

ORIGINAL REPORT

Spontaneously reported adverse reactions in association with complementary and alternative medicine substances in Sweden[†]

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SUMMARY

Purpose Although the safety information is limited, use of complementary and alternative medicine (CAM) products is not without risks. Spontaneous reporting systems may be used in the surveillance of these products. We describe the pattern of spontaneously reported CAM related adverse reactions submitted to the Swedish Medical Products Agency (MPA) and highlight areas of safety concern.

Methods All adverse reactions spontaneously reported to MPA between 1987 and 2006, where at least one CAM substance was a suspected agent, were scrutinised. From each report information about the patient, adverse reaction/s, drug treatment/s, dosage, time relationship and outcome was retrieved.

Results Among a total of 64 493 reports, 778 reports concerned 967 suspected adverse reactions related to 175 different CAM products. The main distribution of suspected adverse reactions was: urticaria (8.3%), exanthema (7.4%) and contact dermatitis (5.7%). The most reported CAM substances were purple coneflower (*Echinacea purpurea*) (8.1%), purple coneflower + siberian ginseng (*Eleutherococcus senticosus*) + malabar nut (*Adhatoda vasica*) (7.3%) and ginkgo leaf (*Ginkgo biloba*) (6.7%). In 221 reports, at least one reaction was categorised as serious, the most frequent being pulmonary embolism (1.7%), mixed liver reaction (2.8%), and anaphylactic reaction (2.0%). Eleven of the serious adverse reactions had a fatal outcome.

Conclusions CAM substances were associated with a variety of adverse reactions. Some of these have previously been unrecognised or poorly documented and suggest further investigations. By stimulating the reporting of adverse reactions of CAM products, the signal detection power of the spontaneous reporting system may increase further. Copyright © 2009 John Wiley & Sons, Ltd.

KEY WORDS—complementary and alternative medicine; herbal drugs; adverse drug reaction; drug interaction; adverse drug reaction reporting systems

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INTRODUCTION

The use of complementary and alternative medicine (CAM) is widespread and increasing.^{1–3} In population surveys use of CAM products has been reported in between 20 and 52% of the general population within 1 year.^{3–5} The popularity of these products can in part be explained by people's beliefs that natural remedies are safe due to the natural origin.⁶ In general there is a lack of high quality data regarding safety

issues for CAM substances. Nevertheless, it is now well established that a number of these agents have the potential to produce minor or major safety problems.^{7,8} Several examples of serious adverse effects, such as hepatic failure, renal failure, neurotoxicity and anaphylaxis, have been associated with CAM substances.^{7,8} There has also been an increased awareness of potential CAM–drug interactions.^{9,10} Other safety issues are variability in biologic potency between preparations, contaminations and counterfeit preparations.¹¹ Moreover, a treatment with documented medical benefits may be delayed due to the use of CAM products.¹¹

In order to capture new and previously unrecognised CAM related adverse reactions the spontaneous

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reporting systems of suspected adverse drug reactions may be an important method. Adverse drug reporting is, or should be, as essential for CAM products as it is for pharmaceuticals in providing post-marketing surveillance. The objective of this study was to describe the pattern of spontaneously reported adverse reactions to the Swedish Medical Products Agency (MPA) where CAM substances were suspected to be implicated and highlight areas of safety concern.

METHODS

Since 1965, there is a national spontaneous reporting system for adverse drug reactions in Sweden. It has been mandatory to report all new or serious suspected adverse reactions to the Swedish MPA since 1975. This comprises pharmaceutical drugs as well as natural remedies and 'certain medicinal products for external use'. The Swedish Pharmacovigilance System consists of a network of six regional centres of pharmacovigilance handling and assessing all reported adverse reactions within their region followed by a re-evaluation at the MPA. The registered data in each report include information about the patient, the treatment suspected to have caused the adverse event, other medications and the reaction(s). This information, as well as the causality assessment and administrative data (e.g. type of report and source), is stored in the national database SWEDIS (Swedish Drug Information System). The World Health Organisation Adverse Reaction Terminology (WHO-ART) is used to categorise all suspected adverse reactions.¹² More than one ADR and/or drug can be included in each report. Causality assessments are done according to the WHO-UMC causality assessment system.¹³ Since causality assessment may be difficult, especially for CAM products, we included all reports in this study independently of the causality assessments.

