

Asteraceae

General Information

The genera in the family of Asteraceae (Table 13) (formerly Compositae) include various types of asters (daisies), arnica, chamomile, goldeneye, marigold, snake-root, tansy, thistle, and wormwood.

Delayed hypersensitivity reactions to the Asteraceae (Compositae) can arise from sesquiterpene lactones. To detect contact allergy to sesquiterpene lactones, a mixture of lactones (alantolactone, costunolide, and dehydrocostus lactone) is used. However, Compositae contain other sensitizers, such as polyacetylenes and thiophenes. In a prospective study, the lactone mixture was complemented with a mixture of Compositae (containing ether extracts of arnica, German chamomile, yarrow, tansy, and feverfew) to detect contact allergy to Compositae (1). Of 346 patients tested, 15 (4.3%) reacted to the mixture of Compositae, compared with eight of 1076 patients (0.7%) who gave positive results with the lactone mixture, indicating the importance of the addition of Compositae allergens to the lactone mixture. However, the authors warned that patch-testing with these mixtures can cause active sensitization.

- Compositae dermatitis occurred in a 9-year-old boy with a strong personal and family history of atopy. Positive patch test reactions were 2+ for dandelion (*Taraxacum officinale*), false ragweed (*Ambrosia acanthicarpa*), giant ragweed (*Ambrosia trifida*), short ragweed (*Ambrosia artemisiifolia*), sagebrush (*Artemisia tridentata*), wild feverfew (*Parthenium hysterophorus*), yarrow (*Achillea millefolium*), and tansy (*Tanacetum vulgare*), and 1+ for *Dahlia* species and English ivy (*Hedera helix*) (2). Patch tests were negative for another 30 plants, including cocklebur (*Xanthium strumarium*), dog fennel (*Anthemis cotula*), fleabane (*Erigeron strigosus*), sneezeweed (*Helenium autumnale*), and feverfew (*Tanacetum parthenium*).

An Austrian study has re-confirmed the importance of testing with not only a mixture of Compositae and a mixture of sesquiterpene lactones, but also with additional plant extracts when there is continuing clinical suspicion of allergy to one of the Compositae (3). By using additional short ether extracts, the authors found two of five patients who had otherwise been overlooked.

Achillea millefolium

Achillea millefolium (yarrow) can cause contact dermatitis (4); a generalized eruption following the drinking of yarrow tea has also been reported (5).

- A female florist from North Germany, who ran a flower shop from 1954 to 1966 had to quit her job because of contact allergy to chrysanthemums and primrose. After a further 12 years she started to suffer occasionally from

Table 13 The genera of Asteraceae

<i>Acamptopappus</i> (goldenhead)
<i>Acanthospermum</i> (starburr)
<i>Achillea</i> (yarrow)
<i>Achyrrachaena</i> (blow wives)
<i>Acmella</i> (spotflower)
<i>Acourtia</i> (desert peony)
<i>Acroptilon</i> (hard heads)
<i>Adenocaulon</i> (trail plant)
<i>Adenostemma</i> (medicine plant)
<i>Adenophyllum</i> (dogweed)
<i>Ageratum</i> (whiteweed)
<i>Ageratina</i> (snakeroot)
<i>Agoseris</i> (agoseris)
<i>Almut aster</i> (alkali marsh aster)
<i>Amberboa</i> (amberboa)
<i>Amblyolepis</i> (amblyolepis)
<i>Amblyopappus</i> (amblyopappus)
<i>Ambrosia</i> (ragweed)
<i>Ampel aster</i> (climbing aster)
<i>Amphipappus</i> (chaffbush)
<i>Amphiachyris</i> (broomweed)
<i>Anacylus</i> (anacylus)
<i>Anaphalis</i> (pearly everlasting)
<i>Ancistrocarphus</i> (nest straw)
<i>Anisocoma</i> (anisocoma)
<i>Antennaria</i> (pussytoes)
<i>Anthemis</i> (chamomile)
<i>Antheropeas</i> (e aster bonnets)
<i>Aphanostephus</i> (doze daisy)
<i>Arctium</i> (burdock)
<i>Arctotheca</i> (capeweed)
<i>Arctotis</i> (arctotis)
<i>Argyroxiphium</i> (silver sword)
<i>Argyranthemum</i> (dill daisy)
<i>Argyrautia</i> (arhyrautia)
<i>Arnica</i> (arnica)
<i>Arnoglossum</i> (Indian plaintain)
<i>Arnoseris</i> (arnoseris)
<i>Artemisia</i> (sagebrush, wormwood)
<i>Asanthus</i> (brickell bush)
<i>Aster</i> (aster)
<i>Astranthium</i> (western daisy)
<i>Atrichoseris</i> (atrichoseris)
<i>Baccharis</i> (baccharis)
<i>Bahia</i> (bahia)
<i>Baileya</i> (desert marigold)
<i>Balduina</i> (honeycombhead)
<i>Balsamorhiza</i> (balsam root)
<i>Balsamita</i> (balsamita)
<i>Baltimora</i> (baltimora)
<i>Barkleyanthus</i> (willow ragwort)
<i>Bartlettia</i> (bartlettia)
<i>Bartlettina</i> (bartlettina)
<i>Bebbia</i> (sweetbush)
<i>Bellis</i> (bellis)
<i>Benitoa</i> (benitoa)
<i>Berkheya</i> (berkheya)
<i>Berlandiera</i> (green eyes)
<i>Bidens</i> (beggar ticks)
<i>Bigelowia</i> (rayless goldenrod)
<i>Blennosperma</i> (sticky seed)
<i>Blepharipappus</i> (blepharipappus)
<i>Blepharizonia</i> (blepharizonia)
<i>Blumea</i> (false ox tongue)

