Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Andrographis paniculata (Andrographis) and anaphylaxis

Updated safety review with adverse event data to 31 December 2024

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Summary

- The TGA has continued to receive a sustained high number of reports of anaphylaxis associated with Andrographis-containing medicines following a large increase in 2019. A fatal case was reported in June 2024.
- The safety concerns of life-threatening anaphylaxis from Andrographis are magnified by the unpredictable nature of the response. Reports describing anaphylactic reactions detail events that happen both after prior use or sensitisation and also on first exposure. Expert advice from a clinical immunologist supports this safety 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.
- From 2005 when the first reports of anaphylaxis associated with Andrographis-containing medicines were received by the TGA 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 10 reports of anaphylaxis related to medicines 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. It is tentatively estimated that anaphylaxis from Andrographis occurs at a rate of 0.01-0.1% per units of Andrographis medicines supplied, which in practical terms means that for every 1000 to 10,000 containers of an Andrographis medicine supplied, an anaphylaxis event can be expected. Several limitations apply to this estimate including incomplete supply data and suspected under-reporting. Nevertheless, this estimate suggests anaphylaxis reactions are expected to occur for Andrographis medicines supplied in similar volumes to those analysed.
- Analyses of reporting data for the 20 most highly supplied Andrographis products in Australia during a defined period 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 associated with Andrographis.
  - most had a rapid onset of symptoms (within 30 minutes).
  - most were treated with adrenaline, and most presented to hospital (emergency department and/or hospital 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 to an extent that is compatible with Andrographis being suitable as an ingredient in listed medicines (see Data analysis of preparation type and Risk mitigation options).
- The number of anaphylaxis adverse events for Andrographis is high when compared with other oral 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 registered medicine ingredients associated with anaphylactic reactions (see Other medicines at risk of anaphylaxis).
- A review of medical literature published since November 2011 on Andrographis and associated adverse events 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 *in vitro* cell-based assay and *in silico* model predictions provide some evidence that some of the active constituents in Andrographis could evoke release of allergenic mediators and potentially result in anaphylactic reactions, while one study found anti-inflammatory actions were observed in mouse models of asthma.
- 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 two have published safety communications on the topic.
- For an ingredient to remain appropriate for use in low-risk 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 health claims 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 a sustained high number of reports of anaphylaxis involving Andrographis-containing listed medicines since 2019, this ingredient is inconsistent with the low-risk medicines regulatory framework.
- 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.
- This updated safety review has concluded that even if additional risk mitigation strategies were adopted, the risk of life-threatening anaphylaxis associated with Andrographis is inconsistent with the low-risk regulatory framework of listed medicines.

Background

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. 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 TGA has undertaken ongoing post-market monitoring activities related to the effectiveness of the risk mitigation. Following the large increase in 2019, the TGA has continued to receive a sustained number of reports of anaphylaxis associated with Andrographis-containing medicines, with no indication of a declining trend. Of particular concern are adverse event reports that describe use 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. In 2024, one medicine sponsor of an Andrographis-containing medicine implemented a strengthened and more prominent label warning to further highlight the risk of anaphylaxis.

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
- 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

[1] Brown, S.G.A., Mullins, R.J. and Gold, M.S. (2006), 2. Anaphylaxis: diagnosis and management. Medical Journal of Australia, 185: 283-289. https://doi.org/10.5694/j.1326-5377.2006.tb00563.x

Andrographis-containing listed medicines to warn about allergic reactions and anaphylaxis.

- The TGA has continued to receive a sustained number of reports of anaphylaxis associated with Andrographis-containing medicines following a large increase in the number of reports in 2019, with no indication of a declining trend.
- A fatal case of anaphylaxis associated with Andrographis was reported to the TGA in June 2024. An updated safety advisory was published in July 2024.
- 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 such that the risk of anaphylaxis would be consistent with the low-risk listed medicines regulatory framework.

Expert advice

The TGA sought expert advice from an independent clinical immunology and allergy specialist advisor. The advice provided is summarised below.

Recognised link between Andrographis and hypersensitivity by health professionals

The expert stated their view that the risk of hypersensitivity reactions including anaphylaxis was not widely appreciated by clinical immunologists and related health professionals until recently. They stated that this was despite adverse reaction reports in Australia since 2015, in New Zealand from 2017, and a 2017 publication in the *Internal Medicine Journal*[2], and noted that more attention was focused on the issue after the 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 which are commonly perceived as safe and are often used without medical oversight.

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

In addressing whether the onset and severity of adverse events reported with Andrographis align with patterns seen in other known allergens in foods or medicines, the expert advice indicated that where details are available, reported reactions to Andrographis are entirely consistent with allergic reactions irrespective of the underlying mechanism.

Reactions that occur after many previous uses of Andrographis are 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

[2] Ahn, Y., & Brewerton, M. P2: When The Common Cold Turns Deadly: Anaphylaxis With Andrographis paniculata. Internal Medicine Journal 2017; 47(S5), 5-5. doi:10.1111/imj.2_13578

demonstrate an allergic reaction, for example with antibiotics. The reasons for reactions occurring after prior tolerance are not fully understood, however factors such as the presence of infection, other medications, concomitant exercise or alcohol ingestion may all act as modulating factors.

Reactions on first exposure suggest either sensitisation through prior contact with the allergen in another form or to non-IgE-mediated hypersensitivity pathways, which can produce clinical presentations indistinguishable from classic anaphylaxis via mast cell or basophil activation, alternative antibody pathways, anaphylatoxin generation or activation of other receptor systems.

The expert advice also commented that judgement of severity based on whether a patient presented to hospital or was administered adrenaline is not a reliable measure, as sometimes adrenaline is not administered when it may have been indicated or may be administered when it is not necessary. In addition, some people choose not to go to hospital preferring to 'wait out' a reaction when the severity of the reaction would suggest presenting to an emergency department is the preferable option.

Risk factors in the context of typical Andrographis use

In response to whether particular risk factors influence the onset of hypersensitivity or anaphylactic reactions associated with Andrographis, the advice indicated that ingestion of an allergen in close proximity to well-recognised cofactors—such as vigorous exercise, alcohol consumption, non-steroidal anti-inflammatory medicine use or concurrent viral infection—can potentiate allergic responses or increase their likelihood. Although full clinical histories of reported cases are not available, it is considered highly probable that many individuals were experiencing a viral illness at the time of ingestion, given common use of Andrographis for upper respiratory infections, and some may also have been using anti-inflammatory medicines.

Role of Echinacea in allergic reactions

In considering whether the presence of Echinacea in medicines containing Andrographis could potentiate or exacerbate hypersensitivity reactions attributed to Andrographis, the expert advice noted the allergenic potential of Echinacea itself[3].

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 advice also noted that while positive skin tests have been seen for Echinacea, the absence of positive skin tests for Andrographis in patients with convincing histories of allergic reactions to Andrographis suggests this compound causes reactions by an IgE-independent mechanism.

Clinical investigations for confirmation of allergy

In addressing whether clinical investigations can confirm allergy to Andrographis and/or Echinacea, the expert advice outlines that assessment begins with a detailed clinical history encompassing the specific preparation used, the timing, symptoms and severity of the reaction, concurrent medications, the presence of viral illness, prior exposure to the ingredient/s and an individual's atopic status or history of asthma or previous allergic reactions.

Several investigative tools may assist in determining the underlying mechanism, including skin testing with extracts of implicated ingredients to assess for possible IgE-mediated processes, basophil activation testing where available, and measurement of serum tryptase within hours of a reaction to identify mast-cell activation in cases of suspected anaphylaxis. Although a supervised challenge

[3] Mullins RJ, Heddle R. Adverse reactions associated with echinacea: the Australian experience. Ann Allergy Asthma Immunol. 2002 Jan;88(1):42-51. doi: 10.1016/S1081-16(10)63591-0. PMID: 11814277.

provides definitive evidence of causation, this is generally not preferred given the avoidable nature of the ingredient/s.

Additional comments

In responding to whether any additional insights are relevant to understanding anaphylaxis associated with Andrographis, the expert advice 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 society. The expert advice also commented on the need for risk-benefit analysis noting that evidence of benefit is equivocal. The expert also commented that data collection regarding harm is needed so that a risk-benefit assessment can be undertaken.

Key points – expert advice

- It appears this safety concern related to Andrographis was not widely known by clinical immunologists and related health professionals until the TGA safety alert and media coverage of the fatal case of anaphylaxis 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 as a treatment for upper respiratory infection, it is highly likely that many 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

The TGA first started receiving anaphylaxis reports for Andrographis-containing medicines in 2005 and to 31 December 2024, the TGA has received 1217 adverse event (AE) reports related to medicines containing Andrographis[4]. The top three reaction terms were ageusia (300), anaphylactic reaction (248) and dysgeusia (232)[5]. 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 a sustained high number of case reports of anaphylaxis related to Andrographis-containing medicines up to 31 December 2024 (Figure 1). Of a total 254 reports received between 2005 and 2024, 184 (72%) were received between 2019 and 2024. 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. Medicine supply data from sponsors has been considered 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 adverse events 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 estimated rate.

