

Spontaneously reported adverse reactions for herbal medicinal products and natural remedies in Sweden 2007-2015 - report from the Medical Products Agency, Drugs – Real World Outcomes, Erika Svedlund<sup>1</sup>, Maria Larsson<sup>2</sup> and Robert Hägerkvist<sup>1</sup>; <sup>1</sup>Department of Herbal Medicinal Products, Medical Products Agency, Uppsala, Sweden, <sup>2</sup>Department of Pharmacovigilance, Medical Products Agency, Uppsala, Sweden. Email: [robert.hagerkvist@mpa.se](mailto:robert.hagerkvist@mpa.se)

**Supplement table1.** WHO's causality criteria (<https://www.who-umc.org/media/2768/standardised-case-causality-assessment.pdf>) for the assessment of adverse drug reactions. Only reports rated as at least possible were included in the study (in green color).

<i>Certain</i>	a clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
<i>Probable/ Likely</i>	a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
<i>Possible</i>	a clinical event including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
<i>Unlikely</i>	a clinical event, including laboratory test abnormality with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
<i>Conditional/ Unclassified</i>	a clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment or the additional data are under examination.
<i>Unassessible/ Unclassifiable</i>	a report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

**Supplement table 2.** Serious reports from healthcare professionals.

Suspected substance	Number of reports	ADR (MedDRA PT)	Concomitant drugs
Black cohosh rhizome ( <i>Cimicifuga racemosa</i> L. Nutt.)	4	Transaminases increased Pancytopenia	lamotrigine, tramadol, paracetamol
		Transaminases increased Jaundice	anti-depressive drug (further information missing)
		Transaminases increased	methylscopolamine/codeine/morphine/noscapine/ /papaverine, esomeprazole, ranitidine
		Transaminases increased Gamma-glutamyltransferase increased Blood alkaline phosphatase increased Pyrexia Headache	naproxen
Gentian root, primula spp flowers, sorrel spp herb, elder flower, verbena herb ( <i>Gentiana lutea</i> L., <i>Primula</i> spp., <i>Rumex</i> spp., <i>Sambucus nigra</i> L., <i>Verbena officinalis</i> L.)	3	Suicide attempt Toxicity to various agents	paracetamol, bromhexine/ephedrine, ibuprofen
		Urticaria Angioedema Oral pruritus Erythema multiforme	
		Hepatitis toxic	
Pollen of maize, rye, cock's-foot, pine ( <i>Zea mays</i> L., <i>Secale cereal</i> L., <i>Dactylis glomerata</i> L., <i>Pinus sylvestris</i> L.)	2	Dizziness Fatigue Arrhythmia	fluoxetine
		Transaminases increased	
Purple coneflower herb, expressed juice ( <i>Echinacea purpurea</i> (L.) Moench)	2	Hepatobiliary disease	losartan/hydrochlorothiazide, paracetamol,
		Hypersensitivity	
Wild indigo root, pale coneflower root, purple coneflower root, white cedar herb ( <i>Baptisia tinctoria</i> (L.), <i>Echinacea pallida</i> (Nutt.) Nutt., <i>Echinacea purpurea</i> (L.) Moench, <i>Thuja occidentalis</i> L.)	1	Liver injury	bendroflumethiazide
Valerian root ( <i>Valeriana officinalis</i> L.)	1	Electrocardiogram QT prolonged Hypotension Intentional self-injury Toxicity to various	naproxen, omeprazol, oxycodone, paracetamol, oxazepam, naloxone/oxycodone

		agents	
Horse-chestnut seed ( <i>Aesculus hippocastanum</i> L.)	1	Dermatitis allergic Pruritus	
Fish oil	1	Cerebral infarction Atrial fibrillation	
Devil's claw root ( <i>Harpagophytum procumbens</i> DC)	1	Acute kidney injury	alfuzosin
St. John's wort ( <i>Hypericum perforatum</i> L.)	1	Thrombocytopenia	etanercept, methotrexate
Adhatoda leaves, purple coneflower root, eleutherococcus root ( <i>Justicia adhatoda</i> L., <i>Echinacea purpurea</i> (L.) Moench, <i>Eleutherococcus senticosus</i> (Rupr. et Maxim.) Maxim)	1	Anaphylactic chock Rash pruritic	
Thyme herb and marshmallow root ( <i>Thymus vulgaris</i> L. and/or <i>Thymus zygis</i> L., <i>Althea officinalis</i> L.)	1	Bronchospasm Dysphagia	metformin, paracetamol, sitagliptin
Saw palmetto fruit ( <i>Serenoa repens</i> (Bartram) Small)	1	Drug interaction Haematoma INR increased	dabigatran (also allopurinol, metoprolol, bendroflumetazid)
<i>Lactobacillus acidophilus</i> , <i>Bifidobacterium animalis</i> , <i>Lactobacillus bulgaricus</i> , <i>Streptococcus thermophilus</i> .	1	Abdominal pain upper Abdominal discomfort	oxycodone, bisoprolol, furosemide, cyanocobalamin, spironolactone, omeprazole, simvastatin, paracetamol, pregabalin, amoxicillin, warfarin, lactulose, aluminium hydroxide/magnesium carbonate/magnesium hydroxide, hydrocortisone, propylene glycol/ lactic acid, oxazepam
<b>Total</b>	<b>21</b>	<b>43</b>	

