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Safety of Herbal Products in Thailand

An Analysis of Reports in the Thai Health Product Vigilance Center Database from 2000 to 2008

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Abstract

Background: The use of herbal products continues to expand rapidly across the world and concerns regarding the safety of these products have been raised. In Thailand, Thai Vigibase, developed by the Health Product Vigilance Center (HPVC) under the Thai Food and Drug Administration, is the national database that collates reports from health product surveillance systems and programmes. Thai Vigibase can be used to identify signals of adverse events in patients receiving herbal products.

Objectives: The purpose of the study was to describe the characteristics of reported adverse events in patients receiving herbal products in Thailand.

Methods: Thai Vigibase data from February 2000 to December 2008 involving adverse events reported in association with herbal products were used. This database includes case reports submitted through the spontaneous reporting system and intensive monitoring programmes. Under the spontaneous reporting system, adverse event reports are collected nationwide via a national network of 22 regional centres covering more than 800 public and private hospitals, and health service centres. An intensive monitoring programme was also conducted to monitor the five single herbal products listed in the Thai National List of Essential Medicines (NLEM), while another intensive monitoring programme was developed to monitor the four single herbal products that were under consideration for inclusion in the NLEM. The database contained patient demographics, adverse events associated with herbal products, and details on seriousness, causality and quality of reports. Descriptive statistics were used for data analyses.

Results: A total of 593 reports with 1868 adverse events involving 24 different products were made during the study period. The age range of individuals was 1–86 years (mean 47 years). Most case reports were obtained from the intensive monitoring programme. Of the reports, 72% involved females. The herbal products for which adverse events were frequently reported were products containing turmeric (44%), followed by andrographis (10%), veld grape (10%), pennywort (7%), plai (6%), jewel vine (6%), bitter melon (5%) and snake plant (5%). Gastrointestinal problems were the most common adverse effect reported. Serious adverse events included Stevens-Johnson syndrome, anaphylactic shock and exfoliative dermatitis.

Conclusions: Adverse event reports on herbals products were diverse, with most of them being reported through intensive monitoring programmes. Thai Vigibase is a potentially effective data source for signal detection of adverse events associated with herbal products.

Background

The use of herbal products continues to expand rapidly across the world. Although some studies have shown the benefits of the use of herbal products,[1,2] adverse events have been increasingly reported.[3-8] Dietary supplements, particularly dietary botanical supplements, are widely used in the US; 13–40% of the population reported the use of 'natural herbs', and the sale of dietary botanical supplements topped $US4 billion.[9-12] Thailand has a similar trend, as indicated by an 11% increase in herbal product consumption from $US27 million in the year 2001 to $US32 million in the year 2003.[13]

There are over 2000 herbal products registered in Thailand;[14] 19 of these (including single- and multiple-ingredient products) are included in the Thai National List of Essential Medicines (NLEM), 2008.[15] Herbal products listed in the NLEM are highly accepted in Thai society because only medicines with clear supporting evidence of their efficacy and safety are selected by the National List of Essential Medicine Selection Committee. In addition, those medicines listed in the NLEM are more widely used because they have a higher chance of being included in drug formulary at hospital settings. Several factors contribute to the increased use of herbal products:[16] (i) easy accessibility; (ii) perception of safety; (iii) the desire for self-medication; and (iv) lower cost. However, herbal products may not be as safe as perceived by consumers.

The safety of herbal products has become a concern to both national health authorities and the general public.[8] Serious adverse events resulting from the use of herbal medicines have been reported, such as hepatotoxicity,[4,7] blood pressure fluctuation,[6] rhabdomyolysis[3] and anaphylactic reactions.[5] Improved reporting of adverse effects is needed in order to gain a perspective of the frequency, severity and causes of adverse effects of herbal products. This can be used to inform healthcare professionals and users of herbal products so that unwanted health effects can be avoided or reduced.

Using an international or national database as a tool for surveillance of adverse effects associated with the use of herbal products is potentially as effective as other passive surveillance methods.[17] In Thailand, the Health Product Vigilance Center (HPVC) was established under the Thai Food and Drug Administration, Ministry of Public Health in 1983 (http://www.fda.moph.go.th/vigilance). It is responsible for monitoring the safety of health products in Thailand, primarily medicines, including herbal and traditional medicines. Thai Vigibase was developed by the HPVC as the national database collating all case reports submitted from both spontaneous reporting

systems and intensive monitoring programmes. However, the classification/summarization of reported data regarding how many adverse events result from herbal products, the types of adverse events that occur and which herbs are the potential causes of adverse events are still limited. To develop an effective surveillance system for herbal products in Thailand, the understanding of characteristics of adverse events should be studied. Therefore, our study aims to describe characteristics of adverse event reports on herbal products using Thai Vigibase.