There were 48 medicines[6] containing Andrographis associated with the 254 total cases of anaphylaxis. Five products, supplied by one sponsor and with the same ingredient formulation and tradename, accounted for 159 (63%) cases of anaphylaxis.

As shown in Figure 1 below, the majority (206/254 [81%]) of the 254 anaphylaxis adverse event cases related to Andrographis are associated with medicines that also contain *Echinacea* species (Echinacea). Importantly, this corresponds with a high supply volume for these medicine types. A subset analysis of volume supplied against adverse events to 31 December 2024 showed that the vast majority (98%) of volume supplied were medicines that also contained Echinacea and other active ingredients in addition to Andrographis (see section on supply data and estimated rate). 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.

[4] Adverse events reported to the TGA are entered into the Adverse Event Management System (AEMS) before publication on the Database of Adverse Event Notifications (DAEN). 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). The AEMS / DAEN is a living database and is constantly updated to reflect the latest adverse event information received. The information in the AEMS / DAEN may change if follow-up information is received for an existing adverse event report, if more than one report relating to the same adverse event is identified as a duplicate and combined into a single report, and/or as part of data quality assurance activities.

[5] Products containing Andrographis are also required to include a label warning about taste disturbance (see Regulatory status).

[6] The number of medicines refers to individual tradenames in the AEMS. This includes medicines with the same tradename but different ARTG (AUST) numbers, and where the suspected medicine was reported as Andrographis, but with insufficient detail to identify the medicine tradename. The suspected medicine in these latter cases has been coded in the AEMS as 'Trade name not specified (*Andrographis paniculata*)' and counted here as a single tradename.

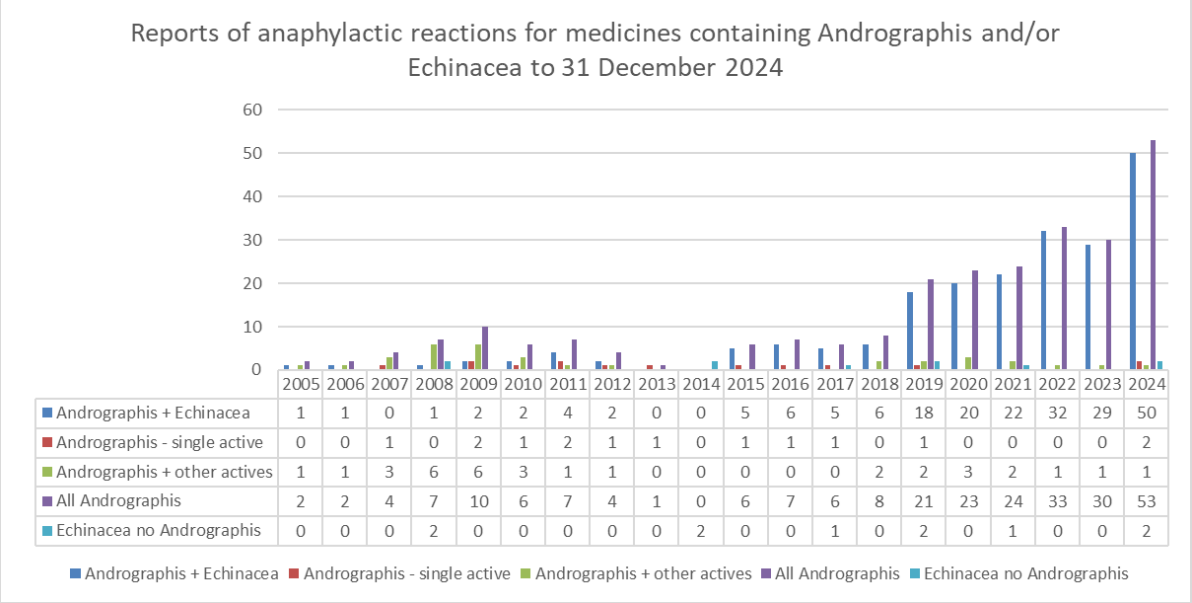
The total number of cases (34/254 [13%]) that involved multi-ingredient Andrographis-containing medicines without Echinacea, along with an additional 14 anaphylaxis reports (14/254 [6%]) received for single active ingredient Andrographis-containing medicines[7], further confirms a signal for the ingredient Andrographis.

This is also supported by the far smaller number of anaphylaxis cases related to medicines containing Echinacea without Andrographis present in the medicine. There have been 8 anaphylaxis reports involving Echinacea in multi-ingredient medicines (no Andrographis, or no Andrographis in a co-suspected medicine) and 2 anaphylaxis reports that involved medicines with Echinacea[8] as the only active ingredient, received by the TGA since 2005.

Notably, in total there have only been 24 listed medicines in the Australian Register of Therapeutic Goods (ARTG) with Andrographis as a single active ingredient. Of these, 22 have now been cancelled from the ARTG. There have been approximately 407 listed medicines in total (current and cancelled, single and multi-active ingredient) included in the ARTG that have contained Andrographis, illustrating the majority have been multi-ingredient formulations. As approximately 94% of Andrographis-containing listed medicines ever included in the ARTG have been multi-ingredient preparations, a higher number of reports for these preparation types can be expected. This is further supported by analysis of supply data against adverse event reports (see below).

In summary, of the total 254 anaphylaxis reports for Andrographis, 81% (206/254) involved medicines that contained both Andrographis and Echinacea, 13% (34/254) involved multi-ingredient Andrographis-containing medicines that did not contain Echinacea and 6% (14/254) contained Andrographis as a single active ingredient.

Figure 1. Reports of anaphylactic reactions for medicines containing Andrographis and/or Echinacea to 31 December 2024[9].



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Andrographis + Echinacea	1	1	0	1	2	2	4	2	0	0	5	6	5	6	18	20	22	32	29	50
Andrographis - single active	0	0	1	0	2	1	2	1	1	0	1	1	1	0	1	0	0	0	0	2
Andrographis + other actives	1	1	3	6	6	3	1	1	0	0	0	0	0	2	2	3	2	1	1	1
All Andrographis	2	2	4	7	10	6	7	4	1	0	6	7	6	8	21	23	24	33	30	53
Echinacea no Andrographis	0	0	0	2	0	0	0	0	0	2	0	0	1	0	2	0	1	0	0	2

[7] This figure was derived from 12 cases with known tradenames and 2 with insufficient detail to identify the tradename, but that were reported as Andrographis. The suspected medicine in these 2 cases has been coded in the AEMS as 'Trade name not specified (*Andrographis paniculata*)'.

[8] The suspected medicines in these 2 cases were reported as 'Echinacea', which have been coded in the AEMS as 'Trade name not specified (*Echinacea* sp.)'.

[9] Figure 1 provides the number of reports since 2005 as this was the first year that anaphylaxis reports associated with Andrographis-containing medicines were received by the TGA.