**Supplement table 3.** Serious reports from patients.

Suspected substance	Number of reports	ADR (MedDRA PT)	Concomitant drugs
Gentian root, primula spp flowers, sorrel spp herb, elder flower, verbena herb ( <i>Gentiana lutea</i> L., <i>Primula spp.</i> , <i>Rumex spp.</i> , <i>Sambucus nigra</i> L., <i>Verbena officinalis</i> L.)	4	Pruritus Urticaria Lip swelling Swelling face Cough Hypoaesthesia oral Asthma Pharyngeal hypoaesthesia	
		Dyspnoea	caffeine/acetylsalicylic acid
		Urticaria Palpitation	
		Dry mouth Hallucination Tinnitus	paracetamol, desogestrel/ethinylestradiol
Pollen of maize, rye, cock's-foot , pine ( <i>Zea mays</i> L., <i>Secale cereal</i> L., <i>Dactylis glomerata</i> L., <i>Pinus sylvestris</i> L.)	2	Pruritus generalised	loratadin
		Anaphylactic reaction	trimethoprim, omega-3, losaratan
St. John's wort ( <i>Hypericum perforatum</i> L.)	1	Confusional state Coordination abnormal Sensory loss Feeling hot Nausea Headache Memory impairment Fatigue Somnolence	
Purple coneflower herb and root ( <i>Echinacea purpurea</i> (L.) Moench)	1	Rash erythematous Hypotension Swelling face	ibuprofen, paracetamol
Candytuft, angelica root, German chamomile flower, caraway fruit, milk thistle fruit, lemon balm leaves, peppermint leaves, celandine herb, licorice root ( <i>Iberis amara</i> L., <i>Angelica archangelica</i> L., <i>Matricaria recutita</i> L., <i>Carum carvi</i> L., <i>Silybum marianum</i> (L.) Gaertn., <i>Melissa officinalis</i> L., <i>Mentha piperita</i> L., <i>Chelidonium majus</i> L., <i>Glycyrrhiza glabra</i> L.)	1	Abdominal pain upper	
Black cohosh rizhorne ( <i>Cimicifuga racemosa</i> L. Nutt.)	1	Pruritus Blisters Liver function tests abnormal White blood cell count increased	
Arctic root root ( <i>Rhodiola rosea</i> L.)	1	Asthenia Dizziness Fatigue Headache Learning disorder Memory impairment Nausea	

		Pain Paraesthesia	
Thyme herb and marshmallow root ( <i>Thymus vulgaris</i> L. and/or <i>Thymus zygis</i> L., <i>Althea officinalis</i> L.)	1	Dyspnoea	Terbutaline, drospirenone/ ethinylestradiol
Valerian root ( <i>Valeriana officinalis</i> L.)	1	Dry mouth Dry eye Mucosal dryness Dry skin Body temperature increased Heart rate increased Muscle disorder Arthropath Asthenia Blood pressure increased Hypohidrosis Tooth disorder	clemastine
<b>Total</b>	<b>13</b>	<b>55</b>	