Methods

Data Source

This retrospective study used the Thai Vigibase, which included all case reports of suspected adverse events submitted by health professionals throughout the country to HPVC from February 2000 to December 2008.

Under the spontaneous reporting system, adverse events reports are collected nationwide via a national network of 22 regional centres covering more than 800 public and private hospitals and health service centres.[18] When adverse events resulting from an actual or potential exposure to a substance are found, healthcare professionals from all health facilities are encouraged to report the suspected adverse events associated with herbal products. Reports can be submitted either via an adverse event reporting form or via an online reporting system. Those reports are then directly sent to the national HPVC or through the regional centre.

Intensive monitoring programmes were undertaken to promote the reporting of adverse events associated with herbal product use. After a total of five single herbal products (*Curcuma longa* [Turmeric], *Andrographis paniculata* [Andrographis], *Zingiber cassumunar* [Plai], *Clinacanthus nutans* [Snake plant] and *Cassia alata* [Wild senna]) were included in the Thai NLEM in 1999, a 2-year intensive monitoring programme of these products was launched in the year 2000. In addition, an intensive monitoring programme was initiated by the Department for Development of Thai Traditional and Alternative Medicine (which is responsible for promoting the use of herbal products in Thailand). This programme focused on four single herbal products that were under consideration for inclusion in the NLEM *Cissus quadrangularis* [Veld grape], *Centella asiatica* [Pennywort], *Derris scandens* [Jewel vine], *Momordica charantia* [Bitter melon]). Data collected under this programme will be crucial information used for considering whether these products are to be listed in NLEM.

When submitting a report to Thai Vigibase, the following information should be provided: report identification; report date; patient's demographics; herbal products and drug use information, including administration, date and time; underlying disease (coded by *International Classification of Diseases, 10th edition*; ICD-10); name of reported source; name of reporter; type of herbal products; and a description of the reported adverse events. Data in Thai Vigibase are in the Microsoft Access® format.

Analyses

All retrieved data regarding adverse events associated with the use of herbal products from Thai Vigibase during the study period were included for analyses. Reports without the name of the herbal product were excluded and patients' demographics and adverse events associated with herbal products were explored. The association between the herbal products and adverse events is not confirmed. Causality assessment was carried out using Naranjo's algorithm by health professionals at the time of report submission.[19] Only reports rated as 'possible' or higher were included in our analysis. The number of reports and adverse events classified by herbal product name were counted. Adverse events from each product were classified and presented by organ system affected. According to the WHO Adverse Reaction Terminology (WHO-ART) classification, each preferred term is categorized into a primary system organ class and up to two subsidiary system organ classes.[20] We used the matched pair of the primary system organ class and preferred term in our analysis. Adverse events were classified as non-serious or serious. Serious adverse events

were subclassified into hospitalization or prolongation of hospitalization, persistent or significant disability/incapacity, and life threatening.

Qualities of reports were classified into four grades (0, 1, 2 and 3) according to WHO-Uppsala Monitoring Centre (WHO-UMC) documentation grading.[21] These four grades of report quality were different in terms of the data completeness. For grade 1, reports must include data on patient identification, at least one suspect drug and at least one adverse reaction term. The reports also have to contain information on onset and treatment dates. For grade 2, indication for treatment must be additionally provided. For grade 3, information on positive rechallenge has to be given. For reports providing information less than grade 1 level, it is rated as grade 0. All variables were analysed using descriptive statistics.

Results

Over the 9-year study period, Thai VigiBase had a total of 593 case reports with 1868 adverse events involving 24 different herbal products.

Table I shows the patients' demographics and characteristics of adverse event reports. Most reported cases involved females (72%). Ages ranged from 1 to 86 years; 62% of patients were aged 31–60 years. Eighty-five percent had no history of drug allergy. Approximately 90% of adverse events that occurred were not classified as serious; however, 4% (25 cases) were serious. Of these serious adverse events, 84% required hospitalization or prolongation of hospitalization, 8% were persistent or resulted in significant disability/incapacity, and 8% were life threatening. When evaluated for causality using Naranjo's algorithm, almost all cases (99.8%) were classified as 'possible' causality. It was found that all 25 serious case reports had causality assessment at the 'possible' level. Regarding quality of reports, most were graded at quality level 2 (58%).