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Table 13 (Continued)

<i>Boltonia</i> (doll's daisy)	<i>Cynara</i> (cynara)
<i>Borrchia</i> (seaside tansy)	<i>Dahlia</i> (dahlia)
<i>Brickellia</i> (brickell bush)	<i>Delairea</i> (capeivy)
<i>Brickelliastrum</i> (brickell bush)	<i>Dendranthema</i> (arctic daisy)
<i>Buphthalmum</i> (ox eye)	<i>Dichaetophora</i> (dichaetophora)
<i>Cacaliopsis</i> (cacaliopsis)	<i>Dicoria</i> (twin bugs)
<i>Calendula</i> (marigold)	<i>Dicranocarpus</i> (dicranocarpus)
<i>Callilepis</i> (ox-eye daisy)	<i>Dimeresia</i> (dimeresia)
<i>Callistephus</i> (callistephus)	<i>Dimorphotheca</i> (cape marigold)
<i>Calotis</i> (calotis)	<i>Ditrichia</i> (ditrichia)
<i>Calycadenia</i> (western rosinweed)	<i>Doellingeria</i> (whitetop)
<i>Calycoseris</i> (tackstem)	<i>Doronicum</i> (false leopardbane)
<i>Calyptocarpus</i> (calyptocarpus)	<i>Dracopis</i> (coneflower)
<i>Canadanthus</i> (mountain aster)	<i>Dubautia</i> (dubautia)
<i>Carduus</i> (plumeless thistle)	<i>Dysodiopsis</i> (dog fennel)
<i>Carlina</i> (carline thistle)	<i>Dyssodia</i> (dyssodia)
<i>Carminatia</i> (carminatia)	<i>Eastwoodia</i> (eastwoodia)
<i>Carphephorus</i> (chaffhead)	<i>Eatonella</i> (eatonella)
<i>Carphochaete</i> (bristlehead)	<i>Echinacea</i> (purple coneflower)
<i>Carthamus</i> (distaff thistle)	<i>Echinops</i> (globe thistle)
<i>Castalis</i> (castalis)	<i>Eclipta</i> (eclipta)
<i>Celmisia</i> (celmisia)	<i>Egletes</i> (tropic daisy)
<i>Centaurea</i> (knapweed)	<i>Elephantopus</i> (elephant's foot)
<i>Centipeda</i> (centipeda)	<i>Eleutheranthera</i> (eleutheranthera)
<i>Centratherum</i> (centratherum)	<i>Emilia</i> (tasselflower)
<i>Chaenactis</i> (pin cushion)	<i>Encelia</i> (brittlebush)
<i>Chaetadelpha</i> (skeletonweed)	<i>Enceliopsis</i> (sunray)
<i>Chaetopappa</i> (least daisy)	<i>Engelmannia</i> (Engelmann's daisy)
<i>Chamaemelum</i> (dog fennel)	<i>Enydra</i> (swampwort)
<i>Chamaechaenactis</i> (chamaechaenactis)	<i>Erechtites</i> (burnweed)
<i>Chaptalia</i> (sun bonnets)	<i>Ericameria</i> (goldenbush)
<i>Chloracantha</i> (chloracantha)	<i>Erigeron</i> (fleabane)
<i>Chondrilla</i> (chondrilla)	<i>Eriophyllum</i> (woolly sunflower)
<i>Chromolaena</i> (thoroughwort)	<i>Erlangea</i> (erlangea)
<i>Chrysactinia</i> (chrysactinia)	<i>Eucephalus</i> (aster)
<i>Chrysoma</i> (chrysoma)	<i>Euchiton</i> (euchiton)
<i>Chrysanthemum</i> (daisy)	<i>Eupatorium</i> (thoroughwort)
<i>Chrysogonum</i> (chrysogonum)	<i>Eurybia</i> (aster)
<i>Chrysopsis</i> (golden aster)	<i>Euryops</i> (euryops)
<i>Chrysothamnus</i> (rabbit brush)	<i>Euthamia</i> (goldentop)
<i>Cichorium</i> (chicory)	<i>Evax</i> (pygmy cudweed)
<i>Cineraria</i> (cineraria)	<i>Facelis</i> (trampweed)
<i>Cirsium</i> (thistle)	<i>Filago</i> (cottonrose)
<i>Clappia</i> (clapdaisy)	<i>Fitchia</i> (fitchia)
<i>Clibadium</i> (clibadium)	<i>Flaveria</i> (yellowtops)
<i>Cnicus</i> (cnicus)	<i>Fleischmannia</i> (thoroughwort)
<i>Columbiadoria</i> (columbiadoria)	<i>Florestina</i> (florestina)
<i>Condylidium</i> (villalba)	<i>Flourensia</i> (tarwort)
<i>Conoclinium</i> (thoroughwort)	<i>Flyriella</i> (brickell bush)
<i>Conyza</i> (horseweed)	<i>Gaillardia</i> (blanket flower)
<i>Coreocarpus</i> (coreocarpus)	<i>Galinsoga</i> (gallant-soldier)
<i>Coreopsis</i> (tickseed)	<i>Gamochoaeta</i> (everlasting)
<i>Corethrogyne</i> (sand aster)	<i>Garberia</i> (garberia)
<i>Cosmos</i> (cosmos)	<i>Gazania</i> (gazania)
<i>Cotula</i> (waterbuttons)	<i>Geraea</i> (desertsunflower)
<i>Crassocephalum</i> (ragleaf)	<i>Gerbera</i> (Transvaal daisy)
<i>Crepis</i> (hawksbeard)	<i>Glyptopleura</i> (glyptopleura)
<i>Critonia</i> (thoroughwort)	<i>Gnaphalium</i> (cudweed)
<i>Crocidium</i> (spring gold)	<i>Gochnatia</i> (gochnatia)
<i>Croptilon</i> (scratch daisy)	<i>Grindelia</i> (gumweed)
<i>Crupina</i> (crupina)	<i>Guardiola</i> (guardiola)
<i>Cyanopsis</i> (knapweed)	<i>Guizotia</i> (guizotia)
<i>Cyanthillium</i> (ironweed)	<i>Gundelia</i> (gundelia)
<i>Cymophora</i> (cymophora)	<i>Gundlachia</i> (gundlachia)
	<i>Gutierrezia</i> (snakeweed)