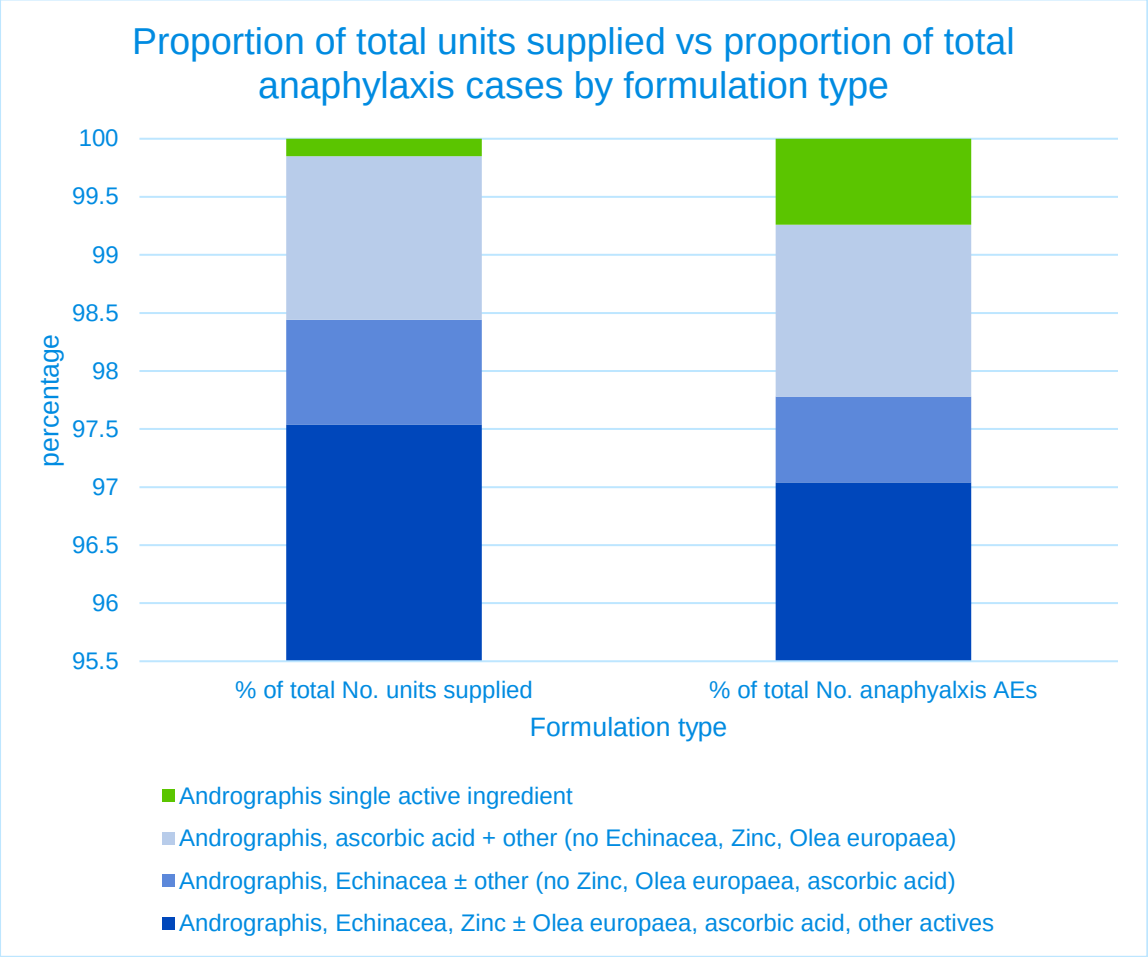
A subset analysis was performed on 135 anaphylaxis adverse event cases that could be linked to supply data grouped by formulation type – see Figure 2 below (more details on the supply data used in this analysis are included below – see Supply data and estimated rate).

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)[10] 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%) when compared to the proportion of supply (0.14%). 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 14 anaphylaxis reports in total for single active ingredient Andrographis medicines, the safety signal for Andrographis as a single active ingredient remains supported. Furthermore, the safety signal cannot be considered stronger for medicines containing Andrographis combined with Echinacea or other active ingredients, compared with single active ingredient Andrographis medicines, once supply data is taken into consideration.

[10] The number of medicines refers to individual tradenames in the AEMS. This includes medicines with the same tradename but different ARTG (AUST) numbers. Each of the medicines in this subset analysis involved medicines listed in the ARTG.

Figure 2 – Formulation analysis: Proportion of supply vs proportion of anaphylaxis cases



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

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 in the 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 the content of andrographolide, the naturally occurring constituent in Andrographis considered largely responsible for therapeutic effects, along with 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 in the ARTG within the previous 5 years (from July 2019 onwards)[11]. The supply data provided by sponsors was

[11] 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.

analysed against TGA's Adverse Event Management System (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.

Under-reporting

Under-reporting is well documented in spontaneous reporting systems[12].

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.

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[13]. 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[13].

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[14], 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 likely higher than the number of reports in the TGA's adverse event database.

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.

[12] Hazell L, Shakir SA. Under-reporting of adverse drug reactions : a systematic review. Drug Saf. 2006;29(5):385-96. doi: 10.2165/00002018-200629050-00003. PMID: 16689555.

[13] Palleria C, Leporini C, Chimirri S, Marrazzo G, Sacchetta S, Bruno L, Lista RM, Staltari O, Scuteri A, Scicchitano F, Russo E. Limitations and obstacles of the spontaneous adverse drugs reactions reporting: Two "challenging" case reports. J Pharmacol Pharmacother. 2013 Dec;4(Suppl 1):S66-72.

[14] Naseri K, Thrimawithana T, Allahham A, Nooney V, de Courten B, Shahin W. Exploring Complementary Medicine Usage, Consumer Perceptions, and Impact of Label Warnings: A Cross-Sectional Study in Melbourne, Australia. Pharmacy (Basel). 2025 Apr 27;13(3):61. doi: 10.3390/pharmacy13030061. PMID: 40407499; PMCID: PMC12101403.

- supply data for non-current Andrographis medicines was only required from sponsors who also had current Andrographis-containing medicines, so there was no supply data for other non-current Andrographis medicines for which adverse event reports have been received.
- 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.

A subset analysis was performed on 135 anaphylaxis adverse event cases that could be linked to supply data provided by sponsors. 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 (1/10,000 [0.01%] to 1/1,000 [0.1%]) or very rarely (<1/10,000 [<0.01%]), which in practical terms means that for every 1000 to 10,000 containers of an Andrographis medicine supplied, an anaphylaxis event can be expected. Therefore, if supply continues at the same volume as analysed in this review, anaphylaxis adverse events can be considered certain to occur.

Furthermore, 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.

Therefore, 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. Importantly, a lower risk profile cannot be attributed to medicines with no reported cases of anaphylaxis if they have been supplied in low volumes.

Figure 3 below 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 4 below shows the overall number of anaphylactic adverse event reports included in the subset analysis for each year from 2019 to 31 December 2024. Anaphylaxis reports were excluded from this subset analysis if the reported Andrographis-containing medicine did not have a definite ARTG (AUST) number associated with it, or the adverse event was likely associated with different supply data not obtained for this analysis. The number of excluded anaphylaxis reports were 17 in 2019, 11 in 2020, and 16 across the remaining years. This may explain the seemingly lower number of anaphylaxis adverse events in 2019 and 2020. While medicine supply data was provided up to 31 May 2024, adverse events that occurred up to December 2024 were included in the subset analysis as it is plausible that the adverse events that occurred during this time were related to product supplied to the market by sponsors up to 31 May 2024.

Figure 3 – Supply data by year: 1 Jan 2019 to 31 May 2024

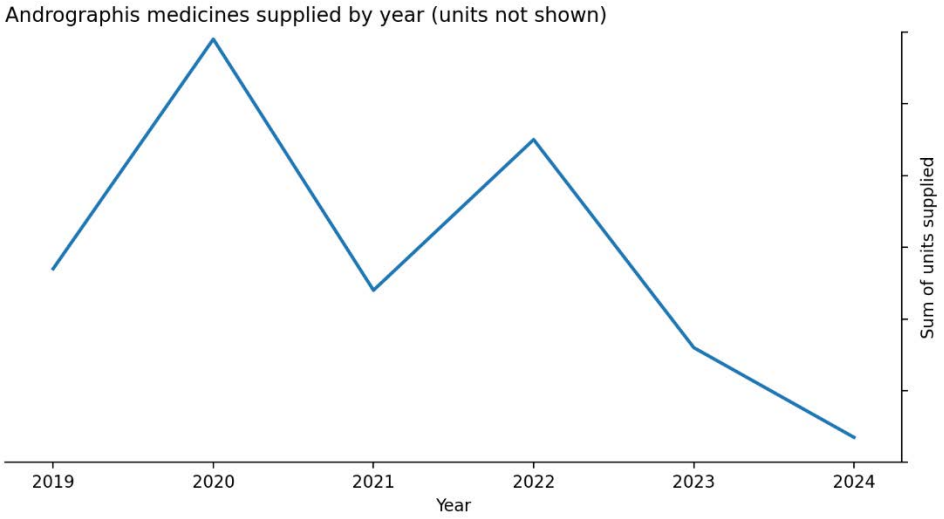


Figure 4 – Subset analysis: Anaphylaxis adverse events that could be linked to supply data (2019-2024)*

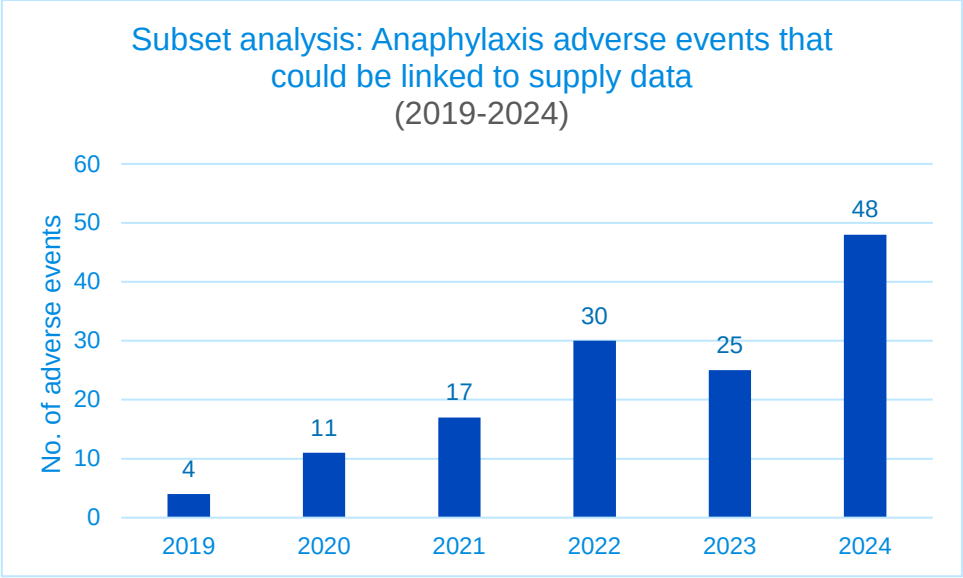


*Figure 4 represents a subset of all anaphylaxis cases associated with Andrographis-containing medicines and only includes cases that involved medicines for which supply data was provided to the TGA, and where the timing of the adverse event correlated with sponsor supply data for the suspected medicine.