Table II shows the number of adverse events and reports for each herbal product. The herbal products for which adverse events were frequently reported were products containing *Curcuma longa* (Turmeric) 44%, followed by *Andrographis paniculata* (Andrographis) 10%, *Cissus quadrangularis* (Veld grape) 10%, *Centella asiatica* (Pennywort) 7%, *Zingiber cassumunar* (Plai) 6%, *Derris scandens* (Jewel vine) 6%,

Table I. Characteristics of patients and adverse event reports

Characteristics	No. (%) [n = 593]
Patients	
Sex	
female	425 (71.6)
male	167 (28.2)
NA	1 (0.2)
Age [y]	47.3 (15.7)[a]
<15	10 (1.9)
15–30	78 (13.2)
31–60	365 (61.5)
>60	121 (20.4)
NA	19 (3.2)
History of drug allergy	
No	503 (84.8)
Yes	72 (12.2)
NA	18 (3.0)
Adverse event reports	
Seriousness[b]	
Serious	25[c] (4.2)
hospitalization or prolongation of hospitalization	21
persistent or significant disability/incapacity	2
life threatening	2
Non-serious	536 (90.4)
NA	32 (5.4)
Causality assessment[d]	
Certain	0 (0.0)
Probable	1 (0.2)
Possible	592 (99.8)
Quality of reports[e]	
Quality 3	31 (5.2)
Quality 2	345 (58.2)
Quality 1	144 (24.3)
Quality 0	73 (12.3)

a Data presented as mean (SD).

b Serious adverse events are those that cause a patient a hospitalization or prolongation of hospitalization, persistent or significant disability/incapacity, or are life threatening.

c Causality assessment of all 25 cases was assessed as 'possible'.

d Naranjo's algorithm.[19]

e WHO-Uppsala Monitoring Centre documentation grading.[21]

NA = not available.

Momordica charantia (Bitter melon) 5% and *Clinacanthus nutans* (Snake plant) 5%.

Eighty percent of the case reports were derived from the intensive monitoring programmes (table II). Of the 593 total reports in this study, 7 reports with 30 adverse events involved *Cassia siamea* (Thai cassia). Among adverse events found, 53.3% were related to liver and biliary system disorders, which were the dominant adverse events leading to the withdrawal of a certain brand product of *Cassia siamea* (Thai cassia) from the market.

Overall, gastrointestinal problems were the most common adverse health effects reported. Serious adverse events included Stevens-Johnson syndrome (one case associated with the use of Andrographis and one with the use of Indian mulberry), anaphylactic shock (one case associated with the use of Andrographis) and exfoliative dermatitis (one case associated with the use of Turmeric, one with the use of Andrographis, one with the use of Pennywort and one with the use of Plai), as shown in table III.

Discussion

This study examined herbal adverse event reports to the HPVC across Thailand from February 2000 to December 2008. Our findings revealed a total of 593 reports with 1868 adverse events involving 24 different single herbal products. The high number of reports received has been attributable to several factors. For example,

Table II. The number and types of reports and adverse events associated with each herbal product submitted to the Health Product Vigilance Center, Thai FDA

Herbs	Reports [n (%)]	Source of reports [n (%)][a]		Adverse events[b] [n (%)]
		spontaneous	intensive	
1. *Curcuma longa* (Turmeric)	260 (43.8)	38 (14.6)	222 (85.4)	805 (43.1)
2. *Andrographis paniculata* (Andrographis)	60 (10.1)	27 (45.0)	33 (55.0)	131 (7.0)
3. *Cissus quadrangularis* (Veld grape)	56 (9.5)	1 (1.8)	55 (98.2)	181 (9.7)
4. *Centella asiatica* (Pennywort)	42 (7.1)	0 (0)	42 (100)	200 (10.8)
5. *Zingiber cassumunar* (Plai)	38 (6.4)	8 (21.1)	30 (78.9)	97 (5.2)
6. *Derris scandens* (Jewel vine)	35 (5.9)	0 (0)	35 (100)	152 (8.1)
7. *Momordica charantia* (Bitter melon)	30 (5.1)	1 (3.3)	29 (96.7)	105 (5.6)
8. *Clinacanthus nutans* (Snake plant)	29 (4.9)	3 (10.3)	26 (89.7)	81 (4.3)
9. *Cassia siamea* (Thai cassia)	7 (1.2)	7 (100)	0 (0)	30 (1.6)
10. *Arthrospira platensis* (Spirulina)	5 (0.8)	5 (100)	0 (0)	8 (0.4)
11. *Cassia alata* (Wild senna)	5 (0.8)	3 (60.0)	2 (40.0)	10 (0.5)
12. *Curcuma xanthorrhiza* (Giant curcuma)	5 (0.8)	5 (100)	0 (0)	12 (0.6)
13. *Morinda citrifolia* (Indian mulberry)	5 (0.8)	5 (100)	0 (0)	7 (0.4)
14. *Allium sativum* (Garlic)	3 (0.5)	3 (100)	0 (0)	8 (0.4)
15. *Ganoderma lucidum* (Ling zhi)	2 (0.3)	2 (100)	0 (0)	9 (0.5)
16. *Gingko biloba* (Gingko)	2 (0.3)	2 (100)	0 (0)	5 (0.3)
17. *Tinospora crispa* (Heart-leaved moonseed)	2 (0.3)	2 (100)	0 (0)	8 (0.4)
18. *Cassia angustifolia* (Indian senna)	1 (0.2)	1 (100)	0 (0)	3 (0.2)
19. *Oenothera biennis* (Evening primrose oil)	1 (0.2)	1 (100)	0 (0)	3 (0.2)
20. *Piper nigrum* (Pepper)	1 (0.2)	1 (100)	0 (0)	1 (0.1)
21. *Pueraria mirifica* (Kwao Krua Kao)	1 (0.2)	1 (100)	0 (0)	2 (0.1)
22. *Solanum trilobatum* (Indian nightshade)	1 (0.2)	1 (100)	0 (0)	2 (0.1)
23. *Talinum paniculata* (Ginseng)	1 (0.2)	1 (100)	0 (0)	2 (0.1)
24. *Zingiber officinale* (Ginger)	1 (0.2)	1 (100)	0 (0)	6 (0.3)
Total	**593 (100)**	**119 (20.1)**	**474 (79.9)**	**1868 (100)**