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Table 13 (Continued)

Gymnosperma (gymnosperma)
Gymnostyles (burrweed)
Gynura (gynura)
Haploesthes (false broomweed)
Haplocarpha (onefruit)
Haplopappus (haplopappus)
Hartwrightia (hartwrightia)
Hasteola (false Indian plaintain)
Hazardia (bristleweed)
Hebeclinium (thoroughwort)
Hecastocleis (hecastocleis)
Hedypnois (hedypnois)
Helenium (sneezeweed)
Helianthell (helianthella)
Helianthus (sunflower)
Helichrysum (strawflower)
Heliopsis (heliopsis)
Heliomeris (false goldeneye)
Hemizonia (tarweed)
Hesperevax (dwarf-cudweed)
Hesperomannia (island aster)
Hesperodoria (glowweed)
Heteranthemis (ox eye)
Heterosperma (heterosperma)
Heterotheca (false golden aster)
Hieracium (hawkweed)
Holocarpha (tarweed)
Holozonia (holozonia)
Hulsea (alpinegold)
Hymenoclea (burrobrush)
Hymenopappus (hymenopappus)
Hymenothrix (thimblehead)
Hymenoxys (rubberweed)
Hypochoeris (cat's ear)
Hypochoeris (cat's ear)
Inula (yellowhead)
Ionactis (aster)
Isocarpha (pearlhead)
Isocoma (golden bush)
Iva (marsh elder)
Ixeris (ixeris)
Jamesianthus (jamesianthus)
Jaumea (jaumea)
Jefea (jefea)
Kalimeris (aster)
Koanophyllon (thoroughwort)
Krigia (dwarf dandelion)
Lactuca (lettuce)
Laennecia (laennecia)
Lagascea (lagascea)
Lagenifera (island daisy)
Lagophylla (hareleaf)
Lapsana (nipplewort)
Lapsanastrum (nipplewort)
Lasianthaea (lasianthaea)
Lasiospermum (cocoonhead)
Lasthenia (goldfields)
Launaea (launaea)
Layia (tidy tips)
Leibnitzia (sun bonnets)
Lembertia (lembertia)
Leontodon (hawkbit)
Lepidospartum (broom sage)
Lessingia (lessingia)