Figure 4 indicates that there may be a slight correlation between the increase in adverse events in the years 2021, 2022 and 2023 following the increase in supply as shown in figure 3. However, the largest spike in adverse events occurred in 2024. Figure 5 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 5 – Subset analysis: Anaphylaxis adverse events reported in 2024#.

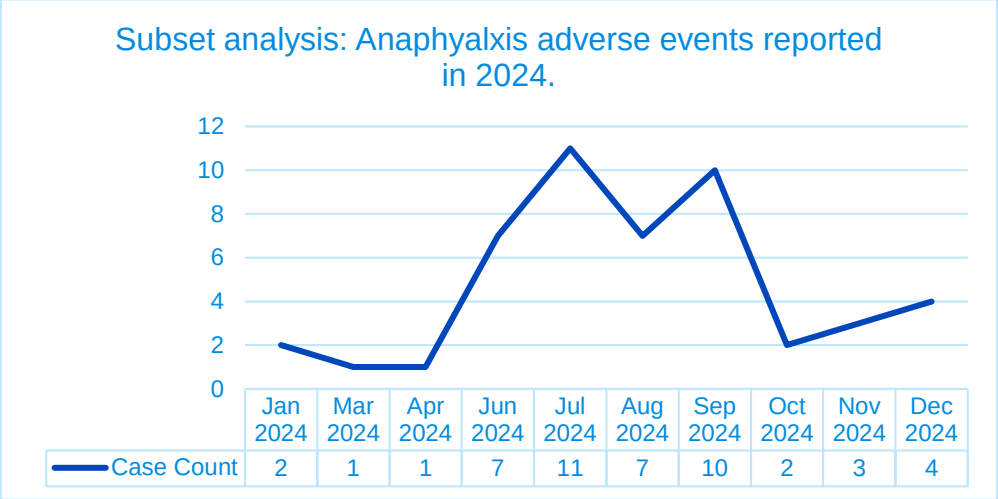


Figure 5 only includes anaphylaxis cases from the subset analysis above, being those that involved medicines for which supply data was provided to the TGA, and where the timing of the event correlated with the sponsor supply data for the suspected medicine.

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. Using the two anaphylaxis-related SMQs, 619 cases were identified. Amongst these cases, the top four reaction terms were anaphylactic reaction (248), pruritis (195), urticaria (150) and rash (138).

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).

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

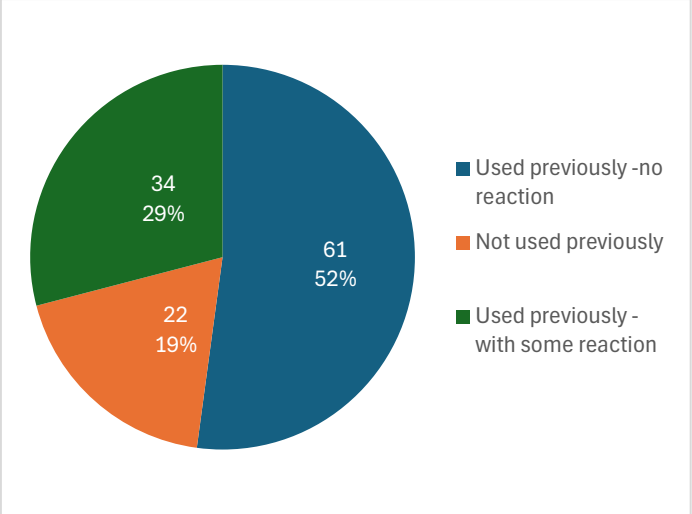
in the narratives. Case review was limited to those cases coded with a reaction term of ‘anaphylactic reaction’ or ‘anaphylactic shock’ and with sufficient information in the narrative to provide some or all of the additional information above. This identified 171 cases for further review where the Andrographis-containing 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 6 – Pie chart showing anaphylaxis cases with history of use of the suspected medicine containing Andrographis



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.

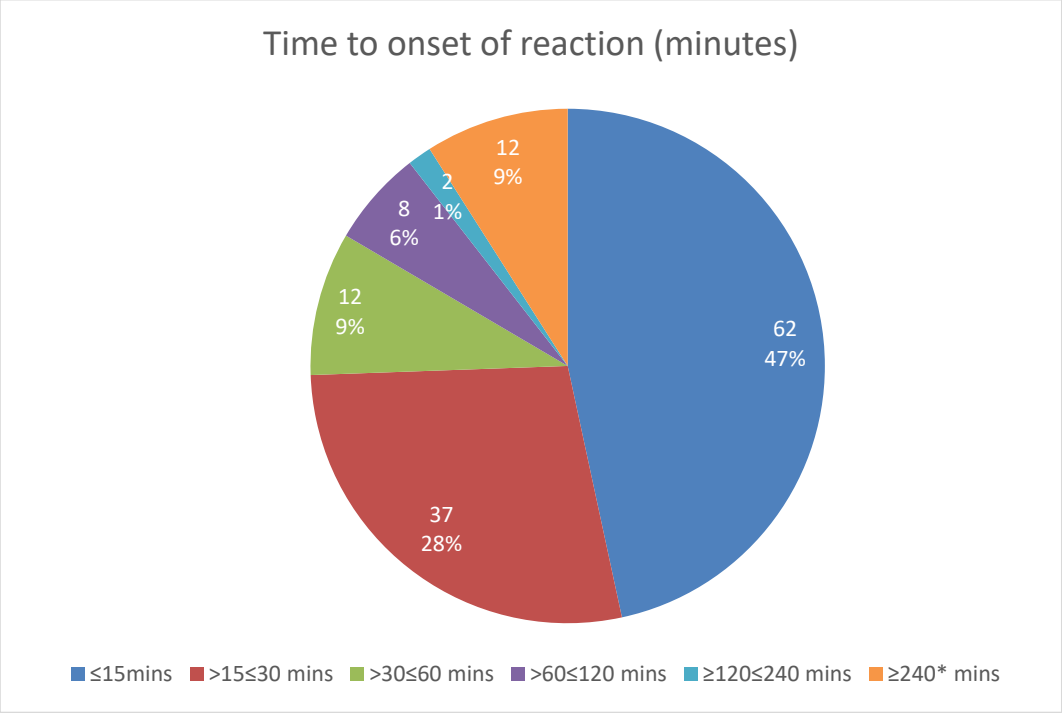
Time to reaction onset

Of the 171 reports, 133 included reaction onset time[15] 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.

