Achillea millefolium

Scientific Name

***Achillea millefolium* L.**

Synonyms

Achillea albida Willd., *Achillea alpicola* (Rydb.) Rydb. (illeg.), *Achillea ambigua* Boiss., *Achillea ambigua* Pollini, *Achillea anethifolia* Fisch. ex Herder, *Achillea angustissima* Rydb., *Achillea arenicola* A.Heller, *Achillea bicolor* Wender., *Achillea borealis* var. *arenicola* J.T.Howell, *Achillea borealis* subsp. *arenicola* (A.Heller) D.D.Keck, *Achillea borealis* subsp. *californica* (Pollard) D.D.Keck, *Achillea borealis* var. *californica* (Pollard) J.T. Howell, *Achillea borealis* f. *fusca* (Rydb.) Hultén, *Achillea californica* Pollard, *Achillea ceretanica* Sennen, *Achillea compacta* Lam., *Achillea coronopifolia* Willd., *Achillea crassifolia* Colla, *Achillea cristata* Hort. ex DC., *Achillea cuspidata* Wall.(inval.), *Achillea dentifera* Rchb., *Achillea eradiata* Piper, *Achillea fusca* Rydb., *Achillea gigantea* Pollard, *Achillea gracilis* Raf., *Achillea haenkeana* Tausch, *Achillea intermedia* Schleich., *Achillea lanata* Lam., *Achillea lanulosa* Nutt., *Achillea lanulosa* subsp. *alpicola* (Rydb.) D.D.Keck, *Achillea lanulosa* var. *alpicola* (Rydb.) Rydb., *Achillea lanulosa* var. *arachnoidea* Lunell, *Achillea lanulosa* var. *eradiata* (Piper) M.Peck, *Achillea lanulosa* subsp. *megacephala* (Raup) Argus, *Achillea lanulosa* f. *peroutkyi* F.Seym., *Achillea lanulosa* f. *rubicunda* Farw., *Achillea laxiflora* A.Nelson, *Achillea laxiflora* Pollard & Cockerell, *Achillea magna* All. (illeg.), *Achillea magna* L. *Achillea magna* Haenke (illeg.), *Achillea marginata* Turcz. ex Ledeb., *Achillea megacephala* Raup, *Achillea millefolilium* E.Mey., *Achillea millefolium* f. *albiflora* Dabrowska, *Achillea millefolium* var. *alpicola* (Rydb.) Garrett, *Achillea millefolium* var. *arenicola* (A.Heller) Nobs, *Achillea millefolium* var. *arenicola* (A.Heller) Ferris, *Achillea millefolium* var. *asplenifolia* (Vent.) Farw., *Achillea millefolium* subsp. *atrotegula* B.Boivin, *Achillea millefolium* subsp. *balearica* Sennen, *Achillea millefolium* var. *borealis* (Bong.) Farw., *Achillea millefolium* var. *californica* (Pollard) Jeps., *Achillea millefolium* f. *californica* (Pollard) H.M.Hall, *Achillea millefolium* var. *colliniformis* Dabrowska, *Achillea millefolium* subsp. *compacta* (Lam.) Bonnier & Layens, *Achillea millefolium* var. *dipetala* Dabrowska, *Achillea millefolium* f. *discolor* B.Boivin, *Achillea millefolium* var. *dissecta* Dabrowska, *Achillea millefolium* var. *fulva*, *Achillea millefolium* var. *fusca* (Rydb.) G.N.Jones, *Achillea millefolium* var. *gigantea* (Pollard) Ferris, *Achillea millefolium* var. *gigantea* (Pollard) Nobs, *Achillea millefolium* f. *iserana* (Podp.) Hayek, *Achillea millefolium* var. *iserana* Podp., *Achillea millefolium* var. *lanata* W.D.J.Koch, *Achillea millefolium* var. *lanulosa* (Nutt.) Piper, *Achillea millefolium* subsp. *lanulosa* (Nutt.) Piper, *Achillea millefolium* var. *litoralis* Ehrenb. ex Nobs, *Achillea millefolium* var. *lobata* Dabrowska, *Achillea millefolium* var. *maritima* Jeps., *Achillea millefolium* var. *megacephala* (Raup) B.Boivin, *Achillea millefolium*

T.K. Lim, *Edible Medicinal And Non-Medicinal Plants: Volume 7, Flowers*,
DOI 10.1007/978-94-007-7395-0_10, © Springer Science+Business Media Dordrecht 2014

var. *nigrescens* E.Mey., *Achillea millefolium* var. *occidentalis* DC., *Achillea millefolium* var. *pacifica* (Rydb.) G.N.Jones, *Achillea millefolium* subsp. *pallidotegula*, *Achillea millefolium* subsp. *pannonica* (Scheele) Hayek, *Achillea millefolium* subsp. *pannonica* (Scheele) Oborny, *Achillea millefolium* var. *parviligula*, *Achillea millefolium* var. *parvula*, *Achillea millefolium* var. *puberula* (Rydb.) Nobs, *Achillea millefolium* var. *puberula* (Rydb.) Ferris, *Achillea millefolium* f. *rhodantha* Lepage, *Achillea millefolium* f. *rosea* (Desf.) E.L.Rand & Redfield, *Achillea millefolium* var. *rosea* (Desf.) Torr. & A.Gray, *Achillea millefolium* f. *roseiflora* B.Boivin, *Achillea millefolium* f. *roseoides* Breitung, *Achillea millefolium* f. *rubicunda* (Farw.) Farw., *Achillea millefolium* var. *russeolata*, *Achillea millefolium* var. *sordida* W.D.J.Koch, *Achillea millefolium* var. *spathulata* Dabrowska, *Achillea nabelekii* Heimerl, *Achillea nigrescens* (E.Mey.) Rydb., *Achillea occidentalis* (DC.) Raf., ex Rydb., *Achillea ochroleuca* Eichw., *Achillea ossica* K.Koch, *Achillea pacifica* Rydb., *Achillea palmeri* Rydb., *Achillea pannonica* Scheele, *Achillea pannonica* f. *laxa* Dabrowska, *Achillea pecten-veneris* Pollard, *Achillea pratensis* Saukel & R.Länger, *Achillea pseudotanitifolia* Wierzb. ex Rchb., *Achillea puberula* Rydb., *Achillea pumila* Schur, *Achillea rosea* Desf., *Achillea seidlii* J.Presl & C.Presl, *Achillea setacea* Schwein., *Achillea sordida* (W.D.J.Koch) Dalla Torre & Sarnth., *Achillea subalpina* Greene, *Achillea subhirsuta* Gilib. (inval.), *Achillea submillefolium* Klokov & Krytzka, *Achillea sylvatica* Becker, *Achillea tanacetifolia* Mill., *Achillea tenuifolia* Salisb. (illeg.), *Achillea tenuifolia* var. *albicaulis* (C.A.Mey.) Trautv., *Achillea tenuis* Schur, *Achillea tomentosa* Pursh (illeg.), *Achillea virgata* Hort. ex DC., *Achillios millefoliatus* St.-Lag., *Alitubus millefolium* (L.) Dulac, *Alitubus tomentosus* Dulac, *Chamaemelum millefolium* (L.) E.H.L.Krause, *Chamaemelum tanacetifolium* (All.) E.H.L.Krause, *Chamaemelum tomentosum* (L.) E.H.L.Krause (illeg.)