Leucanthemum (daisy)
Leucanthemella (leucanthemella)
Liatris (blazing star)
Lindheimera (lindheimera)
Lipochaeta (nehe)
Logfia (cotton rose)
Luina (silverback)
Lygodesmia (skeleton plant)
Machaeranthera (tansy aster)
Madia (tarweed)
Malacothrix (desert dandelion)
Malperia (malperia)
Mantisalca (mantisalca)
Marshallia (Barbara's buttons)
Matricaria (mayweed)
Megalodonta (water marigold)
Melampodium (blackfoot)
Melanthera (squarestem)
Micropus (cottonseed)
Microseris (silver puffs)
Mikania (hemp vine)
Monolopia (monolopia)
Monoptilon (desert star)
Montanoa (montanoa)
Mycelis (mycelis)
Neurolaena (neurolaena)
Nicolletia (hole-in-the-sand plant)
Nothocalais (prairie dandelion)
Oclemena (aster)
Olearia (daisy bush)
Oligoneuron (goldenrod)
Omalotheca (arctic cudweed)
Oncosiphon (oncosiphon)
Onopordum (cotton thistle)
Oonopsis (false goldenweed)
Oreochrysum (goldenrod)
Oreostemma (aster)
Orochaenactis (orochaenactis)
Osmadenia (osmadenia)
Osteospermum (daisy bush)
Packera (ragwort)
Palafoxia (palafox)
Parasenecio (Indian plantain)
Parthenice (parthenice)
Parthenium (feverfew)
Pascalina (Pascalina)
Pectis (cinchweed)
Pentachaeta (pygmy daisy)
Pentzia (pentzia)
Pericome (pericome)
Pericallis (ragwort)
Perityle (rock daisy)
Petasites (butterbur)
Petradoria (rock goldenrod)
Peucephyllum (pygmy cedar)
Phalacroseris (mock dandelion)
Phoebanthus (false sunflower)
Picradeniopsis (bahia)
Picris (ox tongue)
Picrothamnus (bud sagebrush)
Pinaropappus (rock lettuce)
Piptocarpha (ash daisy)
Piptocoma (velvet shrub)
Pityopsis (silk grass)
Platyschkuhria (basin daisy)

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Table 13 (Continued)

<i>Pleurocoronis</i> (pleurocoronis)	<i>Stephanomeria</i> (wire lettuce)
<i>Pluchea</i> (camphorweed)	<i>Stevia</i> (candyleaf)
<i>Polymnia</i> (polymnia)	<i>Stokesia</i> (stokesia)
<i>Porophyllum</i> (poreleaf)	<i>Struchium</i> (struchium)
<i>Prenanthes</i> (rattlesnake root)	<i>Stylocline</i> (nest straw)
<i>Prenantheella</i> (prenantheella)	<i>Symphytotrichum</i> (aster)
<i>Proustia</i> (proustia)	<i>Synedrella</i> (synedrella)
<i>Psacalium</i> (Indianbush)	<i>Syntrichopappus</i> (Fremont's gold)
<i>Psathyrotes</i> (turtleback)	<i>Tagetes</i> (marigold)
<i>Pseudogynoxys</i> (pseudogynoxys)	<i>Tamaulipa</i> (boneset)
<i>Pseudelephantopus</i> (dog's tongue)	<i>Tanacetum</i> (tansy)
<i>Pseudobahia</i> (sunburst)	<i>Taraxacum</i> (dandelion)
<i>Pseudoclapia</i> (false clap daisy)	<i>Tephrosia</i> (groundsel)
<i>Pseudognaphalium</i> (cudweed)	<i>Tetramolopium</i> (tetramolopium)
<i>Psilactis</i> (tansy aster)	<i>Tetranervis</i> (four-nerve daisy)
<i>Psilocarphus</i> (woolly heads)	<i>Tetradymia</i> (horsebrush)
<i>Psilostrophe</i> (paper flower)	<i>Tetragonotheca</i> (nerve ray)
<i>Pterocaulon</i> (blackroot)	<i>Thelesperma</i> (green thread)
<i>Pulicaria</i> (false fleabane)	<i>Thurovia</i> (thurovia)
<i>Pyrrhopappus</i> (desert chicory)	<i>Thymophylla</i> (pricklyleaf)
<i>Pyrocoma</i> (goldenweed)	<i>Tithonia</i> (tithonia)
<i>Rafinesquia</i> (California chicory)	<i>Tolpis</i> (umbrella milkwort)
<i>Raillardella</i> (raillardella)	<i>Tonestus</i> (serpentweed)
<i>Raillardiopsis</i> (raillardiopsis)	<i>Townsendia</i> (Townsend daisy)
<i>Rainiera</i> (rainiera)	<i>Tracyina</i> (Indian headdress)
<i>Ratibida</i> (prairie coneflower)	<i>Tragopogon</i> (goat's beard)
<i>Rayjacksonia</i> (tansy aster)	<i>Trichocoronis</i> (bugheal)
<i>Reichardia</i> (bright eye)	<i>Trichoptilium</i> (trichoptilium)
<i>Remya</i> (remya)	<i>Tridax</i> (tridax)
<i>Rhagadiolus</i> (rhagadiolus)	<i>Tripleurospermum</i> (mayweed)
<i>Rigiopappus</i> (rigiopappus)	<i>Tripolium</i> (sea aster)
<i>Rolandra</i> (yerba de plata)	<i>Trixis</i> (threefold)
<i>Roldana</i> (groundsel)	<i>Tussilago</i> (coltsfoot)
<i>Rudbeckia</i> (coneflower)	<i>Uropappus</i> (silver puffs)
<i>Rugelia</i> (Rugel's Indian plantain)	<i>Urospermum</i> (urospermum)
<i>Sachsia</i> (sachsia)	<i>Vancklevea</i> (vancklevea)
<i>Salmea</i> (bejuco de miel)	<i>Varilla</i> (varilla)
<i>Santolina</i> (lavender cotton)	<i>Venegasia</i> (venegasia)
<i>Sanvitalia</i> (creeping zinnia)	<i>Venidium</i> (venidium)
<i>Sartwellia</i> (glowwort)	<i>Verbesina</i> (crownbeard)
<i>Saussurea</i> (sawwort)	<i>Vernonia</i> (ironweed)
<i>Schkuhria</i> (false threadleaf)	<i>Viguiera</i> (goldeneye)
<i>Sclerocarpus</i> (bone bract)	<i>Wedelia</i> (creeping ox eye)
<i>Sclerolepis</i> (bog button)	<i>Whitneya</i> (whitneya)
<i>Scolymus</i> (golden thistle)	<i>Wilkesia</i> (iliau)
<i>Scorzonera</i> (scorzonera)	<i>Wollastonia</i> (watermeal)
<i>Senecio</i> (ragwort)	<i>Wyethia</i> (mule-ears)
<i>Sericocarpus</i> (whitop aster)	<i>Xanthisma</i> (sleepy daisy)
<i>Serratula</i> (plumeless sawwort)	<i>Xanthium</i> (cocklebur)
<i>Shinnersoseris</i> (beaked skeletonweed)	<i>Xanthocephalum</i> (xanthocephalum)
<i>Sigesbeckia</i> (St Paul's wort)	<i>Xylorhiza</i> (woody aster)
<i>Silphium</i> (rosinweed)	<i>Xylothamia</i> (desert goldenrod)
<i>Silybum</i> (milk thistle)	<i>Yermo</i> (desert yellowhead)
<i>Simsia</i> (bush sunflower)	<i>Youngia</i> (youngia)
<i>Smallanthus</i> (smallanthus)	<i>Zinnia</i> (zinnia)
<i>Solidago</i> (goldenrod)	
<i>Soliva</i> (burrweed)	
<i>Sonchus</i> (sow thistle)	
<i>Sphaeromeria</i> (chicken sage)	
<i>Sphagneticola</i> (creeping ox eye)	
<i>Spilanthes</i> (spilanthes)	
<i>Spiracantha</i> (dogwood leaf)	
<i>Stebbinsoseris</i> (silver puffs)	
<i>Stenotus</i> (mock goldenweed)	