The terminology and definitions used for different CAM therapies have changed over time as well as the legislation of drugs and natural remedies.¹⁴ In the present study CAM products were defined as natural remedies (origin from herbals, animals, bacterial cultures, minerals or salts) not excessively processed or refined and which are intended to be used without a prescription for the purpose of self-treatment according to the Medical Products Agency's code of statutes. For the purpose of this study nutritional supplements and homeopathy products were included in this definition. In Sweden there is no legal restriction regarding where these CAM products may be sold. Trade names are registered in SWEDIS and in order to identify the CAM substances in the reports, multiple sources

were used including literature, staff at the MPA and the website of the MPA. However, in some cases the ingredients were not possible to identify and therefore were labelled according to their trade name.

All spontaneously reported adverse reactions to the Swedish MPA between 1 January 1987 and 31 December 2006 where at least one CAM substance was suspected to be implicated independently of the causality assessments were scrutinised. In order to do this the following information was registered: administered CAM substances and pharmaceutical drugs, suspected adverse reactions, causality assessment, outcome, the patients' sex and age. We also registered profession, sex and age of the reporter who submitted the report. The study complies with the current Swedish laws.

RESULTS

A total of 64 493 reports of suspected adverse reactions were identified in the Swedish pharmacovigilance database during the study period. Of these, 778 (1.2%) concerned 967 adverse reactions reported to be related to CAM products. The number of reports between 1987 and 2006 are shown in Figure 1. In the 778 reports, 249 different suspected adverse reactions were identified and 175 different CAM substances were involved as suspected agents. Of these 778 reports 539 (69%) involved a female subject. The age of all subjects ranged between 0 and 99 years with a median age of 53 years. The typical reporter was a male senior physician aged between 41 and 50 years (Table 1).

The ten most frequently suspected CAM substances were found in 58% of the reports. Common agents were purple coneflower (*Echinacea purpurea*) ($n = 63$; 8.1%), purple coneflower + siberian ginseng (*Eleutherococcus senticosus*) + malabar nut (*Adhatoda vasica*) ($n = 57$; 7.3%), ginkgo leaf (*Ginkgo biloba*) ($n = 52$; 6.7%) and St John's wort (*Hypericum perforatum*) ($n = 44$; 5.6%) (Table 2). The most frequently reported adverse reactions

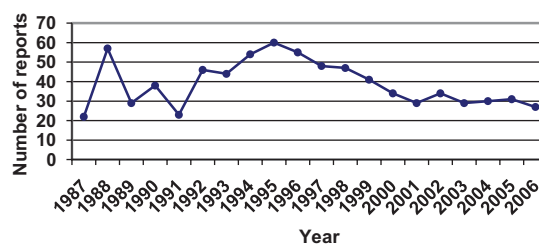


Figure 1. Number of reports of suspected adverse events associated with CAM (complementary and alternative medicine) substances received by the Medical Product Agency in Sweden between 1987 and 2006

SPONTANEOUSLY REPORTED CAM RELATED ADVERSE REACTIONS

Table 1. Characteristics of 778 reporters of suspected ADR to the Swedish adverse drug reaction database (SWEDIS) between January 1987 and December 2006

Reporters	Total number of reports (%)	Reports per 10000 reporter category and years	Number of females* (%)	Age years median [†] (range)
Senior physician	587 (75)	10.5	218 (37)	45 (27–70)
Junior physician	109 (14)	27.7	57 (52)	37 (24–64)
Pharmacists	31 (4)	4.0	24 (77)	55 (41–66)
Drug industry staff	15 (2)	NA	1 (0.7)	36 (33–62)
Nurse	8 (1)	0.03	8 (100)	45 (39–57)
Dentist	2 (0.3)	0.09	1 (50)	58 (58–58)
Medical student	1 (0.1)	NA	1 (100)	32 (32–32)
Unknown	25 (3)		12 (48)	42 (51–26)
All	778 (100)	NA	322 (41)	45 (24–60)

Abbreviation: NA, not available.

*The sex of the reporter was unknown in 14 reports.