a Reports received from the spontaneous reporting or intensive monitoring system.

b Some reports have more than one event.

Table III. Adverse events of reported herbal products classified by organ system according to WHO Adverse Reaction Terminology

Herbs [no. of events]	System Organ Class	n (%)[a]	Detail (n)
Curcuma longa[b] (Turmeric) [805]	Gastrointestinal system disorders	305 (37.9)	Abdominal pain (100), diarrhoea (60), eructation (48), nausea (45), vomiting (40), constipation (4), flatus (3), flatulence (2), cheilitis (1), constipation aggravated (1), gum hyperplasia (1)
	Body as a whole – general disorders	155 (19.3)	Fatigue (60), chest discomfort (45), therapeutic response increased (35), fever (7), chest tightness (3), back pain (2), leg pain (1), oedema mouth (1), pain burning (1)
	Psychiatric disorders	118 (14.7)	Anorexia (111), appetite increased (3), somnolence (3), insomnia (1)
	Central and peripheral nervous system disorders	104 (12.9)	Headache (94), dizziness (6), burning sensation (2), burning skin (2)
	Skin and appendages disorders	53 (6.6)	Pruritus (27), rash (13), rash erythematous (3), rash maculopapular (2), skin dry (2), angioedema (1), **exfoliative dermatitis (1)**, itching (1), macular rash (1), rash bullous (1), uticaria (1)
	Respiratory system disorders	49 (6.1)	Dyspnoea (31), coughing (18)
	Liver and biliary system disorders	6 (0.7)	Jaundice (6)
	Heart rate and rhythm disorders	4 (0.5)	Palpitation (4)
	Metabolic and nutritional disorders	4 (0.5)	Thirst (4)
	Urinary system disorders	4 (0.5)	Micturition frequent (2), urinary frequency (1), urine odour foul (1)
	Endocrine disorders	2 (0.2)	Gynaecomastia (2)
	Special senses other, disorders	1 (0.1)	Taste perversion (1)
Andrographis paniculata[b] (Andrographis) [131]	Skin and appendages disorders	51 (38.9)	Pruritus (13), rash (8), rash maculopapular (7), urticaria (6), sweating increased (4), erythema multiforme (3), angioedema (2), rash erythematous (2), skin exfoliation (2), **exfoliative dermatitis (1)**, dry lips (1), itching (1), **Stevens-Johnson syndrome (1)**
	Body as a whole – general disorders	18 (13.7)	Fatigue (6), oedema periorbital (3), eyelid oedema (2), fever (2), therapeutic response decreased (2), **anaphylactic shock (1)**, flank pain (1), oedema of extremities (1)
	Gastrointestinal system disorders	18 (13.7)	Vomiting (6), nausea (5), abdominal pain (4), diarrhoea (2), throat dry (1)
	Psychiatric disorders	15 (11.5)	Anorexia (12), sleepiness (2), insomnia (1)
	Respiratory system disorders	12 (9.2)	Dyspnoea (5), coughing (4), bronchospasm (2), sputum increased (1)
	Central and peripheral nervous system disorders	9 (6.9)	Headache (6), burning sensation (1), dizziness (1), faintness (1)
	Urinary system disorders	3 (2.3)	Face oedema (2), urinary frequency (1)
	Application site disorders	2 (1.5)	Anaesthesia local (2)
	Vascular (extracardiac) disorders	2 (1.5)	Vasculitis (2)
	Musculoskeletal system disorders	1 (0.8)	Muscle weakness (1)
Cissus quadrangularis (Veld grape) [181]	Gastrointestinal system disorders	100 (55.2)	Flatulence (30), constipation (14), nausea (14), diarrhoea (12), abdominal pain (10), vomiting (6), abdominal discomfort (4), mouth dry (4), constipation aggravated (1), dyspepsia (1), faecal abnormality (1), fullness abdominal (1), stool loose (1), throat dry (1)
	Central and peripheral nervous system disorders	21 (11.6)	Headache (8), dizziness (6), faintness (6), burning sensation (1)