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redness of the pharynx and stomachache after drinking tea prepared from yarrow and camomile. Skin tests were positive to chrysanthemum with cross-reactions to sunflower, arnica, camomile, yarrow, tansy, mugwort, and frullania (a lichen that does not occur in the Northern part of Germany). Patch-testing with primin showed high-grade hypersensitivity to Primula.

A. millefolium contains sesquiterpene lactones, polyacetyles, coumarins, and flavonoids. Extracts have often been used in cosmetics in concentrations of 0.5–10%. *A. millefolium* was weakly genotoxic in *Drosophila melanogaster*. In provocative testing, patients reacted to a mix of *Compositae* that contained yarrow, as well as to yarrow itself. In clinical use, a formulation containing a 0.1% extract was not a sensitizer and alcoholic extracts of the dried leaves and stalks of the flower were not phototoxic (6). However, positive patch tests to *A. millefolium* have been reported (7).

Anthemis species and *Matricaria recutita* (chamomile)

Chamomile is the vernacular name of *Anthemis* genus and *Matricaria recutita* (German chamomile, pinhead). The former are more potent skin sensitizers (delayed-type) than the latter, presumably because they can contain a higher concentration of the sesquiterpene lactone, anthecotullid. Cross-sensitivity with related allergenic sesquiterpene lactones in other plants is possible.

Adverse effects

Internal use of chamomile tea has been associated with rare cases of anaphylactic reactions (8) and its use in eye-washes can cause allergic conjunctivitis (9).

Arnica montana

Arnica montana (arnica) contains a variety of terpenoids and has mostly been used in the treatment of sprains and bruises but is also used in cosmetics.

Ingestion of tea prepared from *Arnica montana* flowers can result in gastroenteritis.

- A 27-year-old woman presented with a rapidly enlarging necrotic lesion on her face and left leg together with malaise and high fever (10). She reported that she had applied a 1.5% arnica cream to her face before these symptoms had occurred. The diagnosis was Sweet's syndrome elicited by pathergy to arnica. She was treated with prednisolone and her skin lesions disappeared within 3 weeks.

Of 443 individuals who were tested for contact sensitization, 5 had a positive reaction to *A. montana* and 9 to *Calendula officinalis* (marigold); a mixture of the two was positive in 18 cases (3). Sensitization was often accompanied by reactions to nickel, *Myroxylon pereirae* resin, fragrance mix, propolis, and colophon.