[†]The age of the reporter was unknown in 60 reports.

were urticaria ($n = 65$; 8.3%), exanthema ($n = 58$; 7.4%), contact dermatitis ($n = 45$; 5.7%) and angioedema ($n = 35$; 4.4%) (Table 3). In 221 (28%) reports, at least one serious suspected adverse reaction was described, the most frequent being pulmonary embolism ($n = 14$; 1.7%), mixed liver reaction ($n = 22$; 2.8%) and anaphylactic reaction ($n = 16$; 2.0%). In total 25 cases of venous thromboembolism were reported. Of these, shark liver oil was implicated as a suspected agent in 15 cases (nine cases of pulmonary embolism, five cases of venous thrombosis in leg and one case of thrombosis in retinal veins). The age of these 15 subjects ranged between 12 and 73 years. In 4 of the 15 cases a malignant disease was reported. Among all 778 cases the adverse reaction had a fatal outcome in 11 (1.41%) cases. In Table 4 five cases (0.64%) where the causality between the ADR and the CAM substances was assessed as at least possible according to WHO criteria¹³ are presented. Only in one of these cases a CAM substance was the sole suspected agent. In that case a fatal liver necrosis was reported in 28-year old male who used *Purple cone flower* 5 days a week for 6 months, instead of the recommended dose and duration of use in association with cold symptoms. No obvious other cause for the liver disorder was identified in this case. In 38 cases a CAM-drug interaction and in one case a CAM-CAM interaction (fish oil and ginkgo leaf) was reported. The 35 cases where causality was assessed as at least possible according to WHO criteria¹³ are shown in Table 5. The most frequent interactions involved warfarin and St John's wort. These interactions resulted in increased INR (International Normalised Ratio). Moreover there were three reports of pregnancy in women who had used oral contraceptives concomitantly with St John's wort. Two of these concerned combined oral contraceptives, which included ethinylestradiol and desogestrel.

DISCUSSION

This study presents the pattern of reported CAM related adverse reactions in Sweden during a 20-year period. The CAM related adverse reactions constituted 1.2% of all reports in the database, a figure that is higher than the corresponding figure of 0.5% of the WHO database of adverse drug reactions. The latter figure was based on a compilation of reports from 55 countries between 1968 and 1997.¹⁴

In this study common CAM-substances suspected of having caused the reported adverse reaction were purple cone flower, ginkgo leaf, shark liver oil, St John's wort, coenzyme Q10 and tea tree oil (*Melaleuca alternifolia*). All these substances have a widespread use in the Swedish population except for shark liver oil that has had a limited use since 1990 (see below). Although a variety of adverse reactions affecting many organ systems were reported, skin and hypersensitivity reactions dominated the panorama, with urticaria, exanthema, contact dermatitis as the reactions most commonly reported. Our findings are in agreement with those reported in a study based on the WHO adverse drug reaction database.¹⁴ In that study skin reactions such as pruritus, rash and urticaria were most frequently reported. In a study of spontaneous reports of suspected adverse reactions in Italy between 2002 and 2007 skin disorders, gastrointestinal disorders and psychiatric disorders were the ADR groups most commonly reported.¹⁶ Of the serious reactions found in our study pulmonary embolism, mixed liver reaction and anaphylactic reaction were most frequently reported. Moreover, in 11 cases the outcome was fatal. Some of the reported ADRs in this study might have been associated with misuse of CAM products such as acute or chronic

Table 2. CAM substances with a minimum of 5 ADR reports* registered in the Swedish adverse drug reaction database (SWEDIS) between January 1987 and December 2006

