of non-serious reactions in RCTs ≤14 days duration and in intensive monitoring studies were similar (35.3 per 1000 patients vs 34.2 per 1000 patients). Skin and subcutaneous reactions were the third most common reaction type in RCTs and the most common reaction type in post-market monitoring studies.

- There have been few published case reports involving oral use of Andrographis and anaphylaxis or reactions consistent with hypersensitivity. Our review identified three cases of anaphylaxis; one reported in Thailand after using a single ingredient Andrographis medicine[17] and two reported in New Zealand after consuming Andrographis-containing medicines (formulation details not provided)[18]. Another literature case report of rash and severe skin itching was reported in a systematic review and meta-analysis[13].

- Details of a further 5 cases of anaphylaxis were published in a conference abstract co-authored by Professor s22 who provided expert advice to the TGA (see Expert advice section below). The abstract summarised 5 cases of anaphylaxis in adults who had consumed ArmaForce[19]. The abstract was presented at the Australasian Society of Clinical Immunology and Allergy (ASCIA) conference in September 2024 to highlight risks to clinical immunologists. Of note was that skin testing was conducted in 4 of the 5 cases, with all 4 showing negative results. In one of the 4 cases, the patient experienced anaphylaxis on rechallenge. This supports the suggestion in the expert advice that the mechanism behind reactions may be IgE-independent, which also noted that more investigation is needed. Due to the limited data presented in the conference abstract, it is unclear whether these cases had been previously reported to the TGA and included in the above AE data, although a search based on reporter (sender) names in the TGA AEMS suggests they have not been reported. Notwithstanding, considering the high number of cases, an additional 5 cases are not expected to change the outcome of this review, indeed they would only serve to further support it.

- Although andrographolide[xxxi] derivative medicines for injection are not currently approved for use in Australia, they are clinically used in China for the treatment of acute infectious diseases[13,20]. Anaphylaxis has been observed in published literature involving these medicine types, including multiple case reports of severe life-threatening reactions, some reporting fatal cases of anaphylactic shock after the use of andrographolide derivative injections[13,20] . Published literature has advised doctors to ask patients about a history of allergy before prescribing andrographolide derivative injections, and to avoid use in patients with a history of allergy to any drug, or with an allergic constitution or family history of allergy, and to closely monitor for adverse reactions in patients who are given the injection for the first time[13,20] .The relevance of the anaphylactic potential of injections to the oral route of administration is currently not clear.

Non-clinical studies

AEMDS requested nonclinical comment on the allergenic potential and immunomodulatory action of Andrographis or its constituents from the Toxicology Section within the Scientific Evaluation Branch.

[xxxi] Andrographolide is naturally occurring in Andrographis paniculata and is considered the main active constituent.

The following is a direct excerpt from the assessment report from the Toxicology Section, with the full file note and reference list provided at Appendix D.

Assessment

Andrographis paniculata contains various compounds including terpenes and flavonoids. Extracts from this plant contain varying compositions of these. The quality of available literature studies was mixed, but most used standard methods for studying allergenicity and anaphylaxis in *in silico*, *in vitro* and *in vivo* systems. For the test articles used, a few of the studies used Andrographis extracts prepared from raw plant material (using different solvents, with composition reported). However, most studies used purified andrographolide, the main active constituent of Andrographis, or derivatives of andrographolide.

Pro-allergenic potential of Andrographis or its constituents

The nature of allergic reactions reported for patients receiving Andrographis extracts are indicative of a Type I (IgE-mediated) hypersensitivity reaction or of a pseudoallergy. The latter does not require sensitisation or antigen-specific IgE and involves direct activation of mast cells, occurs after the first dose and can occur at a higher frequency.

In vitro, andrographolide, dehydroandrographolide and neoandrographolide induced pseudoallergy type reactions in cellular assays. In a study using affinity chromatography with human mast cells as the bait, dehydroandrographolide was the primary component purified from an Andrographis extract. *In silico* docking suggested dehydroandrographolide was capable of binding FcεRI, which could result in direct activation of mast cells. Less affinity was seen with andrographolide.

The studies in animals focused on a typical hypersensitivity reaction mechanism of action (sensitisation and challenge). The popliteal lymph node assay in mice assesses the sensitisation potential (Pieters, 2001) while the active systemic anaphylaxis model in guinea pigs involves both a sensitisation and challenge phase. With components that elicited a pseudoallergenic potential in *in vitro* assays, an immunostimulant effect was seen in the popliteal lymph node assay but negative results were seen in the guinea pig assay. Possible reasons for the negative results in guinea pigs:

- the study design is not optimal to assess pseudoallergy type reactions
- only gross clinical signs of an anaphylaxis response were assessed; additional clinical signs (for example effects on respiratory rate) and histamine release would have provided more sensitive indicators
- guinea pigs may be a less sensitive species for pseudoallergic reactions than other animal species; dogs and minipigs are better species to assess such reactions and there have been reports of drugs eliciting pseudoallergic reactions in dogs with no evidence in rodents[xxxii]
- the doses used may not have been sufficient to elicit a response
- possible competing reactions of pro-allergenic and anti-inflammatory responses.

The *in vitro* data suggest a pseudoallergy and anaphylactoid potential of some components of Andrographis extracts. However, whether these components can elicit a typical hypersensitivity reaction is inconclusive. Likewise, the allergenic potential of other components has not been assessed. It is noted that andrographolide has low oral bioavailability, primarily due to efflux by P-glycoprotein and extensive first-pass metabolism. Co-administered medicines or foods that interact with P-glycoprotein or enzymes involved in the metabolism of andrographolide may increase exposures to andrographolide and increase the risk of allergic reactions. As well as being a

[xxxii] AusPAR for linagliptin: https://www.tga.gov.au/sites/default/files/auspar-trajenta.pdf

component of Andrographis extracts, dehydroandrographolide is also a likely metabolite of andrographolide. The allergenic potential of other andrographolide metabolites has not been assessed.

Anti-allergic/anti-inflammatory potential of Andrographis or its constituents

Andrographis-related compounds showed anti-inflammatory effects *in vitro* and *in vivo* through an inhibitory action on NF-κB/MAPK. Effects were shown *in vitro* in LPS-induced macrophages and *in vivo* in ovalbumin-sensitised mice, under conditions of hypersensitivity and inflammation. Inhibition of NF-κB by Andrographis-related substances was associated with lower gene expression of pro-inflammatory mediators, and reduced production of pro-inflammatory cytokines. In mice, treatment with Andrographis-related compounds improved airway function following ovalbumin challenge, or in response to a bronchoconstrictor. As the studies used purified Andrographis constituents (e.g., andrographolide, dehydroandrographolide) instead of herbal preparations commercially available to the general public, the clinical relevance of these findings is limited. However, these studies provide some understanding of the cellular mechanisms underlying the anti-inflammatory effects of Andrographis constituents.

As components of Andrographis appear to have competing allergenic and anti-inflammatory actions, different extracts with different compositions may affect the balance between these actions.

Predictive value of animal studies for allergenic potential

There are no standard methods for assessing the systemic allergenic potential of chemicals with nonclinical studies. Animal studies have improved understanding of hypersensitivity reactions in humans, but none are able to adequately model anaphylaxis in humans. Whilst rodent models have the advantage of being readily available, can test larger group sizes, and have well-understood physiology, they do not mimic the diversity of the human immune repertoire (i.e., the entirety of immunoglobulins, B cells, T cell receptor population). One suggested solution to address the issue of whether animal responses are representative is to use multiple animal models, each with their own strengths (Kanagaratham *et al.,* 2018). Another commentary suggested that seeking clinical similarity in allergenic responses is less important, relative to the larger goal of assessing relative allergenicity (and anaphylactic potential) of known allergens versus non-allergens (Lehrer and McClain, 2009). Thus, the value of animal studies on allergenicity lies more in better understanding mechanisms than in being used to accurately predict allergenic and anaphylactic reactions to substances.

Conclusions

The published nonclinical studies provide some evidence that:

- Some of the active ingredients in *A. paniculata* could be capable of evoking release of allergenic mediators, potentially resulting in anaphylactoid reactions. Evidence is based on *in vitro* cell-based assay and *in silico* model predictions. The lack of allergic reaction in animals raised questions about the adequacy of the animal models.
- Anti-inflammatory actions of *A. paniculata* extract and main active andrographolide was observed in mouse models of asthma.

Key points – literature

- There have been very few reported cases of anaphylactic reactions associated with Andrographis in clinical studies, noting most studies published to date have methodological limitations for detecting rare adverse events.
- A small number of case reports of anaphylaxis or severe allergic reactions have been published in the literature.
- Published nonclinical studies provide some evidence that some of the active constituents in Andrographis could evoke allergenic mediators potentially resulting in anaphylactoid reactions.
- Anti-inflammatory actions of Andrographis and andrographolide have been observed in a mouse model.

Regulatory status

Australia

Andrographis is permitted for use in listed medicines in Australia. Listed medicines are regulated as low risk medicines and are therefore only permitted to contain low risk ingredients unless any unacceptable risks can be appropriately reduced, such as through communication to consumers via label warnings. Further controls can be applied to ingredients with identified risks to ensure the risk remains low.

Listed medicines are not evaluated for efficacy or benefits and only low-level indications can be used that are appropriate for self-selection and self-administration without medical advice or supervision. Listed medicines can be supplied for purchase by consumers from retail outlets without health professional advice. Therefore, the risk of each Andrographis-containing medicine must be sufficiently low to remain appropriately regulated as a listed medicine.

There are limitations when considering the risk-benefit of any particular ingredient within the context of the listed medicines regulatory framework. The benefits of an ingredient may change depending on the indications and the formulation of the medicine in which it is used. There are no limits on how many ingredients or indications can be applied to each listed medicine. Restrictions on the preparation type of an ingredient, dosage regime or population are relatively few for listed medicine ingredients, and do not apply to Andrographis. Therefore, listed medicines that contain an ingredient of concern such as Andrographis can be considerably varied in composition, dose and indications. It is the responsibility of each sponsor to ensure the risk-benefit profile of each of their medicines remain appropriate.

Notwithstanding, where a safety concern is identified for an ingredient that suggests the risk-benefit of all medicines that contain that ingredient may no longer be favourable for a listed medicine, it is the regulator's role to take appropriate action to mitigate consumer risk. The purported benefits of Andrographis were considered as part of the 2015 review and have not been replicated here, noting only low-risk indications are permitted for listed medicines. The availability of other ingredients with similar benefits was also considered in the 2015 review and these ingredients remain available for use in listed medicines.

Approximately 84 listed medicines in the ARTG contain Andrographis. These products frequently have indications such as relief of cold and flu symptoms, or immune support. Only 8/84 listed medicines include indications in their ARTG entries unrelated to symptom relief for viral illnesses or

general immune support. These include gastrointestinal and /or liver support, skin support or anti-inflammatory / joint pain relief[xxxiii].

In addition to the label warning for allergic reactions / anaphylaxis, listed medicines that contain Andrographis are also required to display the label warning:

> '*Andrographis may cause taste disturbance including loss of taste. If you develop any adverse symptoms - stop use and seek medical advice*.' (or words to that effect)

There are no other restrictions that apply to this ingredient when used in listed medicines in Australia.

One of the required certifications for listing a medicine on the ARTG, is that it is safe for its intended purpose. This certification may not be correct for Andrographis-containing listed medicines where indications are for use during infections, considering this has the potential to increase the risk of occurrence and severity of allergic reactions.

International regulation

International jurisdictions do not always regulate herbal medicines in the same way as other medicines, therefore safety evaluations and pharmacovigilance data are not always available. Nevertheless, some have received adverse event reports of anaphylaxis and hypersensitivity reactions associated with Andrographis, mostly in multi-ingredient preparations, some have related label warning requirements, and one has published a safety communication on the topic. Details for each regulator are provided below in Table 8 and in Appendix E.

Table 8. Summary of International regulation

Regulator	Regulates Andrographis as a medicine	Received reports of anaphylaxis or hypersensitivity/allergic-type reactions associated with Andrographis	Requires label warnings related to allergy	Published safety communications
s33				

[xxxiii] According to reporter search for Andrographis in listed medicines on 18 June 2025 (D25-2622002).

s33

Regulation in Thailand

In Thailand, Andrographis is on the National List of Essential Medicines (NLEM) in Thailand for non-infectious diarrhoea and respiratory tract infection (sore throat and common cold)[8].

s33

s33

Key points – regulatory status

- Andrographis is permitted for use in listed medicines in Australia without restrictions apart from the requirements to display label warnings about:
  - risks of allergic reactions including anaphylaxis, and
  - taste disturbance.
- Andrographis is present in approximately 86 listed medicines.
- Listed medicines are regulated as low risk medicines and are not evaluated by the TGA for efficacy. Listed medicines can only claim low-level benefits appropriate for self-administration without medical advice or supervision. Therefore, any risks must be sufficiently low to remain appropriate for use in low risk listed medicines.
- One of the required certifications for listing a medicine on the ARTG, is that it is safe for its intended purpose. This certification may not be correct for Andrographis-containing listed medicines where indications are for use during infections, considering this has the potential to increase the risk of occurrence and severity of allergic reactions.
- Andrographis is widely used in Thailand and has a long history of use, s33
s33
-

Conclusion

The increasing number of anaphylaxis adverse events reported to the TGA since 2019 is concerning, as is the unpredictable manner in which they are occurring.

Serious reactions are occurring after first exposure, but also after previous use on multiple occasions without prior reaction, in people with no history of allergy or asthma. Therefore, contraindications for certain populations would not provide effective risk mitigation.

The typical use of Andrographis for viral infections, carries inherent risk as viral infections can potentiate allergic reactions or make them more likely to occur. Risks can also be increased from concurrent use of NSAIDs, possibly taken for symptomatic relief during viral infections as discussed in the expert advice. Although concurrent use of NSAIDs was not commonly reported in the adverse event cases analysed for this review, it remains possible that this could occur. Additionally, milder reactions may go unnoticed as symptoms of the virus being treated rather than identified by consumers as a risk factor for a more severe reaction on subsequent exposure.

As most anaphylactic reactions are occurring within 30 minutes of consuming the medicine, and typically progress rapidly, the label warning to seek immediate medical attention is likely of limited value even if it was more prominent.

Data analyses of Andrographis medicines supplied in high volumes did not identify any convincing trends for Andrographis ingredient preparation types or extract types that were not associated with adverse events. Therefore, there is no evidence to support that restrictions on the ingredient preparation or extract would provide effective risk mitigation.

For an ingredient to remain appropriate for use in listed medicines, it should be safe for self-administration without the need for medical advice or supervision. With only limited benefits permitted for listed medicines, the risk must also remain sufficiently low. As the risk of life-threatening anaphylaxis cannot be predicted or reliably mitigated, with an increasing number of reports involving Andrographis-containing listed medicines, this ingredient cannot be considered low risk. Justification for continued use in listed medicines could not be identified.

To conclude, the evidence considered in this updated safety review did not support strengthened risk mitigation as an effective option to reduce the risk of anaphylaxis from Andrographis.

The risk of anaphylaxis that cannot be reliably mitigated, and the increased risk of severe allergic reaction posed by an indication for the ingredient indicates Andrographis is not a low-risk ingredient and therefore does not appear appropriate to be permitted for use in listed medicines.

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ADDENDUM

Advisory committee on complementary medicines (ACCM) 37th meeting 31 July 2025

As stated in the Recommendations above, advice was sought from ACCM at their 37th meeting on 31 July 2025. See meeting minutes (D25-4920412) for a detailed summary.

ACCM advice and resolutions

ACCM advised the TGA Delegate of the Minister and Secretary that, in relation to each requested advice question:

1. Whether the Committee agrees that, based on the available evidence, when Andrographis is used in listed medicines:

    a. there is increased risk posed to the consumer because the presence of viral illness can increase the likelihood or severity of an allergic reaction, and these products are mainly used for symptomatic treatment of viral illnesses.

    Yes, the committee agrees.

    b. anaphylaxis adverse events have been sudden and unpredictable and therefore the risk of anaphylaxis is difficult to mitigate.

    Yes, the committee agrees.

    c. further risk minimisation measures to strengthen label warnings, restrict formulations or publish further education are unlikely to mitigate the risk of anaphylaxis.

    Yes, the committee agrees.

2. Whether there is:

    a. any additional evidence that has not been considered by the TGA, or in the recent published literature that provides compelling evidence as to whether a specific preparation, use, dose, source of herbal material, or herbal constituent, is responsible for anaphylaxis observed with Andrographis.

    b. any other evidence pertaining to Andrographis and anaphylaxis that has not been considered by the TGA in this safety review.

    The committee advised that they were unable to comment on whether any additional evidence was available. However, they highlighted that factors related to data analysis and an analysis of single ingredient Andrographis medicines vs combination products, as well as dose, preparation (modern extractions vs traditional use), risk/benefit, and the use of

Andrographis in combination with other ingredients needs to be given further consideration before the risk of Andrographis as a single listed ingredient can be clearly determined.

Further consideration of each of these factors, and TGA's conclusion following ACCM 37, is provided below.

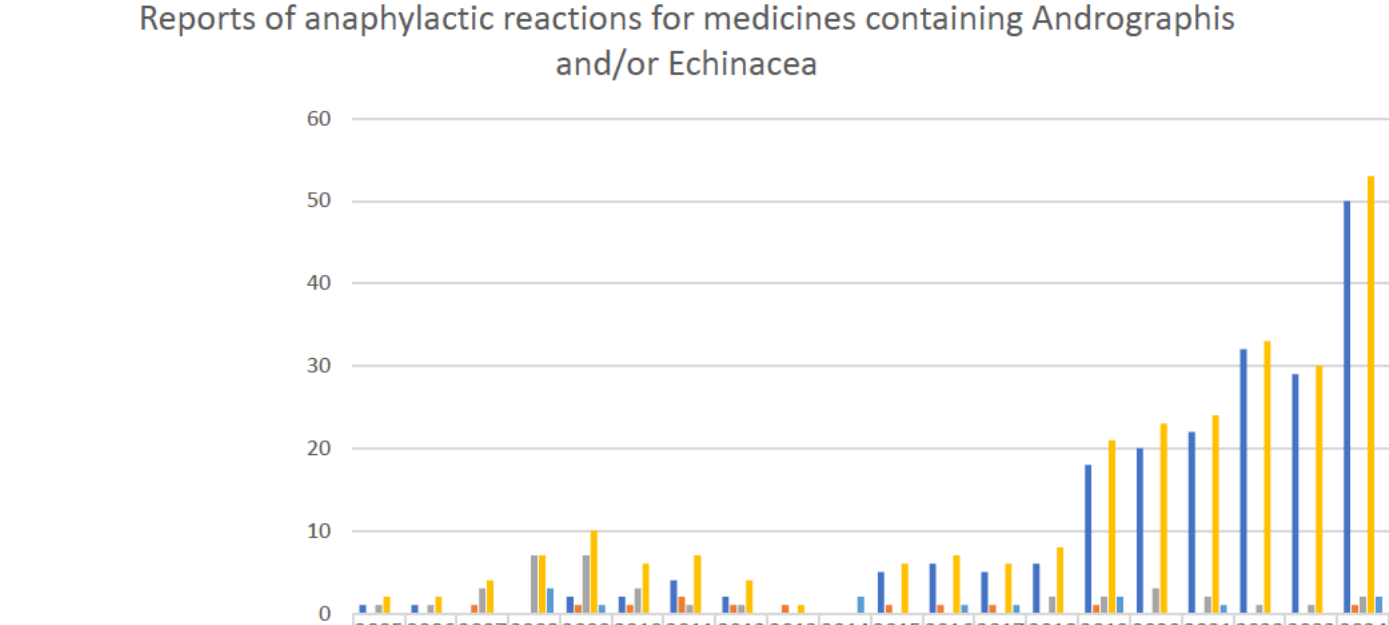
Signal analysis for single ingredient Andrographis medicines and use in combination with other ingredients

- In total there have been 24 listed medicines in the ARTG with Andrographis as the single active ingredient. 22 of these are now cancelled. s47G s47G .
- The TGA has received one anaphylaxis report associated with the current single active ingredient Andrographis medicine that has been supplied (AUST L 302367 Nature's Sunshine Andrographis), s47G s47G s47G), noting limitations for estimating a rate of occurrence.
- s47G s47G . The TGA has received 11 anaphylaxis adverse event reports for 2 of the Blackmores Cold Combat ARTG listings, however the TGA does not hold supply data for these medicines over the period the reactions occurred (since 2007)[xxxiv].