**Supplement table 4.** Non-serious reports from healthcare professional.

Suspected substance	Number of reports	ADR (MedDRA PT)	Concomitant drugs		
Purple coneflower herb, expressed juice ( <i>Echinacea purpurea</i> (L.) Moench)	7	Oedema			
		Nausea			
		Dizziness			
		Cold sweat			
		Blood pressure decreased			
		Dyspnoea			
		Abdominal pain upper			
		Transaminases increased Blood alkaline phosphatase increased	prednisolone, azathioprine		
Pollen of maize, rye, cock's-foot , pine ( <i>Zea mays</i> L., <i>Secale cereal</i> L., <i>Dactylis glomerata</i> L., <i>Pinus sylvestris</i> L.)	4	Uterine haemorrhage			
		Transaminases increased	levothyroxine, gabapentin, zolpidem,		
		Transaminases increased	desloratadine		
		Transaminases increased	dexametason, bortezomib, pamidronic acid		
Valerian root ( <i>Valeriana officinalis</i> L.)	4	Drug interaction Drug ineffective	methadone		
		Fall Tremor	ibuprofen, tramadol		
		Nightmare			
		Dry skin Rash			
		Gentian root, primula spp flowers, sorrel spp herb, elder flower, verbena herb ( <i>Gentiana lutea</i> L., <i>Primula spp.</i> , <i>Rumex spp.</i> , <i>Sambucus nigra</i> L., <i>Verbena officinalis</i> L.)	3	Urticaria	
Oesophagitis	alendronic acid, atenolol, calcium/cholecalciferol				
Angioedema	loratadine				
Pollen of rye, timothy, maize ( <i>Secale cereale</i> L., <i>Phleum pratense</i> L., <i>Zea mays</i> L.)	3	Dyspepsia Sleep disorder			
		Drug therapeutic incompatibility	lithium (decreased Serum-lithium concentration), (also ginseng ( <i>Panax ginseng</i> C.A.Mey.), omega-3 )		
		Urticaria	saw palmetto fruit ( <i>Serenoa repens</i> (Bartram) Small)		
Thyme herb and marshmallow root ( <i>Thymus vulgaris</i> L. and/or <i>Thymus zygis</i> L., <i>Althea officinalis</i> L.)	3	Diarrhoea			
		Hypoaesthesia oral Lip swelling			
		Feeling hot Pruritus Swelling face			
		Devil's claw root ( <i>Harpagophytum procumbens</i> DC)	2	Transaminases increased	
		Muscular weakness Myalgia			
Saw palmetto fruit ( <i>Serenoa repens</i> (Bartram) Small)	2	Hypertension	enalapril, acetylsalicylic acid, amlodipine, furosemide, bisoprolol		
		INR increased	warfarin, paracetamol (also		

			metoprolol, nicotine, glyceryl trinitrate, fentanyl, simvastatin, enalapril)
Black cohosh rhizome ( <i>Cimicifuga racemosa</i> L. Nutt.)	2	Paraesthesia	cholecalciferol/calcium carbonate
		Tinnitus	sulfasalazine, hydroxychlorquine, methotrexate, folic acid, terbutaline, paracetamol, naproxen
Wild indigo root, pale coneflower root, purple coneflower root, white cedar herb ( <i>Baptisia tinctoria</i> (L.), <i>Echinacea pallida</i> (Nutt.) Nutt., <i>Echinacea purpurea</i> (L.) Moench, <i>Thuja occidentalis</i> L.)	2	Angioedema	omega-3
		Syncope	acetylsalicylic acid, cyanocobalamin
Fish oil	1	Hypertriglyceridaemia	atorvastatin, metformin, estradiol, loratadine, citalopram
Ginkgo leaves ( <i>Ginkgo biloba</i> L.)	1	Transaminases increased	glucosamine, zolmitriptan, desloratadine
Agnus castus fruit ( <i>Vitex agnus-castus</i> , L)	1	Urticaria	
Eleutherococcus roots and rhizome, schisandra fruit ( <i>Eleutherococcus senticosus</i> (Rupr. et Maxim) Maxim, <i>Schisandra chinensis</i> (Turcz.) Baill.	1	Angioedema Steven Johnson syndrome	levofloxacin, bendroflumethiazide, rosuvastatin
Two different suspected herbal medicinal products containing: 1. Black cohosh rhizome ( <i>Cimicifuga racemosa</i> L. Nutt.) 2. Arctic root root ( <i>Rhodiola rosea</i> , L)	1	Transaminases increased	levothyroxine, paracetamol, propranolol, zopiklon
Candytuft, angelica root, German chamomile flower, caraway fruit, milk thistle fruit, lemon balm leaves, peppermint leaves, celandine herb, licorice root ( <i>Iberis amara</i> L., <i>Angelica archangelica</i> L., <i>Matricaria recutita</i> L., <i>Carum carvi</i> L., <i>Silybum marianum</i> (L.) Gaertn., <i>Melissa officinalis</i> L., <i>Mentha piperita</i> L., <i>Chelidonium majus</i> L., <i>Glycyrrhiza glabra</i> L.)	1	Dyspepsia	
Arctic root root ( <i>Rhodiola rosea</i> , L)	1	Anxiety	citalopram, hydroxyzine, propiomazine
Valerian root ( <i>Valeriana officinalis</i> L.), Hop strobile	1	Abdominal pain	

<i>(Humulus lupulus L.),</i> Melissa leaves ( <i>Melissa</i> <i>officinalis L.</i> )			
<b>Total</b>	<b>40</b>	<b>53</b>	