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

Figure 7 – Reaction onset time



*including same day or longer

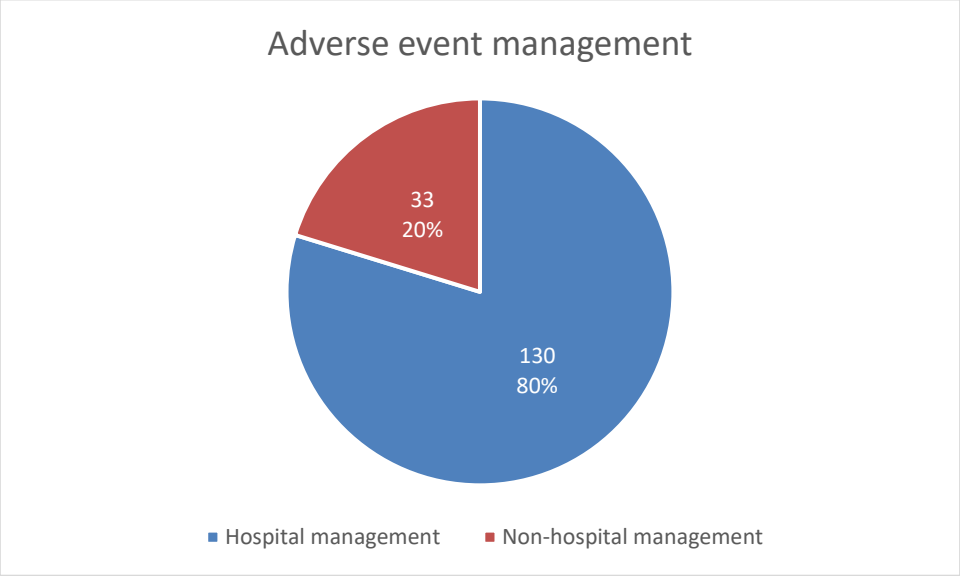
Of the cases that reported time to onset, it is concerning that the time to onset occurred in 30 minutes or less in most cases (99/133 [74%]). This may not provide sufficient time to access treatment, nor to look for the possible cause and instructions on a label warning once a reaction has commenced, 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 and/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 8 – Adverse event management

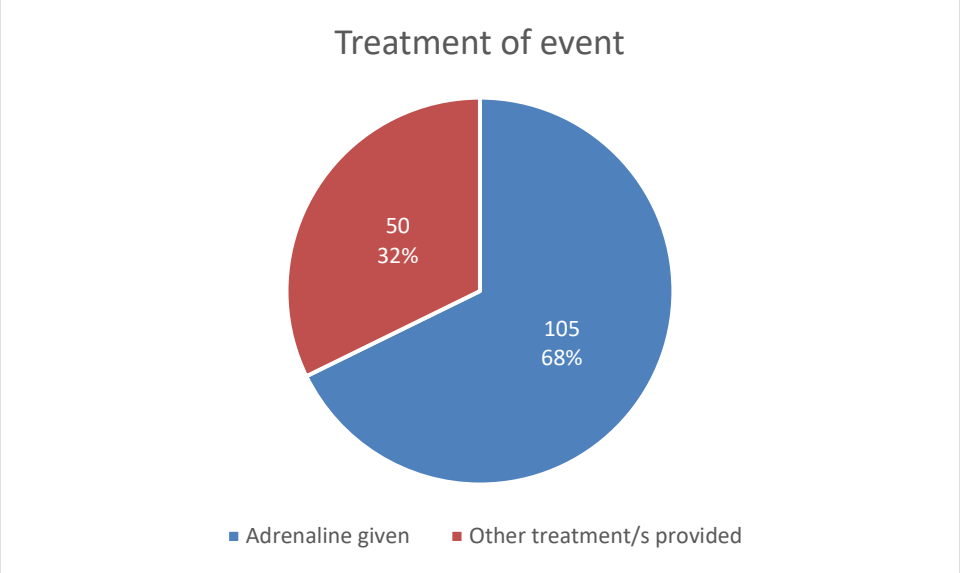


Treatment of event

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 9 – Treatment of event

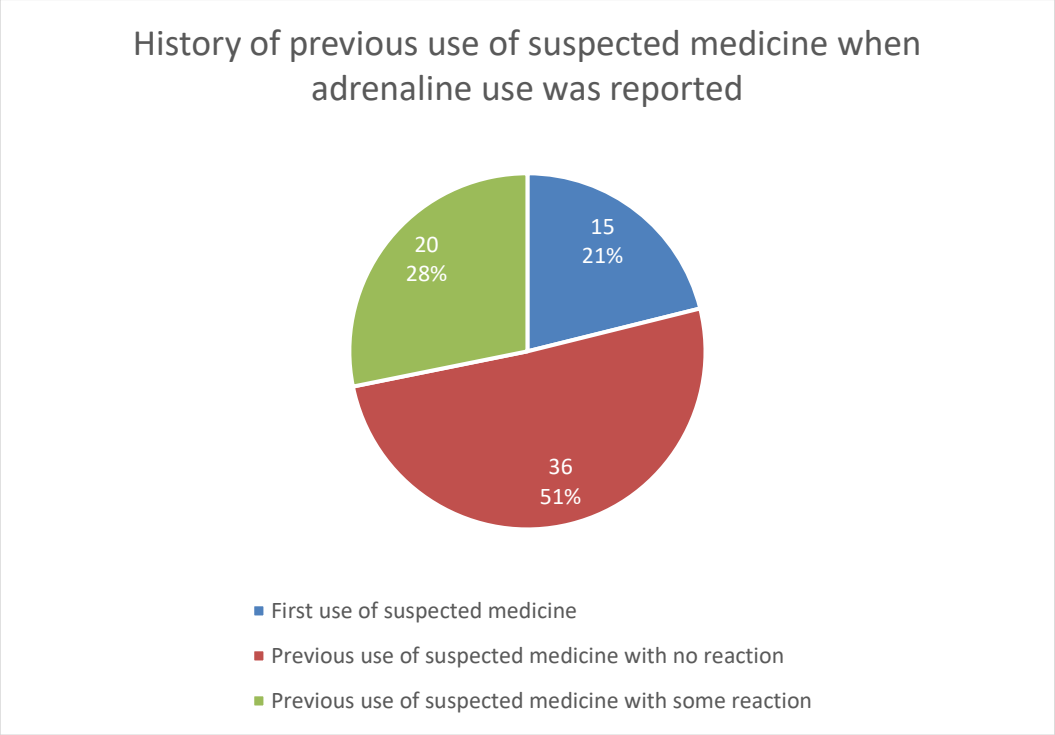


- Of the 50 cases where treatment other than adrenaline was reported, treatments included antihistamines, corticosteroids, IV fluids or hospital observation. Of these:
  - 24 cases reported attendance at hospital with 8 of these also reporting ambulance attendance.
- Of the 105 cases that reported use 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 10 – 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 10). This indicates that a precautionary approach of carrying an adrenaline auto-injector for individuals who have previously experienced a reaction would potentially only help in 28% of cases. Notwithstanding, the need to carry an adrenaline 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[16].

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

[16] Allergy & Anaphylaxis Australia. Signs and symptoms of an allergic reaction. [accessed online 6 March 2025]. https://allergyfacts.org.au/signs-and-symptoms-of-an-allergic-reaction/

- 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/adrenaline/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 at most have prevented less than half of cases, while a contraindication for those with asthma would at most have prevented only 23% of 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 are 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 Andrographis-containing medicines in Australia.

Summary of Australian adverse events

There has been a sustained high reporting trend for the number of Andrographis-associated anaphylaxis cases received by the TGA between 2019 and 31 December 2024, with 72% (184/254) of total reports received during this time.

The majority of cases involved medicines with both Andrographis and Echinacea; there were 31 different Andrographis-containing medicines[17] for which anaphylaxis cases were reported that also contained an Echinacea ingredient. Echinacea is also associated with allergic reactions. However, supply of these Andrographis-Echinacea combination medicines was also far higher than supply of medicines containing Andrographis without Echinacea. Notwithstanding, 19% (48/254) of Andrographis-related anaphylaxis cases involved medicines that did not contain Echinacea. Since 2005 there have only been 10 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.

[17] The number of medicines refers to individual tradenames in AEMS. This includes medicines with the same tradename but different ARTG (AUST) numbers.

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, and that if Andrographis-containing medicines continue to be supplied at similar volumes as those analysed, more anaphylaxis cases can be considered certain to occur.

Although there is a slight correlation between the increased number of adverse event reports and an increase in supply of Andrographis-containing medicines during the Covid-19 pandemic, the 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 the contention that under-reporting of adverse events due to lack of awareness is likely.

A detailed review of anaphylaxis case narratives associated with Andrographis 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 the medicine 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 department attendance and/or hospital admission).
- Less than half (41/88 [47%]) had history of allergy while less than a quarter (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[18] data up to 31 December 2024 identified 52 cases of anaphylactic reaction, anaphylactic shock, anaphylactoid reaction or anaphylactoid shock that involved oral[19] Andrographis as the sole suspected single ingredient, excluding Australian cases.

Although the number of anaphylaxis cases for sole suspected oral Andrographis appears quite low, VigiBase data up to 31 December 2024 showed positive disproportionality scores for Andrographis and the adverse events anaphylactic reaction (3.5) and anaphylactic shock (2.3) using the information

[18] 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 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.

[19] 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.

component model and its lower limit of a 95% credibility interval (IC_{025})[20,21]. This indicates a higher-than-expected number of reports when considering all reported reactions for Andrographis, all reports of anaphylactic reaction or anaphylactic shock for all active ingredients, and all reactions for all ingredients. It should be noted that these disproportionality scores were based on all routes of administration and were not limited to the oral route and were based on reports for all geographical locations including Australia.

A search of VigiBase data up to 31 December 2024 was also performed for oral[22]**Error! Bookmark not defined.** 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.