We have updated Figure 1 (see Reporting pattern section) below to show medicines with Andrographis as the single active ingredient.

[xxxiv] The requirement for sponsors to provide information to the TGA under section 31(2) of the Act applies to the preceding 5-year period. The requirement to retain records of distribution (see Therapeutic Goods (Listed Medicines - Conditions of Listing) Determination 2022) also applies to a period of 5 years. Therefore, supply data cannot be obtained from the sponsor for these medicines under the provisions of the Act.

Figure 1U. Reports of anaphylactic reactions for medicines containing Andrographis and/or Echinacea.



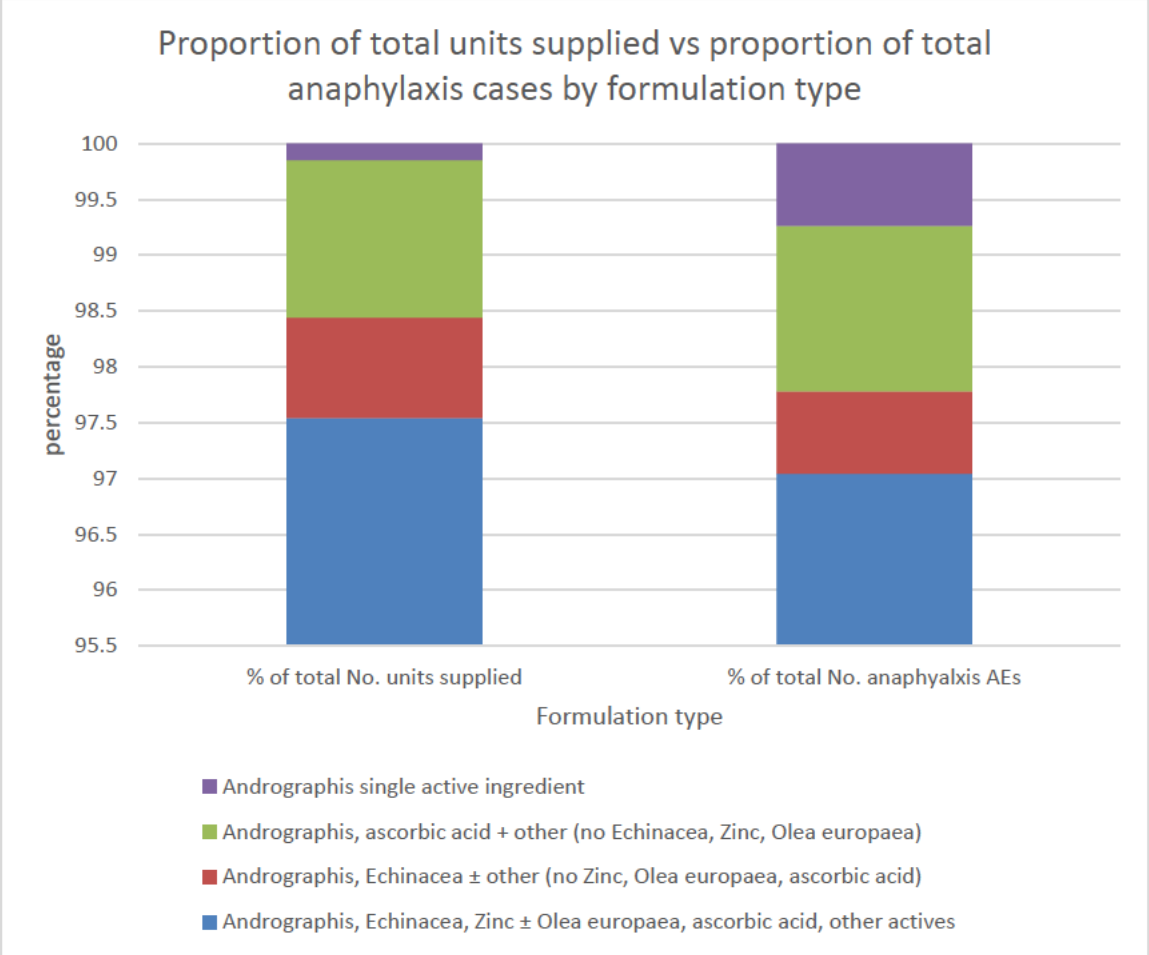
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Andrographis and Echinacea	1	1	0	0	2	2	4	2	0	0	5	6	5	6	18	20	22	32	29	50
Andrographis - single active	0	0	1	0	1	1	2	1	1	0	1	1	1	0	1	0	0	0	0	1
Andrographis with other active's	1	1	3	7	7	3	1	1	0	0	0	0	0	2	2	3	2	1	1	2
All Andrographis	2	2	4	7	10	6	7	4	1	0	6	7	6	8	21	23	24	33	30	53
Echinacea without Andrographis	0	0	0	3	1	0	0	0	0	2	0	1	1	0	2	0	1	0	0	2

The proportion of cases for medicines with Andrographis and Echinacea is high. This corresponds with a high supply volume for these medicine types. The analysis of volume supplied against adverse events showed that the vast majority (98%) of volume supplied were medicines that also contained Echinacea and other active ingredients in addition to Andrographis. Although supply data was not available for all products, this does provide some indication of the prevalence of the combination of these two ingredients in the market. Further analysis was performed on 135 anaphylaxis adverse event cases that could be linked to supply data (see supply data limitations above) grouped by formulation type – see Figure 9 and Table 9 below.

Due to the high number of different ingredient combinations, frequently combined active ingredients were grouped together for the formulation analysis. More granular grouping introduced too many variables and limited the ability to identify the effect of each variable, particularly considering the high number of unique formulations (10) of the total number of medicines (15) in the analysis. Andrographis combined with Echinacea and Zinc were most consistently present together (12/15 [80%]) with various other ingredients. Other grouping compared data for formulations with Andrographis and Echinacea, but without zinc or other common active ingredients such as *Olea europaea* and ascorbic acid. The analysis also compared data for formulations where Echinacea was not present, and where Andrographis was present as a single active ingredient.

The proportion of supply volume for each formulation type was compared to the proportion of anaphylaxis cases for each formulation type. From the analysis, it is evident that the proportion of total anaphylaxis cases for each formulation type largely correlates with the proportion of total supply for that formulation type, with the exception of Andrographis single active ingredient medicines, which had a higher proportion of anaphylaxis cases (0.74% [1/135]) when compared to the proportion of supply (0.14%s47 (D25-3808836). This trend indicates a higher number of anaphylaxis cases might be expected if higher volumes of single active ingredient Andrographis medicines were supplied. Considering this, in addition to the 12 anaphylaxis reports in total for single active ingredient Andrographis medicines, the signal for Andrographis as a single active ingredient remains supported. Furthermore, the signal cannot be considered stronger for medicines containing Andrographis combined with Echinacea or other active ingredients once supply data is taken into consideration.

Figure 9 – Formulation analysis: Proportion of supply vs proportion of anaphylaxis cases



* Other active ingredients were one or more of the following: *Curcuma longa*, *Sambuccus nigra*, citrus bioflavonoids extract, colecalciferol, retinol palmitate, *Eleutherococcus senticosus*, *Ocimum tenuiflorum*, calcium ascorbate dihydrate, sodium ascorbate.

Table 9 – Formulation analysis: Proportion of supply vs anaphylaxis cases

Formulation Type	No. units supplied	% of total No. units supplied	No. anaphylaxis AEs	% of total No. anaphylaxis AEs	No. medicines
Andrographis, Echinacea, Zinc ± *Olea europaea*, ascorbic acid, other actives	s47	s47G			
Andrographis, Echinacea ± other (no Zinc, *Olea europaea*, ascorbic acid)					
Andrographis, ascorbic acid + other (no Echinacea, Zinc, *Olea europaea*)					
Andrographis single active ingredient					
Total					

*Other active ingredients were one or more of the following: *Curcuma longa*, *Sambuccus nigra*, citrus bioflavonoids extract, colecalciferol, retinol palmitate, *Eleutherococcus senticosus*, *Ocimum tenuiflorum*, calcium ascorbate dihydrate, sodium ascorbate.

The ACCM committee also commented on Table 7 in the updated review and considered data should be presented for Andrographis as a single active ingredient when comparing to data for other medicines that appeared to relate to single active ingredient medicines. However, it should be noted that data for all medicines in the analysis included some with multi-ingredient formulations. Nevertheless, an updated version of Table 7 is provided below (Table 7U) to provide Australian data for single active ingredient medicines only, noting that VigiBase data remains unchanged as this was based on single ingredient medicines. As demonstrated above, the lower number of anaphylaxis cases for single ingredient Andrographis medicines in Australia is likely due to lower supply of these medicines, with only one being supplied in Australia at the time of our targeted investigation. Notwithstanding, the number of anaphylaxis reports for single ingredient Andrographis medicines up to March 2025 is still higher than the number reported for the Schedule 4 Prescription Only antibiotic medicine moxifloxacin.

As Echinacea was also raised as an ingredient that might be implicated in anaphylaxis cases by Committee members, Echinacea as a single active ingredient has also been included in Table 7U below. There has been only 1 Australian anaphylaxis case for a 'single' Echinacea ingredient medicine that was reported to contain 2 Echinacea ingredients as the only active ingredients: *E. purpurea* and *E. angustifolia*. The title of Table 7U has been updated below to reflect that Echinacea may be associated with anaphylaxis rather than known to cause anaphylaxis.

Table 7U. Comparison with other single active ingredient medicines associated with anaphylaxis

Drug name	No. sole suspect, single active ingredient medicine anaphylaxis[xxxv] reports in AEMS	No. sole suspect, single active ingredient medicine anaphylaxis[xxxvi] reports in VigiBase[xxxvii]	Disproportionality IC^{025} values from VigiBase
Andrographis	12	s33	
Echinacea angustifolia, *Echinacea purpurea*, and/or *Echinacea pallida*	1[xxxviii]		
aspirin & acetylsalicylic acid	31		
ibuprofen	97		
paracetamol	44		

[xxxv] Qlik AEMS search: data up to 16 March 2025, default bookmark on, sole suspect filter on, reaction terms anaphylactic shock, anaphylactic reaction, anaphylactoid shock, anaphylactoid reaction. Medicine ingredient names searched: Andrographis paniculata, aspirin and acetylsalicylic acid (D25-1090187), ibuprofen (D25-1090207), paracetamol (D25-1090214), amoxicillin, amoxycillin, amoxicillin sodium, amoxicillin trihydrate, amoxycillin trihydrate (D25-1090197), moxifloxacin (D25-1090222). **Multi-active ingredient medicines excluded.**

[xxxvi] VigiBase search: Global data up to 16 March 2025, reaction terms: anaphylactic shock (preferred term [PT]), anaphylactic reaction (PT), anaphylactoid shock (PT), anaphylactoid reaction (PT), role: sole suspect or sole suspect with concomitant (non-suspected) combinations only. Individual active ingredient names searched: Andrographis paniculata (D25-1090179), acetylsalicylic acid (D25-1090187), ibuprofen (D25-1090207), paracetamol (D25-1090214), amoxicillin (D25-1090197) and moxifloxacin (D25-1090222).

[xxxvii] Reasons for the low number of reports globally for Andrographis include that VigiBase has limited functionality for multi-ingredient medicines. Additionally, herbal medicines are mostly not regulated as medicines in other jurisdictions, therefore AE data is not collected and reported to VigiBase. Where AEs are collected for herbal medicines, ingredient level data may not be collected, particularly for multi-ingredient medicines. s33
s33

[xxxviii] D25-4153923

[xxxix] VigiLyze search 24 September 2025, Ingredients names: Echinacea angustifolia, Echinacea purpurea, Echinacea pallida. Reaction terms: anaphylactic shock (preferred term [PT]), anaphylactic reaction (PT), anaphylactoid shock (PT), anaphylactoid reaction (PT). Role: sole suspect or sole suspect with concomitant combinations only (D25-4221203).

Drug name	No. sole suspect, single active ingredient medicine anaphylaxis[xxxv] reports in AEMS	No. sole suspect, single active ingredient medicine anaphylaxis[xxxvi] reports in VigiBase[xxxvii]	Disproportionality IC^{025} values from VigiBase
amoxicillin, amoxycillin, amoxicillin sodium, amoxicillin trihydrate, amoxycillin trihydrate.	232	s33	
moxifloxacin	9		

s33
s33 . A retrospective post-market study of AE data held in Thailand's adverse event database confirmed that all cases associated with Andrographis discussed in the report involved Andrographis as a single agent[8] (cross ref: Suwankesawong 2014).

The top 20 medicines by supply volume were also re-examined for any formulation or ingredient trends for the 7 medicines with no reported anaphylaxis cases. No difference in formulation for these 7 medicines could be identified to suggest they were in some way lower risk. All contained Andrographis, Echinacea and/or Zinc, as well as other active ingredients, as per the formulations with reported anaphylaxis cases.

No other evidence was provided by ACCM nor could be located as part of the updated safety review to suggest that the risk is greater when Andrographis is combined with other ingredients, or that certain formulations were lower risk.

Dose / preparation (modern extractions vs traditional use)

Dose, preparation and a comparison of modern extracts with traditional preparations were not discussed in detail during the ACCM meeting. However as per the meeting Minutes, one member questioned the role of formulation, extraction solvents, concentration/dose of certain constituents, and manufacturing practices in adverse events and the uncertainty of whether in contrast to traditional preparations, modern day formulations pose a higher risk due to different extraction methods and consequently, different constituent profiles and enrichments.

The Committee's concluding remarks about giving consideration to dose is therefore taken to relate to risks from exposure to different quantities of certain constituents, and how these may differ from traditional preparations.

As provided in the Risk profile section above, a detailed analysis of medicines supplied in higher volumes[xl] was conducted to determine any trends relating to formulations or extract ingredient manufacturers and adverse events of anaphylaxis. Importantly, a lower risk profile cannot be attributed to medicines with no reported cases of anaphylaxis if they have been supplied in low volumes. Considering anaphylaxis from Andrographis is possibly rare (1/1,000 [0.1%) to 1/10,000 [0.01%]) to very rare (<1/10,000 [<0.01%]), an absence of anaphylaxis reports where less than 10,000 units have been supplied is not unexpected and does not suggest a lower risk preparation.

Of the top 20 medicines by supply volume, no trends could be identified to suggest the risk of anaphylaxis was greater for preparations with extracts:

- made by certain manufacturers
- with certain concentration ratios (e.g. highly concentrated extracts)
- made using particular solvents
- with a particular andrographolide content per dose
- made from particular plant parts

The 7 medicines in the top 20 medicines by supply volume with no reported cases of anaphylaxis were included in the data analysis. No clear trends were identified to suggest they were lower risk based on any of the parameters above, including andrographolide dose.

The TGA does not hold supply data for other Andrographis medicines, including traditional preparations for which reports of anaphylaxis have been received. However we have received a report of anaphylaxis associated with an s47 s47 and is considered a traditional preparation[xli]. This indicates traditional preparations cannot be considered without risk.

Andrographis crude powder in capsule and tablet dosage forms has been widely sold in Thai markets and distributed to hospitals for the treatment of cold, fever and Covid-19[xlii]. Considering multiple cases of anaphylaxis have been reported to Thai authorities, and that use of traditional crude leaf preparations is widespread in Thailand, risks from traditional preparations cannot be considered absent. Published literature on cases in Thailand refer to reactions associated with powdered leaf[8]. s33

The composition of Andrographis extracts and crude Andrographis preparations has been the subject of some published literature. For example, a recent study from Thailand examined the concentration and dissolution of 4 diterpenoids (andrographolide, 14-deoxy-11,12-didehydroandrographolide, neoandrographolide and 14-deoxyandrographolide) in four Andrographis extract products and three Andrographis crude powder products[xlii]. One of the extract products was labelled as an aqueous extract. Other extract types were not confirmed however authors commented that the commercially available Andrographis extracts are typically prepared using ethanolic extracts. The study found that the concentration of diterpenoids was greater in

[xl] Analysis was conducted on the 'top 20 medicines' equating to products supplied in volumes above 46,000 units between 2019 and 2024.

s47

[xlii] Rangkadilok N, Pholphana N, Akanimanee J, et al. Comparison of diterpenoid contents and dissolution profiles of selected Andrographis paniculata crude and extract capsules. Phytochemical Analysis. 2024;35(6): 1309-1322. doi:10.1002/pca.3364. (D25-3931247)

extracts compared to crude powder products, however there were inconsistencies in the proportions of each. Authors commented that lower andrographolide content and inconsistent quantities in crude powder can be dependent on different seasons and sources. The study also conducted dissolution testing and found the extract labelled as an aqueous extract had the highest dissolution rate of all the extracts (>80% for all 4 diterpenoids). It also found 2 of the crude powder products had high dissolution rates for all 4 diterpenoids (>70% within 15 minutes), and that all crude powder products had higher dissolution rates than extracts, with the exception of the aqueous extract. As dissolution has potential implications for pharmacokinetics, these findings indicate that preparation type may influence clinical outcomes. Authors commented that the aqueous extract maybe more soluble and likely to release all diterpenoids compared to products using other extraction techniques, but also noted that other factors such as lubricants, diluents, disintegrants, amount of extract used in the formulation, particle size and humidity may affect the dissolution of extracts.

Another earlier study from Thailand also found variance in andrographolide content and dissolution rates in seven Andrographis products made from dried ground plant material and one extract product[xliii]. It also noted degradation rates varied considerably, possibly due to different formulations, manufacturing processes, source of raw materials, particle size and remaining moisture content.

Furthermore, the pharmacological activity of Andrographis is likely due to a complex interplay and possible synergy between multiple constituents beyond andrographolide and other main diterpenoids, as found in a recent study that conducted LC-ESI-MS/MS[xliv] and a network pharmacology analysis on a concentrated ethanolic Andrographis leaf extract[xlv]. These studies show that multiple variables can potentially affect composition, stability, pharmacokinetics and ultimately pharmacological activity, and highlight the complexities involved in any attempts to identify formulations that could potentially be higher risk, which at this stage has not been well studied in published literature.