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Table III. Contd

Herbs [no. of events]	System Organ Class	n (%)[a]	Detail (n)
	Body as a whole – general disorders	14 (7.7)	Chest tightness (7), fatigue (4), eyelid oedema (2), oedema of extremities (1)
	Application site disorders	10 (5.5)	Anaesthesia local (10)
	Skin and appendages disorders	10 (5.5)	Rash erythematous (4), pruritus (3), urticaria (2), rash bullous (1)
	Urinary system disorders	10 (5.5)	Polyuria (3), urine abnormal (3), face oedema (2), urine discolouration (1), urine flow decreased (1)
	Psychiatric disorders	9 (5.0)	Anorexia (3), insomnia (3), hunger abnormal (1), sleepiness (1), somnolence (1)
	Heart rate and rhythm disorders	6 (3.3)	Palpitation (6)
	Vision disorders	1 (0.6)	Conjunctivitis (1)
Centella asiatica (Penny wort) [200]	Gastrointestinal system disorders	95 (47.5)	Abdominal pain (16), flatulence (16), constipation (12), mouth dry (10), nausea (10), vomiting (10), diarrhoea (8), throat dry (5), abdominal discomfort (2), dyspepsia (2), flatus (2), fullness abdominal (1), stool black (1)
	Psychiatric disorders	33 (16.5)	Anorexia (21), insomnia (5), appetite increased (3), sleepiness (2), bulimia (1), somnolence (1)
	Central and peripheral nervous system disorders	24 (12.0)	Dizziness (13), headache (6), faintness (3), burning sensation (2)
	Body as a whole – general disorders	14 (7.0)	Fatigue (8), syncope (3), abdominal distention gaseous (1), chest tightness (1), feeling cold (1)
	Heart rate and rhythm disorders	12 (6.0)	Palpitation (12)
	Urinary system disorders	10 (5.0)	Polyuria (7), micturition frequency (2), urine discolouration (1)
	Skin and appendages disorders	7 (3.5)	Pruritus (2), urticaria (2), **exfoliative dermatitis (1)**, hot dry skin (1), rash maculopapular (1)
	Application site disorders	4 (2.0)	Anaesthesia local (4)
	Reproductive disorders, female	1 (0.5)	Leukorrhoea (1)
Zingiber cassumunar[b] (Plai) [97]	Gastrointestinal system disorders	21 (21.6)	Abdominal pain (6), vomiting (6), nausea (5), diarrhoea (4)
	Body as a whole – general disorders	20 (20.6)	Therapeutic response decreased (15), fatigue (4), fever (1)
	Skin and appendages disorders	18 (18.6)	Pruritus (7), Rash (5), rash erythematous (2), dermatitis (1), **exfoliative dermatitis (1)**, erythema multiforme (1), papulovesicular rash (1)
	Psychiatric disorders	15 (15.5)	Anorexia (15)
	Central and peripheral nervous system disorders	14 (14.4)	Headache (12), burning sensation (1), burning skin (1)
	Respiratory system disorders	7 (7.2)	Dyspnoea (5), coughing (2)
	Urinary system disorders	1 (1.0)	Urinary frequency (1)
	Vision disorders	1 (1.0)	Conjunctival discolouration (1)
Derris scandens (Jewel vine) [152]	Gastrointestinal system disorders	78 (51.3)	Abdominal pain (16), constipation (10), mouth dry (10), diarrhoea (8), flatulence (8), Vomiting (8), throat dry (7), nausea (6), faeces discoloured (2), abdominal discomfort (1), faecal abnormality (1), fullness abdominal (1)
	Psychiatric disorders	17 (11.2)	Anorexia (6), sleepiness (4), appetite increased (3), insomnia (3), somnolence (1)
	Body as a whole – general disorders	15 (9.9)	Chest tightness (6), fatigue (3), syncope (3), back pain (2), feeling cold (1)