The only positive IC_{025} disproportionality score for any *Echinacea* spp. and adverse event terms specific to anaphylaxis was *Echinacea purpurea* and anaphylactic shock (1.1). There was no disproportionate reporting for other *Echinacea* species and adverse event terms specific to anaphylaxis.

Therefore, international adverse event data indicates that disproportionate reporting for anaphylactic reactions (3.5) and anaphylactic shock (2.3) for single ingredient Andrographis products is greater than for Echinacea, which only showed disproportionately high reporting for anaphylactic shock with *Echinacea purpurea* (1.1), and with a lower IC_{025} disproportionality score than for Andrographis.

A broader search of VigiBase data up to 31 December 2024 for Andrographis and andrographolide using SMQs Anaphylactic reaction (Broad) and Anaphylactic/anaphylactoid shock conditions (Broad) identified 371 case reports involving oral[22] use of Andrographis, excluding Australian cases[23]. There were no cases that involved andrographolide. This shows there were far more cases globally that were possibly related to anaphylaxis than those reported with anaphylaxis-specific reaction terms alone.

Of the 371 cases, 334 involved Andrographis as the sole suspected single ingredient[24]. Of the 334 cases:

- 49 were characterised as serious:
  - 4 of these were reported as life threatening,
  - 40 caused or 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),
- 147 cases did not report on the seriousness,
- no cases reported a fatal outcome.

[20] 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).

[21] The READUS-PV guidelines and checklist were considered when utilising disproportionality data: The Reporting of a Disproportionality Analysis for Drug Safety Signal Detection Using Individual Case Safety Reports in PharmacoVigilance (READUS-PV): Development and Statement | Drug Safety | Springer Nature Link and Table 3 | The Reporting of a Disproportionality Analysis for Drug Safety Signal Detection Using Individual Case Safety Reports in PharmacoVigilance (READUS-PV): Development and Statement | Drug Safety | Springer Nature Link.

[22] 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

[23] Filters: Active ingredients: *Andrographis paniculata*, andrographolide, Reaction: SMQs Anaphylactic reaction (Broad) and Anaphylactic/anaphylactoid shock conditions (Broad), Country of primary source: Australia unchecked, Route of admin: oral, suspected duplicate reports excluded, data up to 31 December 2024.

[24] Filters as above (see Footnote 23) but with number of suspecting/interacting drugs: 1.

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 that 4.7% of reported cases were attributed to Andrographis[25]. Interestingly, another study using WHO VigiBase data from the same time period found that Andrographis was the third most-frequently reported herbal medicine associated with immediate allergic-like reactions, when strict inclusion criteria were 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[26].

Thailand

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[27, 28].

A retrospective post-market study of adverse event 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[27]. 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. All cases discussed in the report involved Andrographis as a single agent, which further supports the signal for the single ingredient Andrographis.

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[28]. 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%]). 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

[25] 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.

[26] 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.

[27] 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.

[28] 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.

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 72% (184/254) of total reports up to 31 December 2024 received since 2019.
- Although most reports are for medicines that also contain Echinacea, supply data shows these medicines were supplied in far higher numbers than single ingredient Andrographis medicines. Notwithstanding, 48 (19%) cases involved Andrographis-containing medicines with no Echinacea. The number of anaphylaxis cases for Echinacea-containing medicines without Andrographis is low, with only 10 reports received since 2005.
- The sustained high number of anaphylaxis cases between 2019 and 2024 may relate to an increase in supply of Andrographis-containing medicines 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 the medicine 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 less than a quarter (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 of anaphylaxis associated with 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 as described in literature.

Risk profile

Data analysis of preparation type

The TGA's adverse event data to 31 December 2024 for anaphylaxis reports for Andrographis-containing medicines along with data provided by sponsors was analysed for trends 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 for trends is not reliable. Therefore, analyses were conducted on the 'top 20' products by supply volume.

Of these top 20 Andrographis-containing medicines by supply volume, 13 had associated anaphylaxis adverse event reports.

Andrographis extract ingredient manufacturer

There were 8 different manufacturers of Andrographis extract ingredients for the 20 medicines supplied in highest volumes. Adverse events were noted for products with extracts from 5 of these 8 manufacturers (63%). Although there were no adverse events reported for medicines that contained extracts from 3 of the 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 from other extracts or less likely to cause adverse events. Therefore, no clear trends could be identified for anaphylactic adverse events associated with any particular extract ingredient manufacturers.

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. 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 1). No clear trends could be identified for anaphylactic adverse events associated with particular extract ingredients, extract solvents or extract concentration ratios.

Table 1. Proportion of products with anaphylaxis adverse events using extracts made with certain solvents

Solvent	Number 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[29]. 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 Andrographis-containing medicines supplied in highest volumes, adverse events were reported for products that used each of these plant parts (see Table 2). 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[30] (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

[29] United States Pharmacopeia (USP-NF) 2025. Monographs: Andrographis, Powdered Andrographis Extract, Powdered Andrographis. [accessed 7 April 2025].

[30] TGA approved terminology for therapeutic goods

Table 2. Proportion of products with anaphylaxis adverse events using different plant parts

Plant part	Number 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 (see Table 3).

Table 3. Proportion of products with anaphylaxis adverse events for certain andrographolide doses

Andrographolide content per single dose (to nearest whole number) (mg)	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%)

Andrographis-containing medicines without reported anaphylaxis cases

The top 20 Andrographis-containing medicines by supply volume were also examined for any formulation or ingredient trends for the seven medicines with no reported anaphylaxis cases. No difference in formulation for these seven 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.

Comments on dose from the literature

A systematic review and meta-analysis on the safety of Andrographis reported no significant difference in incidence of serious adverse events between low dose and high dose oral andrographolide (≤120 mg/day vs >120 mg/day), however only five serious adverse event 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[31].

In contrast, an earlier reported dose escalation study involving oral Andrographolide reported one anaphylactic reaction in a patient with HIV in week four of the study, after the dose was increased from 5mg/kg to 10mg/kg[32]. 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 unrelated to dose.

With regard to dose, the retrospective post-market study of adverse event data held in Thailand's adverse event database confirmed that the safety signal for Andrographis cannot be attributed to higher doses, as 7 of 13 Andrographis critical hypersensitivity cases (according to 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[33]. 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.

Composition of Andrographis extracts

The ARTG does not capture the full constituent profile of Andrographis extracts nor the complexity of how they are manufactured.

The United States Pharmacopeia (USP) monograph for *Powdered Andrographis Extract* includes a limit of no more than 15% for the diterpenoid constituent 14-deoxy-11,12-didehydroandrographolide, a restriction not applied in other USP monographs for Andrographis (*Andrographis* [dried stems or leaves], *Powdered Andrographis*)[34].The rationale for this limit is unclear, and existing literature does not indicate that this constituent poses a higher risk of anaphylaxis than others.

A systematic review and meta-analysis of andrographolide-derivative injectable medicines used in China found multiple cases of anaphylaxis across products[35]. However, the authors did not identify any derivative injection medication as higher risk. Notwithstanding, the relevance of injectable formulations to oral Andrographis extracts is limited.

The TGA has received a report of anaphylaxis from a traditional herbal liquid extract preparation, indicating that traditional preparations cannot be considered without risk. International experience

[31] 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.

[32] Calabrese C, Berman SH, Babish JG, et al. A phase I trial of andrographolide in HIV positive patients and normal volunteers. Phytother Res 2000; 14: 333-8.

[33] 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.

[34] United States Pharmacopeia (USP-NF) 2025. Monographs: Andrographis, Powdered Andrographis Extract, Powdered Andrographis. [accessed 7 April 2025].

[35] 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.

supports this: Andrographis crude powder in capsule and tablet dosage forms has been widely sold in markets in Thailand and distributed to hospitals for the treatment of cold, fever and Covid-19[36], multiple cases of anaphylaxis have been reported to Thai authorities, published literature on cases in Thailand refer to reactions associated with powdered leaf[37].

Published literature on the chemical composition of Andrographis products shows variability in diterpenoid content and dissolution rates between extracts and crude powders. Extraction solvents (e.g., ethanolic vs aqueous), formulation excipients, particle size, moisture content and other manufacturing factors all likely influence final composition, dissolution and resulting pharmacokinetics and clinical outcomes[36,38].

Research also suggests that Andrographis' pharmacological activity likely arises from multiple interacting constituents, not just the diterpenoid andrographolide, adding further complexity to determining safety or risk profiles[39].

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.

A TGA review of published non-clinical studies that examined the allergenic and anti-inflammatory effects of various Andrographis extracts and purified constituents noted that the *in vitro* data suggest a pseudoallergy and anaphylactic potential of some components of Andrographis extracts. However, whether these components can elicit a typical hypersensitivity reaction was inconclusive. In addition, the allergenic potential of other components was not assessed. The toxicological review further noted there are no standard methods for assessing the systemic allergenic potential of chemicals with nonclinical studies. It pointed out that the value of animal studies is that they contribute to better understanding mechanisms of hypersensitivity reactions in humans, but they are not able to adequately model anaphylaxis in humans.