As included in the updated safety review, the TGA toxicology section evaluated published non-clinical studies examining the allergenic and anti-inflammatory effects of various Andrographis extracts and purified constituents. The toxicological evaluation noted that the *in vitro* data suggest a pseudoallergy and anaphylactoid potential of some components of Andrographis extracts. However, whether these components can elicit a typical hypersensitivity reaction is inconclusive. Likewise, the allergenic potential of other components was not assessed. Furthermore, the toxicological evaluation noted there are no standard methods for assessing the systemic allergenic potential of chemicals with nonclinical studies. It also commented that the value of animal studies lies more in better understanding mechanisms than in being used to accurately predict allergenic and anaphylactic reactions to substances.

The evaluation also noted that components of Andrographis appear to have competing allergenic and anti-inflammatory actions, and that different extracts with different compositions may affect the balance between these actions. However, it also noted that many of the studies used purified

[xliii] Daodee S, Wnagboonskul J, Jarukamjorn K et al. The consideration of quality control criteria for Andrographis paniculata product. KKU Res J. Oct - Dec 2006; 11(4) https://so01.tci-thaijo.org/index.php/APST/article/view/83985/66872 (D25-3981587)

[xliv] LC-ESI-MS/MS = liquid chromatography electrospray ionisation tandem mass spectrometry.

[xlv] Banerjee S, Kar A, Mukherjee PK, Haldar PK, Sharma N, Katiyar CK. Immunoprotective potential of Ayurvedic herb Kalmegh (Andrographis paniculata) against respiratory viral infections - LC-MS/MS and network pharmacology analysis. Phytochem Anal. 2021 Jul;32(4):629-639. doi: 10.1002/pca.3011. Epub 2020 Nov 9. PMID: 33167083. (D25-4020160)

Andrographis constituents (e.g., andrographolide, dehydroandrographolide) instead of herbal preparations commercially available to the general public, therefore the clinical relevance of these findings is limited. Importantly, isolated Andrographis constituents are not currently permitted ingredients in listed medicines.

Therefore, while it is possible that the allergenic potential of Andrographis may in some way relate to certain constituents or their proportions within Andrographis-containing medicines, there is currently no available evidence to establish higher or lower risk preparations. While further research in this area may improve understanding of the allergenic mechanism behind Andrographis, a delay to regulatory action in anticipation of further evidence is not considered appropriate for a well-documented life-threatening reaction associated with medicines regulated as low risk products.

With regard to dose, the retrospective post-market study of AE data held in Thailand's adverse event database confirmed that the signal cannot be attributed to higher doses, as 7 of 13 Andrographis critical hypersensitivity cases (WHO criteria) where the product's brand name was reported involved single active ingredient Andrographis dry powder with doses ranging from 353 mg to 1750 mg[8] (cross ref: Suwankesawong 2014). This wide variance in dose is consistent with the findings of the TGA analysis of Andrographolide doses associated with anaphylaxis cases which also varied widely from <20mg -140mg.

Therefore, this additional consideration of dose and composition of Andrographis extracts and traditional Andrographis preparations further confirms the findings of the updated safety review that there is insufficient evidence that risk can be attributed to certain doses or preparation types. Therefore, restrictions on dose, composition or preparation are not appropriate risk mitigation options for Andrographis in listed medicines at this stage. Although the exact mechanism remains uncertain, a precautionary approach is appropriate considering the life-threatening nature of anaphylaxis.

Risk / benefit

Discussion of risk-benefit for the ingredient Andrographis when used in listed medicines was included in both the 2015 safety review (R15/746298) and in the above updated safety review.

The 2015 review explained that a comprehensive risk-benefit analysis could not be conducted as the efficacy of Andrographis had not been evaluated by the TGA, and that methodology for the safety review comprised an analysis of adverse event data held by the TGA, as well as available information on adverse events and safety issues in published literature and from international pharmacovigilance activities. Notwithstanding, the putative and established benefits were considered against the possible risk of allergic-type and anaphylactic reactions and concluded that the number of reported of adverse events along with the severity of these types of reactions (potentially life-threatening) appeared to present a significant enough risk to warrant further action.

Similarly as included in the updated review above, when considering the balance of risk against benefit, it is important to note that listed medicines are only permitted to use low-level indications that are appropriate for self-selection and self-administration without medical advice or supervision. Therefore, any risks must also be appropriately low in order of the risk benefit profile to remain favourable for a low risk listed medicine. The risk of a life-threatening reaction such as anaphylaxis is unacceptable for medicines indicated for low – level benefits only. As such, this review finds Andrographis inappropriately positioned in the regulatory framework for listed medicines. Higher risk medicines must be registered on the Australian Register of Therapeutic Goods (ARTG), which involves individually evaluating the quality, safety and effectiveness of the product.

During the ACCM meeting, one speaker noted safety concerns around Andrographis combination formulas and concurred with the TGA that the identified concerns do not support Andrographis as a low-risk ingredient. Another member commented that risks appear to outweigh benefits. Other members commented that risk-benefit, including implications for other traditional practitioners utilising the herb should be considered, and that traditional uses of Andrographis are broader than treating upper respiratory tract infections.

Implications for the use of Andrographis by traditional practitioners is outside the scope of this safety review. However, the use of Andrographis in extemporaneously compounded medicines prescribed for patients by traditional practitioners would not be impacted by regulatory changes to the Permissible Ingredient Determination as these medicines are not required to be included in the ARTG.

The updated safety review acknowledged uses of Andrographis for conditions other than upper respiratory tract infections. However, only 8 of 84 listed medicines included indications without reference to respiratory symptoms or immune boosting (see section on Regulatory Status – Australia above). Therefore, in the majority of situations when Andrographis is being used by consumers as per the indication, there is an increased risk of severe allergic reactions. When used for indications other than respiratory or viral infections, the associated risk is reduced but remains sufficiently high to preclude restricting use solely to non-respiratory or non-viral indications.

Conclusion

At ACCM 37 the committee supported the TGA's view that there is increased risk posed to the consumer because the presence of viral illness can increase the likelihood or severity of an allergic reaction, and these products are mainly used for symptomatic treatment of viral illnesses; that anaphylaxis adverse events have been sudden and unpredictable and therefore the risk of anaphylaxis is difficult to mitigate; and that further risk minimisation measures to strengthen label warnings, restrict formulations or publish further education are unlikely to mitigate the risk of anaphylaxis.

The committee raised several factors requiring further exploration, including additional analysis of the available data, with these addressed above in this addendum.

This updated safety review of Andrographis, including advice from ACCM37, concludes that Andrographis is not a low-risk ingredient and therefore is not appropriate to be permitted for use in listed medicines.

Erratum

<table>
<tr><th>Page</th><th>Error</th><th>Correction</th></tr>
<tr><td>1</td><td>‘the TGA has only received 13 reports of anaphylaxis related to products containing Echinacea without Andrographis.’</td><td>‘the TGA has only received 10 reports of anaphylaxis related to products containing Echinacea without Andrographis’.</td></tr>
<tr><td>2</td><td>‘and one has published a safety communication on the topic’</td><td>‘and two have published safety communications on the topic’</td></tr>
<tr><td>9</td><td>‘There were 47 products associated with the 254 cases of anaphylaxis’</td><td>‘There were 48 products associated with the 254 cases of anaphylaxis’</td></tr>
<tr><td>9</td><td>‘(205/254 [81%])’</td><td>‘(206/254 [81%])’</td></tr>
<tr><td>9</td><td>‘(49/254 [19%])’</td><td>‘(48/254 [19%])’</td></tr>
<tr><td>9</td><td>‘with only 13 reports received by the TGA since 2005.’</td><td>‘with only 10 reports received by the TGA since 2005.’</td></tr>
<tr><td>9</td><td colspan="2">s47G</td></tr>
<tr><td>9</td><td colspan="2"></td></tr>
<tr><td>10</td><td>Figure 1 data:
<table><tr><th></th><th>2008</th><th>2009</th><th>2016</th><th>2024</th></tr><tr><td>Andrographis and Echinacea</td><td>0</td><td>2</td><td>6</td><td>50</td></tr><tr><td>Andrographis without Echinacea</td><td>7</td><td>8</td><td>1</td><td>2</td></tr><tr><td>Echinacea without Andrographis</td><td>3</td><td>1</td><td>1</td><td>2</td></tr></table></td><td><table><tr><th></th><th>2008</th><th>2009</th><th>2016</th><th>2024</th></tr><tr><td>Andrographis and Echinacea</td><td>1</td><td>2</td><td>6</td><td>50</td></tr><tr><td>Andrographis without Echinacea</td><td>6</td><td>8</td><td>1</td><td>3</td></tr><tr><td>Echinacea without Andrographis</td><td>2</td><td>0</td><td>0</td><td>2</td></tr></table></td></tr>
<tr><td>21</td><td>‘Notwithstanding, 19% (49/254)’</td><td>‘Notwithstanding, 19% (48/254)’</td></tr>
<tr><td>21</td><td>‘Since 2005 there have only been 13’</td><td>‘Since 2005 there have only been 10’</td></tr>
<tr><td>25</td><td>‘Notwithstanding, 49 (19%) cases’</td><td>‘Notwithstanding, 48 (19%) cases’</td></tr>
<tr><td>25</td><td>‘with only 13 reports received’</td><td>‘with only 10 reports received’</td></tr>
<tr><td>46</td><td colspan="2">s33</td></tr>
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<tr><td>53</td><td>Figure 1U data
<table><tr><th></th><th>2008</th><th>2009</th><th>2016</th><th>2024</th></tr><tr><td>Andrographis and Echinacea</td><td>0</td><td>2</td><td>6</td><td>50</td></tr><tr><td>Andrographis – single active</td><td>0</td><td>1</td><td>1</td><td>1</td></tr><tr><td>Andrographis with other active’s</td><td>7</td><td>7</td><td>0</td><td>2</td></tr><tr><td>Echinacea without Andrographis</td><td>3</td><td>1</td><td>1</td><td>2</td></tr></table></td><td><table><tr><th></th><th>2008</th><th>2009</th><th>2016</th><th>2024</th></tr><tr><td>Andrographis and Echinacea</td><td>1</td><td>2</td><td>6</td><td>50</td></tr><tr><td>Andrographis – single active</td><td>0</td><td>2</td><td>1</td><td>2</td></tr><tr><td>Andrographis with other actives</td><td>6</td><td>6</td><td>0</td><td>1</td></tr><tr><td>Echinacea without Andrographis</td><td>2</td><td>0</td><td>0</td><td>2</td></tr></table></td></tr>
<tr><td>54</td><td>‘in addition to the 12 anaphylaxis reports’</td><td>‘in addition to the 14 anaphylaxis reports’</td></tr>
<tr><td>55</td><td>‘There has been only 1 Australian anaphylaxis case for a ‘single’ Echinacea ingredient medicine that was reported to contain 2 Echinacea ingredients as the only active ingredients: E. purpurea and E. angustifolia.’</td><td>‘There have been only 3 Australian anaphylaxis cases for a ‘single’ Echinacea ingredient medicine. One was reported to contain 2 Echinacea ingredients as the only active ingredients: E. purpurea and E. angustifolia. The suspected medicines in the other 2 cases were reported as Echinacea with insufficient detail to identify the tradename or formulation, therefore they have been coded in the AEMS as ‘Trade name not specified (Echinacea sp.)’.</td></tr>
<tr><td>56</td><td>Table 7U
<table><tr><td>(Drug name)</td><td>(No. sole suspect, single active ingredient medicine anaphylaxis reports in AEMS)</td><td>(No. sole suspect, single active ingredient medicine anaphylaxis reports in VigiBase)</td></tr><tr><td>Echinacea angustifolia, Echinacea purpurea, and/or Echinacea pallida</td><td>1</td><td>1</td></tr></table></td><td><table><tr><td>(Drug name)</td><td>(No. sole suspect, single active ingredient medicine anaphylaxis reports in AEMS)</td><td>(No. sole suspect, single active ingredient medicine anaphylaxis reports in VigiBase)</td></tr><tr><td>Echinacea angustifolia, Echinacea purpurea, Echinacea pallida and/or Echinacea spp.</td><td>3</td><td>5</td></tr></table></td></tr>
<tr><td>56</td><td>Footnote ‘xxxv’
‘Medicine ingredient names searched: Andrographis paniculata,’</td><td>Footnote ‘xxxv’
Medicine ingredient names searched: Andrographis paniculata (D25-1090179),’</td></tr>
</table>

56	Footnote ‘xxxviii’ ‘D25-4153923’	Footnote ‘xxxviii’ ‘Qlik AEMS search: data up to 16 March 2025, default bookmark on, sole suspect filter on, reaction terms anaphylactic shock, anaphylactic reaction, anaphylactoid shock, anaphylactoid reaction. Medicine ingredient names searched: Echinacea angustifolia, Echinacea purpurea, Echinacea pallida and/or Echinacea spp. (D25-4153923)’
56	Footnote ‘xxxix’: ‘Ingredients names: Echinacea angustifolia, Echinacea purpurea, Echinacea pallida.	Footnote ‘xxxix’: ‘Ingredients names: Echinacea angustifolia, Echinacea purpurea, Echinacea pallida, Echinacea spp.’
56	Footnote ‘xxxix’: (D25-4221203)	Footnote ‘xxxix’: (D26-1078916)

APPENDIX A: EXPERT ADVICE FROM CLINICAL IMMUNOLOGY AND ALLERGY SPECIALIST (D24-3402126)

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TGA REPORT: *Andrographis paniculata* and anaphylactic reactions

Report prepared by s.22

August 2024

1.Until very recently, I don't believe that adverse reactions to *Andrographis* have been widely appreciated despite adverse reaction reports following *Andrographis* use notified by the TGA from 2015, in New Zealand from 2017 [1] and in a publication in the Internal Medicine Journal in 2017 [2]. The recent alert from the TGA, 2 July 2024, has focussed more attention on this matter as has the media report in June 2024 of a fatality likely due to anaphylaxis caused by *Andrographis*. To further highlight the risk of allergic reactions to this herbal preparation, particularly in Armaforce, to our colleagues, our unit will report a further five cases we have seen at the forthcoming national Australasian Society of Clinical Immunology and Allergy conference in September [3].

The cases reported to date may be a significant underestimate of possible reactions as those suffering milder reactions may not come to the attention of the medical community nor might they seek any assistance, so the reaction goes unreported. It is well established that there is general under-reporting of adverse reactions to drugs,[4] and this is even more so with herbal products as the public generally regards these as safe and acquires them independent from any medically qualified practitioner [5].

2. The reactions we have identified as well as those documented in the Delegate's report where details are available, are entirely consistent with allergic reactions regardless of the mechanisms underpinning those reactions.

Comments are made in the Delegate's report regarding the frequency of ingesting this compound before the reported reaction. Some reactions occurred after many previous uses and some on first ever use. The former is no different from any allergic reaction regardless of cause - an IgE-mediated reaction requires prior sensitisation before a reaction occurs. This is seen with many drug reactions where patients take repeated courses, for example, of an antibiotic, before they demonstrate an allergic reaction. Factors causing a reaction at a particular time when the substance has been tolerated previously are not entirely clear but modifying factors such as presence of infection, other medications, concomitant exercise or alcohol ingestion may all act as modulating factors.

A reaction occurring on the first ever use suggests either that sensitisation has occurred by prior exposure to the allergen in another form, or that the reaction has been caused by non-IgE-mediated hypersensitivity. Non IgE-mediated pathways can induce symptoms indistinguishable from classic anaphylaxis and may do so via mast cell or basophil activation, via other antibodies, generation of anaphylatoxins, or via other receptors such as G-coupled receptors [6].

Judgement of reaction severity by noting whether an individual presents to a hospital or receives adrenaline for treatment of the reaction is an unreliable measure. Many patients present to an emergency department and don't receive adrenaline when they should and likewise, occasionally adrenaline is given when it was not necessary. Some individuals choose not to go to hospital and "wait out" a reaction when the severity of the reaction would dictate the wisdom of presenting to Emergency.

3. In general terms, there are known risk factors that can potentiate an allergic reaction or act as co factors to make a reaction more likely. These include ingestion/exposure to the allergen in close proximity to vigorous exercise, ingestion of alcohol or non-steroidal anti -inflammatory medications and in the context of viral infections. The full history of those who have had reactions and have been reported is not known but as this "supplement" is used as a treatment for upper respiratory infection, it is highly likely that most had a viral illness at the time and it is also possible that some anti-inflammatory medication may have been used as well. In the cases seen in our unit all five patients had ingested Armaforce in the setting of an infection.

4. In 2002 Mullins and Heddle[7] described five patients who had likely allergic, adverse reactions to Echinacea; two had anaphylaxis and two had asthma immediately after ingestion with the fifth having a delayed skin rash. Three of five had positive skin tests to Echinacea suggesting an IgE - mediated mechanism.

At that time there had been 51 adverse reaction reports to the TGA, 26 of which were suggestive of an allergic mechanism, some very serious. People with a background of atopy were over represented in this group.

In 2011 The New Zealand Medicines and Medical Devices Authority issued a warning after four case reports of likely allergic reactions.

Therefore, it is possible that some of the present reports represent adverse reactions to the Echinacea component or are a result of synergy between the two compounds. However, there are reports of reactions to *Andrographis* alone so both herbal compounds are implicated in reactions. Furthermore, from the reports available, positive skin tests were achieved with Echinacea but none of the patients seen in our unit with convincing histories of allergic reactions to *Andrographis* or Armaforce had positive skin tests which suggests that perhaps this compound causes reactions by an IgE-independent mechanism. Further investigations will be required to elucidate the culprits and the mechanism(s) underpinning the observed adverse reactions such as direct mast cell histamine release or mechanisms via stimulation of other pathways or receptors.

5. Several steps can be taken to explore the nature and causes of the reported allergic reactions. As with all investigations in allergy practice this begins with a detailed **history**. Important factors to explore include:

Preparation used

Timing, symptoms and severity of any reaction

Other medications taken at the time

The general state of the individual – were they "treating" a viral infection or was the compound taken for another reason?

Had they used the preparation previously?

An individual's personal status – are they atopic? Do they have asthma? Have they experienced previous allergic reactions?

Investigations: Skin testing with extracts of all implicated ingredients will assist in identifying whether the reaction might be IgE-mediated; some research laboratories offer BAT (basophil activation testing) and this could be set up and conducted on blood samples; measurement of serum tryptase within hours of the reaction if anaphylaxis has occurred can be very useful in determining whether there is mast cell activation. Ultimately a supervised challenge can be conducted as the "ultimate proof" of causation, however most specialists and patients would be reluctant to undertake this particularly for such a dispensable compound that is easily avoided!

Of the five cases reported by our unit; 4/5 were skin tested and were negative; the 5th declined testing. One patient did want a challenge and promptly reacted.

6. My final comments on this matter concern risk-benefit analysis for this compound. I appreciate that this herbal preparation has been used in China and India for centuries, however we have no knowledge about the constituents that have been used medicinally, or what parts of the plant were used, or the concentrations of active ingredients and many other factors regarding the chemistry of the final product. Similarly with the unregulated product that is available for the public to use in our society, we do not know anything about standardisation of manufacture and other relevant details.