***Artemisia* species**

There are about 60 different species of *Artemisia*, of which the principal are *Artemisia absinthium*, *Artemisia annua*, *Artemisia cina*, and *Artemisia vulgaris*.

Artemisia absinthium

The volatile oil of *A. absinthium* (wormwood), which gives the alcoholic liqueur absinthe its flavor, can damage

the nervous system and cause mental deterioration. This toxicity is attributed to thujones (alpha-thujone and beta-thujone), which constitute 0.25–1.32% in the whole herb and 3–12% of the oil. Alcoholic extracts and the essential oil are forbidden in most countries.

Artemisia annua

Artemisia annua, known in China as Qinghaosu, contains artemisinin, which has antimalarial activity. Several derivatives of the original compound have proved effective in the treatment of *Plasmodium falciparum* malaria and are currently available in a variety of formulations: artesunate (intravenous, rectal, oral), arteminate (oral), artemisinin (intravenous, rectal, oral), dihydroartemisinin (oral), artemether (intravenous, oral, rectal), and artemotil (intravenous). Artemisinic acid (qinghao acid), the precursor of artemisinin, is present in the plant in a concentration up to 10 times that of artemisinin. Several semisynthetic derivatives have been developed from dihydroartemisinin (11).

Artemisia cina

Artemisia cina (wormseed) contains the toxic lactone, santonin, which was formerly used as an antihelminthic drug, but has now been superseded by other less toxic compounds.

Artemisia vulgaris

Artemisia vulgaris (common wormwood) contains the toxic lactone, santonin, which was formerly used as an antihelminthic drug, but has now been superseded by other less toxic compounds. Depending on the origin of the plant, 1,8-cineole, camphor, linalool, and thujone may all be major components. Allergic skin reactions (12) and abortive activity have been described.

Calendula officinalis

Calendula officinalis (marigold) contains a variety of carotenoids, saponins, steroids, sesquiterpenoids, and triterpenoids.

Of 443 individuals who were tested for contact sensitization, five had a positive reaction to *A. montana* and nine to *C. officinalis*; a mixture of the two was positive in 18 cases (3). Sensitization was often accompanied by reactions to nickel, *Myroxylon pereirae* resin, fragrance mix, propolis, and colophon.

Callilepis laureola

Callilepis laureola (impila, ox-eye daisy) contains the toxic compound atractyloside and related compounds. The plant is responsible for the deaths of many Zulu people in Natal, who use its roots as a herbal medicine.

Adverse effects

Necropsy records of 50 children who had taken herbal medicines made from *C. laureola* showed typical hepatic and renal tubular necrosis (13). In young Black children the plant causes hypoglycaemia, altered consciousness, and hepatic and renal dysfunction. This syndrome can be hard to distinguish from Reye's syndrome.

Acute renal insufficiency has been attributed to *C. lauroleola* (14).

Chrysanthemum vulgare

Chrysanthemum vulgare (common tansy) contains essential oils and thujone in such amounts that even normal doses can be neurotoxic (15).

Cynara scolymus

Cynara scolymus (artichoke) contains a variety of flavonoids, phenols, and sesquiterpenoids, including cynarapicrin, cynaratriol, cynarolide, and isoambrin. It has been used to lower serum cholesterol, with little evidence of efficacy (16).

Adverse effects

Two vegetable warehouse workers developed occupational rhinitis and bronchial asthma by sensitization to *C. scolymus* (17). Skin prick tests to artichoke were positive and IgE specific for artichoke was found. Nasal challenge with artichoke extract triggered a reduction in peak nasal inspiratory flow of 81 and 85%. One patient had a reduction in peak expiratory flow rate of up to 36% after exposure to artichoke in the workplace.

Allergic contact dermatitis (18) and occupational contact urticaria (19) have also been reported.

***Echinacea* species**

The three most commonly used species *Echinacea* are *E. angustifolia*, *E. pallida*, and *E. purpurea*. *Echinacea* is recommended for the prevention and treatment of the common cold.

Echinacea species (coneflower, black Sampson hedgehog, Indian head, snakeroot, red sunflower, scurvy root) have become increasingly popular, particularly for the prophylaxis and treatment and prevention of cold and flu symptoms. However, the claimed efficacy of *Echinacea* in the common cold has not been confirmed in a randomized, double-blind, placebo-controlled trial (20) or a systematic review (21). *Echinacea* is claimed to have antiseptic and antiviral properties and is under investigation for its immunostimulant action. The active ingredients are glycosides (echinacoside), polysaccharides, alkaloids, and flavonoids.