Family

Asteraceae

Common/English Names

Bad Man's Plaything, Bloodwort, Carpenter's Weed, Common Yarrow, Devil's Nettle, Devil's Plaything, Fernweed, Gordaldo, Knight's Milfoil, Milfoil, Musk Milfoil, Nosebleed, Nosebleed Plant, Old Man's Pepper, Plumajillo, Sanguinary, Sneezewort, Soldier's Friend, Soldier's Woundwort, Staunchweed, Thousand-Seal, Thousand-Seal Bad Man's Plaything, Thousand Weed, Thousand-Leaf, Thousand-Seal, Thousand Weed, Thousand-Leaf, Western Yarrow, Woundwort, Yarrow, Yarrow Bloodwort, Yarrow Milfoil, Yarroway

Vernacular Names

Argentina: Milhojas (Spanish)
Azerbaijan: Adi boymadərən
Brazil: Aquileia, Mil em Folhas, Mil-Folhas
Burmese: hta.ri:hpweing
Catalan: Milfulles
Chinese: Shi, Shi Cao, yang shi cao
Croatian: Armanj, Božja haluga, Božje drvce, Hajdučka trava, Hrb, Jezičec, Jutrocel, Kačak, Kačak, Koromačić, Kostenica, Kostret, Kostretica, kostrešica, koštenica, Malankovica, Mali stozlat, mekušica, Mesečina, Mrmanj, Mrmonj, Paprac, Rebrac, Reza, Rman Vodeni sporiš, Spor, Sporić-stolistak, sporiš, Stolika, Stoliska, Stolist, Stolista, Stolistak, Stolistac, Stolisnik, Tučija trava
Czech: Řebříček obecný, Řebříček obecný pravý
Danish: Almindelig røllike, Finbladet røllike, Røllike, Soldaterurt, Tømrerurt
Dutch: Duizendblad, Gewoon duizendblad
Eastonian: Harilik raudrohi
Egypt: Om alf waraka (Arabic)
Esperanto: Akileo milfolia, Milfolio
Finnnish: Aivastusjuuri, Akantupakki, Hurstinkukka, Pietarinkukka, Pyörtänäpöllö, Pyörtänöpöllö, Siankärsäheinä, Siankärsämö
French: Achillée, achillée mille-feuille, Herbe à Dinde, Herbe aux charpentiers, Herbe aux cochers, Herbe aux Militaires, Herbe de Saint-Jean, Herbe de St-Jean, Mille feuille
Gaelic: Athair thalún

German: Achillenkraut, Augenbraue der Venus, Bauchwehkraut, Blutkraut, Blutstillkraut, Feldscharfgarbe, Frauendank, Frauenkraut, Garbenkraut, Gebenkraut, Gemeine Schaf garbe, Gerwel, gewöhnliche Schafgarbe, Gliedkraut, Gotteshand, Grillengras, Katzen kraut, Katzenschwanz, Lämmerzunge, Marga retenkraut, Schafgarbe, Schafrippen, Schaf zunge, Tausendblatt, Tausendblättchen, Teekraut, Wiesen-Schafgarbe, Wiesen-Schafgarbe

Hungarian: Egérfarkfû, Közönséges cickafark, Mezei cickafark

Icelandic: Vallhumall

India: Biranjasipha, Gandana, Gandrain, Puthkanda, Bhut Kesi (Hindi), Bimjasif (Joshimath), Rajmari (Konkani), Rojmaari (Marathi), Achchilliya (Tamil), Tukhm gandana, Buiranjasif, Brinjasuf (Urdu)

Italian: Achillea, Achillea millefoglie, millefoglio, Millefoglio montano

Japanese: Seiyou no kogirisou, Yaroo

Kashmir: Momadrichopandiga

Korean: seoyangtobpul

Ladakh: Chabu, Chuang

Mexico: Alcanfor, Ciento en rama (Spanish)

Norwegian: Bakkeryllik, Broksjit, Hardhaus, Jordhumle, Kanelblom, Krydderblom, Ølkong, Røllik, Rølløkka, Ryllik, Soldaturt, Teblom, Tobakksblomst, Vanlig Ryllik

Persian: biranjasib, bu-l-maderan

Polish: Krwawnik pospolity

Portuguese: Aquiléia, Espuma-do-mar, Mil-em-rama, Mil-folhas, milefólio

Russian: tysâčelistnik obyknovennyj

Serbian: Ajdučica, Ajdučka trava, Aspra, Beli ravanj, Belo ivansko cveće, Hajdučica, Hajdučka trava, Jalova mesečina, Jalovi mesečnjak, Jalovo mesečje, Krvavac, Kunica, Kunji rep, Kučja trava, Ljutica, Mesečina, Moračika, Paprac, Petrovsko cveće, Ravan, Ravanj, Ravunika, Spor, Sporiš, Sporiševina, Stolistnik, Stolisnik, Tintorova trava