Suspected CAM substance	Number of reports (%) n = 778	ADRs
Purple coneflower (<i>Echinacea. Purpurea</i>) [†]	63 (8.1)	Exanthema (13), urticaria (11), increased hepatic enzymes (5), angioedema (4), elevated transaminase ALP/GT (2), liver necrosis (2), various (26)
Purple coneflower + siberian ginseng (<i>Eleutherococcus senticosus</i>) + Malabar nut (<i>Adhatoda vasica</i>) [‡]	57 (7.3)	Urticaria (16), angioedema (14), anaphylactic reaction (7), exanthema (5), increased hepatic enzymes (2), fever (2), various (11)
Ginkgo leaf (<i>Ginkgo biloba</i>)	52 (6.7)	Exanthema (9) haemorrhage (4), urticaria (3), headache (3), palpitations (2), tachycardia (2), vasculitis (2), nausea (2), convulsions (2), various (23)
St John's wort (<i>Hypericum perforatum</i>)	44 (5.6)	Increased prothrombin (10), urticaria (4), unintended pregnancy (4), pulmonary embolism (2), thrombocytopenia (2), dizziness (2), increased therapeutic effect (2), various (18)
Shark liver oil	42 (5.3)	Pulmonary embolism (9), thrombosis leg (5), fever (3), thrombocytopenia (3), exanthema (3), urticaria (2), leukopenia (2), thrombocytosis (2), hepatitis (2), elevated transaminases (2), various (9)
Coenzyme Q10	42 (5.3)	Increased prothrombin (5), exanthema (3), decreased prothrombin (2), erythema multiforme (2), pulmonary embolism (2), leukopenia (2), mixed liver reaction ¹⁵ (2), elevated transaminases ALP/GT (2), fever (2), vasculitis (2), various (18)
Korean ginseng (<i>Panax ginseng</i>)	42 (5.3)	Angioedema (3), urticaria (3), erythema multiforme (2), headache (2), nausea (2), elevated transaminases ALP/GT (2), elevated transaminases (2), anxiety (2), various (24)
Tea tree oil (<i>Melaleuca alternifolia</i>)	41 (5.2)	Contact dermatitis (27), exanthema (5), eczema (4), various (5)
Black cohosh (<i>Actaea racemosa</i>)	38 (4.8)	Endometrial hyperplasia (6), bleeding gynaecologic (4), menstrual disorder (3), increased blood pressure (3), elevated transaminases (3), other various hepatic reactions (3), various (16)
Fish oil	32 (4.1)	Elevated transaminases ALP/GT (3), angioedema (2), eczema (2), hypercalcaemia (2), increased creatinine (2), hepatitis (2), various (19)
Purple cone flower + wild indigo (<i>Baptisia tinctoria</i>) + thuja (<i>Thuja. occidentalis</i>)	17 (2.1)	Fever (3), urticaria (3), angioedema (2), various (9)
Saw palmetto (<i>Serenoa repens</i>)	17 (2.1)	Decreased prothrombin (5), thrombocytopenia (2), vertigo (2), various (8)
Evening primrose oil (<i>Oenothera biennis</i>)	15 (1.9)	Thrombosis venous (2), concentration impaired (2), various (15)
Cape aloe (<i>Aloe vera</i>)	15 (1.9)	Eczema (2), palpitations (2), hepatitis (2), various (9)
European mistletoe (<i>Viscum album</i>)	14 (1.7)	Anaphylactic reaction (3), irit (2), various (9)
Ginseng [§]	14 (1.7)	Exanthem (2), mixed liver reaction (2), elevated transaminases ALP/GT (2), various (8)
Thymus extract	13 (1.6)	Application site reaction (5), fever (2), soft tissue abscess (2), various (4)
Dandelion (<i>Taraxacum officinalis</i>) + bearberry (<i>Arctostaphylos uva ursi</i>) +, peppermint (<i>Mentha Piperita</i>)	10 (1.2)	Hypokalaemia (2), various (8)
Bee wax + spruce resin	7 (0.9)	Contact dermatitis (5), eczema (2).
Magnolia Vine (<i>Schisandra chinensis</i>)	7 (0.9)	Various ADRs
Eucalyptus + (peppermint)	6 (0.7)	Contact dermatitis (5), eczema (1).
Garlic (<i>Allium sativum</i>)	6 (0.7)	Liver reactions (3), other (3)
Horsetail (<i>Equisetum arvense</i>)	6 (0.7)	Various ADRs
Soy beans	5 (0.6)	Various ADRs

Abbreviation: CAM, complementary and alternative medicine; ADRs, adverse drug reactions; GT, gamma-glutamyltransferase (liver enzymes); ALP, phosphatase alkaline increased.

*Causality was not assessed and the suspected ADRs are not necessarily associated with the reported CAM substances.

[†]14 different products were reported, Echinagard 34 reports, Echinaforce 7 reports, Friggs echinacea 4 reports, Echinacea 5 reports, other 13 reports.

[‡]Fifty-one of 57 reports concerned the product Kan Jang.