When considering benefit, there are numerous papers, predominantly in the Chinese literature, detailing experimental evidence for the activity of various ingredients on various biochemical pathways, but there are very few publications detailing the benefits as assessed in randomised, placebo-controlled, clinical trials (RCTs), the standard to which western medicines is held. The best accessible publication to this end is Hu et al.[7], a systematic review and meta-analysis. This paper outlines accepted processes for assessing the scientific standard of publications. Thirty-three RCTs were included in the systematic review. The conclusion of these authors was that there was poor study quality and heterogeneity and that well-designed trials are needed to secure evidence of benefit in the treatment of upper respiratory infections.

s47G
s47G Every effort should be made to collect as much data as possible regarding the harm around ingestion of this product so that a risk-benefit assessment can be undertaken.

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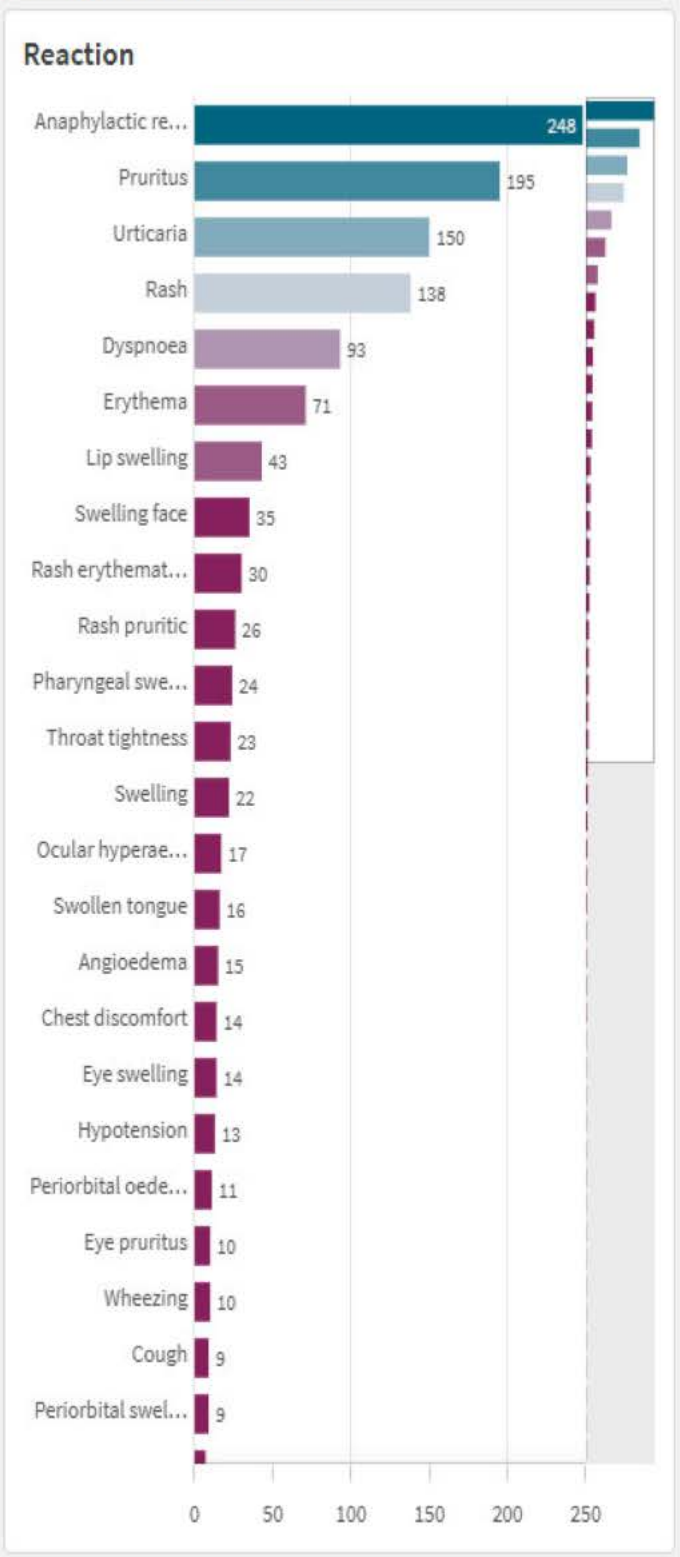
APPENDIX B(1): ANAPHYLACTIC REACTIONS AND ANAPHYLACTIC /ANAPHYLACTOID SHOCK CONDITIONS SMQ REACTION TERMS & CASE COUNT:

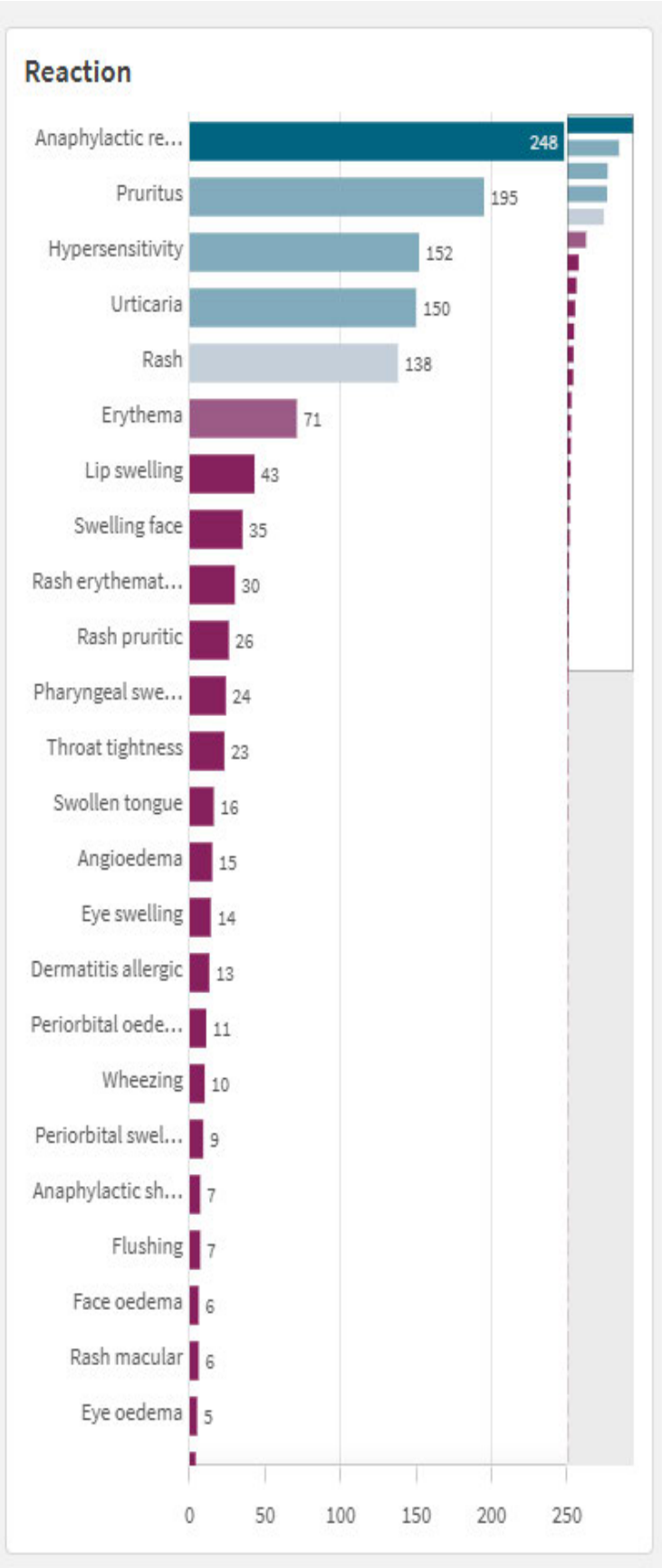
Reaction Term	Case Count
Anaphylactic reaction	248
Pruritus	195
Urticaria	150
Rash	138
Dyspnoea	93
Erythema	71
Lip swelling	43
Swelling face	35
Rash erythematous	30
Rash pruritic	26
Pharyngeal swelling	24
Throat tightness	23
Swelling	22
Ocular hyperaemia	17
Swollen tongue	16
Angioedema	15
Chest discomfort	14
Eye swelling	14
Hypotension	13
Periorbital oedema	11
Eye pruritus	10
Wheezing	10
Cough	9
Periorbital swelling	9
Anaphylactic shock	7
Flushing	7
Face oedema	6
Eye oedema	5
Blood pressure decreased	4
Sneezing	4
Cyanosis	3
Pharyngeal oedema	3
Respiratory distress	3
Swelling of eyelid	3
Asthma	2
Blood pressure immeasurable	2
Lip oedema	2
Mouth swelling	2
Oedema	2
Skin swelling	2
Anaphylactoid reaction	1
Choking sensation	1
Circulatory collapse	1
Eyelid oedema	1
Oedema mouth	1
Oral mucosal eruption	1
Rash papular	1
Shock	1
Stridor	1
Tongue oedema	1



Note some reports contain multiple reaction terms.

APPENDIX B(2): HYPERSENSITIVITY SMQ REACTION TERMS & CASE COUNT:

Reaction Term	Case Count
Anaphylactic reaction	248
Pruritus	195
Hypersensitivity	152
Urticaria	150
Rash	138
Erythema	71
Lip swelling	43
Swelling face	35
Rash erythematous	30
Rash pruritic	26
Pharyngeal swelling	24
Throat tightness	23
Swollen tongue	16
Angioedema	15
Eye swelling	14
Dermatitis allergic	13
Periorbital oedema	11
Wheezing	10
Periorbital swelling	9
Anaphylactic shock	7
Flushing	7
Face oedema	6
Rash macular	6
Eye oedema	5
Ear swelling	4
Sneezing	4
Pharyngeal oedema	3
Rash papular	3
Respiratory distress	3
Skin exfoliation	3
Swelling of eyelid	3
Asthma	2
Blister	2
Dermatitis	2
Drug hypersensitivity	2
Erythema multiforme	2
Generalised oedema	2
Lip oedema	2
Mouth swelling	2
Skin swelling	2
Stomatitis	2
Anaphylactoid reaction	1
Choking sensation	1
Circulatory collapse	1
Conjunctival oedema	1
Dermatitis exfoliative	1
Eyelid oedema	1
Localised oedema	1
Oedema mouth	1
Oral mucosal eruption	1
Prurigo	1
Rash maculo-papular	1
Rash vesicular	1
Seasonal allergy	1
Shock	1
Skin reaction	1
Stevens-Johnson syndrome	1
Stridor	1
Tongue oedema	1



Note some reports contain multiple reaction terms.

APPENDIX C: LITERATURE REVIEW (FULL TEXT ARTICLES) NOVEMBER 2011 TO 17 JUNE 2024 - ANDROGRAPHIS PANICULATA AND ANAPHYLAXIS / HYPERSENSITIVITY

Search strategies

The TGA's previous safety review of this issue considered articles published up to November 2011, therefore a targeted literature search was conducted for articles published after this date. The search was limited to articles that referred to *Andrographis paniculata*, adverse events and anaphylaxis / anaphylactic reactions / allergic reactions / hypersensitivity.

The search was conducted in 2 parts:

1. November 2011 to December 2013 inclusive:
Search for: remove duplicates from 19 [16 or 18]
Results: 24

Embase, Ovid MEDLINE(R)			
#	**Search Statement**	**Results**	**Annotation**
1	Andrographis paniculata.mp. or exp Andrographis paniculata/	4095	
2	Andrographis.mp.	4563	
3	(allergic reaction or allergy).mp. or exp allergy/	771405	
4	exp anaphylaxis/ or Anaphyla*.mp.	122196	
5	exp hypersensitivity/ or Hypersensitiv*.mp.	1263201	
6	1 or 2	4563	
7	3 or 4 or 5	1360124	
8	6 and 7	191	
9	limit 8 to (human and english language and yr="2014 -Current")	69	
10	remove duplicates from 9	66	
11	limit 8 to english language	187	
12	limit 11 to human	131	
13	limit 8 to english language	187	
14	limit 13 to human	131	
15	limit 14 to yr="2011 - 2013"	26	
16	limit 14 to dc="20110111-20131231"	24	
17	limit 14 to dt="20110111-20131231" [Limit not valid in Embase; records were retained]	121	
18	from 17 keep 120-121	2	
19	16 or 18	26	
20	remove duplicates from 19	24	

2. 2014 to 17 June 2024:
Search for: remove duplicates from 9 [limit 8 to (human and english language and yr="2014 - Current")]
Results: 66

Embase, Ovid MEDLINE(R)			
#	**Search Statement**	**Results**	**Annotation**
1	Andrographis paniculata.mp. or exp Andrographis paniculata/	4034	
2	Andrographis.mp.	4493	
3	(allergic reaction or allergy).mp. or exp allergy/	766679	
4	exp anaphylaxis/ or Anaphyla*.mp.	121291	
5	exp hypersensitivity/ or Hypersensitiv*.mp.	1254051	
6	1 or 2	4493	
7	3 or 4 or 5	1350150	
8	6 and 7	191	
9	limit 8 to (human and english language and yr="2014 -Current")	69	
10	remove duplicates from 9	66	

Methodology

Abstracts were reviewed and only articles directly relevant to Andrographis and adverse events and/or anaphylaxis / hypersensitivity were obtained for full review. During the review, if additional citations appeared relevant, full text articles were obtained for further review. Articles that were not specific to Andrographis, or that did not appear to describe adverse events, were excluded from further review.
A high-level summary of the published literature is provided in the Published literature section of the safety review. The following provides a more detailed summary and critique of each article that was reviewed.

Articles

Systematic reviews / meta-analyses

Worakunphanich W, Thavorncharoensap M, Youngkong S, Thadanipon K, Thakkinstian A. Safety of Andrographis paniculata: A systematic review and meta-analysis. Pharmacoepidemiology and Drug Safety. 2021 Jun;30(6):727-39. - *D24-2492468*

Comments / summary

This systematic review and meta-analysis aimed to estimate the incidence of AEs associated with the use of Andrographis in Upper Respiratory Tract Infection (URTI), noninfective diarrhoea and autoimmune disease. The authors also aimed to compare the incidence of AEs to that of standard treatment or placebo.

Relevant studies published up to 31 August 2018 were identified from six databases, with unpublished reports from FDA Thailand and Department of Thai Traditional and Alternative Medicine also considered. A total of 13 studies were identified that met the inclusion criteria:

- either a RCT, cohort study or post-marketing study;
- investigated AEs; and
- involved Andrographis as oral monotherapy for the treatment of upper respiratory tract infection (URTI), noninfective diarrhoea or autoimmune disease.

There were 10 RCTs identified for inclusion and three post-marketing (intensive monitoring) studies. The authors identified six serious AEs: 1 of haematochezia resulting in hospitalisation and 1 of pregnancy, however details of the other 4 were not provided. The most common non-serious AEs identified in the 10 RCTs related to gastrointestinal disorders (n = 52), followed by nervous system disorders (n = 17), and skin and subcutaneous disorders (n = 12), respectively. Where details of non-serious reactions were reported in the RCT, details were provided in Supplement table 1 and included 3 AEs of urticaria and 9 AEs of pruritis / rash. The authors reported that the meta-analysis of RCTs found that serious AEs among patients receiving Andrographis were very rare (<1/10000) or 0.02 per 1,000 patients. While the incidence of nonserious AEs was found to be very common (≥1/10) or 102.6 per 1000 patients in base-case analysis, authors commented that was likely a slight overestimation as one patient could experience more than one AE.

The authors reported that no significant difference in terms of incidence of serious AEs occurred between low dose and high dose of andrographolide (≤120 mg/day vs >120 mg/day), although it should be noted that only 5 serious AE reports were identified in the analysis. Notwithstanding, the authors concluded that this was consistent with the current evidence, which indicated that serious AEs usually were immunological-allergic responses, which were unlikely to be related to the dose. The most common AEs in the three post-marketing studies were non-serious skin and subcutaneous disorders, with the pooled incidence of all non-serious AEs calculated by the study authors as 34.2 per 1000 patients (95% CI: 0.0–229.6 per 1000 patients; I^2 = 97.61%). No serious AEs were identified from the three intensive monitoring studies. Authors noted that the pooled incidence of nonserious AEs from RCTs for treatment duration ≤14 days was similar to that of the pooled incidence from intensive monitoring (35.3 per 1000 patients vs 34.2 per 1000 patients).

The authors commented that a possible reason that anaphylactic shock was not identified in this study was that such serious AEs usually occur very rarely so were less likely to be identified from RCTs or small-scale intensive monitoring studies. The authors further commented that spontaneous reports remain an important method to identify serious AEs, with meta-analyses a useful complement to provide more precise estimates of risk. They also noted another possible reason why anaphylactic shock was not identified in this review was that only studies using oral monotherapy with Andrographis were included, and that previous studies found intravenous administration of Andrographis to be associated with higher risk of anaphylaxis. Authors also commented that the association between Andrographis and anaphylactic shock found in spontaneous reports might be subject to confounders such as contamination or patient characteristics rather than to the herb itself.

Other limitations noted by the study authors were that only three indications were used as inclusion criteria, which resulted in a limited pool of studies. In addition, the authors commented that the sample size of the included RCTs was small and the duration of the studies relatively short, and that many studies were of unclear risk of bias. Authors also noted that patients with any known allergy to Andrographis were excluded from RCTs, which may have resulted in an underestimate of pooled incidence of AEs.

Therefore, although this study did not identify serious cases of anaphylaxis or hypersensitivity reactions, this may have been due to multiple limitations. Nevertheless, the study did find that the pooled incidence of non-serious reactions in RCTs ≤14 days duration and intensive monitoring

studies was common (>1/100 to <1/10) with skin and subcutaneous reactions the third most common reaction type in RCTs and the most common reaction type in post-market monitoring studies.

Hu XY, Wu RH, Logue M, Blondel C, Lai LY, Stuart B, Flower A, Fei YT, Moore M, Shepherd J, Liu JP. Andrographis paniculata (Chuān Xīn Lián) for symptomatic relief of acute respiratory tract infections in adults and children: A systematic review and meta-analysis. PloS one. 2017 Aug 4;12(8):e0181780. - *D24-3922849*

Comments / summary

This systematic review and meta-analysis were conducted to evaluate the efficacy and safety of oral Andrographis used for symptomatic relief of acute URTI in adults and children. The final review included 33 randomised controlled trials (RCTs) comprising 7175 patients. The authors stated that all but 10 trials reported on AEs or safety. There were no reported cases of anaphylaxis or severe hypersensitivity. The authors noted that these results were not consistent with the TGA's safety review of 2015 which revealed that the most common AEs associated with Andrographis were hypersensitivity or allergic reactions. They acknowledge that a lack of proportionate data on each AE in each group limited a comprehensive risk-benefit assessment.

The authors stated that no serious AEs were reported in the included trials and AEs appeared to be mainly gastrointestinal. However, they noted that the quality of included trials was generally lower than desired as many were poorly designed, underpowered, inadequately blinded and there was high heterogeneity among trials due to variations in population and outcomes.

Therefore, this article does not provide compelling evidence of safety or absence of AEs.