Slovašcina: Arman, Armanc, Erman, Grenki rman, Hrman, Jermanec, Kaček, Kačjek, Korancelj, Korocelj, Mezinec, Mezinic, Navadni rman, Rman navadni, Rmanc, Runica, Skorejca, Zavrelec, Zevrelčec

Slovencina: Rebříček obyčajný

Spanish: Aquilea, Aquillea, Artemisa bastarda, Cientoenrama, Flor de la pluma, Hierba de las heridas, Hierba de los carpinteros, Hierba de San José, Meona, Mil hojas, milenrama, Milfohas, Milfullas, Milhojas, Milorri

Swedish: Backhumle, Jordhumle, Karibacka, Näsegräs, Näsgräs, Rölleka, Röllika

Turkish: Beyaz civanperçemi, civanperçemi, Civanpercemiotu, Kandil Çiçek

Vietnamese: Cỏ thi, Cúc vạn diệp, Dương kỳ thảo, Xương cá

Welsh: Milddail, Gwilffrai, Llys Y Gwaedlif, Llysiau Marwolaeth, Llysiau'r Gwaedlin, Llysiau'r Gwaedlif, Milfyd, Milfydd, Minfel, Wrisgan Llwyd

Origin/Distribution

The plant is indigenous to temperate and alpine areas in Eurasia, including most of Europe and many parts of Asia (i.e., from Turkey eastwards to Siberia and northwestern India). It has been introduced into North America, China, New Zealand and Australia.

Agroecology

Yarrow is a cool climate plant; it is occasionally grown in the cooler highland parts of subtropical regions. In its native range, it grows at low or high altitudes, up to 3,500 m above sea level. It grows in disturbed habitats, neglected gardens, waste areas, grasslands, woodlands, pastures, turfed areas, gullies and along roadsides in relatively moist locations. It grows in full sun to partial shade, on acidic to alkaline soils. It is frost and drought tolerant.

Edible Plant Parts and Uses

The flowers and leaves are edible (Uphof 1968; Grieve 1971; Facciola 1990; Roberts 2000; Schofield 2003). An aromatic tea is made from the dried flowers and leaves. An essential oil

extracted from the flowering heads is used as a flavouring for soft and alcoholic beverages. Yarrow flowers can be fried with butter sprinkled with sugar or orange juice. The bitter leaves are eaten raw or cooked as spinach or in soups and are best used when young and tender. They are also used in mixed salads. Yarrow leaves were part of a herbal mixture known as 'gruit' used in the flavouring and preservation of beer prior to the use of hops. The leaves are also used as a substitute for tobacco, nutmeg, cinnamon and hops.

Botany

An erect, branched herbaceous perennial, 20–100 cm high with rhizomatous or stoloniferous growth form and sparingly branched or unbranched tomentose or glabrous stems. Leaves are petiolate; large near the middle and bottom or sessile, cauline and smaller towards the tip. Leaf blades lanceolate or oblong-lanceolate, 3.5–25 cm × 5–3.5 cm, bipinnate or tripinnate, feathery and arranged spirally on the stem, glabrous to sparsely tomentose or densely lanate (Plates 1 and 2). Inflorescence heads 10 to >100, in terminal, simple or compound, slightly rounded or flat-topped corymbs on the expanded end (receptacle) of the flower stalk (Plate 2). Involucre oblong or subovoid with 20–30 phyllaries (involucral bracts) in 3 overlapping series, ovate to lanceolate and hairy. Each flower head (capitulum) contains ray florets (female) and disk florets (bisexual) which are white and cream to pink to deep purple (Plate 3). There are generally 3–8 ray florets that are ovate to round. Disk florets 10–20, at the centre of the flower head, tubular, and greyish white or cream. Fruit tiny, oblong achenes, 2 mm, with broadly winged margins and no pappus.

Nutritive/Medicinal Properties

Plant Phytochemicals

Sesquiterpenes and sesquiterpene lactones found in the leaf and flowering head included acetylbalchanolide, millefolide, and an unknown lactone

Plate 1 Juvenile plant with fine, feathery pinnately compound leaves

with mp 138 °C (Hochmannová et al. 1961); leucodin and achillin (Romo de Vivar and Olmos 1968); desacetylmatricarin, matricarin and millefin (Kasymov and Sidyakin 1972); austricin (deacetylmatricarin), millefin, 8-hydroxyachillin and an isomer of matricarin (Adekenov et al. 1979; Kasymov and Sidyakin 1972); and artecanin, estafiatin, leucomisin and balchanolide from the plant (Konovalov and Chelombit'ko 1991). Achillicin, the major proazulene (prochamazulene) of *Achillea millefolium*, was isolated and identified as 8-acetoxyartabsin (Cuong et al. 1979a); chamazulene (2, 13–15) and chamazulene carboxylic acid were also isolated (Cuong et al. 1979b). Other sesquiterpenes isolated included proazulenes, 8-acetoxyartabsin, 8-anelooxyartabsin, 2,3-dihydrodeacet oxymatricin, (Verzár-Petri et al. 1979a) and azulene (Verzár-Petri et al. 1979b). Three main azulenogene sesquiterpene lactones were isolated from *A. millefolium* plant and identified as 8-acetoxy-artabsine, 8-angeloxy-artabsine and

Plate 2 White-flowering head

Plate 3 Purple flowering head

2,3-dihydro-desavetoxy-matricin (Verzár-Petri et al. 1980). Ulubelen et al. (1990) isolated a new sesquiterpene lactone, achillifolin, together with known sesquiterpene lactones, dihydroparthenolide and dihydroreynosin, from the aerial parts. Known flavonoids, terpenoids and vanillic acid were also isolated. Ohir et al. (1991) isolated desacetylmatricarin, two sesquiterpene lactones of a new 3-oxa-guaianolide type, 8-acetyl egelolide and 8-angeloyl egelolide from the aerial parts. The structures of 8 α-angeloxy-, 8 α-tigloxy- and 8 α-acetoxy-10-epi-artabsin (achillicin) as well as of the respective 3-oxa-analogues were revised by Schröder et al. 1994). On the basis of 2D-NMR spectral data, it was shown unequivocally that these compounds were artabsin derivatives. *Achillea millefolium* was reported to contain α-peroxyachifolid, dehydromatricaria ester, pontica epoxide (Rücker et al. 1991; Hausen et al. 1991) and isoachifolidiene, a precursor of guaianolide peroxides (Rücker et al. 1992). Three new antitumor sesquiterpenoids, achimillic acids A, B and C, were isolated as methyl esters from *Achillea millefolium* (Tozyo et al. 1994) Three new sesquiterpenes which were trivially named as sesquiterpene lactone esters A and B (1 and 2) and sesquiterpene lactone-diol (3) were isolated from the plant (Farooq et al. 2012).