[§]A substance was assigned as ginseng if not stated that panax ginseng was in the product.

^{||}Mixed liver reaction was defined according to Benichou.¹⁵

overdoses of self-selected CAM products. Such use may in part be explained by the belief that natural remedies are safe due to the natural origin.⁶

Purple cone flower derived from several species of a flowering plant and has become increasingly used to relieve symptoms of cold. In general purple cone flower has been considered relatively safe^{17,18}

although concerns over allergic reactions have previously been reported.^{7,18} In this study we found several cases of exanthema, urticaria and anaphylaxis reported in association with use of purple cone flower products which give further support for the occurrence of hypersensitivity reactions in relation to purple cone flower products. Atopic individuals have been

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Table 3. CAM substance–ADR* combinations with a minimum of 10 reports registered in the Swedish adverse drug reaction database (SWEDIS) between January 1987 and December 2006

ADRs	Number of reports (%) n = 778	Suspected CAM substance
Skin reactions		
Urticaria	65 (8.3)	Purple coneflower (<i>Echinacea purpurea</i>) + siberian ginseng (<i>Eleutherococcus senticosus</i>) + malabar nut (<i>Adhatoda vasica</i>) (16), purple coneflower (11), St John's wort (<i>Hypericum perforatum</i>) (4), Korean ginseng (<i>Panax ginseng</i>) (3), ginkgo leaf (<i>Ginkgo biloba</i>) (3), purple coneflower, wild indigo (<i>Baptisia tinctoria</i>), thuja (<i>Thuja occidentalis</i>) (3), pollen extract (2), hawthorn (<i>Crataegus oxyacantha</i>) + peppermint (<i>Mentha Piperita</i>) + paprika+ seed of pumpkin + milfoil (<i>achillea millefolium</i>) + rosemary (<i>Rosmarinus officinalis</i>) + vitamins (2), fish oil (2), shark liver oil (2), various substances (17)
Exanthema	58 (7.4)	Purple coneflower (13), ginkgo leaf (9), purple coneflower + siberian ginseng + malabar nut (5), tea tree oil (<i>Melaleuca alternifolia</i>) (5), shark liver oil (3), Coenzyme Q10 (3), pollen extract (2), ginseng (2), various substances (16)
Contact dermatitis	45 (5.7)	Tea tree oil (27), spruce, bee wax (5), broad-leaved paperbark (<i>Melaleuca Quinquenervia</i>) + peppermint oil (5), bee wax (2), arnica (<i>Arnica montana</i>) (2), various substances (4)
Angioedema	35 (4.4)	Purple coneflower + siberian ginseng + malabar nut (14), purple coneflower (4), Korean ginseng (3), purple coneflower + wild indigo (<i>Baptisia tinctoria</i>) + thuja (2), fish oil (2), various substances (10)
Pruritus	28 (3.5)	Ginkgo leaf (7), purple coneflower + wild indigo + thuja (2), pollen extract (2), siberian ginseng (2), tea tree oil (2), various substances (13)
Erythema multiforme	12 (1.5)	Coenzyme Q 10 (2), Korean ginseng (2), various substances (8)
Liver and biliary system disorders		
Hepatic enzymes increased	31 (3.9)	Purple coneflower (5), black cohosh (4), shark liver oil (2), purple coneflower + siberian ginseng + malabar nut (2), various substances (18)
Transaminase ALP/GT elevated	26 (3.3)	Valerian (<i>Valeriana officinalis</i>) (5), fish oil (3), horsetail (2), unspecified homeopathic drug (2), Korean ginseng (2), Purple coneflower (2), ginseng (2), pollen extract (2), Coenzyme Q10 (2), various substances (4)
Mixed liver reaction ¹⁵	22 (2.8)	Ginseng (2), fish oil (2), Coenzyme Q10 (2), green tea extract (2), ginkgo leaf (2), various substances (12)
Hepatitis	12 (1.5)	Cape aloe (<i>Aloe vera</i>) (2), shark liver oil (2), fish oil (2), various substances (6)
General symptoms		
Fever	20 (2.5)	Unspecified homeopathic drug (3), shark liver oil (3), pollen extract (2), purple coneflower + siberian ginseng + malabar nut (3), European mistletoe (2), Coenzyme Q10 (2), various substances (5)
Anaphylactoid reaction	16 (2.0)	Purple coneflower + siberian ginseng + malabar nut (7), European mistletoe (<i>Viscum album</i>) (3), various substances (6)
Headache	12 (1.5)	Ginkgo leaf (7), Korean ginseng (2), various substances (3)
Blood disorders		
Prothrombin increased	20 (2.5)	St John's wort (10), Coenzyme Q10 (5), various substances (5)
Bleeding gynaecologic	10 (1.2)	Black cohosh (6), various substances (4).
Prothrombin decreased	10 (1.2)	Saw palmetto (<i>Serenoa repens</i>) + seed of pumpkin (5), Coenzyme Q10 (2), purple coneflower (2), various substances (1)
Cardiovascular disorders		
Pulmonary embolism	14 (1.7)	Shark liver oil (9), St John's wort (2), Coenzyme Q10 (2), various substances (1)
Palpitations	11 (1.4)	Cape aloe (2), sou tsian (2), Ginkgo leaf (2), various substances (5)
Gastro-intestinal disorders		
Abdominal pain	12 (1.5)	Purple coneflower + siberian ginseng + malabar nut (2), various substances (10)
Neurologic disorders		
Vertigo	11 (1.4)	Saw palmetto (2), various substances (9)