Shang YX, Shen C, Stub T, Zhu SJ, Qiao SY, Li YQ, Wang RT, Li J, Liu JP. Adverse effects of andrographolide derivative medications compared to the safe use of herbal preparations of andrographis paniculata: results of a systematic review and meta-analysis of clinical studies. Frontiers in Pharmacology. 2022 Jan 28;13:773282. - *D24-3071917*

Summary

This systematic review and meta-analysis aimed to evaluate the safety of andrographolide derivative injections and oral Andrographis and andrographolide preparations including analysis of reported adverse events. Anaphylaxis and skin and subcutaneous tissue disorders featured strongly amongst AEs to injections, warranting caution, while authors concluded that the AEs to herbal (oral) Andrographis preparations suggested they were essentially safe.

It included data from 262 studies, including 125 randomised controlled trials (RCTs), 23 non-RCTs, six case series and 108 case reports. Authors stated that sample sizes ranged from 20 to 2000 participants, except for case reports. However, an included study with a sample size of 2000 was not obvious; the largest one evident was1000. Most studies related to injections, while only 10 related to oral Andrographis preparations. AEs were graded according to severity based on the information reported in the articles, which authors commented was limited in some cases resulting an unclear grading.

The authors noted that AEs were different depending on study type, with more severe reactions (mainly anaphylactic reactions and anaphylactic shock) reported in case reports where single patients took the drug. In contrast, a small number of AEs were reported across all patients who took the drug in RCTs, non-RCTs and case series, which were the data authors used to calculate the incidence of AEs.

Andrographolide injections

Case reports included in the review involved 152 patients, of which 97 patients developed anaphylaxis after being treated with injections of andrographolide derivatives. Of these 39 cases were graded as severe, 55 were graded as life-threatening while another three had a fatal outcome. The meta-analysis of RCTs, non-RCTs and case series performed by the authors included 9490 patients treated with andrographolide derivative injections, of whom 383 patients (4.04%) experienced a total of 383 AEs. These were mainly gastrointestinal disorders, skin and subcutaneous tissue disorders, followed by anaphylaxis, general disorders and abnormal administration site conditions and nervous system disorders. The majority of these AEs were reported as mild to moderate, but a small number of patients experienced severe or life-threatening AEs. The 20 reports of anaphylaxis and an additional 24 reports of unspecified anaphylactic reaction represented 5.22% and 6.27% of all reported reactions in this analysis respectively.

A comparison of doses was not conducted. Authors reported that in several studies it was unclear whether dosages were in accordance with instructions. This limited any analysis of dosage trends.

Authors reported on different salts of andrographolide derivative injections and adverse events for each. The three most frequently used in were andrographolide sulfonate (AS), potassium sodium dehydroandrographolide succinate (PSDS), and potassium dehydroandrographolide succinate (PDS).

The meta-analysis revealed a similar rate of adverse events for PDS and Andrographolide sulfonate (AS) injections and noted 11 cases of anaphylaxis for AS and 17 unspecified anaphylactic reactions for PSDS in randomised controlled trials (RCTs), non-RCTs and case series. An analysis of case reports identified a further 97 cases of anaphylaxis (AS: 30 cases, PSDS: 21 cases, PDS:45 cases, and andrographolide sodium bisulfite (ASB): 1 case). Of these, 55 were life-threatening anaphylactic shock (CTCAE grade 4[xlvi]), and three patients died (CTCAE grade 5), one each using AS, PSDS and PDS (see Figure 10 below). Authors did not identify any derivative injection medicine as higher risk.

Figure10. Tables 1, 2 and 4 from Shang et al 2022.

[xlvi] CTCAE = Common Terminology Criteria for Adverse Events, G1 = mild, G2 = moderate, G3 = severe or medically significant, G4 = life-threatening, G5 = lethal.

TABLE 1 | ADR incidence of andrographolide derivative injections.

Andrographolide derivative injections	Number of ADRs with CTCAE grading						Total number of ADRs	ADR incidence	Dosage (whether according to instructions)			
	G1	G2	G3	G4	G5	Unclear			Lower	Yes	Higher	Unclear
Andrographolide sulfonate (AS, trade name: Xiyanping injection)	60	9	1	0	0	128	198	5.48% [4.47%, 6.72%]	12	174	6	6
Potassium sodium dehydroandrographolide succinate (PSDS, trade name: Yanhuning injection)	34	16	0	0	0	96	146	3.69% [2.59%, 4.94%]	0	15	6	125
Potassium dehydroandrogrpholide succinate (PDS, trade name: Chuanhuning injection)	9	0	0	0	0	17	26	5.33% [3.68%, 7.72%]	0	13	0	13
Andrographolide sodium bisulfite (ASB, trade name: Lianbizhi injection)	0	0	0	0	0	1	1	0.67% (1/150)	0	0	0	1
Andrographis paniculata (AP, trade name: Chuanxinlian injection)	0	0	0	0	0	2	2	3.45% (2/58)	0	0	0	2
Other[a]	0	0	0	0	0	6	6	LiangRJ 1998 Liang, (1998): 15.00% (6/40)	0	0	0	6
	4	0	0	0	0	0	4	YuCC 2010 Yu et al. (2010): 1.54% (4/260)	0	0	0	4

[a]*In these 2 articles, the authors only reported that they used injections containing andrographolide, and did not specify the name of the injection, so the active ingredients of these injections were unknown.*

TABLE 2 | ADRs of andrographolide derivative injections reported in the included RCTs, non-RCTs and case series.

Andrographolide derivative injections	ADRs							
	Gastrointestinal disorders	Skin and subcutaneous tissue disorders	Anaphylaxis	General disorders and abnormal administration site conditions	Nervous system disorders	Blood and lymphatic system disorders	Abnormal investigation (medical examination) results	Unspecified anaphylactic reaction
AS	101	64	11	3	3	1	8	7
PSDS	54	51	0	13	3	0	8	17
PDS	11	6	5	0	4	0	0	0
ASB	0	1	0	0	0	0	0	0
AP	0	2	0	0	0	0	0	0
Other	0	0	4	0	2	0	4	0

TABLE 4 | ADRs of andrographolide derivative injections reported in the included case reports.

Andrographolide derivative injections	ADRs								
	Anaphylaxis	Skin and subcutaneous tissue disorders	General disorders and abnormal administration site conditions	Gastrointestinal disorders	Nervous system disorders	Respiratory, thoracic and mediastinal disorders	Renal and urinary disorders	Cardiac disorders	Abnormal investigation (medical examination) results
AS	30	12	7	4	1	3	0	0	0
PSDS	21	2	3	7	5	0	0	2	0
PDS	45	27	6	4	2	3	0	3	13
ASB	1	0	0	0	0	0	4	0	0
Other	0	0	0	0	0	0	2	0	0

Oral Andrographis paniculata

The authors reviewed 10 studies that reported AEs after using oral Andrographis preparations. Seven of the preparations used in these studies were Andrographis extracts while two were powdered Andrographis, however no extract details were provided to enable dosage comparison. The authors stated that meta-analysis on the incidence of AEs was unable to be performed on these studies due to different preparations being used. The reported AEs for oral Andrographis preparations were mainly gastrointestinal disorders (nausea, diarrhea, vomiting, abdominal pain, dyspepsia, flatulence, constipation) and skin and subcutaneous tissue disorders (rash, pruritis, urticaria). A total of 165 AEs were reported in the included studies, with the severity ranging from mild to moderate in 47 AEs. The authors stated that the remaining 118 AEs could not be clearly graded due to insufficient information provided in the original studies.

The authors reported that of the included case reports involving oral Andrographis, one patient experienced rash and skin itching which was graded as severe and resolved after symptomatic treatment and product cessation. Another two patients experienced dizziness which was graded as mild.

Oral andrographolide

Two studies also investigated the use of oral andrographolide. In one study (Ciampi *et al* 2020), oral andrographolide was used at 140 mg, twice daily for patients with not active progressive multiple sclerosis. AEs reported in this study include pruriginous rash, dysgeusia and gastroesophageal reflux, which were possibly related to the medication. In the other study (Calabrese *et al* 2000), oral andrographolide (PN355) was used in HIV positive patients and normal volunteers at 5 mg/kg, 3 times/ day for 3 weeks, escalating to 10 mg/kg, 3 times/day for 3 weeks, and to 20 mg/kg, 3 times/day for a final 3 weeks[12]. Shang *et al*. reported that AEs in this study included pruritis/rash, headache, fatigue, loose stools/diarrhea, allergic reaction, bitter taste, tender lymph nodes, nausea, metallic taste, dry tongue, decreased sex drive, eyes sensitive to light, decreased short term memory, dizziness, heartburn, decreased/no taste, and lymphadenopathy[13]. Notably, Shang *et al.* did not mention that the trial was ceased early after 6 weeks, due to the AEs experienced, including an anaphylactic reaction during week 4 of the study in a HIV positive subject and a body rash and headache during week 2 in one of the 5 HIV negative patients. The anaphylaxis patient was treated in the emergency room with (IV) Benadryl, prednisone and adrenaline. However, despite the treatment, the symptoms continued, diminishing gradually over a few days.

Concluding comments

Authors concluded that andrographolide injections should be used with caution as a small number of patients can experience life-threatening or lethal anaphylactic shock after using these injections, being of particular importance in patients with a history of allergy. They recommended that prescribers of these medicines should check the allergy history of patients carefully before prescribing. Conversely, the authors concluded that the AEs associated with 'herbal preparations' of Andrographis suggest they are essentially safe, presumably referring to oral preparations. However, the included studies for these preparation types were mainly small sample sizes (the largest being 200) and were therefore under-powered to detect rare adverse events.

Another limitation was that some important AEs of the oral andrographolide HIV study by Calabrese *et al* were omitted by the authors, who also omitted the fact that the trial was ceased early due to the incidence of AEs. No comment on the safety of oral andrographolide was provided by the authors.

Authors noted that the included studies had methodological deficiencies with the exception of only a few studies, and that higher quality studies are needed to evaluate the safety of andrographolide derivatives. Authors also acknowledged that their review and analysis was limited by only including studies that reported the occurrence of AEs but did not include studies that clearly reported that patients did not have AEs after taking andrographolide injections or herbal preparations of Andrographis. Authors commented that this could skew the apparent incidence of AEs associated with andrographolide injections resulting from the meta-analysis to be slightly higher than the true AE incidence. Authors did not comment on the number of excluded studies that did not collect or reported AE data as opposed to those that collected AE data but had no AEs reported.

The emphasis on AEs from injectable andrographolide-derivatives limits the relevance of this study to this investigation as injectable dosage forms are not permitted for use in listed medicines. However, it does highlight the risk of anaphylaxis with this dosage form, with the number of anaphylaxis cases alarmingly high both in case reports and in the meta-analysis of RCTs, non-RCTs

and case series. While the authors did not observe a similar risk with herbal oral Andrographis preparations, the reviewed data was too limited to provide compelling evidence for the authors conclusions of apparent safety.

Ding B, Fang B, Li J, Liu Q, Lv C, Yu X, Zhao X. Expert consensus guidelines on clinical use of Xiyanping injection for acute infectious diseases. Asian Pacific Journal of Tropical Medicine. 2020 Apr 1;13(4):152-61. - D24-3084394

Comments / summary

This paper has been presented as expert consensus guidelines on the clinical use of Xiyanping (andrographolide sulfonate) injection in treating acute infectious diseases, based on findings of a systematic review of the literature. The guidance elucidates the safety, precautions and contraindications of Xiyanping injection and also provides recommendations around the intervention time, usage and dosage, course of treatment and combined use of Xiyanping injection.

In the *Safety of Xiyanping injection* section, authors reported that severe AEs of Xiyanping injection account for about 3.72% of the total reported AEs identified in a literature review, spontaneously reported data and large-scale prospective active monitoring data. Authors reported the main clinical manifestations of severe AEs were anaphylactic shock, shiver and expiratory dyspnoea. They also noted that there was a higher risk of severe AEs for patients with a history of drug allergy to use Xiyanping injection.
The authors recommended to inquire about a history of drug allergy before using Xiyanping injection in patients. Authors also noted that close attention should be paid to observe and monitor the medication response in patients who are given the injection for the first time. Authors also advised that patients with a history of allergy to Xiyanping or other drugs, or that had an allergic constitution or family history of allergy should not be given Xiyanping injection.

The paper appears to have limited relevance to this investigation which is focused on oral use. However, it does highlight the risk of anaphylaxis with this dosage form of andrographolide sulfonate.

Clinical trials

Dimpfel W, Schombert L, Keplinger-Dimpfel IK, Panossian A. Effects of an adaptogenic extract on electrical activity of the brain in elderly subjects with mild cognitive impairment: A randomized, double-blind, placebo-controlled, two-armed cross-over study. Pharmaceuticals. 2020 Mar 14;13(3):45. - D24-3084225

Comments / summary

This RCT pilot study was designed to provide preliminary data to determine whether Adaptra® Forte is an effective and safe treatment for impaired cognitive functions, memory, learning ability, sleep disorders and electrical activity of the brain, and the durability of any beneficial effects. Adaptra® Forte is an oral herbal product consisting of standardised extracts of Andrographis herb and *Withania somnifera* (WS) roots and leaf.

A major limitation of this pilot study for the purposes of the safety review was that one of the exclusion criteria was known allergy to any of the plant constituents or other ingredients of the investigational product or clinically relevant allergic symptoms. Furthermore, as the product involved in this study consisted of a combination of Andrographis and WS, the causality of any observed AE would be confounded and therefore of limited relevance for this safety review.

Further limitations included the relatively small sample size resulting in a lack of adequate power, although the authors noted that the study was a 'pilot study designed to provide preliminary data to power a future large-scale study of Adaptra® Forte efficacy for cognitive impairment' and that 'the significance of the results could be improved in a future study by increasing the number of subjects.

Other noted limitations included inconsistencies in descriptions of the wash out period ('about 4 weeks' vs '4 weeks') and inclusion criteria ('mild cognitive impairment' vs 'cognitive deficits'). There was also insufficient detail regarding the screening process and methodology for determination and assessment of subjects 'suffering from cognitive deficits' as per the inclusion criteria. There also appeared to be a relatively short follow-up period (two weeks) and short trial period (four weeks) to establish long term effects.

The authors reported three (AEs) in the patient group during the treatment with Adaptra® Forte: one allergic reaction in a patient using the antihistamine cetirizine and hypertension in two subjects (12% of the sample size) concomitantly using hypotensive drugs irbesartan and candesartan. One of these patients discontinued the treatment after 32 days of repeated administration of Adaptra® Forte. Authors concluded that all AEs presumably resulted from possible interactions with concomitant treatments. Authors reported 'no serious adverse events or other significant side effects' in this study.

Notwithstanding one allergic AE, due to the limitations described above, this study did not provide compelling evidence to either support or refute the association between Andrographis and anaphylaxis / hypersensitivity.

Case reports

Joob B, Wiwanitkit V. Anaphyloid Reaction Due to Andrographis Paniculata Capsule. International Journal of Research. 2019;4(9):17-8. - D24-3082363

Comments / summary

In this case report from Thailand, the authors described a case of a 58-year-old patient who presented with generalised urticaria and respiratory difficulty. Low blood pressure of 90/50 mm Hg and palpitation ('110/minute') were reported by the authors. The patient was reported to have developed symptoms within minutes of taking an oral Thai Government Pharmaceutical Organisation (GPO) Andrographis capsule, and was diagnosed as an anaphylactoid case. The patient was treated with IV corticosteroids and recovered within one day.

The authors commented that the Andrographis medicine involved in this case is locally made and included in the Thai NLEM. The authors noted that another study by Richard *et al*. (2017) had shown no anaphylactic reaction to Andrographis. While the authors provided no further comment, our review of the non-clinical study by Richard *et al*. found limitations in the study design and its findings (see Toxicology comment – File note). Notwithstanding, the authors noted that the present case of anaphylaxis showed a strong association with the use of Andrographis. The authors also referred to the modernisation of traditional medicines and the need for studies on safety with regard to allergy and anaphylactic reactions and post market surveillance systems for modified traditional medicine products. The authors concluded that this case of anaphylaxis was due to Andrographis, and that although Andrographis is claimed to be safe, the possibility of adverse effects should not be forgotten.

Ahn Y, Brewerton M. P2: WHEN THE COMMON COLD TURNS DEADLY: ANAPHYLAXIS WITH ANDROGRAPHIS PANICULATA. Internal Medicine Journal. 2017 Sep;47:5 - D24-3071475

Comments / summary

This poster abstract was presented at the Australasian Society of Clinical Immunology and Allergy (ASCIA) 2017 conference. The authors were from New Zealand (NZ) and presented case details for two patients who experienced anaphylaxis after consuming Andrographis-containing medicines. The first patient consumed two different medicines six months apart, Good health's Viralex Attack and Blackmores Immunoshield respectively, and both times experienced immediate Ig-E mediated symptoms with the second episode resulting in anaphylaxis. The second patient had also consumed Good health's Viralex Attack and also experienced anaphylaxis. Both patients were reported to have been treated with intramuscular adrenaline and admitted to hospital for observation. Formulation details of the suspected Andrographis-containing products were not provided in the abstract.

The authors noted that Medsafe NZ issued a warning in March 2017 and Andrographis has since been removed from some products. Current online advertising suggests the formulation of Good Health's Viralex Attack may no longer contain Andrographis[xlvii]. The authors also noted a discussion on the options and limitations of tests available to allergists for novel allergens. Unfortunately, these details were not included in the abstract.
The positive rechallenge in the first patient supports a causal association, and although limited details were included, this poster abstract presents another two cases of possible Andrographis associated anaphylaxis.

Katelaris C, Keat K, West, T. ASCIA Conference Abstract: Risk Alert-Anaphylaxis Following ArmaForce Ingestion. Internal Medicine Journal, 2024; 54(S4), 5-6. https://doi.org/10.1111/imj.16556 D25-899174

Comments / summary (contains confidential case details not for publication)

This conference abstract was coauthored by Professor s22 who provided expert advice to the TGA (refer to Appendix A: Expert advice above). It was presented at the Australasian Society of Clinical Immunology and Allergy (ASCIA) conference in September 2024 and provided an overview of five case reports of anaphylaxis AEs associated with ArmaForce. The five cases occurred in adults aged between 19-50 years who had taken ArmaForce to assist with viral upper respiratory infections or for immune support post infection.

Authors reported the following details:

- 3 patients required treatment of adrenaline, and one patient required a combination of prednisolone and antihistamine,
- 4 patients had follow-up skin allergy tests after their AE, the results of which were all negative,
- one patient experienced anaphylaxis when rechallenged with '1/8 tablet',
- 2 patients were noted as having 'previous use' of the herb, however it is unclear whether they had previously used ArmaForce or another Andrographis product. Authors did not report whether the patients had experienced any adverse reactions after the previous use.

Authors also noted;

- previous TGA publications on Andrographis and anaphylaxis/allergic reactions in 2015,
- a number of AEs associated with Andrographis in New Zealand and internationally,
- a significant increase in AEs to Andrographis since 2019 and
- a recent death from anaphylaxis after ArmaForce ingestion has highlighted the risk.

[xlvii] Viralex® Attack, Immune Support Supplements - Goodhealth NZ [accessed 23 January 2025].

To conclude, the authors emphasised the importance of notifying possible adverse reactions from ArmaForce for effective monitoring and informing further regulatory action, such as labelling or removal of this product.

The negative skin testing results reported in 4 cases supports the suggestion in the expert advice that the mechanism behind reactions may be IgE-independent.