Adverse effects

Between July 1996 and November 1998, the Australian Adverse Drug Reactions Advisory Committee received 37 reports of suspected adverse drug reactions in association with *Echinacea* (22). Over half of these ($n = 21$) described allergic-like effects, including bronchospasm ($n = 9$), dyspnea ($n = 8$), urticaria ($n = 5$), chest pain ($n = 4$), and angioedema ($n = 3$). The 21 patients were aged 3–58 (median 31) years and 12 had a history of asthma ($n = 7$) and/or allergic rhinitis/conjunctivitis/hayfever ($n = 5$). *Echinacea* was the only suspected cause in 19 of the 21 cases. The symptoms began at variable times, within 10 minutes of the first dose to a few months, and all but two cases occurred

within 3 days of starting treatment. At the time of reporting 17 of the patients had recovered, 2 had not yet recovered, and the outcome was unknown in the other two cases.

A systematic review of all clinical reports of adverse events in clinical trials, post-marketing surveillance studies, surveys, spontaneous reporting schemes, and to manufacturers, the WHO, and national drug safety bodies has suggested that short-term use of *Echinacea* is associated with a relatively good safety profile, with a slight risk of transient, reversible, adverse events, of which gastrointestinal upsets and rashes occur most often (23). In rare cases, *Echinacea* is associated with allergic reactions, which can be severe.

Hematologic

Possible leukopenia has been associated with long-term use of *Echinacea* (24).

Skin

Recurrent erythema nodosum has been attributed to *Echinacea*.

- A 41-year-old man, who had taken *Echinacea* intermittently for the previous 18 months, had four episodes of erythema nodosum, preceded by myalgia and arthralgia, fever, headache, and malaise (25). The skin lesions resolved within 2–5 weeks and responded to oral prednisolone. He was advised to discontinue *Echinacea* and 1 year later remained free from further recurrence.

Echinacea has been reported to have caused a flare up of pemphigus vulgaris (26).

- A 55-year-old man with pemphigus vulgaris in remission self-administered *Echinacea* for an upper respiratory tract infection. Within 1 week he developed an acute exacerbation of the pemphigus vulgaris. Withdrawal of *Echinacea* resulted in improvement of his symptoms, but he had to be treated with prednisolone, azathioprine, and dapsone to achieve a partial remission.

The authors suggested that the immunostimulatory properties of *Echinacea* may have caused this flare up.

Immunologic

Intravenous administration of *Echinacea* has been associated with severe allergic reactions. Oral ingestion can cause allergic skin and respiratory responses (27).

Five cases of adverse drug reactions have been attributed to oral *Echinacea* extracts (28). Two of the patients had anaphylaxis and one had an acute attack of asthma. The authors also tested 100 atopic subjects and found that 20 of them, who had never before taken *Echinacea*, had positive reactions to skin prick tests.

An anaphylactic reaction to *Echinacea angustifolia* has been reported (29).

- A 37-year-old woman who took various food supplements on an irregular basis self-medicated with 5 ml of an extract of *E. angustifolia*. She had immediate burning of the mouth and throat followed by tightness of the chest, generalized urticaria, and diarrhea. She made a full recovery within 2 hours.

The basis for this anaphylactic reaction was hypersensitivity to *Echinacea*, confirmed by skin prick and RAST testing. However, others have challenged the notion of a causal relation in this case (30). Nevertheless, the author affirmed his belief that *Echinacea* was the causal agent and reported that at that time *Echinacea* accounted for 22 of 266 suspected adverse reactions to complementary medicines reported to the Australian Adverse Drug Reaction Advisory Committee (30).

Sjögren's syndrome has been attributed to *Echinacea* (31).

- A 36-year-old woman developed generalized muscle weakness (31). She was found to have hypokalemia, which was treated with electrolyte replacement. Her muscular complaints disappeared but she then complained of joint stiffness, dry mouth, and dry eyes. The diagnosis of Sjögren's syndrome was confirmed by laboratory tests.

She had been taking a herbal mixture that included *Echinacea*, which is known to stimulate the immune system, and the authors speculated that *Echinacea* had aggravated a pre-existing autoimmune disease.

Teratogenicity

Of 412 pregnant Canadian women who contacted a specialized information service between 1996 and 1998 with concerns about the use of *Echinacea* during pregnancy, 206 had already taken the remedy and the other 206 eventually decided not to use it (32). In the *Echinacea* group, 54% had taken it during the first trimester of pregnancy; 12 babies had malformations, six major and six minor. The figures in the control group were seven and seven respectively. Thus, there was no difference in the incidence of birth defects. However, the study lacked sufficient power to generate reliable data.

Eupatorium species

Several *Eupatorium* species, such as *Eupatorium cannabinum* (hemp agrimony) and *Eupatorium purpureum* (gravel root), have hepatotoxic potential due to the presence of pyrrolizidine alkaloids, which are covered in a separate monograph.

There is no evidence of pyrrolizidine alkaloids in *Eupatorium rugosum* (white snakeroot) but this plant also has poisonous properties, which are attributed to an unstable toxin called tremetol. Transfer from cow's milk to humans can produce a condition known as milk sickness, including trembles, weakness, nausea and vomiting, prostration, delirium, and even death.