Several species of the polyploid *A. millefolium* group, however, could be characterized by their distinct sesquiterpene pattern (Montsko et al. 2008). *A. millefolium* was characterized by the presence of 8-desacetylmatricarin, santonin, matricarin, achillicin and artabsins; *A. pratensis* by arglanin, 4-hyperoxy-arglanin, santonin and santamarin; and *A. collina* by 8-desacetylmatricarin, santonin, matricarin, achillicin, 3-oxa-achillin, 8α-angeloxy-artabsin, 8α-angeloxy-3-oxa-art absin, 8α-tigloxy–artabsin and 8α-tigloxy–3-oxa-artabsin.

Five sesquiterpenoid, i.e., seco-pseudo guaianolides (paulitin, isopaulitin, psilostachyin C,

desacetylmatricarin and sintenin) and five flavonoids (apigenin, luteolin, centaureidin, casticin and artemetin) were isolated and identified from the aerial parts of the *Achillea millefolium* aggregate (Csupor-Löffler et al. 2009). Flavonoids found in the plant included rutin, apigenin, luteolin and the 7-glucosides of apigenin and of luteolin, cosmosiin and luteolin 7-*O*-β-D-glucopyranoside (Kaloshina and Neshta 1973). The main flavonoid constituents of leaf and flower heads of *Achillea millefolium* subspecies were found to be apigenin and luteolin, mainly found as 7-*O*-glucosides and 7-malonylglucosides (Guédon et al. 1993). This represented the first report of flavone glycoside malonylesters in *Achillea* genus. White-flowering populations, i.e., the ssp. *millefolium* and *ceretanum*, showed a similar distribution of flavonoid compounds, whereas the presence of rutin in the leaves of the *alpestris* ssp. appeared to be characteristic. The flowering tops of this taxon were distinguished from the other two by their amount of schaftoside and isoschaftoside. The following sesquiterpenoids were isolated from *A. millefolium* group (*A. collina* and *A. pratensis*): achillicin, 8α-tigloxy-artabsin, 8α-angeloxy-artabsin, arglanin and santamarin (Glasl et al. 1999).

The flavonoids found in *A. millefolium* of the section *Millefolium* comprised of flavonoid aglycones and flavonoid glycosides—C-glycosylflavones, flavonol and flavones O-glycosides (Ivancheva et al. 2002). The flavonoid aglycones comprised large amounts of quercetagetin 3,6,7-trimethyl ether (chrysophenol-D), quercetagetin 3,6,7,3′,4′-pentamethyl ether (artemetin); small amounts of scutellarein 6,7, 4′-trimethyl ether (salvigenin), quercetagetin 3,6, 4′-trimenthyl ether (centaureidin); and traces of scutellarein 6-methyl ether (hispidulin), scutellarein 6,7-dimethyl ether (cirsimarin) and 6-hydroxyluteolin 6-methyl ether (nepetin). The flavonoid glycosides comprised small amounts of vitexin (5,7,4′-trihydroxyflavone-8-C-glycosyl), vicenine 2 (5,7,4′-trihydroxyflavone-6,6-di-C-glycosyl) and swertjponin (5,3′,4′-trihydroxy-7-OMeflavone-6-C-glycosyl) and traces of swertisin (5,4′-dihydroxy-7-OMeflavone-6-C-glycosyl). The flavonol and flavones *O*-glycosides were large amount of quercetin-3-*O*-glycoside, small amount of quercetin-3-*O*-*rhamnoglycoside*, and traces of luteolin-7-*O*-glycoside, diosmetin-7-*O*-glycoside and kaempferol-3-*O*-glycoside. The flavonoid casticin was isolated from *Achillea millefolium* (Haïdara et al. 2006). The following flavonoid compounds were found in *Achillea* species belonging to the *A. millefolium* L. group (Gherase et al. 2004): rutin, apigenin-7-*O*-*glucoside* and luteolin-7-*O*-glucoside were found in the methanol extract. The free aglycones, apigenin and luteolin, were also detected. Total phenolic contents reported for *A. millefolium* herb were 9.55 mg GAE/100 g DW (Wojdyło et al. 2007). Major phenolic compounds (mg/100 g DW) found were phenolic acids, 429 mg caffeic acid, 118 mg neochlorogenic acid and 35 mg ferulic acid, and flavonoids, 103 mg luteolin and 84.3 mg apigenin. The following phenolic compound were isolated from the methanol extract of *A. millefolium*: chlorogenic acid (1), rutin (2), luteolin 7-*O*-glucoside (3); 1,3-dicaffeoylquinic acid (4); 1,4-dicaffeoylquinic acid (5); 3,4-dicaffe oylquinic acid (6); apigenin 4′-*O*-glucoside (7); apigenin 7-*O*-glucoside (8); luteolin 4′-*O*-glucoside (9); and 3,5-dicaffeoylquinic acid (10) (Vitalini et al. 2011). Polyphenolic compounds (g/kg dry matter) in the aerial yarrow plant parts were determined as follows: chlorogenic acid 8.12 g, 3,5-DCQA (dicaffeoylquinic acid) 21.59 g, 1,5-DCQA 8.88 g, 4,5, DCQA 3.31 g, total caffeoyl derivatives 41.90 g, total dihydroxycinnamic acid derivatives 52.67 g, total flavonoids 12.92 g, total dihydroxycinnamic acid derivatives + flavonoids 65.59 g and total polypenolic compounds 63.06 g (Fraisse et al. 2011).