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Table III. Contd

Herbs [no. of events]	System Organ Class	n (%)[a]	Detail (n)
	Central and peripheral nervous system disorders	15 (9.9)	Dizziness (6), headache (6), faintness (3)
	Urinary system disorders	9 (5.9)	Polyuria (6), urine discolouration (2), urine frequency (1)
	Heart rate and rhythm disorders	6 (3.9)	Palpitations (6)
	Skin and appendages disorders	5 (3.3)	Pruritus (2), rash (1), rash maculopapular (1), urticaria (1)
	Respiratory system disorders	3 (2.0)	Coughing (2), throat irritation (1)
	Application site disorders	2 (1.3)	Anaesthesia local (2)
	Reproductive disorders, female	1 (0.7)	Leukorrhoea (1)
	Special senses other, disorders	1 (0.7)	Taste loss (1)
Momordica charantia (Bitter melon) [105]	Gastrointestinal system disorders	50 (47.6)	Diarrhoea (22), nausea (8), flatulence (6), vomiting (6), abdominal pain (2), mouth dry (2), throat dry (2), abdominal distress (1), stool loose (1)
	Central and peripheral nervous system disorders	20 (19.0)	Dizziness (8), headache (4), faintness (3), anaesthesia mouth (1), anaesthesia tongue (1), burning sensation (1), numbness localized (1), paraesthesia (1)
	Heart rate and rhythm disorders	10 (9.5)	Palpitation (10)
	Skin and appendages disorders	7 (6.7)	Pruritus (3), rash erythematous (2), rash (1), rash bullous (1)
	Urinary system disorders	5 (4.8)	Face oedema (2), urine abnormal (2), urine discolouration (1)
	Application site disorders	4 (3.8)	Anaesthesia local (4)
	Body as a whole – general disorders	4 (3.8)	Fatigue (2), fever (1), oedema of extremities (1)
	Psychiatric disorders	4 (3.8)	Appetite increased (3), insomnia (1)
	Respiratory system disorders	1 (1.0)	Throat sore (1)
Clinacanthus nutans[b] (Snake plant) [81]	Skin and appendages disorders	24 (29.6)	Pruritus (14), rash (7), hot dry skin (2), pruritus aggravated (1)
	Gastrointestinal system disorders	16 (19.8)	Abdominal pain (4), diarrhoea (4), nausea (4), vomiting (4)
	Central and peripheral nervous system disorders	15 (18.5)	Headache (12), burning (3)
	Body as a whole – general disorders	13 (16.0)	Therapeutic response decreased (8), fatigue (4), fever (1)
	Psychiatric disorders	6 (7.4)	Anorexia (6)
	Respiratory system disorders	5 (6.2)	Dyspnoea (3), bronchospasm (2)
	Application site disorders	1 (1.2)	Anaesthesia local (1)
	Vision disorders	1 (1.2)	Conjunctival discolouration (1)
Cassia siamea[b] (Thai cassia) [30]	Liver and biliary system disorders	16 (53.3)	Jaundice (8), hepatic enzymes increased (3), hepatic function abnormal (2), hepatitis (2), hepatic pain (1)
	Psychiatric disorders	12 (40.0)	Anorexia (12)
	Body as a whole – general disorders	2 (6.7)	Fatigue (2)
Arthrospira platensis (Spirulina) [8]	Skin and appendages disorders	3 (37.5)	Rash (1), rash maculopapular (1), urticaria (1)
	Central and peripheral nervous system disorders	1 (12.5)	Numbness (1)
	Liver and biliary system disorders	1 (12.5)	Liver function test abnormality (1)
	Musculoskeletal system disorders	1 (12.5)	Myalgia (1)
	Reproductive disorders, female	1 (12.5)	Menstrual disorder (1)
	Respiratory system disorders	1 (12.5)	Coughing (1)