Inula helenium

Large doses of the root of *Inula helenium* (elecampane) can cause vomiting, diarrhea, cramps, and paralytic symptoms.

Petasites species

Petasites species have hepatotoxic potential, owing to the presence of pyrrolizidine alkaloids, which are covered in a

separate monograph. Extracts of *Petasites hybridus* (butterdock, bog rhubarb, butterbur, butterdock) contain little in the way of these alkaloids (33). Butterbur has been used to treat allergic rhinitis and asthma and in the prevention of migraine.

Senecio species

Many species of *Senecio*, such as *Senecio jacobaea* (ragwort) and *Senecio longilobus* (thread leaf groundsel), contain hepatotoxic amounts of pyrrolizidine alkaloids (which are covered in a separate monograph). Honey made from *Senecio* plants also contains pyrrolizidine alkaloids (34).

Adverse effects

Veno-occlusive disease has been attributed to *Senecio* after chronic use (35,36).

- Hepatic veno-occlusive disease occurred in a 38-year-old woman who had occasionally consumed "Huamanripa" (*Senecio tephrosioides*) as a cough remedy for many years (37). She had abdominal pain, jaundice, and anasarca. A hepatic biopsy showed pronounced congestion with a centrilobular predominance, foci of necrosis, and in some areas a reversed lobulation pattern. During the next 13 months she was hospitalized four times with complications of portal hypertension.
- An infant developed hepatic veno-occlusive disease after having been fed a herbal tea known as gordolobo yerba, commonly used as a folk remedy among Mexican-Americans; there was acute hepatocellular disease and portal hypertension, which progressed over 2 months to extensive hepatic fibrosis (38).

In one case hepatic damage due to *Senecio* mimicked Reye's syndrome (39).

Silybum marianum

Silybum marianum (holy thistle, lady's thistle, milk thistle, St. Mary's thistle) has been used to treat liver problems, such as hepatitis, and prostatic cancer. It contains a variety of lignans, including silandrin, silybin, silychristin, silydianin, silymarin, and silymonin.

Adverse effects

- A 57-year-old Australian woman presented with a 2-month history of intermittent episodes of sweating, nausea, colicky abdominal pain, fluid diarrhea, vomiting, weakness, and collapse (40). She was taking ethinylestradiol and amitriptyline and had taken milk thistle for 2 months. A thorough check-up showed no abnormalities. On reflection she realized that all her attacks had invariably occurred after taking the milk thistle. She stopped taking it and had no symptoms until a few weeks later, when she tried another capsule and had the same symptoms.

This idiosyncratic reaction to milk thistle seems to be a rarity. The Australian authorities knew of only two other adverse drug reactions associated with milk thistle.

Immunologic

Anaphylactic shock has been reported after the use of a herbal tea containing an extract of the fruit of the milk thistle (41).

Drug-drug interactions

Indinavir

Milk thistle inhibits CYP3A4 and uridine diphosphoglucuronosyl transferase in human hepatocyte cultures (42).

In 10 healthy subjects silymarin 160 mg tds had no effect on the pharmacokinetics of indinavir 800 mg tds (43). In a similar study silymarin 175 mg tds had no effect on the pharmacokinetics of indinavir 800 mg tds (44).

Tanacetum parthenium

Tanacetum parthenium (feverfew, bachelor's buttons, motherherb) has been used in the prevention of migraine, with some benefit (45), and for rheumatoid arthritis, without (46).

Adverse effects

As *Tanacetum parthenium* is rich in allergenic sesquiterpene lactones, such as parthenolide, it is not surprising that contact dermatitis has been observed (SEDA-11, 426). The most common adverse effect of oral feverfew is mouth ulceration. A more widespread inflammation of the oral mucosa and tongue, swelling of the lips, and loss of taste have also been reported.

Feverfew inhibits platelet aggregation (47), and its concomitant use with anticoagulants such as warfarin is therefore not advised.

Tussilago farfara

Tussilago farfara (coltsfoot) has hepatotoxic potential owing to the presence of pyrrolizidine alkaloids (see separate monograph).

- An 18-month-old boy who had regularly consumed a herbal tea mixture since the 3rd month of life developed veno-occlusive disease with portal hypertension and severe ascites (48). Histology of the liver showed centrilobular sinusoidal congestion with perivenular bleeding and parenchymal necrosis without cirrhosis. The child was given conservative treatment only and recovered completely within 2 months.

The tea contained peppermint and what the mother thought was coltsfoot (*T. farfara*), analysis of which revealed high amounts of pyrrolizidine alkaloids. Seneciphylline and the corresponding *N*-oxide were identified as the major components, and the child had consumed at least 60 µg/kg/day of the toxic pyrrolizidine alkaloid mixture over 15 months. Macroscopic and microscopic analysis of the leaf material indicated that *Adenostyles alliariae*

(Alpendost) had been erroneously gathered by the parents in place of coltsfoot. The two plants can easily be confused especially after the flowering period.

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