Thirty-five compounds were isolated from various fractions of the ethanol extract of the dried plant material of *Achillea millefolium* (Tunón et al. 1994). From the C:1 fraction, adenine, betaine, betonicine, choline, homostachydrine, mandelonitrile glucoside, rutin, staydrine and trigonelline were isolated; from fraction C:2, caffeic acid, chlorogenic acid, ferulic acid, mandelic acid, salicylic acid and vanillic acid; and from fraction F:2, apigenin, capric acid methyl ester, caprylic acid methyl ester, carvacrol, eugenol, gallic acid, hydroquinone, isorhamnetin, linoleic acid ethyl ester, linoleic acid methyl

ester, linolenic acid methyl ester, luteolin, palmitic acid ethyl ester, palmitic acid methyl ester, phloroglucinol, protocatechuic acid, pyrocatechol, quercetin, tannic acid and undecylenic methyl ester were isolated.

Beta-sitosterol was identified as the major sterol and α-amyrin as the major triterpene of *A. millefolium* (Chandler et al. 1982b). The sterols stigmasterol, campesterol and cholesterol; and the triterpenes β-amyrin, taraxasterol and pseudotaraxasterol were also identified.

From above ground parts of *Achillea collina* within the *A millefolium* group, proline, stachydrine, betonicine, betaine and choline were isolated as the major nitrogen containing compounds (Mehlführer et al. 1997). The TLC screening of 11 different species belonging to *A. millefolium* group showed qualitatively identical betaine patterns but quantitative differences were observed.

From the lipophilic extract of subterranean parts of *Achillea millefolium* s.str. 17 different alkamides together with (+)-sesamin were isolated and identified (Greger and Hofer 1989). Besides a rare decadienoic acid tyramide and the corresponding novel *p*-methoxy derivative, the amide pattern was especially characterized by the dominating olefinic piperideides. Greger and Werner (1990) compared the alkamides from the subterranean parts of different members of the *Achillea millefolium* group. They found that the European representatives (*A. millefolium*, *A. pannonica*, *A. collina*, *A. asplenifolia*, *A. setacea*) were predominated by deca-2 *E*,4 *E*,6*Z*-trienoic piperideide with some cytotypes accumulating two isomeric decatetraenoic piperideides and (+)-sesamin. The alkamide patterns of the Asian and North American members (*A. asiatica*, *A. lanulosa*) were characterized by a preponderance of decadienoic acid-derived isobutylamide and piperideide.

Thirteen compounds were identified in the essential oil: borneol, camphene, camphor, 1,8 cineole, α-pinene, *p*-cymene, furfuryl alcohol, isobutyl acetate, isovaleric acid, limonene, menthol, sabinene and terpinene-4-ol (Bejnarowicz and Smolenski 1968). Haggag et al. (1975) reported the following constituents in the essential oil: azulene, caryophyllene, eucalyptol, borneol, bornyl acetate, α-pinene, β-pinene, limonene and α-thujone. The major components of the essential oil hydrodistilled from the stems, leaves and inflorescences were found to be β-thujone (8.3–21.7 %), camphor (8.6–11.7 %), 1, 8-cineole (7.7–15.2 %), β-pinene (3.8–7.8 %) and sabinene (5.7–8.9 %) (Hachey et al. 1990). More than 60 components have been identified, 40 of which were mainly oxygenated compounds. Several monoterpenes and sesquiterpenes were identified in the essential oil of wild *Achillea millefolium* complex in northern Greece, although the main component was ascaridole (47.2 %) (Chatzopoulou et al. 1992). Lesser amounts of 1, 8-cineole (10.5 %), *p*-cymene (7.4 %), α-terpinene (7.0 %) and camphor (8.1 %) were found. Bélanger and Dextraze (1993) reported the following as main components (range) in the essential oils of *A. millefolium* plants: chamazulene (51.3–1.16 %), germacrene D (54.7–5.6 %), β-thujone (35.1–0 %), α-thujone (20.7–0 %), α-phellandrene (17.4–0 %), sabinene (17.2–0.29 %), myrcene (14.7–0.10 %), β-pinene (9.74–0.2 %), β-caryophyllene (7.68–0.54 %), camphor (6.7–0.2 %), 1,8-cineole (6.45–0.26 %) *p*-cymene (1.73–0 %), bornyl acetate (3.88–0 %), camphene (2.68–0.11 %), limonene (3.11–0 %) and γ-terpinene (5.5–0.2 %).

The main volatile constituents found in *Achillea millefolium* growing wild in Greece were 1,8-cineole, camphor, borneol and lavandulol (Kokkalou et al. 1992). A comparison of the main volatile constituents currently found in *A. millefolium* oils revealed that great infraspecific variation occurred. One hundred twenty-three components were identified in the oil of aerial parts of *A. millefolium* from Kazakhstan representing 93.1 % of the oil (Suleimenov et al. 2001). Camphor (16 %), 1,8-cineole (8.7 %), borneol (6.2 %), β-eudesmol (6.1 %), α-terpineol (5.9 %), α-bisabolol (5.5 %) and terpinen-4-ol (3.1 %) were found as the major compounds.

Twenty components were identified in the essential oil of aerial parts of *A. millefolium* grown in Siberia (Smelcerovic et al. 2010). Major constituents were 1,8-cienole (28.8 %), camphor (11 %), borneol (5.9 %), β-pinene (5,4 %), caryophyllene oxide (3.3 %), β-caryophyllene (3.1 %),

α-elemol (3 %) and α-terpineol (2.9 %). Other components included α-pinene (2.5 %), terpinen-4-ol (2.3 %), camphene (0.7 %), sabinene (0.1 %), *p*-cymene (1.9 %), germacrene D (0.7 %), γ-terpinene (0.5 %), humulene (0.4 %), (*Z*)-β-farnesene (0.3 %), α-muurolene (0.2 %), cadina-3,9-diene (0.1 %) and hexahydrofarnesyl acetone (0.1 %). 1,4-dimethyl azulene, chamazulene, chamazulenecarboxylic acid and achillin were also found.