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Table III. Contd

Herbs [no. of events]	System Organ Class	n (%)[a]	Detail (n)
Cassia alata (Wild senna) [10]	Body as a whole – general disorders	3 (30.0)	Therapeutic response decreased (2), eyelid oedema (1)
	Gastrointestinal system disorders	3 (30.0)	Vomiting (2), nausea (1)
	Central and peripheral nervous system disorders	2 (20.0)	Headache (2)
	Skin and appendages disorders	2 (20.0)	Urticaria (2)
Curcuma xanthorrhiza (Giant curcuma) [12]	Urinary system disorders	6 (50.0)	Face oedema (6)
	Gastrointestinal system disorders	2 (16.7)	Abdominal pain (2)
	Skin and appendages disorders	2 (16.7)	Erythema multiforme (1), urticaria (1)
	Body as a whole – general disorders	1 (8.3)	Eyelid oedema (1)
	Reproductive disorders, female	1 (8.3)	Leukorrhoea (1)
Morinda citrifolia (Indian mulberry) [7]	Urinary system disorders	5 (71.4)	Blood urea nitrogen increased (2), creatinine clearance decreased (1), renal failure acute (1), renal function abnormal (1)
	Skin and appendages disorders	2 (28.6)	Papular rash (1), **Stevens-Johnson syndrome (1)**
Allium sativum Linn. (Garlic) [8]	Body as a whole – general disorders	2 (25.0)	Back pain (2)
	Gastrointestinal system disorders	2 (25.0)	Eructation (2)
	Skin and appendages disorders	2 (25.0)	Pruritus (1), rash maculopapular (1)
	Central and peripheral nervous system disorders	1 (12.5)	Dizziness (1)
	Respiratory system disorders	1 (12.5)	Dyspnoea (1)
Ganoderma lucidum (Ling zhi) [9]	Gastrointestinal system disorders	4 (44.4)	Abdominal pain (2), diarrhoea (2)
	Central and peripheral nervous system disorders	2 (22.2)	Dizziness (1), faintness (1)
	Skin and appendages disorders	2 (22.2)	Photosensitivity toxic reaction (2)
	Liver and biliary system disorders	1 (11.1)	Hepatitis (1)
Gingko biloba (Gingko) [5]	Body as a whole – general disorders	3 (60.0)	Oedema legs (3)
	Liver and biliary system disorders	1 (20.0)	Hepatic enzymes increased (1)
	Skin and appendages disorders	1 (20.0)	Rash (1)
Tinospora crispa (Heart-leaved moonseed) [8]	Gastrointestinal system disorders	5 (62.5)	Abdominal pain (2), constipation (2), abdominal discomfort (1)
	Body as a whole – general disorders	2 (25.0)	Chest tightness (2)
	Liver and biliary system disorders	1 (12.5)	Hepatitis (1)
Cassia angustifolia (Indian senna) [3]	Cardiovascular disorders, general	2 (66.7)	Hypotension (2)
	Body as a whole – general disorders	1 (33.3)	Therapeutic response decreased (1)
Onethera Biennis (Evening primrose oil) [3]	Central and peripheral nervous system disorders	1 (33.3)	Dizziness (1)
	Psychiatric disorders	1 (33.3)	Insomnia (1)
	Respiratory system disorders	1 (33.3)	Dyspnoea (1)
Piper nigrum (Pepper) [1]	Skin and appendages disorders	1 (100.0)	Rash maculopapular (1)
Pueraria mirifica (Kwao Krua Kao) [2]	Reproductive disorders, female	1 (50.0)	Leukorrhoea (1)
	Skin and appendages disorders	1 (50.0)	Macular rash (1)

Continued next page

Table III. Contd

Herbs [no. of events]	System Organ Class	n (%)[a]	Detail (n)
Solanum trilobatum (Indian nightshade) [2]	Skin and appendages disorders	2 (100.0)	Pruritus (1), rash (1)
Talinum paniculata (Ginseng) [2]	Skin and appendages disorders	2 (100.0)	Rash acneiform (1), rash erythematous (1)
Zingiber officinale (Ginger) [6]	Psychiatric disorders	3 (50.0)	Appetite increased (3)
	Body as a whole – general disorders	1 (16.7)	Fatigue (1)
	Gastrointestinal system disorders	1 (16.7)	Nausea (1)
	Skin and appendages disorders	1 (16.7)	Pruritus (1)

a Percentage of each herbal product.

b Indications by the List of Herbal Medicine Products in Thailand[15] (*Curcuma longa* [Turmeric]: dyspepsia; *Andrographis paniculata* [Andrographis]: non-infectious diarrhoea, sore throat and common cold; *Zingiber cassummunar* [Plai]: muscle pain and inflammation; *Clinacanthus nutans* [Snake plant]: herpes simplex, herpes zoster, aphthous ulcer, urticaria and rash; *Cassia alata* [Wild senna]: constipation).

Bold indicates serious adverse event.

the HPVC has provided guidelines for reporting adverse events associated with herbal products to network health centres. In addition, a 2-year intensive monitoring programme was conducted to specifically monitor the five single herbal products (*Curcuma longa* [Turmeric], *Andrographis paniculata* [Andrographis], *Zingiber cassumunar* [Plai], *Clinacanthus nutans* [Snake plant] and *Cassia alata* [Wild senna]) that have been listed in the Thai NLEM since 1999. Furthermore, the Department for Development of Thai Traditional and Alternative Medicine has been collecting effective and safety data of four herbal products (*Cissus quadrangularis* [Veld grape], *Centella asiatica* [Pennywort], *Derris scandens* [Jewel vine], *Momordica charantia* [Bitter melon]) that are under consideration to be listed in the Thai NLEM. Data collected under this programme will be crucial information used for approving these products to be listed in NLEM. The eight top reported herbal products (table II) are mainly the results from such a programme.

Curcuma longa (Turmeric) and *Andrographis paniculata* (Andrographis) were the two most frequently reported herbal products. This is because they have been widely known and listed in the NLEM in Thailand. *Curcuma longa* (Turmeric), in particular, is the product with the highest number of reports because it is promoted to serve as a substitute for products used to treat flatulence. Most importantly, both products are available at drug stores and are easily accessible.