The review also indicated 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 is important to note that many of the studies used purified 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.

Overall, the available evidence highlights:

- Variability across preparation methods and final product composition
- The presence of anaphylaxis risk across different preparations including traditional extracts and crude preparations
- Limited understanding of which constituents contribute to hypersensitivity
- Significant gaps in published research

[36] 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.

[37] 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. https://doi.org/10.1186/1472-6882-14-515

[38] 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.

[39] 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.

- Lack of compelling evidence to identify any specific composition as higher risk

Conclusions on evidence of risk based on preparation

Of the top 20 Andrographis-containing 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.

A review of published literature on Andrographis also did not identify compelling evidence that greater risk could be attributed to certain preparations, constituents or doses.

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 currently regulated as low-risk products. While the exact mechanism remains uncertain, a precautionary approach is appropriate considering the life-threatening nature of anaphylaxis.

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)[40, 41, 42, 43] . 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[44]. This pattern was observed in Andrographis-associated anaphylaxis cases that reported on reactions to previous

[40] Wolbing et al., About the role and underlying mechanisms of cofactors in anaphylaxis. Allergy 2013; 68: 1085–1092, DOI:10.1111/all.12193.

[41] Muñoz-Cano, et al. "Mechanisms, cofactors, and augmenting factors involved in anaphylaxis." *Frontiers in Immunology* 8 (2017): 1193, https://doi.org/10.3389/fimmu.2017.01193.

[42] Cardona et al., World Allergy Organization Anaphylaxis Guidance 2020, World Allergy Organization Journal, V13, Iss 10, 2020,100472, ISSN 1939-4551, https://doi.org/10.1016/j.waojou.2020.100472.

[43] Niggemann & Beyer, Factors augmenting allergic reactions. Allergy 2014; 69: 1582–1587, DOI:10.1111/all.12532.

[44] Allergy & Anaphylaxis Australia. Signs and symptoms of an allergic reaction. [accessed online 6 March 2025]. https://allergyfacts.org.au/signs-and-symptoms-of-an-allergic-reaction/

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[45], 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 Qualitative case review of narratives in a subset of anaphylaxis cases, consumer subgroups at greater risk could not be conclusively identified.

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 aged 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 that a preparation is 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 associated with 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

[45] Allergy & Anaphylaxis Australia. Signs and symptoms of an allergic reaction. [accessed online 6 March 2025]. https://allergyfacts.org.au/signs-and-symptoms-of-an-allergic-reaction/

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: Data analysis of preparation type).

Other ingredients that require an allergy warning when used in listed medicines are propolis and pollen. There has been one 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 adverse event reporting.

Other medicines known to commonly trigger anaphylaxis include NSAIDs such as ibuprofen and acetyl salicylic acid (aspirin), as well as paracetamol and the antibiotics amoxicillin and moxifloxacin[46]. 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. Australian anaphylaxis adverse event data for each of these ingredients, as well as for Echinacea, were compared. Table 4 provides the total number of Australian anaphylaxis adverse events recorded in the AEMS database up to 31 December 2024 for each ingredient where only a single suspected medicine (or sole suspected medicine) was involved in the reaction. This includes where the sole suspected medicine contained the ingredient as the only active ingredient or when present with other active ingredients in the suspected medicine formulation. Additional details are provided about the number cases that did and did not involve Echinacea combined with Andrographis.

Table 4. Comparison of Australian adverse events for ingredients associated with anaphylaxis

Drug name	No. anaphylaxis[47] reports in AEMS – sole suspected medicine reports only
Andrographis	244
- Andrographis with Echinacea	(197)
- Andrographis without Echinacea	(47)
Echinacea angustifolia, *Echinacea purpurea*, *Echinacea pallida* and/or *Echinacea* spp.	207
- Echinacea without Andrographis	(10)
aspirin & acetylsalicylic acid	36
ibuprofen	100

[46] Montañez MI, Mayorga C, Bogas G, Barrionuevo E, Fernandez-Santamaria R, Martin-Serrano A, Laguna JJ, Torres MJ, Fernandez TD, Doña I. Epidemiology, Mechanisms, and Diagnosis of Drug-Induced Anaphylaxis. Front Immunol. 2017 May 29;8:614. doi: 10.3389/fimmu.2017.00614. PMID: 28611774; PMCID: PMC5446992.

[47] TGA AEMS search: all data included in the AEMS from 1971 up to 31 December 2024 was searched, sole suspect filter on, reaction terms anaphylactic shock, anaphylactic reaction, anaphylactoid shock, anaphylactoid reaction. Includes all routes of administration, noting that all Andrographis and Echinacea cases involved oral medicines only. Medicine ingredient names searched: *Andrographis paniculata*, *Echinacea angustifolia*, *Echinacea purpurea*, *Echinacea pallida* and/or *Echinacea* spp., aspirin and acetylsalicylic acid, ibuprofen, paracetamol, amoxicillin, amoxycillin, amoxicillin sodium, amoxicillin trihydrate, amoxycillin trihydrate, moxifloxacin.

Drug name	No. anaphylaxis[47] reports in AEMS – sole suspected medicine reports only
paracetamol	65
amoxicillin, amoxycillin, amoxicillin sodium, amoxicillin trihydrate, amoxycillin trihydrate.	418
moxifloxacin	9

Similarly, a comparison of global data reveals disproportionality scores for Andrographis that are higher than those for Echinacea and ingredients used in registered medicines known to cause anaphylaxis as shown in Table 5. This further supports the finding of this safety review, that Andrographis may not be appropriately positioned in the Australian regulatory framework for use in listed medicines.

Table 5. Comparison of global adverse event data and disproportionality IC^{025} values for ingredients associated with anaphylaxis up to 31 December 2024.

Drug name	No. sole suspect, single active ingredient anaphylaxis reports in VigiBase[48] (oral[49])	No. sole suspect, single active ingredient anaphylaxis reports in VigiBase (route of admin: all / not reported)[50]	Disproportionality IC^{025} values from VigiBase[51]
Andrographis	55	71[52]	Anaphylactic reaction (PT): 3.5 Anaphylactic shock (PT): 2.3
Echinacea angustifolia,	4	12[52]	Anaphylactic shock (PT): 1.1 (*Echinacea purpurea*)

[48] VigiBase search: Global data up to 31 December 2024, reaction terms: anaphylactic shock (preferred term [PT]), anaphylactic reaction (PT), anaphylactoid shock (PT), anaphylactoid reaction (PT). Individual active ingredient names searched: *Andrographis paniculata*, *Echinacea angustifolia*, *Echinacea purpurea*, *Echinacea pallida*, *Echinacea* spp., acetylsalicylic acid, ibuprofen, paracetamol, amoxicillin and moxifloxacin. Number of suspecting/interacting drugs: 1, all geographical locations, suspected duplicate reports excluded, route of admin: oral. Figures are provided for adverse events involving single active ingredient suspected medicines only as VigiBase is not suitable for extracting data for multiple-ingredient medicines when there are many different medicines for an ingredient, which is the case for Andrographis.

[49] 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.

[50] VigiBase search: As above without 'Oral' filter.

[51] Disproportionality scores considered were IC^{025} values generated from VigiBase for global data up to 31 December 2024, calculated using all reports for all ingredients/medicines. Reaction terms: anaphylactic shock (preferred term [PT]), anaphylactic reaction (PT), anaphylactoid shock (PT), anaphylactoid reaction (PT). Individual active ingredient names searched: *Andrographis paniculata*, *Echinacea angustifolia*, *Echinacea purpurea*, *Echinacea pallida*, *Echinacea* spp., acetylsalicylic acid, ibuprofen, paracetamol, amoxicillin and moxifloxacin. Only positive IC^{025} values are reported here.

[52] Reasons for the low number of reports globally for Andrographis and Echinacea include that VigiBase has limited search 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. Nevertheless, the higher disproportionality scores for Andrographis indicates the number of anaphylaxis cases for Andrographis is disproportionately high when compared to all reactions for Andrographis, and to all cases of anaphylaxis for all ingredients relative to the total number of adverse events in the global database.