Trans-nerolidol (1–31.9 %), caryophyllene oxide (2.1–23 %), β-pinene (0.5 –20.0 %), 1,8-cineole (0.5–11.9 %) were found to be the first predominant constituents in all 20 leaves and flower oils of white- and pink-flowering *A. millefolium* plants (Judzentiene and Mockute 2010). Other components found in all 20 samples included β-caryophyllene (1.7.7 %), α-pinene (0.1–6.3 %), sabinene (0.1–8.0 %), α-terpinene (tr – 0.6 %), borneol (tr – 8.4 %), terpinen-4-ol (tr – 2.8 %), α-terpineol (tr – 0.9 %), bornyl acetate (0.1–6.0 %), α-humulene (tr – 1.2 %), germacrene D (tr – 3.8 %) and (2Z,6*E*)-farnesyl acetate (tr – 3.5 %). Selin-11-en-4-α-ol (tr – 10.4 %) was also dominant and found in both leaf and flowers of ten pink- and seven white-flowered plants. 10-epi-γ-eudesmol was also dominant in 17 samples comprising 10 samples (tr – 12.2 %) in both flower and leaves of white cultivars and seven samples (0.8–5.8 %) in both flower and leaves of pink cultivars. Spathulenol was also dominant in 19 samples (tr – 10.2 %) in 10 white- and 9 pink-flowering plants. Other compounds found in 17–19 samples (leaf and flowers) included camphene (tr – 3.7 %), myrcene (tr – 1.1 %), *p*-cymene (tr – 2.4 %), γ-terpinene (0.1–1.4 %), terpinolene (tr – 2.3 %), camphor (tr – 6.7 %), *cis*-chrysanthenol (tr – 0.9 %), β-bourbonene (tr – 0.3 %), β-bisabolene (tr – 2.6 %), δ-cadinene (tr – 7.6 %), α/β-caryophylla—4(14), 8(15)-dien-5-ol (tr – 6.7 %) and (2Z,6*E*)-farnesol (tr – 1.7 %). Chamazulene was found in five samples (tr – 1.4 %) of the leaf and flower of the pink-flowered plants and one sample in the flower of white-flowered plant (2.7 %). 1-epi-cubenol was only found in white-flowered plants (nine out of ten samples, tr – 2.7 %). (2*E*, 6*E*)-farnesol was only found in pink-flowered plants (tr – 1.9 %). Chrysanthenone and carvotanacetone were found only in the flower (7.2, 2.1 %) and leaf (7.6, 2.6 %) samples, respectively, of pink-flowered plant in the same one locality. Significant qualitative and quantitative variations were also found in the total content of monoterpenes (1.2–57.2 %) and sesquiterpenes (39.9–98.8 %).

Studies in Norway reported that the essential oil content of *Achillea millefolium* differed greatly between the vegetative stage (0.13 %) and the stage of full bloom (0.34 %) (Rohloff et al. 2000). Changes in the composition of yarrow essential oil were found to be related to maturation of the plant, with increasing amounts of monoterpenes in relation to the sesquiterpene. A clear trend was detected only for the monoterpenic compounds with increasing levels of α-pinene and β-pinene and α-thujone and decreasing levels of sabinene, borneol and bornyl acetate. Previously reported as major compounds, chamazulene and germacrene D could be found only in insignificant amounts. Sesquiterpenic compounds such as β-bisabolene, α-bisabolol and δ-cadinene were detected in substantial amounts by solid-phase microextraction (SPME) in contrast to the steam-distilled samples.

Twenty-one volatile constituents were isolated from the oil of Iranian *A. millefolium* (Afsharypuor and Asgary 1996). The oil possessed a high percentage (55.4 %) of sesquiterpenes. The major components of this fraction were α-bisabolol (22.9 %), spathulenol (12.4 %), *cis*-nerolidol (5.7 %), *cis*-carveol (5 %) and *trans,trans*-farnesol (4.0 %). Other components included phenol (3.9 %), *trans*-carveol (3.7 %), $C_{IO}H_{18}O_2$ (3.5 %), *cis*-sabinol (2.5 %), *cis-β-farnesene* (2.7 %), α-patchoulene (2.2 %), 2-pentyl- 5-propylresorcinol (1.8 %), campherenone (1.7 %), C_{15} H_{26} O (1.7 %), bornyl acetate (1.3 %), β-himachalene (1.2 %), geranyl acetate (0.9 %), caryophyllene (0.9 %), 4-oxo-3,4-dihydro-2,3-diazaphenoxathiin (0.9 %),6,10,14-trimethyl pentadecan-2-one (0.8 %) and neryl acetate (0.7 %). The percentage of sesquiterpenes in the oil obtained from flowers and leaves of the plants grown in Portugal was much lower (up to 8.5 %) and was dominated by germacrene-D. The oil obtained from

Iranian *A. millefolium* ssp. *millefolium* possessed a high percentage of sesquiterpenes (55.4 %) in which α-bisabolol was the main compound, while no proazulene or 1,8-cineole was detected (Saeidnia et al. 2004). The major components of the oil were α-copaene (11.1 %) and (*E*)-nerolidol (8.8 %). The main constituents of *A. millefolium* essential oil from the Balkans (21 compounds) were β-pinene (32.63 %), β-caryophyllene (16.52 %), sabinene (11.48 %) and chamazulene (5.86 %), and these four compounds constituted 66.49 % of the oil (Boskovic et al. 2005). Other constituents included 1,8-cineole (4.57 %), caryophyllene oxide (3.74 %), bicyclogermacrene (2.70 %), α-pinene (2.52 %), bornyl acetate (2.42 %), germacrene D (2.12 %), α-humulene (2.12 %), α-phellandrene (0.76 %), α-terpinene (0.47 %), α-copaene (0.75 %), α-thujene (0.51 %), terpinolene (0.42 %), β-bourbonene (0.41 %), γ-terpinene (0.39 %), 4-terpineol (0.36 %), β-longipinene (0.20 %) and borneol (1.68 %). A total of 102 components were identified from the essential oil of *A. millefolium* plants from various European countries (Orav et al. 2006). The quantitatively most important components of yarrow were sabinene, β-pinene, 1,8-cineole, artemisia ketone, linalool, α-thujone, β-thujone, camphor, borneol, fenchyl acetate, bornyl acetate, (*E*)-β-caryophyllene, germacrene D, caryophyllene oxide, β-bisabolol, δ-cadinol, chamazulene and others.