Despite the reports of adverse events in Thai Vigibase, this does not necessarily mean that the adverse events are caused by the herbal products. It is important to note that having adverse events reported does not imply direct causation. Such events could be related to other contributing factors. The lack of direct causation also applies to gastrointestinal problems, which were the most commonly reported adverse events. *Curcuma longa* (Turmeric) is the herbal product most commonly reported to the HPVC. Its indication is for dyspepsia. The reported gastrointestinal problems might be due to clinical conditions, other contributing factors or genuine adverse effects. Thai Vigibase is a good source for identifying signals of potential interest that could lead to further studies or investigations.

In order to detect a rare adverse event associated with a particular herbal product, a sufficiently large sample of persons exposed to a particular herbal product may be necessary to detect significant signal observations.[22,23] Thai Vigibase serves nearly the entire Thai population; thus, Thai Vigibase data are possibly a large enough source of information in Thailand to help in the detection of rare adverse events involving herbal products. Spontaneous reports in Thai Vigibase have demonstrated their importance, for example, in the withdrawal from the market of a certain brand product of *Cassia siamea* (Thai cassia) following reports of hepatotoxicity. It is

important to note that such hepatotoxicity would not have been detected without the use of safety information provided by Thai Vigibase.[18] Thai Vigibase can detect and monitor adverse events of all users of certain products, especially rare events. It can serve as an important tool in hypothesis generation and implementation of more specific surveillance activities.[24]

However, there are limitations that need to be considered when interpreting our results. First, as Thai Vigibase data are mostly acquired from a passive adverse event surveillance system, adverse events reported to HPVC can be underreported. However, underreporting is normally expected in spontaneous reporting.[25-28] One of the potential reasons for underreporting is the lack of healthcare providers' awareness of the patient's herbal usage. It was also possible that healthcare providers did not know that herbal products could cause adverse events.[23,29] Another issue is that most usage of herbal products is self-directed, with patients mostly buying products from the community pharmacy. If a non-serious adverse event occurs, the patient may not go to hospital. The likely channel is that they may share information with community pharmacists. This makes a community pharmacist a feasible person who is exposed to information and able to report such events. However, there has been a paucity of reports submitted by community pharmacists despite their exposure to users of herbal medicines who experience adverse events.[30]

Second, the data of adverse events associated with herbal products sent to the HPVC is frequently incomplete. Recommendations for an adverse event report should include the following variables: (i) product name; (ii) demographic data; (iii) succinct clinical description of the adverse events (including confirmatory/relevant test/laboratory result); (iv) confounding factors such as concomitant medical products and medical history; (v) temporal information (including the date of event onset and start/stop dates for use of medical product); (vi) dose/frequency of use; (vii) biopsy/autopsy result; (viii) dechallenge/rechallenge information; and (ix) outcome.[24] Likewise, the HPVC recommends the same variables mentioned above in the Thai Vigibase. However, some reports sent to the HPVC are still incomplete because no information was available on some variables, such as concomitant drug use, dosage regimen and dechallenge/rechallenge information. The reports shown in this study were graded in quality level 3 (5%), quality level 2 (58%) and quality level 1 (24%). Despite data incompleteness, the quality of the Thai Vigibase is sufficient for signal detection, as demonstrated by the successful detection of a Thai cassia product-related adverse event, resulting in its withdrawal from the market.

Third, the distribution of the reports does not necessarily represent the incidence of events associated with herbal products because some herbal product reports were from intensive monitoring programmes.[18] The herbal products included in these programmes were *Curcuma longa* (Turmeric), *Andrographis paniculata* (Andrographis), *Capsicum frutescens* (Chili), *Zingiber officinale* (Ginger), *Cassia alata* (Wild senna), *Centella asiatica* (Pennywort), *Clinacanthus nutans* (Snake plant) and *Zingiber cassumunar* (Plai). These could partly explain the high number of reports of these products in our Thai Vigibase system.

Despite these limitations, however, Thai Vigibase can provide insights into adverse experiences with herbal products. Such a system can serve as an important surveillance mechanism for adverse events involving herbal products. Underreporting and incompleteness in the reports are key limitations of the Thai Vigibase system. Encouraging reporting can contribute to improving awareness among health personnel and patients about the benefit-harm profile of the herbal products.

Conclusions

We found that a majority of adverse event reports on herbal products was obtained through intensive monitoring programmes. In addition, a variety of herbal product-related adverse events was also reported. Considering the wide use of herbal products, it is important to have a surveillance system for monitoring the safety of these products. Our research findings demonstrated that

the Thai Vigibase is an important source of information that can be used as part of the surveillance system of herbal products. Further studies are continually required to further explore herbal product-specific adverse events using this database.

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