There was insufficient information provided in the abstract to confirm if the presented case reports have been received by the TGA and lodged in the AEMS database. Professor s22 was encouraged to report any cases to the TGA but did not confirm whether the cases in the abstract had been submitted. s22
s22
s22 , therefore does not align with any of the 5 cases described in the conference abstract. There were no other Andrographis related anaphylaxis reports in the TGA AEMS with sender details that corresponded to other study authors, however it cannot be ruled out that senders other than study authors may have submitted these cases to the TGA.

Other literature

Meincke R, Pokladnikova J, Straznicka J, Meyboom RH, Niedrig D, Russmann S, Jahodar L. Allergy-like immediate reactions with herbal medicines in children: A retrospective study using data from VigiBase®. Pediatric Allergy and Immunology. 2017 Nov;28(7):668-74. - D24-3134146

Comments / summary

This retrospective study extracted data from VigiBase® between the start of the WHO's international pharmacovigilance program in 1968 and August 2014, to identify hypersensitivity reactions to herbal medicines in children and adolescents. The patient age was limited to <18 years and time of AE onset was ≤1 day to distinguish reports of immediate hypersensitivity (type I) reactions from delayed onset hypersensitivity reactions (type IV). Reports were only included if causality was assessed as being either possible, probable or certain. Of the total data set, 79 cases were identified as meeting the inclusion criteria. The total number of reported AEs of allergy-like and asthma-like in the study population of 79 cases was 107, representing 1.35 reported AEs per unique case report ID and suspect herbal.

Andrographis was reported as a suspect herbal medicine associated with AEs, contributing to 4.7% (n=5) of all reported AEs (n=107). The most commonly reported suspect herbal medicines were mixed herbals, *Hedera helix*, and *Echinacea purpurea*, contributing to 51.4% (n=55), 15.0% (n=16), and 5.6% (n=6) of all reported AEs, respectively. The authors did not provide details of the reactions attributed to individual suspect herbal medicines, with seven reports of anaphylaxis recorded in the total 107 reported AEs. The authors noted that there were no reports of fatal AEs to herbals and that the nine AEs reported as "not recovered," rash and urticaria were most commonly caused by various herbal medicines.

The limitations of this study include the specific and restrictive inclusion criteria which resulted in the majority of reports being excluded by the authors. The authors also noted that the cases used for the study came from a variety of sources and the likelihood that the suspected adverse reactions are drug-related is not the same in all cases.

The authors acknowledged that:

- there are limitations of using spontaneous reporting as a source of pharmacovigilance data.

- another limitation may have been the manual selection process of reaction terms that indicate hypersensitivity and the overall exclusion of all GIT-related symptoms.
- the use of comedications may have influenced study results and confounded the data.
- they did not know whether any of the physicians who reported the AEs were allergist or complementary medicine specialists, and therefore it was not clear how far reporter type may have confounded the data.
- the selection of AE reaction terms used by reporters to code adverse events may have been influenced by semantics.

Notwithstanding these limitations, this study found that Andrographis was a suspect herbal medicine in 4.7% of reported immediate hypersensitivity reactions associated with herbal medicines in children and adolescents, with a causality assessment of possible, probable or certain.

Pokladnikova J, Meyboom RH, Meincke R, Niedrig D, Russmann S. Allergy-like immediate reactions with herbal medicines: a retrospective study using data from VigiBase®. Drug safety. 2016 May;39:455-64 - D19-6459538

Comments / Summary

The aim of this retrospective study was to provide an overview of immediate allergic-like reactions associated with herbal medicines reported in the WHO international pharmacovigilance database VigiBase.

The researchers retrieved historical case reports included in the VigiBase database between 1969 and August 2014. The inclusion criteria included exposure to a herbal medicine considered suspect, a documented causality assessment of 'possible', 'probable' or 'certain', a latency time of no more than 1 day from herbal exposure to AE onset and manual selection of WHO-ART preferred terms indicating likely symptoms of an immediate hypersensitivity reaction. WHO-ART terms were further divided into asthma-like and allergy-like reaction groups. The reaction terms used in the inclusion criteria ranged from skin reactions to potentially more serious adverse reactions, including anaphylaxis.

After applying the inclusion criteria, 757 unique case reports containing 1039 reported reactions were retrieved. The authors further categorised these into two groups, allergic-type reactions and asthma-like reactions. Allergic-type reactions accounted for 95.2% (n=989) of all 1039 reported reactions, while asthma-like reactions accounted for 4.8 % (n=50). The most frequently reported suspected medicines were mixed herbals (36% [374/1039]), followed by *Phleum pratense* (6.5% [68/1039]) then Andrographis (5.0% [52/1039]).

Andrographis and urticaria was listed as a frequently reported herbal medicine and allergic reaction combination (n=11 reports). However, the study only listed the most frequently reported herbal medicine – reaction combinations where 10 or more reports had been received for each specific combination. This could be a potential limitation as although Andrographis was linked to urticaria, there may have been other allergic reactions such as anaphylactic reactions attributed to Andrographis that may have been excluded because they were below the authors' reporting threshold (≥10 reports). A disproportionality analysis using the information component (IC) model did not show disproportionate reporting for Andrographis and urticaria.

The most frequent reporters were physicians (32.1%), hospital staff (24.7%) and pharmacists (14.1%). However, the authors highlighted that there is a high number of underreporting of herbal AEs by both patients and healthcare professionals. They suggested that this may be due to the lack of awareness among health professionals regarding the potential safety issues associated with herbal use.

The authors noted the following limitations:

- use of VigiBase:
  - extracted reports did not contain original detailed free-text descriptions by the primary reporters,
  - formal causality assessment was not available for the earliest reports
  - a standardised reaction term can be different to a clinical diagnosis based on established clinical diagnostic criteria), and
- a restrictive study design that emphasised high specificity with regard to the likely diagnosis of immediate allergic reactions.

Authors commented that these limitations resulted in the majority of reports from the extracted original raw dataset being excluded.

The authors acknowledged that although such a conservative approach implies reduced sensitivity for signal detection, overall it improves the interpretability of their findings. However, this could be considered a limitation of the study as their inclusion criteria may have been too restrictive. For example, the authors excluded cases with single reaction terms (including dyspnoea, pruritus, and gastrointestinal symptoms), which may be considered symptoms related to acute allergic-type reactions.

The authors noted that due to insufficient herbal product regulations, some AEs may be attributable to a lack of standardisation, contamination, adulteration, plant misidentification/substitution as well as improper use of herbal medicines including their inappropriate labelling rather than the pharmacological/toxicology effects of the herbals themselves.

The authors also acknowledged the limitations of spontaneous reporting data, noting that it does not provide information on the actual exposure to herbals in a population nor on the incidence of related AEs, however the primary strength of spontaneous reporting systems are the qualitative descriptive analyses and signal detection for previously unknown drug safety issues, rather than quantitative analyses.

Notwithstanding these limitations, this study reveals that Andrographis was the third most frequently reported herbal medicine associated with immediate allergic-like reactions in VigiBase up to 2014, when strict inclusion criteria was applied, although a disproportionate number of reports for Andrographis was not observed.

Wechwithan S, Suwankesawong W, Sornsrivichai V, McNeil EB, Jiraphongsa C, Chongsuvivatwong V. Signal detection for Thai traditional medicine: examination of national pharmacovigilance data using reporting odds ratio and reported population attributable risk. Regulatory Toxicology and Pharmacology. 2014 Oct 1;70(1):407-12. - D24-2436924

Comments / summary

This post-market study analysed AE reports from the Thai FDA database from 2002 to 2013. The authors aimed to quantify the contribution of Thai traditional medicine (TTM) to AE reports and to assess the association between TTMs and serious AEs. The authors conducted disproportionality analysis for signal detection using reporting odds ratio (ROR) as measurement, and commented that

medicines 'with a high ROR and/or causing a high number of ADRs are considered as having public health importance'.

Reports were analysed to determine the percentage of serious AEs when compared with all reports for each individual TTM. Although authors reported the TTMs with the highest percent of serious AEs (among all reports involving each TTM) as Andrographis (24.6%; n=44 out of 179 total reports for Andrographis), *Derris scandens* (19.2%) and *Curcuma longa* (14.6%), this appears to be misreported by study authors Table 2 in the paper suggested Andrographis had the highest *number* of serious reports (and total reports) for single herbal medicines, however other single herbal medicines had higher *percentages* of serious reports, albeit some with only 1 or 2 reports, with 100% of these being serious. Six reports for Andrographis were of anaphylactic shock which had a significant crude ROR (2.32 [95% CI: 1.03, 5.21]) and adjusted ROR (2.68 [95% CI: 1.19, 6.04]). ROR).. Authors also calculated the reported population attributable risk (RPAR) and commented that this 'indicates the proportion of a specific ADR in the whole dataset that could be avoided if the medicine is removed from use'. The authors reported that the RPAR for Andrographis was very low (0.05%) compared to Western medicine due to the low number of reports in the dataset. Authors also provided ROR and RPAR values for reports of anaphylactic shock for the three most reported conventional medicines and also for Penicillin G. The adjusted ROR for Andrographis was higher than for all except for Penicillin G. Authors commented that the adjusted ROR values for the three most common drugs causing anaphylactic shock was not high (lower than 2) as these drugs also caused other adverse events. Authors reported that the RPAR value was lower for Andrographis than for all four conventional medicines reported in the paper. Nevertheless, the authors concluded that the association Andrographis had with anaphylactic shock was weak but significant.

Suwankesawong W, Saokaew S, Permsuwan U, Chaiyakunapruk N. Characterization of hypersensitivity reactions reported among Andrographis paniculata users in Thailand using Health Product Vigilance Center (HPVC) database. BMC complementary and alternative medicine. 2014 Dec;14:1-7. - D24-3071628

Comments / summary

This retrospective post-marketing study analysed AE data from the Thai Vigibase and considered hypersensitivity cases reported by health care professionals from February 2001 to December 2012 related to oral Andrographis as the sole suspected medicine.

The article also provided background about the Health Product Vigilance Centre (HPVC) which commenced intensive monitoring of oral Andrographis after it was added to Thailand's National List of Essential Medicines (NLEM) in 1999 for use in the indications of non-infectious diarrhea and pharyngotonsillitis, with the indication for common cold added in 2006. Andrographis has been subject to intensive monitoring by the HPVC at different times following inclusion in the NLEM list, as well as subject to routine monitoring.

Of the 170 case reports identified that involved Andrographis for oral use as the sole suspected medicine, 106 cases included reaction terms consistent with hypersensitivity reactions. Of these, authors reported that 13 included critical reaction terms according to WHO criteria.

Key points reported by the authors for the 106 hypersensitivity cases were that 87% of cases recorded no previous documented history of drug allergy. 17% (18 cases) were classified as serious with 16 cases requiring hospitalisation. None of these cases were reported as being fatal, but two were described as life-threatening. Time of exposure was less than a day in 48% of cases, with time to onset of symptoms reported as being the first day of use in 57.6% of cases, with the shortest onset timeframe being reported as 5 minutes in one serious case**.** Time to exposure was reported as

the second day of administration in 22.6% of cases, while reactions still developed on or after 4 days of use in 4.7% of cases.

Of the 106 hypersensitivity cases, the 13 cases with critical reaction terms included anaphylactic shock (5 cases), anaphylactic reaction (4 cases) or angioedema (5 cases). Authors reported a history of drug allergy was present in two patients who developed angioedema. One patient was allergic to tetracycline, while another one was allergic to ibuprofen. The time to onset ranged from 5 minutes to 1 day. The authors considered that 11 of the 13 cases with critical reaction terms were serious and reported causality assessment for these cases as certain in 3 cases, probable in 7 cases and possible in 1 case. Seven case reports detailed the product's brand name. Interestingly, six different brands were reported among the seven case reports. The brand names were checked, and all were dry powder with differing doses ranging from 352 mg to 1,750 mg. Of the 13 cases with critical reaction terms, the authors included details of whether the event occurred after the first dose ('1 time used') (6 cases) or second dose ('2 time used') (1 case) where reported.

One of the strengths of this study was that it was limited to case reports involving Andrographis as a single agent, removing some potential confounding. Case reports were also limited to oral therapy and did not include IV use. Authors noted that reports were submitted from various settings with different brand products and commented that this cumulative evidence supported the association between Andrographis and hypersensitivity, as it was the likely cause in the majority of cases.

The authors also commented that the issue of Andrographis and hypersensitivity had caught the attention of the Thai FDA. However, the Signal Detection and Assessment Working Group and Drug Safety (pharmacovigilance) subcommittee under the Thai FDA decided to make no changes on product labelling at the time of publication because the causation of the signal could not be confirmed, but recommended a future pharmacoepidemiology study to determine whether the association between hypersensitivity reactions and Andrographis-containing products is confirmed. It is unclear whether this has occurred.

Although the authors concluded that the oral use of Andrographis may be associated with a risk of acute hypersensitivity reactions, they have tempered this conclusion by stating that it was not possible to draw a direct causal relationship from this study, due to the possibility that such reactions could be related to product contamination or lack of standardisation across brands. They state that further studies are needed to investigate this association in the future.

APPENDIX D (not for publication): D24-3784569 (reproduced in full below)

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

NONCLINICAL COMMENT ON ALLERGENIC POTENTIAL OF *ANDROGRAPHIS PANICULATA* OR ITS CONSTITUENTS

Subject: Nonclinical comment on studies related to the allergenic potential of *Andrographis paniculata* and/or its constituents
Tox File No.: 2012/008550
TRIM Reference: D24-3784569
Evaluator: (name redacted)
Date: 18 October 2024

To: (name redacted) AEMDS

The Adverse Events and Medicines Defects Section (AEMDS) has requested nonclinical comment on a number of studies identified as relevant to the allergenic potential of *Andrographis paniculata* (Andrographis) and its active constituents.

AEMDS is re-examining the safety of the herbal ingredient Andrographis in listed medicines due to a continued high number of reports of anaphylaxis and other severe allergic reactions. To better understand the mechanisms behind these reactions, AEMDS is also reviewing the current state of the science on Andrographis-related allergenicity, and have identified several nonclinical studies of uncertain relevance that require comment by the Toxicology Section.

Advice was sought to determine whether the studies:

- provide supportive evidence of allergenic potential of Andrographis and active constituents
- provide supportive evidence of protective effects against allergic reactions
- are useful at identifying possible mechanisms for anaphylaxis/hypersensitivity of Andrographis-containing products for oral use in humans
- more broadly whether animal studies provide value in characterising risk of allergenic potential during drug development and whether findings can be extrapolated to humans.

An overview of hypersensitivity reactions and current methods for evaluating allergenicity findings in nonclinical studies are provided in the Appendix, followed by a summary of findings from the identified nonclinical studies and relevance to risk characterisation of Andrographis use in humans.

ASSESSMENT

Published articles identified by the AEMDS and additional studies sourced by the Nonclinical Evaluator related to the allergenic potential and immunomodulatory action of Andrographis or its constituents have been summarised in Table 3 and **Table 4**.

Andrographis paniculata contains various compounds including terpenes and flavonoids. Extracts from this plant contain varying compositions of these. The quality of available literature studies was mixed, but most used standard methods for studying allergenicity and anaphylaxis in *in silico*, *in vitro* and *in vivo* systems. For the test articles used, a few of the studies used Andrographis extracts prepared from raw plant material (using different solvents, with composition reported). However, most studies used purified andrographolide, the main active constituent of Andrographis, or derivatives of andrographolide.

Pro-allergenic potential of Andrographis or its constituents

The nature of allergic reactions reported for patients receiving Andrographis extracts are indicative of a Type I (IgE-mediated) hypersensitivity reaction or of a pseudoallergy. The latter does not require sensitisation or antigen-specific IgE and involves direct activation of mast cells, occurs after the first dose and can occur at a higher frequency.

In vitro, andrographolide, dehydroandrographolide and neoandrographolide induced pseudoallergy type reactions in cellular assays. In a study using affinity chromatography with human mast cells as the bait, dehydroandrographolide was the primary component purified from an Andrographis extract. *In silico* docking suggested dehydroandrographolide was capable of binding FcεRI, which could result in direct activation of mast cells. Less affinity was seen with andrographolide.

The studies in animals focused on a typical hypersensitivity reaction mechanism of action (sensitisation and challenge). The popliteal lymph node assay in mice assesses the sensitisation potential (Pieters, 2001) while the active systemic anaphylaxis model in guinea pigs involves both a sensitisation and challenge phase. With components that elicited a pseudoallergenic potential in *in vitro* assays, an immunostimulant effect was seen in the popliteal lymph node assay but negative results were seen in the guinea pig assay. Possible reasons for the negative results in guinea pigs:

- the study design is not optimal to assess pseudoallergy type reactions
- only gross clinical signs of an anaphylaxis response were assessed; additional clinical signs (for example effects on respiratory rate) and histamine release would have provided more sensitive indicators
- guinea pigs may be a less sensitive species for pseudoallergic reactions than other animal species; dogs and minipigs are better species to assess such reactions and there have been reports of drugs eliciting pseudoallergic reactions in dogs with no evidence in rodents[xlviii]
- the doses used may not have been sufficient to elicit a response
- possible competing reactions of pro-allergenic and anti-inflammatory responses.

The *in vitro* data suggest a pseudoallergy and anaphylactoid potential of some components of Andrographis extracts. However, whether these components can elicit a typical hypersensitivity

[xlviii] AusPAR for linagliptin: https://www.tga.gov.au/sites/default/files/auspar-trajenta.pdf

reaction is inconclusive. Likewise, the allergenic potential of other components has not been assessed. It is noted that andrographolide has low oral bioavailability, primarily due to efflux by P-glycoprotein and extensive first-pass metabolism. Co-administered medicines or foods that interact with P-glycoprotein or enzymes involved in the metabolism of andrographolide may increase exposures to andrographolide and increase the risk of allergic reactions. As well as being a component of Andrographis extracts, dehydroandrographolide is also a likely metabolite of andrographolide. The allergenic potential of other andrographolide metabolites has not been assessed.

Anti-allergic/anti-inflammatory potential of Andrographis or its constituents

Andrographis-related compounds showed anti-inflammatory effects *in vitro* and *in vivo* through an inhibitory action on NF-κB/MAPK. Effects were shown *in vitro* in LPS-induced macrophages and *in vivo* in ovalbumin-sensitised mice, under conditions of hypersensitivity and inflammation. Inhibition of NF-κB by Andrographis-related substances was associated with lower gene expression of pro-inflammatory mediators, and reduced production of pro-inflammatory cytokines. In mice, treatment with Andrographis-related compounds improved airway function following ovalbumin challenge, or in response to a bronchoconstrictor. As the studies used purified Andrographis constituents (e.g., andrographolide, dehydroandrographolide) instead of herbal preparations commercially available to the general public, the clinical relevance of these findings is limited. However, these studies provide some understanding of the cellular mechanisms underlying the anti-inflammatory effects of Andrographis constituents.

As components of Andrographis appear to have competing allergenic and anti-inflammatory actions, different extracts with different compositions may affect the balance between these actions.