Another study on the essential oil of *Achillea millefolium* subsp. *millefolium* in Iran identified 20 volatile components (Srabi and Meshkatalsadat 2010). The predominant compounds were geraniol (33.43 %), neryl acetate (17.48 %), farnesol (7.61 %), benzyl benzoate (6.08 %), nerolidol (5.61 %), limonene (5.38 %) and linalool (3.15 %). Other constituents included neral (2.93 %), geranyl butyrate (2.67 %), α-pinene (2.53 %), 1,8-cineole (1.93 %), chrysanthenone (1.77 %), δ-elemene (1.00 %), β-pinene (0.68 %), α -terpineol (0.57 %), nerol oxide (0.54 %), *cis*-jasmone (0.47 %), sabinene (0.34 %), camphor (0.27 %) and geranial (0.11 %). The Italian volatile extracts (SFE (supercritical extraction with CO2) and essential oil) of aerial parts were predominantly composed by α-asarone (25.6–33.3 %), and in the SFE extract and in the HD oil, respectively, β-bisabolene (27.3–16.6 %) and α-pinene (10.0–17.0 %), whereas the main components of the Portuguese extracts were *trans*-thujone (31.4–29.0 %), *trans*-chrysanthenyl acetate (19.8–15.8 %) and β-pinene (1.2–11.1 %) (Falconieri et al. 2011).

The populations *Achillea millefolium* from two different high-altitude Himalayan habitats (1,600 m, 2,850 m) proved to represent two different ecotypes: the 1,8-cineole type and the borneol type with appreciable differences in the contents of oils and mono- and sesquiterpenes (Agnihotri et al. 2005). The major components were characterized as β-pinene (10.6–17.7 %), 1,8-cineole (3.0–15.1 %), borneol (0.2–12.1 %), and β-caryophyllene (8.5–16.2 %). Thirty components were identified in the essential oil of *A. millefolium* cultivated under the tropical conditions of Delhi, India, comprising 93.43 % of the oil content (Nadim et al. 2011). The predominant constituents were sabinene (17.58 %), 1,8-cineole (13.04 %), borneol (12.41 %), bornyl acetate (7.98 %), α-pinene (6.28 %), β-pinene (6.26 %), terpinine-4-ol (6.17 %) and chamazulene (5.28 %). Other minor components included: β-caryophyllene (2.31 %), camphene (2.07 %), germacrene D (1.49 %), limonene (1.27 %), δ-terpinene (1.19 %), *p*-cymene (1.11 %), α-terpineol (1.04 %), methanol (1.03 %), α-thujone (1.00 %), δ-cadinene (0.94 %), α-cadinol (0.90 %), azulen (0.85 %), myrcene (0.81 %), thujanol (0.54 %), pentadecanoic acid (0.49 %), *trans*-carveol (0.44 %), myristic acid (0.23 %), dodecane (0.18 %), α-thujenal (0.16 %), α-copaene (0.13 %), myrtenol (0.13 %) and cyclohexene (0.12 %).

The terpenoid profile of homeopathic tincture prepared from fresh *A. millefolium* plant material comprised 1,8-cineole (18.28 %), α-pinene (11.96 %), germacrene D (11.62 %), phytol (11.20 %) and *trans*-caryophyllene (10.52 %), as dominant components (Lyakina 2002). Other components were sabinene (4.93 %), 1,4-terpineole (3.08 %), camphor (2.57 %), *trans*-sabinene hydrate (2.49 %), β-fenchol (2.49 %), lavandyl acetate (1.85 %), α-humulene (1.26 %) and 4-thujen-2-α-yl-acetate (1.07 %). In contrast, the terpenoid

profile of homeopathic tincture prepared from dried plant material comprised 1-limonene (29.92 %), sabinene (9.44 %), *trans*-caryophyllene (8.78 %) and phytol (7.59 %) as dominant components. The minor components were 1,8-cineole (5.27 %), lavandyl acetate (5.19 %), germacrene D (5.09 %), β-pinene (3.59 %), pseudocumene (3.20 %), episonarene (3.14 %), caryophyllene oxide (2.54 %), α-pinene (2.42 %), α-humulene (1.27 %), γ-selinene (0.94 %), α-longipinene (0.60 %) and camphene (0.24 %).

The terpenoid profile of homeopathic tincture prepared from fresh *A. millefolium* plant material comprised 1,8-cineole (18.28 %), α-pinene (11.96 %), germacrene D (11.62 %), phytol (11.20 %) and *trans*-caryophyllene (10.52 %), as dominant components (Lyakina 2002). Other components were sabinene (4.93 %), 1,4-terpineole (3.08 %), camphor (2.57 %), *trans*-sabinene hydrate (2.49 %), β-fenchol (2.49 %), lavandyl acetate (1.85 %), α-humulene (1.26 %) and 4-thujen-2-α-yl-acetate (1.07 %). In contrast, the terpenoid profile of homeopathic tincture prepared from dried plant material comprised of 1-limonene (29.92 %), sabinene (9.44 %), *trans*-caryophyllene (8.78 %) and phytol (7.59 %) as dominant components. The minor components were 1,8-cineole (5.27 %), lavandyl acetate (5.19 %), germacrene D (5.09 %), β-pinene (3.59 %), pseudocumene (3.20 %), episonarene (3.14 %), caryophyllene oxide (2.54 %), α-pinene (2.42 %), α-humulene (1.27 %), γ-selinene (0.94 %), α-longipinene (0.60 %) and camphene (0.24 %).