Abbreviation: CAM, complementary and alternative medicine; ADRs, adverse drug reactions; GT, gamma-glutamyltransferase (liver enzymes); ALP, phosphatase alkaline increased.

*Causality was not assessed and the suspected ADRs are not necessarily associated with the reported CAM substances. More than one CAM substance/drug could be suspected to have contributed to the reaction.

considered over-represented in those experiencing these reactions¹⁹ although one cannot rule out that there are differences in this respect between different purple cone flower products. In this study we also found that purple cone flower was associated with a number of liver reactions such as increased hepatic enzymes, liver necrosis and decreased prothrombin. In one case a fatal liver necrosis occurred in a 28-year old

male who used purple cone flower for several months instead of the recommended dose and duration of use in association with cold symptoms. No other obvious cause for the liver disorder was identified in that case. In this case the CAM substance was the sole suspected agent. A few liver and biliary adverse reactions have been reported previously within other spontaneous reporting programmes¹⁸ but very limited information

Table 4. Cases where a CAM substance (alone or in combination with conventional pharmaceutical drugs) was suspected to cause or contribute to a fatal ADR* and registered in the Swedish adverse drug reaction database (SWEDIS) between January 1987 and December 2006

ADRs	Suspected substances	Gender	Age
Mixed liver reaction, hypercalcaemia, creatinine increased	Shark liver oil, cyclophosphamide, bleomycin, etretinate, mesna	Male	64
Bleeding	Thymus extract, dicoumarol	Male	77
Arterial cerebral thrombosis	Shark liver oil, cisplatin, etoposide	Male	54
Coagulation disorder	Fish oil, acetylsalicylic acid	Male	68
Liver necrosis	Purple coneflower (<i>Echinacea purpurea</i>)	Male	28

*Only ADRs where the causality was assessed as at least possibly¹³ related to a CAM substance (alone or in combination with conventional pharmaceutical drugs) were included.

regarding these cases is available. In order to further elucidate the association between purple cone flower and liver reactions more studies are needed.

Ginkgo leaf is used primarily to alleviate symptoms in old age such as memory impairment but is also used in the management of intermittent claudication.^{7,20} Although adverse effects are usually mild, transient and reversible, ginkgo leaf may potentiate the anti-

platelet activity²⁰ and cause prolongation of bleeding time, thus increasing the risk of haemorrhage.²¹ We found four reports of bleedings where ginkgo leaf was a suspected agent for the reaction with further supports that this association should be studied further.