Predictive value of animal studies for allergenic potential

There are no standard methods for assessing the systemic allergenic potential of chemicals with nonclinical studies. Animal studies have improved understanding of hypersensitivity reactions in humans, but none are able to adequately model anaphylaxis in humans. Whilst rodent models have the advantage of being readily available, can test larger group sizes, and have well-understood physiology, they do not mimic the diversity of the human immune repertoire (i.e., the entirety of immunoglobulins, B cells, T cell receptor population). One suggested solution to address the issue of whether animal responses are representative is to use multiple animal models, each with their own strengths (Kanagaratham *et al.,* 2018). Another commentary suggested that seeking clinical similarity in allergenic responses is less important, relative to the larger goal of assessing relative allergenicity (and anaphylactic potential) of known allergens versus non-allergens (Lehrer and McClain, 2009). Thus, the value of animal studies on allergenicity lies more in better understanding mechanisms than in being used to accurately predict allergenic and anaphylactic reactions to substances.

CONCLUSIONS

The published nonclinical studies provide some evidence that:

- Some of the active ingredients in *A. paniculata* could be capable of evoking release of allergenic mediators, potentially resulting in anaphylactoid reactions. Evidence is based on *in vitro* cell-based assay and *in silico* model predictions. The lack of allergic reaction in animals raised questions about the adequacy of the animal models.
- Anti-inflammatory actions of *A. paniculata* extract and main active andrographolide was observed in mouse models of asthma.

APPENDIX to Nonclinical File note from Toxicology

Background

Andrographis paniculata (Andrographis) is a herb commonly used in Indian and Chinese medicine and may also go by the names 'king of bitters' and 'kalmegh'. There are currently 90 products for oral use listed on the ARTG that contain Andrographis, generally in multi-ingredient herbal medicine formulations, that are marketed for relief of cold and flu symptoms, or for immune support.

Since 2005, the TGA has received well over 300 reports of anaphylaxis and/or hypersensitivity reactions to products containing Andrographis. TGA has issued safety advisories[xlix] and mandated labelling requirements for statements that warn users of products that contain Andrographis of the risk of allergic reactions in some people. *Andrographis paniculata* is listed in the Therapeutic Goods (Permissible Ingredients) Determination (No. 2)[l] and can be used as an active ingredient or as a homoeopathic preparation ingredient in medicines with the following warning statement on the label:

- 'Andrographis may cause allergic reactions in some people. If you have a severe reaction (such as anaphylaxis), stop use and seek immediate medical attention' (or words to that effect).

When for oral use, the following warning statement is required on the medicine label:

- 'Andrographis may cause taste disturbance including loss of taste. If you develop any adverse symptoms, stop use and seek medical advice' (or words to that effect).

The allergic-type reactions reported for patients taking Andrographis include hypersensitivity, dyspnoea, urticaria, pruritis, paraesthesia, rash, periorbital oedema, lip swelling, face oedema, angioedema, erythema, auricular swelling, throat tightness, wheezing, palpitations, hyperhidrosis, respiratory rate increased, hypoxia, erythematous rash, pruritic rash.[xlix] Because little is currently known about the risk factors behind these hypersensitivity reactions, AEMDS is re-examining the safety profile of Andrographis and undertaking a review of the current literature. In the process they have identified some published nonclinical studies relevant to Andrographis and allergenicity, and have asked for comment on whether the studies shed light on mechanisms for these hypersensitivity reactions. As well, they have asked for broader comment on the role of nonclinical studies in assessing allergenic potential during drug development, and whether findings from allergenicity tests in animals can be extrapolated to humans.

Immune responses and hypersensitivity

Allergic reactions consist of a sensitisation phase and an elicitation phase. Sensitisation is the initial priming phase of the immune system when the allergen is initially encountered. While sensitisation itself does not yet lead to an allergic response, repeated exposure to sufficient amounts of the allergen is needed to elicit an allergic reaction. Allergic (or hypersensitivity) reactions are categorised into four types based on pathogenesis mechanisms (Dispenza, 2019) (**Table 1**). Allergic-type reactions similar to Type I hypersensitivity can also occur independently of IgE, where mast cells or basophils can be activated by IgG/antigen complexes, by complement-derived peptides, or by drugs that directly activate surface receptors to cause mast cell degranulation with release and secretion of vasoactive mediators, enzymes and cytokines (Finkelman *et al.,* 2016). Pseudoallergy does not require a sensitisation phase and can occur on the first dose. Andrographis was reported to induce a pseudoallergic reaction (Zhang *et al.,*

[xlix] Medicines containing Andrographis paniculata safety advisory – 2 July 2024

[l] Therapeutic Goods (Permissible Ingredients) Determination (No. 2) – 4 June 2024

2018), though no specific details were contained in the publication. The profile of allergic-type reactions seen in patients who have taken Andrographis is consistent with Type I hypersensitivity or with pseudoallergy.

Table 1. Comparison of the four types of hypersensitivity and pseudoallergy[li]

	Type I	Type II	Type III	Type IV	Pseudoallergy
Induction	Antibody-mediated	Antibody-mediated	Antibody mediated	Cell-mediated	Direct, via complement
Onset	Immediate	Immediate	Immediate	Delayed	Immediate
Immune reactant	IgE	IgG, IgM	IgG	Th1 cells, Th2 cells, cytotoxic T cells	–
Effector cells	Mast cells, basophils	Phagocytes, natural killer cells	Phagocytes, natural killer cells	CD4+ T cells, CD8+ T cells, macrophages, eosinophils	Mast cells, basophils
Primary mediators	Vasoactive amines	Complement, membrane attack complex	Antigen–antibody–complement complex	IFN-μ, IL-4, IL-5, IL-12, eotaxin	Vasoactive amines
Secondary mediators	Leukotrienes, prostaglandin D_2, platelet-activating factor, cytokines	Lysosomal enzymes, perforin	Lysosomal enzymes	Lymphokines, chemokines, cytokines, cytotoxins	Leukotrienes, prostaglandin D_2, platelet-activating factor, cytokines
Physiologic effects	Increased vascular permeability, vasodilation, bronchial spasm, mucous secretion	Antibody/ complement-mediated lysis, or antibody-dependent cell-mediated cytotoxicity	Immune-complex-mediated injury: immune complex deposition, PMN accumulation, lysosomal enzyme release and tissue injury	Oedema, infiltration by lymphocytes and macrophages at local site, erythema, induration	Increased vascular permeability, vasodilation, bronchial spasm, mucous secretion
Example of hypersensitivity reaction	Systemic anaphylaxis, urticaria, asthma, allergic rhinitis	Drug allergy, Goodpasture's syndrome, Rh incompatibility	Serum sickness, Arthus reaction	Contact dermatitis, chronic asthma, chronic allergic rhinitis, tuberculin reaction	Systemic anaphylaxis, angioedema, urticaria, bronchospasm, gastrointestinal signs, skin flushing

Symptoms of anaphylaxis develop rapidly, with skin rash and swelling of mucosal tissue being early signs, followed by acute onset of hypotension, tachy- or bradycardia, syncope, shallow breathing, bronchoconstriction and bronchospasm, gastrointestinal distress, and cardiac arrest at it severest and life-threatening form (Cardona *et al.,* 2020).

In regard to hypersensitivity reactions, while it is well-recognised that proteins can evoke immune responses, for small molecule substances, there are several accepted mechanisms of how they become immunoreactive (Pallardy *et al.,* 2024). These include:

- haptenisation of small molecules, which are complexed or covalently bound to certain proteins, and taken up by antigen-presenting cells (APCs), potentially leading to T-cell recognition and activation;
- direct activation of T-cell receptors;

[li] Adapted from: Chapter 12. TYPE I, II, III, AND IV HYPERSENSITIVITY. In: Immunology Guidebook. 2004. Ed. J.M. Cruse, R.E. Lewis, H. Wang, Academic Press, Pages 405-412, https://doi.org/10.1016/B978-012198382-6/50036-4.

- binding interactions that alter the conformation of self-peptide ligands presented by APCs;
- T-cell receptors already sensitised to a pathogen becoming cross-reactive to drugs used during infection to that pathogen; or
- under conditions of enhanced immunoreactivity and exposures to co-stimulatory signals (e.g., chemical or viral).

Some of these mechanisms rely on characteristics specific to the chemical (e.g., protein reactivity and haptenisation), but factors specific to an individual may also play a role, such as: genetic differences (e.g., polymorphisms of HLAs or CYPs), history of atopic disease (e.g., eczema, asthma), health status and concomitant use of medications, the existing T-cell receptor repertoire, variations in immune tolerance mechanisms, altered gut microbiome and patterns of exposure to antigen.

With respect to Andrographis, mechanisms to explain possible allergenicity have not been elucidated, and it is unclear whether there are factors inherent to the plant itself or its chemical constituents that are predictive of immunogenic potential, or if there are determining factors unique to individuals predisposing them to a greater risk of hypersensitivity, including anaphylaxis.

Nonclinical methods of assessing allergenicity and anaphylaxis

The current state of investigational tools available to evaluate allergenic potential of substances include *in vitro*, *in silico* and *in vivo* methods (reviewed by Pallardy *et al.,* 2024).

In silico and in vitro

Evaluating protein reactivity of small molecule substances is the first step in establishing whether a substance can be haptenised and capable of sensitisation. Methods to assess protein reactivity of substances include the *in chemico* direct peptide reactivity assay (OECD Test guideline 442C), which monitors the extent that a test chemical covalently binds to a lysine or cysteine-containing peptide. There are also *in silico* tools available (e.g., OECD QSAR toolbox, Case Ultra, TOPKAT), which screen chemicals for alerting structures capable of forming protein adducts, or that can perform molecular docking analysis to establish interaction potential with key proteins (e.g., FcεRI on mast cells; Teubner *et al.,* 2013). *In silico* tools have use in a regulatory context; for example AICIS considers data based on *in silico* models[lii] for skin and respiratory sensitisation potential in chemical risk assessments. ELISA/immunoblotting and mass spectrometry can also be used to confirm and quantify chemical-protein interactions. A major limitation of *in silico* methods is that while they may indicate the ability to bind proteins, they cannot determine if binding interactions are likely to cause sufficient sensitisation to lead to an immunogenic response.

In vitro assays for IgE-mediated hypersensitivity measure antigen-specific IgE or activation of basophil cells in whole blood. However, these assays are not used to assess if a drug is allergenic. They are used primarily to ascertain if an individual's allergic reaction is attributable to a specific test item. Prior exposure (sensitisation) has already occurred. There are no suitable *in vitro* assays to assess if a drug is allergenic. An adaptation of the basophil activation test can be used to assess the potential of a drug to elicit a pseudoallergic reaction. The assay assumes a direct action on mast cells and monitors the release of histamine, lysosomal enzymes or cytokines, or monitors cellular surface markers of mast cell activation. Indeed, non-IgE-mediated mast cell activation has been demonstrated with traditional Chinese medicine preparation containing ginseng, Xue-Sai-Tong injection (Xiang *et al.,* 2013).

[lii] AICIS – In silico predictions for categorisation

In vivo

There are no routine animal studies that are used to assess the *systemic* allergenic potential of small molecule pharmaceuticals. Guinea pig and mouse local lymph node assays have been developed to assess the skin sensitisation potential of medicines that are applied to the skin (OECD Test guideline 429; EMA guideline on non-clinical local tolerance testing of medicinal products[liii]) but no guidelines cover the systemic allergenic potential of small molecule pharmaceuticals in animals. Indeed, the FDA guidance on immunotoxicity[liv] states that, while systemic hypersensitivity reactions are significant potential drug-related adverse reactions, there are currently no standard nonclinical assays available to reliably evaluate potential risks. The guideline goes on to say, "*fit-for-purpose assays and/or a weight-of-evidence assessment may be considered only if appropriate to the specific pharmaceutical and scientifically justified*".

Several animal models have been developed and used to assess allergy to orally administered compounds. Of these, rodents are the most frequently used model and best understood, with respect to processes of sensitisation and elicitation; however, guinea pig, dog, sheep and swine models of allergy have also been developed (Gouel-Chéron *et al.,* 2023). Phenotypes of anaphylaxis can be extrapolated reasonably well to human reactions, with some rodents showing elevated levels of antigen-specific IgE, and release of biomarkers indicating mast cell activation (histamine, leukotrienes, cytokines). Clinical signs due to mast cell activation are seen in mice, with strain-specific observations including decreases in core body temperature/hypothermia, diarrhoea (correlating to intestinal mast cells) and reduced activity (Gouel-Chéron *et al.,* 2023). However, the suitability of responsiveness to allergens in laboratory animals species (*cf*. human response) depends on numerous factors including (EFSA, 2010; Gouel-Chéron *et al.,* 2023; Lehrer and McClain, 2009):

- the animal species, strains, genetic background and/or age;
- the oral sensitisation protocol (necessary to replicate the conditions of intestinal exposure to food allergens in humans);
    - the use of adjuvants (e.g., Freund's complete adjuvant [CFA], lipopolysaccharides [LPS], alum) to circumvent oral tolerance to protein immunogens;
- the allergen preparation (e.g., crude extracts, purified substances or combined with other ingredients) (Bøgh et al., 2016);
- the route, dose, timing, frequency and duration of allergen administration.

Transgenic mouse models have also been developed, where altered expression profiles of specific cytokine mediators (e.g., IL-4, IL-13), effector cells (e.g., regulatory T cells, Treg) or proteins (e.g., CCR4, FcεRI), or in humanised mouse models expressing human FcεRI or engrafted with human peripheral blood mononuclear cells (PBMCs), have facilitated understanding of the role of these factors in anaphylaxis and hypersensitivity (EFSA, 2010; Kanagaratham *et al.,* 2018; Gouel-Chéron *et al.,* 2023), but are currently not widely used for allergen testing.

[liii] EMA/CHMP/SWP/2145/2000 Rev. 1, Corr. 1 – Guideline on non-clinical local tolerance testing of medicinal products

[liv] FDA Guidance for Industry – Nonclinical evaluation of the immunotoxic potential of pharmaceuticals. June 2023

Although animal models are useful tools to gain understanding of allergenicity and anaphylaxis pathophysiology, they do have several limitations which can affect the model reproducibility and translation to human (Gouel-Chéron *et al.,* 2023; Kazemi *et al.,* 2023; Lehrer and McClain, 2009; Santoro and Marsella, 2014):

- Interspecies differences in the pharmacokinetics of the compounds (e.g. bioavailability, metabolism)
- Inter- and intra-species differences in immune systems with resulting variability in immune response to allergens.
- Animal models do not entirely reproduce human pathophysiology and clinical signs of allergy/anaphylaxis:
    - anaphylaxis with low amounts of orally administered allergen has not been demonstrated in mice (*cf.* humans and peanut allergies for example);
    - not all animal models display fatal anaphylaxis;
    - some animal species/rodent strains are not suitable anaphylaxis models due to their inability to produce antigen-specific IgE.
- In some animal models, the oral route of exposure might not be suited to effectively identify the sensitising potential of an allergen (partly attributable to the development of oral tolerance in most animal species).
- Similarly, the use of adjuvants to sensitise the animals and bypass oral tolerance to immunogens might not be suitable to identify the sensitising potential of an allergen.

Animal models developed to date are not standardised and validated. Therefore, as concluded by Lehrer and McClain (2009) "*an animal model should be regarded as a biological test system rather than a human surrogate since it is practically impossible to duplicate the human allergic disease process in an animal.*"

Andrographis constituents and methods of extraction

Whilst evidence associating use of Andrographis-containing products to allergic reactions (including anaphylaxis) is certain, constituents responsible for these reactions have not been identified. Many of the adverse reactions reports for Andrographis products reported to the TGA have come from multi-ingredient preparations – although Andrographis was considered the sole suspected ingredient for most of those reports (TGA, 2015). A role for other ingredients in allergic reactions cannot be excluded; however, further exploration is outside the scope of this enquiry.

Andrographis paniculata has various compounds in its aerial parts and roots, including terpenes and flavonoids (**Table 2**) as well as arabinogalactan proteins, polyphenols and xanthones (Chao and Lin, 2010; Okhuarobo *et al.,* 2014). Andrographolide is the main diterpenoid, present in leaves, dried whole plant and stems, and the active component most investigated for bioactivity. Most of the compounds are insoluble in water. Investigational studies on Andrographis have typically involved the use of extracts of dried raw plant material that have been prepared using various solvents (e.g., alcohols, ether, water). Extracts have been used neat in *in vitro* assays and *in vivo* in animals, or have been separated to purify the active constituent of interest (usually andrographolide). Some studies have also used commercial preparations of Andrographis, containing a specified quantity of Andrographis bioactive/s. Differences in chemical composition of extracts can result from differences in the plant composition due to geographical regions, environment or harvest time, as well as differences in extraction methods.

Table 2. Chemicals found in *A. paniculata*

Compound	Type	Plant part
Terpenes		
Andrographolide	Diterpenoid lactone	Leaves/aerial
Neoandrographolide	Diterpenoid lactone	Leaves/aerial
14-deoxyandrographolide	Diterpenoid lactone	Aerial parts
Andrographoside	Diterpene	Leaves/aerial
14-deoxy-11, 12-didehydroandrographolide	Diterpenoid lactone	Aerial parts
19-O-β-D-glucopyranosyl-ent-labda-8(17), 13-dien-15, 16, 19-triol	Ent-labdane diterpenoid lactone	Aerial parts
8α-methoxy-14-deoxy-17β- hydroxyandrographolide	Ent-labdane diterpenoid lactone	Aerial parts
Andrographolactone	Diterpenoid lactone	Aerial parts
3, 13, 14, 19-tetrahydroxy- ent-labda-8(17), 11-dien-16, 15 olide and 3, 19 isopropylidene- 14-deoxy- ent-labda-8(17), 13-diene-16, 15-olide	Diterpenoid lactone	Aerial parts
14-deoxy-15-isopropylidene-11,12-didehydroandrographolide	Unusual Terpenoid	Aerial parts/roots
3,7,19-trihydroxyl-8,11, 13- ent-labdatriene-15, 16-olide and 8α,17β-epoxy-3, 19-dihydroxy-11,13-ent-labdatrien-15, 16-olide	Diterpene lactone	Aerial parts
Andrograpanin	Diterpene	Leaves
Flavonoids		
5, 7, 2', 3'-tetramethoxyflavone	Flavonone	Whole plant
5-hydroxy-7, 2', 3'-trimethoxy flavones	Flavone	Whole plant
5-hydroxy-7, 2', 6'trimethoxyflavone	Flavone	Root
7-O-methyldihydrowogonin	Flavone	Root/aerial part
7-O-methylwogonin	Flavone	Root/aerial part/whole plant
Flavone-1, 2'methylether	Flavone	Root/aerial part/whole plant
7-O-methylwogonin-5-glucoside	Flavones	Root/aerial part
Flavone-1, 2'-O-glucoside	Flavonoids	Root/aerial part/whole plant
5-hydroxy-7, 8, 2', 5'-tetramethoxyflavone	Flavonoids	Whole plant
Dihydroskullcapflavone	Flavone	Whole plant
5-hydroxy-7, 8, 2, 3' tetramethoxyflavone	Flavone	Whole plant

Pharmacokinetics

One consideration regarding the predictive ability of findings in animals to potential effects in human subjects is the comparison of the pharmacokinetic profile of the test item between species. Given the complex composition of Andrographis, an extensive comparison of the pharmacokinetics of each component between human subjects and different animal species has not been performed. A limited focus on the pharmacokinetics of andrographolide, the main diterpenoid in Andrographis and its extracts is described below.