**Supplement table 5.** Non-serious reports from patients.

Suspected substance	Number of reports	ADR	Concomitant drugs
Black cohosh rizhome ( <i>Cimicifuga racemosa</i> L. Nutt.)	8	Genital haemorrhage	
		Menorrhagia Abdominal pain upper Chromaturia Peripheral swelling Urine odor abnormal	
		Abdominal pain upper Chromaturia Peripheral swelling	
		Pruritus Urticaria	
		Pruritus	
		Heart rate irregular Palpitations	
		Abdominal pain upper Vomiting Diarrhea	
		Urticaria	
		Pollen of maize, rye, cock's-foot , pine ( <i>Zea mays</i> L., <i>Secale cereal</i> L., <i>Dactylis glomerata</i> L., <i>Pinus sylvestris</i> L.)	5
Depression Mental disorder Fat tissue increased			
Migraine Dizziness	citalopram		
Abdominal distension Feeling abnormal			
Somnolence Anxiety Dissociation	agomelatine		
St. John's wort ( <i>Hypericum perforatum</i> L.)	5	Panic attack Tinnitus Mouth swelling Swelling face Dyspnoea Speech disorder Tremor Hyperhidrosis Nausea Pallor	
		Eczema Pruritus	
		Aesthenopia Fatigue Headache Ocular hyperaemia Somnolence Vison blurred	budesonide
		Weight increase	
		Acne Pigmentation disorder Pruritus Erythema	
Purple coneflower, herb, expressed juice ( <i>Echinacea</i>	4	Hypersensitivity Oral herpes	

<i>purpurea</i> (L.) Moench)		Condition aggravated	
		Urticaria	
		Urticaria Pruritus generalised Peripheral swelling	
		Urticaria Pruritus Dry skin Swelling face Skin fissures Insomnia	hydroxyzine
Arctic root root ( <i>Rhodiola rosea</i> L.)	3	Dermatitis allergic Pruritus	
		Tremor Headache Nausea Malaise	
		Headache	etilefrine
Gentian root, primula spp flowers, sorrel spp herb, elder flower, verbena herb ( <i>Gentiana lutea</i> L., <i>Primula</i> spp., <i>Rumex</i> spp., <i>Sambucus nigra</i> L., <i>Verbena officinalis</i> L.)	2	Menorrhagia	
		Urticaria	etonogestrel/ethinylestradiol
Saw palmetto fruit ( <i>Serenoa repens</i> (Bartram) Small)	3	Erectile dysfunction	
		Testicular pain Penile pain	
		Anal pruritus	
Horse-chestnut seed ( <i>Aesculus hippocastanum</i> L.)	2	Thinking abnormal Nausea Headache Abnormal sensation in eye Overdose	Additional use of homemade tea and ointment from horse chestnut (bark and leaves) and <i>Andrographis paniculata</i> (unknown form)
		Limb discomfort Pain Pain in extremity Restless legs syndrome	
Valerian root ( <i>Valeriana officinalis</i> L.), Hop strobile ( <i>Humulus lupulus</i> L.), Melissa leaves ( <i>Melissa officinalis</i> L.)	2	Agitation Heart rate increased	
		Dizziness Fatigue Hallucination Abdominal pain upper Pollakiuria	levothyroxine, cholecalciferol
Echinacea (further information missing)	1	Abdominal pain Pain of skin Pruritus	
Candytuft, angelica root, German chamomile flower, caraway fruit, milk thistle fruit, lemon balm leaves, peppermint leaves, celandine herb, licorice root ( <i>Iberis amara</i> L., <i>Angelica archangelica</i> L., <i>Matricaria recutita</i> L., <i>Carum carvi</i> L., <i>Silybum</i>	1	Feeling drunk Disturbance in attention	methylphenidate

<i>marianum</i> (L.) Gaertn., <i>Melissa officinalis</i> L., <i>Mentha piperita</i> L., <i>Chelidonium majus</i> L., <i>Glycyrrhiza glabra</i> L.)			
Valerian root ( <i>Valeriana officinalis</i> L.)	1	Hyperhidrosis	
Devil's claw root ( <i>Harpagophytum procumbens</i> DC)	1	Ocular hyperaemia	glucosamine
Thyme herb and marshmallow root ( <i>Thymus vulgaris</i> L. and/or <i>Thymus zygis</i> L., <i>Althea officinalis</i> L.)	1	Flatulence	
<i>Lactobacillus acidophilus</i>	1	Vulvovaginal ulceration	
Ginkgo leaves ( <i>Ginkgo biloba</i> L.)	1	Blood pressure decreased Dizziness	
Adhatoda leaves, purple coneflower root, eleutherococcus root ( <i>Justicia adhatoda</i> L., <i>Echinacea purpurea</i> (L.) Moench, <i>Eleutherococcus senticosus</i> (Rupr. et Maxim.) Maxim)	1	Anxiety	paroxetine
<b>Total</b>	<b>42</b>	<b>108</b>	