Shark liver oil contains a number of substances including alkylglycerol and squalmine, both of which are believed to act as potential complements to

Table 5. Cases, where a drug/CAM or CAM/CAM interaction was suspected to have caused an ADR*, and registered in the Swedish adverse drug reaction database (SWEDIS) between January 1987 and December 2006

ADR	Suspected CAM substance	Suspected pharmaceutical substance	Number of reports
Pharmacokinetic interactions			
Decreased prothrombin	Coenzyme Q10	Coumarin acid	2
Increased prothrombin	Coenzyme Q10	Warfarin	2
Increased prothrombin	Purple coneflower (<i>Echinacea purpurea</i>)	Warfarin	1
Increased prothrombin	Purple coneflower + siberian ginseng (<i>Eleutherococcus senticosus</i>) + malabar nut (<i>Adhatoda vasica</i>)	Warfarin	1
Increased prothrombin	Fish oil	Warfarin	1
Increased lithium concentration	Ginkgo leaf (<i>Ginkgo biloba</i>)	Lithium	1
Increased prothrombin	Saw palmetto (<i>Serenoa repens</i>)	Warfarin	1
Decreased prothrombin	Saw palmetto + seed of pumpkin	Warfarin	4
Increased prothrombin	St John's wort (<i>Hypericum perforatum</i>)	Warfarin	9
Decreased therapeutic response/pregnancy	St John's wort	Ethinylestradiol/levonorgestrel	2
Decreased therapeutic response/pregnancy	St John's wort	Levonorgestrel	1
Decreased therapeutic response/pregnancy	St John's wort	Ethinylestradiol/desogestrel	1
Decreased therapeutic response/pregnancy	St John's wort	Atorvastatin	1
Decreased therapeutic response/pregnancy	St John's wort	Clozapine	1
Pharmacodynamic interactions			
Bleeding	Purple coneflower + wild indigo (<i>Baptisia tinctoria</i>) + thuja (<i>Thuja occidentalis</i>)	Warfarin	1
Decreased therapeutic response	Horsetail (<i>Equisetum arvense</i>)	Tamoxifen	1
Bleeding	Fish oil	Warfarin	1
Bleeding	Fish oil	Acetylsalicylic	1
Decreased therapeutic response	Fish oil	Warfarin	1
Bleeding	Fish oil and Ginkgo leaf [†]		1
Hyperglycaemia	Magnolia Vine (<i>Schisandra chinensis</i>) + siberian ginseng + arctic root (<i>Rhodiola rosea</i>)	Insulin	1

Abbreviations: CAM, complementary and alternative medicine; ADRs, adverse drug reactions.

*Only ADRs where the causality was assessed as at least possibly related to a CAM substance were included.

[†]CAM/CAM interaction.

traditional cancer treatment and as immune boosting agents.²² Noteworthy in 9 of the 15 reported cases of pulmonary embolus in total, shark liver oil was implicated as a suspected agent. Shark liver oil was also associated with venous thrombosis in the leg (five cases) and thrombosis in retinal veins (one case). Although shark liver oil is regarded as safe, very limited safety information has been published. All reports found in the Swedish spontaneous reporting system concerned adverse events occurring between 1987 and 1991 during treatment with the shark liver oil product Ecomer. Due to these and other reports received by the MPA of serious adverse events such as liver reactions (three cases), the manufacturer withdrew Ecomer in Sweden in 1990 following legal procedures.²³ Nevertheless, the product was not withdrawn from other countries. Moreover, other shark liver oil products have been and are still marketed in Sweden and elsewhere. Since shark liver oil products may be used as an adjunctive agent in cancer therapy it may be possible that venous thromboembolism is secondary to a malignant disease rather than the use of shark liver oil. However, a malignant disease was only reported in 4 of the 15 cases with venous thromboembolism occurring during use of shark liver oil.

Tea tree oil, extracted from *M. alternifolia*, is a widely used agent with suggested antimicrobial, anti-inflammatory and anti-cancer effects. Tea tree oil was associated with skin reaction such as contact dermatitis, exanthema and eczema. Although it is generally considered that the topical use of the oil is relatively safe,^{7,24} we identified 27 cases of contact dermatitis after use of tea tree oil. In an Australian study of retrospectively reviewed patch test data over a 4.5-year period at a dermatological clinic 41 cases of positive reactions to oxidised tea tree oil of 2320 people patch-tested were identified, giving a prevalence of 1.8%.²⁵ In 41% of the patients a tea tree oil reaction was considered relevant to the presenting dermatitis. Allergic reactions to tea tree oil occur in predisposed individuals and have been associated with various oxidation products that are formed by exposure of the oil to light and/or air.