Andrographolide has low oral bioavailability (2.7% in rats and estimated 6.3% in human subjects) primarily due to first-pass metabolism and efflux transporters; andrographolide is a substrate for P-glycoprotein (Ye *et al.*, 2011; Talapphetsakun *et al.*, 2022). Andrographolide undergoes extensive metabolism, including oxidation, dehydration, reduction and conjugation with glucuronide, sulfate or cysteine (Cui *et al*., 2004; 2005; reviewed in Talapphetsakun, 2022). Species differences in metabolism (extent and metabolites formed) in liver microsomes were noted with some human specific metabolites identified (Zhao *et al.*, 2013). In rats, the main circulating metabolite is 14-deoxy-12-sulfo-andrographolide, which is formed in the gastrointestinal tract and levels can reach ~20 times andrographolide levels in blood as well as tissues (Ye *et al.*, 2011).

In rats, dehydroandrographolide had an oral bioavailability of ~12%, was not a substrate for P-glycoprotein or BCRP and did not undergo significant metabolism in intestinal perfusates (Ye *et al.*, 2012). Dehydroandrographolide is a component of Andrographis as well as being a metabolite of andrographolide.

Published studies on Andrographis paniculata and allergenicity

Nonclinical comment was requested for a number of published literature reports regarding Andrographis and/or its active constituents and allergenicity. Some studies assessed the allergenicity (Table 3) while others assessed the anti-allergic or anti-inflammatory properties Andrographis and/or its active constituents (**Table 4**).

Table 3. Summary findings of literature reports assessing allergenicity

<table>
<tr><th>Experimental details</th><th>Results and comments</th></tr>
<tr><td colspan="2">Richard et al. (2017)
Is Andrographis paniculata extract and andrographolide anaphylactic?</td></tr>
<tr><td>
Rat basophilic leukaemia cells (RBL-2H3)
± anti-dinitrophenyl IgE sensitisation followed by incubation with test item for 10–60 min

Guinea pig (Dunkin-Hartley; 6–7 weeks old; n = 5 ♂/group)
<table>
<tr><th>Sensitisation (daily for 5 days)</th><th colspan="2">Challenge</th></tr>
<tr><td rowspan="2">A. paniculata extract 25 mg/kg (PO)</td><td rowspan="2">A. paniculata extract</td><td>12.5 mg/kg (PO)</td></tr>
<tr><td>2.5 mg/kg (IV)</td></tr>
<tr><td rowspan="2">Andrographolide 8 mg/kg (PO)</td><td rowspan="2">Andrographolide</td><td>4 mg/kg (PO)</td></tr>
<tr><td>0.8 mg/kg (IV)</td></tr>
<tr><td rowspan="2">DMSO 10 mL/kg (PO)</td><td>DMSO (10%)</td><td>10 ml/kg (PO)</td></tr>
<tr><td>DMSO (1%)</td><td>1 ml/kg (IV)</td></tr>
<tr><td>Ovalbumin + CFA 2.5 mg/kg (SC)</td><td>Ovalbumin</td><td>1.67 mg/kg (IV)</td></tr>
</table>
Test items:
• A. paniculata (coarse ground leaves) methanol & water extract containing predominantly andrographolide (>30% w/w), 14-deoxy-11,12-didehydroandrographolide (≤5% w/w), neoandrographolide (>1% w/w), isoandrographolide & andrograpanin (>0.3% w/w each) and skullcapflavone I & 7-O-methylwogonin (>0.05% w/w each)
• andrographolide (purity >98%)
• control: DMSO
</td><td>
In vitro:
A. paniculata extract did not release histamine, LTC4, tryptase or β-hexosaminidase in either IgE-sensitised or non-sensitised cells

Andrographolide induced release of histamine and LTC4 in IgE-sensitised cells, and LTC4, β-hexosaminidase & tryptase in non-sensitised cells (direct activation in non-sensitised cells suggests anaphylactoid response)

In vivo:
Following sensitisation with A. paniculata extract or andrographolide, challenge with A. paniculata extract or andrographolide (PO or IV) did not induce clinical signs of anaphylaxis in guinea pigs

Positive controls (ovalbumin & CFA) induced anaphylaxis under the tested conditions

Limitations:
Lack of in vivo evidence of allergenic potential by A. paniculata extract or andrographolide (uncertainty about the adequacy of sensitisation method)

The in vivo study did not assess histamine levels and assessment of an allergic reaction was by examination of clinical signs and anaphylaxis

The A. paniculata extract and andrographolide doses used for sensitisation and challenge may not reflect human exposure

Long-term exposure or re-challenge to A. paniculata extract and andrographolide not investigated, which could be relevant to addressing the anaphylactic potential of A. paniculata or its constituents in humans
</td></tr>
</table>

<table>
<tr><th>Experimental details</th><th>Results and comments</th></tr>
<tr><td colspan="2">Hu et al. (2015)
Evaluation of the anaphylactoid potential of Andrographis paniculata extracts using the popliteal lymph node assay and P815 cell degranulation in vitro</td></tr>
<tr><td>Murine mastocytoma cell line (P815) degranulation assessed by incubating cells with test items for 45 min (vehicle: Tyrode solution, positive control: C48/80)
Parameters measured: histamine levels, ammonia glycosidase release rate & cell degranulation levels
Mouse (BALB/c; n = 10 ♀/group)
single SC administration of 50 µL Andrographis (commercially sourced), 2 mg in 50 µL AE, EAE, NBE, AEE, 1 mg in 50 µL NAD, DDA, AND or vehicle on the hind footpads and sacrificed on day 7, with popliteal lymph node (PLN) weights & cellularity assessed & compared
Test items:
•Andrographis (commercially sourced MingXing Pharmaceutical Factory)
• A. paniculata (stems and leaves) extracts: alcohol extract (AEE; containing 8.45:3.37:2.85 AND:NAD:DDA), ethyl acetate extract (EAE; 6.32:3.30:2.88 AND:NAD:DDA), n-butanol extract (NBE; 2.22:0:0 AND:NAD:DDA) & aqueous extract (AE; 0:0:0 AND:NAD:DDA)
• EAE fractions (purity >98%): andrographolide (AND), neoandrographolide (NAD) & dehydroandrographolide (DDA)
• vehicle: saline or DMSO</td><td>In vitro:
AEE, EAE & NBE (but not AE) directly induced mast cell degranulation and release of histamine and/or ammonia glycosidase suggesting IgE-independent mast cell activation (anaphylactoid reaction):
<table>
<tr><th>Test item</th><th>Histamine release</th><th>Ammonia glycosidase release</th><th>Cell degranulation</th></tr>
<tr><td>AND</td><td>✓</td><td>×</td><td>×</td></tr>
<tr><td>DDA</td><td>✓</td><td>✓</td><td>✓</td></tr>
<tr><td>NAD</td><td>✓</td><td>×</td><td>✓</td></tr>
<tr><td>AEE</td><td>×</td><td>✓</td><td>✓</td></tr>
<tr><td>EAE</td><td>✓</td><td>✓</td><td>✓</td></tr>
<tr><td>AE</td><td>×</td><td>×</td><td>×</td></tr>
<tr><td>NBE</td><td>×</td><td>✓</td><td>×</td></tr>
</table>
In vivo:
Andrographis (commercially sourced) increased PLN weight cf. vehicle; morphological differences included high number of endothelial venules, increased cross-section area and larger number of mature transformed cells
AEE, EAE & BNE (but not AE), AND, DDA & NAD, also increased PLN weight & cellularity indices
Limitations:
The full chemical composition of the extracts was not provided. This may explain some differences seen between extracts and isolated test items.
In vivo immunostimulant effects of A. paniculata and andrographolide observed in the PLN assay were not interrogated for specificity (i.e., only measured changes to lymph gland size and lymphocyte proliferation but did not monitor biomarkers)
Only a single dose of A. paniculata extracts or of fractions was administered (may not reflect human exposure) by a non-clinically relevant route (SC)</td></tr>
</table>

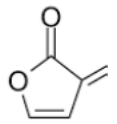
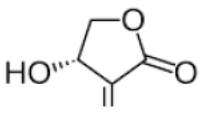
Experimental details	Results and comments
Lin *et al.* (2017) The human mast cell line-1 cell membrane chromatography coupled with HPLC-ESI-MS/MS method for screening potentical (*sic*) anaphylactic components from chuanxinlian injection	
Affinity chromatography purification Membranes from human mast cell line 1 (HMC-1)/CMC column coupled with HPLC-ESI-MS/MS to identify components bound *Test item:* • chuanxinlian injection solution (made from extracts from *A. paniculata*) **Human mast cell line 1** (HMC-1) Degranulation assessed by incubating cells with test items for 30 min *Parameters measured:* β-hexosaminidase & histamine release *Test items:* • dehydroandrographolide (12.5–200 µM)	The mass spectrum & proposed fragmentation pattern of the fraction of *A. paniculata* that was retained on the HMC-1/CMC column matched dehydroandrographolide Dehydroandrographolide increased β-hexosaminidase & histamine release from HMC-1 cells
Yang *et al.* (2019) Crystal structure and anti-inflammatory and anaphylactic effects of andrographolide sulphonate E in Xiyanping, a traditional Chinese medicine injection	
***In silico* analysis — AutoDock4.2 software** potential allergenicity of andrographolide, ASE and dehydrated andrographolide (DA) — molecular docking with FcεRI receptor (plays role in histamine release from mast cells) *Test items:* • andrographolide • andrographolide sulfonate E (ASE; sodium 9-dehydro-17-hydroandrographolide-19-yl sulfate dihydrate) • dehydrated andrographolide (assumed to be dehydroandrographolide)	*In silico:* Andrographolide and ASE displayed similar low binding affinity for FcεRI receptor (*cf.* reference ligand); suggesting that andrographolide and ASE have lower risk of allergic reactivity The interaction mode analysis showed that FcεRI receptor reference ligand formed a hydrogen bond with amino acid residue Trp113 on FcεRI receptor. The authors suggested that this bond could be responsible for anaphylactic effect of andrographolide analogues. Neither andrographolide nor ASE demonstrated hydrogen bonding to Trp113; hydrophobic interactions were demonstrated. Analysis with DA showed hydrogen bonding with Trp113 via the -C=O on the 5-membered ring; suggesting allergenic potential of DA (*cf.* andrographolide). A comparison of the structure of this ring between DA, andrographolide and ASE is shown below:  DA  Andrographolide & ASE **Limitations:** The study contained limited detail on the ligand-docking results. The protein interaction results do not necessarily indicate this will lead to an allergic reaction.

Table 4. Summary findings of literature reports assessing anti-allergic, anti-inflammatory or immunomodulatory activity

Experimental details	Results and comments
Guan *et al.* (2011) Protective Role of 14-Deoxy-11,12-didehydroandrographolide, a Noncytotoxic Analogue of Andrographolide, in Allergic Airway Inflammation	
Mouse (BALB/c; 6–8 weeks old; ♀) Sensitised with ovalbumin (OVA; IP on Day 0 & 14) and challenged with OVA aerosol on Days 22, 23 & 24; 0.1, 0.5, 1 mg/kg 14-DDA or DMSO administered IP 2 h before and 10 h after each OVA aerosol challenge *Test items:* • 14-deoxy-11,12-didehydroandrographolide (14-DDA; purity >98%) • andrographolide (purity >98%) • vehicle: DMSO • negative control: saline aerosol	*In vivo:* 14-DDA dose-dependently inhibited NF-kB activation and reduced cytokines levels (IL-4, IL-5, IL-13, eotaxin) in bronchoalveolar lavage fluid in OVA-sensitised mice *cf.* OVA only or DMSO 14-DDA reduced total IgE & OVA-specific IgE serum levels in OVA-sensitised mice *cf.* OVA only or DMSO 14-DDA reduced mucus production & prevented mast cell degranulation in OVA-sensitised mice *cf.* OVA only or DMSO 14-DDA also reduced airway resistance & restored airway dynamic compliance after ovalbumin-challenge Andrographolide was not assessed *in vivo* due to cytotoxicity *in vitro* **Limitations:** The study only investigated the role of a single *A. paniculata* analogue. The potential combinatorial effect of other constituents of *A. paniculata* was not investigated. 14-DDA was given to mice IP, which is not the clinical route. It is unknown if there are differences in the metabolism (or bioavailability) of 14-DDA by the different routes of administration.
Lim *et al.* (2016) A semisynthetic diterpenoid lactone inhibits NF-κB signalling to ameliorate inflammation and airway hyperresponsiveness in a mouse asthma model	
Human lung epithelial (A549) incubated with test items (30 µM) for 4 h **Mouse** (BALB/c; 6–8 weeks old) sensitised with OVA (200 µg/mL) in alum on Days 0 & 14 and challenged with OVA aerosol for 30 min on Days 22, 23 & 24 IP administration of SRS27 (0.1, 0.3, 1, 3 mg/kg) or vehicle 1 h prior & 11 h after each OVA aerosol challenge *Test item:* • Andrographolide (isolated and purified from *A. paniculata*) • 14-deoxy-11,12-didehydroandrographolide (DDAG; isolated and purified from *A. paniculata*) • 3,19-diacetyl-14-deoxy-11,12-didehydroandrographolide (SRS27; synthetic compound) • Vehicles: DMSO	*In vitro*: Andrographolide, DDAG and/or SRS27 suppressed TNF-α induced nuclear translocation of p65 subunit of NF-κB and DNA binding in nucleus SRS27 suppressed TNF-α induced up-regulation of NF-κB dependent genes (i.e., IL-6, IL-8, CCL5 & MCP-1) [andrographolide and DDAG were not investigated] *In vivo:* In OVA challenged mice, SRS27 (3 mg/kg) decreased — total cell, macrophage, eosinophils, lymphocyte, and neutrophil counts and pro-inflammatory cytokines levels (IL-4, IL-5, IL-13) in bronchoalveolar lavage (BAL) fluid *cf.* OVA + DMSO group — serum IgE levels and mucus secretion *cf.* OVA + DMSO group — lung tissue gene expression of oxidative stress, inflammatory and/or airway remodelling markers (SOD-2, 5-LOX, E-selectin, VCAM-1, CCL5, CCL2, TNFα, AMCase, Ym2, YKL-40, iNOS) *cf.* OVA + DMSO group SRS27 (3 mg/kg) increased IFN-γ levels in BAL fluid *cf.* OVA + DMSO group SRS27 reduced methacholine-induced airway resistance in ovalbumin-challenged mice and moderately improved airway compliance *cf.* OVA + DMSO group **Limitations:** Mice were dosed *A. paniculata* derivative SRS27 using the IP route, which is not clinically relevant for either route or test item.

Experimental details	Results and comments
Che *et al.* (2019) Dehydroandrographolide inhibits IgE-mediated anaphylactic reactions *via* calcium signaling pathway	
Allergic disease 2 (LAD2) human mast cells treated for 20 min with DA (12.5, 25, 50 µM); DNP-IgE sensitised, DNP-BSA challenged *Parameters measured:* β-hexosaminidase, histamine, chemokine release, phosphorylated kinase release **Mouse** (C57BL/6; 8–10 weeks old; *n* = 6 ♂/group) Intragastric administration of 0.25, 0.5, 1 mg/kg DA (7 days post-sensitisation with OVA [IV]) 1 h prior to OVA challenge into the left paw followed by hind paw swelling and extravasation measurement and mast cell staining or OVA challenge IV followed by histamine and chemokines serum level measurement *Test items:* • dehydroandrographolide (DA; purity ≥98%) • negative control: saline	*In vitro:* DA did not induce LAD2 cell degranulation (no increase in β-hexosaminidase or histamine release), but inhibited degranulation induced by DNP-BSA. DA reduced the release of IgE-mediate cytokines (IL-8, IL-13, MCP-1) by LAD2 cells, and downregulated phosphorylation of proteins involved in mast cell degranulation and cytokine release (p38α, AKT1/2/3 & PLC-γ1) induced by DNP-BSA. Noting that PLC-γ1 is involved in calcium signalling pathway and FcεRI pathway. *In vivo*: DA reduced (dose-dependently) extent of IgE-mediated swelling & extravasation (indicating anaphylaxis) in paws of OVA-sensitised mice following OVA challenge DA also reduced serum histamine, TNF α, MCP-1, IL-13 and IL-4, in OVA-sensitised mice following OVA challenge
Yang *et al.* (2019) Crystal structure and anti-inflammatory and anaphylactic effects of andrographolide sulphonate E in Xiyanping, a traditional Chinese medicine injection	
Mouse mononuclear macrophage (RAW264.7) incubated with test items (2.5–80 µM) + LPS for 6-24 h followed by measurement of inflammatory cytokines (NO & TNF-α) **Mouse** (Kunming; *n* = 10 ♂/group) administered 12.5, 25, 50 mg/kg/day andrographolide or ASE, or 2 mg/kg/day dexamethasone IV for 3 days. Xylene applied 40 min after last dose to each ear and oedema assessed *Test items:* • andrographolide • andrographolide sulfonate E (ASE; sodium 9-dehydro-17-hydroandrographolide-19-yl sulfate dihydrate) • vehicle: saline	*In vitro:* Andrographolide and ASE concentration-dependently reduced release of NO (IC_{50} values 9.8 µM & 26.5 µM, respectively) and TNFα (IC_{50} values 11.4 µM & 40.1 µM) by LPS-stimulated macrophages *In vivo:* Both andrographolide and ASE dose-dependently reduced xylene-induced ear oedema in mice (up to 67% and 64%, respectively *cf.* dexamethasone 71%) **Limitations:** Mice were administered andrographolide analogues using a non-clinically relevant route (IV)
Puri *et al.* (1993) Immunostimulant agents from *Andrographis paniculata*	
Mouse (BALB/c; *n* = 4 [♂ &/or ♀]/group) *Treatment:* • 25 mg/kg/day *A. paniculata* ethanolic extracts PO for 7 days prior to immunisation with sheep RBC • 1 mg/kg/day purified crystalline compounds PO for 7 days prior to immunisation • 4 mg/kg purified crystalline compounds IP 7 & 4 days prior to immunisation *Test items*: • *A. paniculata* ethanolic extract (composition not stated) • purified andrographolide • purified neoandrographolide	all test items increased the immune response and delayed hypersensitivity reaction to sheep RBCs

Experimental details	Results and comments
Li *et al.* (2017) Andrographolide Inhibits Inflammatory Cytokines Secretion in LPS-Stimulated RAW264.7 Cells through Suppression of NF-κB/MAPK Signaling Pathway	
Mouse mononuclear macrophage (RAW264.7) incubated with andrographolide (6.25, 12.5, 25 µg/mL) for 1 h followed by LPS (1 µg/mL) stimulation for 18 h *Parameters measured:* cytotoxicity, mRNA and protein levels of pro-inflammatory cytokine release (TNF-α, IL-1β, IL-6), nuclear level of NF-κB, NF-κB, p38, ERK, and JNK protein levels	• Andrographolide inhibited LPS-induced mRNA expression & production of TNFα, IL-6, and IL-1β Andrographolide inhibited LPS-induced increase in nuclear levels of NF-kB and inhibited the LPS-induced NF-kB activation and phosphorylation of p65, IkBa, ERK1/2, JNK and p38 **Limitations:** The purity of the andrographolide used was not specified

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