Drug name	No. sole suspect, single active ingredient anaphylaxis reports in VigiBase[48] (oral[49])	No. sole suspect, single active ingredient anaphylaxis reports in VigiBase (route of admin: all / not reported)[50]	Disproportionality IC$_{025}$ values from VigiBase[51]
Echinacea purpurea, and/or *Echinacea pallida*			
aspirin & acetylsalicylic acid	787	1770	Anaphylactic reaction (PT): 0.3
ibuprofen	2554	3735	Anaphylactic reaction (PT): 1.6 Anaphylactic shock (PT): 0.7
paracetamol	886	1570	Anaphylactic reaction (PT): 0.4 Anaphylactoid shock (PT): 0.4 Anaphylactic shock (PT): 0.1
amoxicillin, amoxycillin, amoxicillin sodium, amoxicillin trihydrate, amoxycillin trihydrate.	3632	6493	Anaphylactic reaction (PT): 2.2 Anaphylactic shock (PT): 2.2 Anaphylactoid reaction (PT): 0.8 Anaphylactoid shock (PT): 0.9
moxifloxacin	1405	3367	Anaphylactic reaction (PT): 2.4 Anaphylactic shock (PT): 2.6 Anaphylactoid reaction (PT): 2.0

Key points – risk profile

- 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.
- A review of published literature on Andrographis also did not identify compelling evidence that greater risk could be attributed to certain preparations, constituents or doses.
- Factors inherent to the typical use of Andrographis that may increase risk 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 safety signal for anaphylaxis and Andrographis is greater than that for certain registered medicine ingredients known to trigger anaphylaxis, which further supports the conclusion of this review that Andrographis may not be appropriately positioned within the regulatory framework for use in low risk listed medicines.

Risk mitigation options

Strengthened label warnings

The current label warning requirement, implemented for all Andrographis-containing listed medicines in May 2020, 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)[53].

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:

- That reactions are occurring because consumers do not read the current warning.

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

- 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.
- A strengthened label warning implemented for one Andrographis-containing medicine in 2024 has not resulted in a reduction in the number of anaphylaxis reports received by the TGA.
- 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, the available evidence did not support a restriction on any of these parameters based on adverse event 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 in June 2024. 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 received from 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 or 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 of anaphylaxis associated with Andrographis 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.

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-level 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 listed 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 perceived 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 as listed medicines. These registered medicines 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 listed complementary medicines and indeed for most oral prescription medicines that are highly regulated. The data also indicates that the anaphylactic 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 necessarily result in quicker access to treatment and reduced risk of death.
- 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.

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.

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)[54, 55]. 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[54, 55, 56, 57].

- While one meta-analysis of randomised controlled trials (RCTs) involving oral Andrographis reported that serious adverse events were very rare (<1/10,000) 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 adverse events and anaphylaxis in particular[54]. 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[58] and two reported in New Zealand after consuming Andrographis-containing medicines (formulation details not provided)[59]. Another literature case report of rash and severe skin itching was reported in a systematic review and meta-analysis[60].
- Details of a further 5 cases of anaphylaxis in adults who had consumed ArmaForce® were published in a conference abstract[61]. The abstract was presented at the 34th annual conference of the Australasian Society of Clinical Immunology and Allergy (ASCIA) in September 2024 to communicate risks to the audience of 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 re-challenge. 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 adverse event data. Notwithstanding, considering the high number of cases overall, an additional 5 cases are not expected to change the outcome of this review, indeed they would only serve to further support it.

[54] 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.

[55] 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.

[56] 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.

[57] 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.

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

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

[60] 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.

[61] Katelaris C, Keat K, West, T. ASCIA Conference Abstract: Risk Alert-Anaphylaxis Following ArmaForce® Ingestion. Internal Medicine Journal, 2024; 54(S4), 5-6.

- Although andrographolide[62] 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[63, 64]. 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[63, 64]. 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 a predisposition or family history of allergy, and to closely monitor for adverse reactions in patients who are given the injection for the first time[63, 64].The relevance of the anaphylactic potential of injections to the oral route of administration is currently not clear.

Non-clinical studies

A TGA review of published non-clinical reports on the allergenic potential and immunomodulatory action of Andrographis is summarised below.

Andrographis contains various compounds including terpenes and flavonoids. Extracts from this plant contain varying compositions of these. The quality of available non-clinical 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.

Overall, the published non-clinical studies provide some evidence that:

- Some of the active ingredients in Andrographis could be capable of evoking release of allergenic mediators, potentially resulting in anaphylactic reactions. Evidence is based on in vitro cell-based assay and in silico model predictions. The lack of allergic reaction in some animal studies raised questions about the adequacy of study design to assess pseudoallergy type reactions and whether the animal species used may have been less sensitive animal species for pseudoallergic reactions.
- 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.
- Anti-inflammatory actions of Andrographis extract and main active andrographolide were observed in mouse models of asthma.

As most 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.

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

[63] 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.

[64] 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.

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 evidence that some of the active constituents in Andrographis could evoke release of allergenic mediators from mast cells, potentially resulting in anaphylactic reactions.
- Anti-inflammatory actions of Andrographis and andrographolide have been observed in mouse models.

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 by the TGA 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 constraints on how many ingredients or indications can be applied to each listed medicine provided they comply with the Permissible Ingredients Determination and the Permissible Indications Determination. 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.

Approximately 84 listed medicines in the ARTG contain Andrographis at the time of this review. These products frequently have indications such as relief of cold and flu symptoms, or immune support. Only 8 out of the 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.

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 in the ARTG, is that it is safe for the purpose for which it is to be used. This certification may not be correct for Andrographis-containing listed medicines, particularly where indications are for use during infections as this has the potential to increase the risk of occurrence and severity of allergic reactions.

Risk / benefit

Discussion of risk-benefit for the ingredient Andrographis when used in listed medicines was included in the 2015 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 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.

The purported benefits reviewed in the 2015 have not been replicated here, particularly considering 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 for the risk-benefit profile to remain favourable for a low-risk listed medicine. The risk of life-threatening anaphylaxis observed for Andrographis is considered unacceptable for medicines indicated for low–level benefits only.

Furthermore, in the majority of situations when Andrographis is being used by consumers as per the indication (i.e. for immune support or symptomatic relief during viral illness), there is an increased risk of severe allergic reactions. When used for indications other than immune support, respiratory or viral symptoms, the associated risk may be reduced, however it remains sufficiently high to preclude restricting use solely to indications unrelated to immune support, respiratory or viral symptoms as a suitable option. The availability of other ingredients with indications similar to those for Andrographis was also considered in the 2015 review and these ingredients remain available for use in listed medicines.

As such, this review indicates that Andrographis presents risk of life-threatening anaphylaxis that is inconsistent with the low-risk listed medicines regulatory framework. Higher risk medicines must be registered in the ARTG, which involves individually evaluating the quality, safety and effectiveness of the product.

Implications for the use of Andrographis by traditional practitioners is outside the scope of this safety review.

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 two have published safety communications on the topic[65].

[65] Reminder: Allergic reactions with Andrographis paniculata [accessed 02 February 2026], Health Product InfoWatch, September 2020 - Canada.ca [accessed 02 February 2026].

In Thailand, Andrographis is on the National List of Essential Medicines (NLEM) for non-infectious diarrhoea and respiratory tract infection (sore throat and common cold)[66].

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 in the ARTG is that it is safe for its intended purpose. Given the risk of allergic reactions including anaphylaxis, this certification may not be appropriate for Andrographis-containing listed medicines.

Advisory committee on complementary medicines (ACCM)

Advice was sought from ACCM at their 37th meeting on 31 July 2025 following completion of the updated safety review.

The committee agreed that there is increased risk posed to the consumer by Andrographis-containing medicines 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 or for ‘immune boosting’ where viral illness could be present.

The committee agreed that anaphylaxis adverse events have been sudden and unpredictable and therefore the risk of anaphylaxis is difficult to mitigate.

The committee agreed 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 advised that they were unable to comment on whether any additional evidence was available that had not already 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.

However, the committee 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

[66] 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.

ingredients needs to be given further consideration before the risk of Andrographis as a single listed ingredient can be clearly determined. Further consideration was subsequently given to each of these factors and has been incorporated into this review and further support the conclusions.

Conclusion

Following a large increase in 2019, the TGA has continued to receive a sustained high number of reports of anaphylaxis associated with Andrographis-containing medicines with no sign of a declining trend. Case narratives often illustrate the unpredictable manner in which they occur.

Serious reactions are occurring after first exposure, but also after previous use on multiple occasions without prior reaction, and 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 unrecognised and assumed to be symptoms of the virus being treated rather than identified by consumers as an indication of risk for a more severe reaction on subsequent exposure.

As most anaphylactic reactions associated with Andrographis occur 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, the available evidence does not 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 is inconsistent with the low-risk listed medicines regulatory framework.

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.

At the 37th ACCM meeting the committee agreed 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 for further consideration, including additional analysis of the available data, which have been incorporated into this review and further support the conclusions.

This updated safety review of Andrographis, including advice from ACCM, concludes that the life-threatening risk of anaphylaxis associated with Andrographis cannot be effectively mitigated to be consistent with the low-risk listed medicines regulatory framework.

Version history

Version	Description of change	Author	Effective date
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