Cimicifuga racemosa (also known as black cohosh or squawroot) is considered a safe alternative for women in whom oestrogen therapy is contraindicated.²⁶ The scientific support for these claims is however limited.²⁷ Several reports of endometrial hyperplasia (six reports), gynaecologic bleeding (four reports) and menstrual disorder (three reports) in association with black cohosh were found in the Swedish database of adverse drug reactions. These reports are in contrast with studies showing that black cohosh used

alone or as part of a multibotanical product, had no effects on vaginal epithelium, endometrium or reproductive hormones.^{28,29} In addition, several reports of different adverse liver reactions in subjects using black cohosh have been received by authorities in several countries, including six reports from Sweden (Table 2).

In the Swedish pharmacovigilance database a total of 39 drug interactions were identified in this study. In general many reports of herb-induced interactions lack important documentation on temporal relations and concomitant drug use, therefore are many of them inconclusive. Fifteen of the 35 reports, where causality was assessed as at least possible, involved use of St John's wort. Of these, 11 concerned decreased effect of warfarin and with an increase in INR values and 3 reports of pregnancy in females using oral contraceptives. Interactions between prescription medicines and St John's wort are well recognised and the mechanism is through induction of the cytochrome P450 enzymes.³⁰

Although spontaneous reporting of possible adverse reactions by health care professionals is one of the fundamental methods in pharmacovigilance³¹ a number of limitations should be acknowledged when interpreting such data. Information in the reports is often incomplete making it difficult or impossible to establish causal relationships between a CAM product and an event. There are also problems with categorising CAM products. Several different names are used for the same herbal product and different herbal products may have the same name. Moreover, herbal products may differ considerably regarding the content of pharmacologically active chemicals and identified safety problems may not be relevant for other similar products. Moreover, there is a substantial under-reporting of adverse events and the reporting is often skewed. Adverse reactions and drug interactions related to CAM substances are often unrecognised.³² Clinicians often do not ask the patients about CAM use, patients do not always regard CAM use as important and often do not perceive CAM substances as medicines. In one study 72% had not informed their caregivers about their CAM use.³³ In addition a widespread knowledge may be lacking among clinicians that adverse drug reactions and drug interactions related to CAM substances can and should be reported. Of all reports received during the study period approximately 1% concerned a reaction where at least one CAM substance was a suspected agent. Considering the wide use, this reporting rate of CAM related adverse reactions seems rather low.

To better capture new and previously unrecognised CAM related adverse reactions a more frequent

KEY POINTS

- In approximately 1% of adverse drug reactions reported to the national Swedish pharmacovigilance system a complementary and alternative medicine (CAM) product is involved in the reaction.
- Purple coneflower (*Echinacea purpurea*), Ginkgo leaf (*Ginkgo biloba*) and St John's wort (*Hypericum perforatum*) are the substances most often reported.
- Urticaria, exanthema, contact dermatitis and angioedema are the reaction most often reported.
- Pulmonary embolism, mixed liver reaction and anaphylactic reaction are the serious reactions most often reported.
- The reporting of CAM-related adverse drug reactions should be stimulating to further improve the safety monitoring of these products.

reporting of adverse events and drug interactions associated with CAMs is desirable. By stimulating the reporting the signal detection power of spontaneous reporting systems would increase. Others have suggested that new monitoring systems are needed since conventional health care providers are usually not involved in the patients' use of CAM substances.³⁴ Therefore it has been suggested that consumers and CAM providers should have the ability to report adverse events during such therapy. In Sweden a system with consumer reporting of adverse drug reactions was started in 2008. Similar systems are also available in several other countries.³⁵

CONCLUSION

Adverse reaction of CAM products is an important albeit neglected subject which deserves further systematic investigation. Spontaneously reported adverse drug reaction data could be used in monitoring the safety of these products. By analysing such data from Sweden we found a variety of CAM related adverse reactions that have previously been unrecognised or poorly documented and deserve further investigations. Of all adverse drug reaction reports submitted during the study period only 1% concerned a reaction where at least one CAM substance was a suspected agent. Considering the wide use of CAM substances the reporting rate of suspected ADRs appears to be rather low. By stimulating the reporting the ADR-signal detection power of spontaneous

reporting system may increase. It seems feasible that also consumers and CAM providers should have the ability to report adverse events during CAM-therapy.

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