Leaf Phytochemicals

Rutin was isolated from the leaves (Neshta et al. 1972). 6-Hydroxyflavones, 6-hydroxyflavonols, and their methyl ethers predominated in the leaf exudates in various combinations in 78 collections of species forming the *Achillea millefolium* group (Valant-Vetschera and Wollenweber 1988). Leaves of field-grown plants accumulated higher concentrations (%w/w dw) than those of hydroponic grown plants in apigenin glycosides (0.25 versus 0.07 %) and total flavonoids (apigenin, luteolin and apigenin glycosides) (0.26 versus 0.08 %) but lower amount of aglycone flavonoids of luteolin and apigenin (0.009 versus 0.012 %), respectively (Pedneault et al. 2002).

During the flowering period of *Achillea millefolium*, the leaf oil consisted mainly of monoterpenes (about 80 %);1,8-cineole was the dominant component (18 %) followed by *trans*-sabinene hydrate (10 %) (Figueiredo et al. 1992a). The sesquiterpene fraction was dominated by germacrene-D (7 %). In the essential oil isolated from leaves collected during the vegetative phase, the monoterpene fraction was small (<3 %), whereas sesquiterpenes amounted to 92 %, germacrene-D being the major component (65 %) of the oil. Forty-two compounds were identified in the leaf oil of Cuban *A. millefolium*; caryophyllene oxide (20 %) was the major volatile constituent (Pino et al. 1998).

The major volatile aroma components of the leaf (area units divided by 100,000 per g dry matter) was α-pinene (96) and the rest were detected in very small to trace amounts: propanal, 2-methyl; butanal, 2-methyl; butanal, 3-methyl; pentanal; α-thujene; hexanal; β-pinene; sabinene; 1,8-cineole; and *p*-cymene (Dokhani et al. 2005). Total phenolics in the leaves were 32.7 mg/g dm and total tartaric esters were 11.7 mg/g dm.

Flower Phytochemicals

Three flavones, 5-hydroxy-3,6,7,4′-tetramethoxyflavone, artemetin and casticin, were isolated from the petroleum ether extract of the flowering heads of *Achillea millefolium* (Falk et al. 1975). From the ether extract of *Achillea millefolium* flowers, two guaianolides with a peroxide bridged cyclopentane ring and an α-methylene-γ-butyrolactone structure were isolated and the compounds were designated α-peroxyachifolid and β-peroxyisoachifolid. Three flavonoid aglycones, one triterpene, one germacranolide and five guaianolides were isolated and characterized from the dichloromethane extract of flower heads of a Hungarian taxon of the *Achillea millefolium* group (Glasl et al. 2002, 2003). Besides apigenin, luteolin and centaureidin, β-sitosterol, 3β-hydroxy-

11α,13-dihydrocostunolide, desacetylmatricarin (= austricin, austrisin), leucodin (= desacetoxymatricarin, leucomisin), achillin, 8α-angeloxyleucodin and 8α-angeloxy-achillin were isolated. Eight phenolic compounds—chlorogenic acid and flavonoids—namely, vicenin-2, luteolin-3′,7-di-*O*-glucoside, luteolin-7-*O*-glucoside, rutin, apigenin-7-*O*-glucoside, luteolin and apigenin, were identified in the extracts from yarrow (*Achillea millefolium*) flowers (Benetis et al. 2008). The total amount of the identified phenolics in yarrow flowers from different populations varied from 13.290 to 27.947 mg/g.

Achillinin A (2β,3β-epoxy-1α,4β,10α-trihydroxyguai-11(13)-en-12,6α-olide), a new guaianolide, was isolated from the flower (Li et al. 2011). Ten 1,10-secoguaianolides were isolated from the flowers of *Achillea millefolium* (Li et al. 2012a). Three of them (millifolides A–C) including two dimeric sesquiterpenoids exhibit new skeletons. Seco-tanapartholide A was found to be cytotoxic. Sesquiterpene dimers, Achillin B and C, were isolated from the flowers (Li et al. 2012b)

Inflorescences of *A. millefolium* grown in the Sibiu district, Romania was found to contain between 0.18 and 0.59 % (mean 0.34 %) volatile oil (Popescu and Pop-Hakkel 1980). The azulenes from the oil varied between 1.5 and 19.6 % (mean 7.04 %). The following components were identified in the volatile oil: caryophyelene, chamazulene, linalyl, acetate, bornyl acetate, limonen, 1,8-cineole, linaleol, borneol, terpineol and geraniol. Two of the samples showed a different chemical composition, one of them lacking 1,8-cineole, the other bornyl acetate. During the flowering period of *Achillea millefolium*, the flower oil consisted mainly of monoterpenes (about 80 %);1,8-cineole was the dominant component followed secondly by sabinene (15 %) (Figueiredo et al. 1992a). The sesquiterpene fraction was dominated by germacrene-D (0.7 %). The monoterpene fraction was dominant in the oils (ca 80 %) from two populations of *Achillea millefolium* L. ssp. *millefolium*, growing in the Botanical Garden of Lisbon (BGL) and in the Caneco Garden of Almada (CGA) (Figueiredo et al. 1992b). The main components differed: sabinene and 1,8-cineole were dominant in the BGL oils, while camphor, 1,8-cineole and β-pinene were the main constituents of CGA oils. Germacrene-D was the major component of the sesquiterpene fraction of all the oils analyzed. Chamazulene was only detected in the oils from the flower heads collected in CGA; its amount decreases through flower-head development.

The major volatile aroma flower components of *A. millefolium* grown in Iran (expressed as area units divided by 100,000 per g dry matter) were α-pinene (1,350), 1,8-cineole (950), β-pinene (674), sabinene (400), β-pinene (381), γ-terpinene (325), *trans*-caryophyllene (328), α-terpinene (205) and DL-limonene (200) (Dokhani et al. 2005). Other minor components included propanal, 2-methyl; butanal, 2-methyl; butanal, 3-methyl; pentanal; α-thujene; α-fenchene; camphene; hexanal; α-phellandrene; β-phellandrene; 3,7-dimethyl-1,3,6-octatriene; *p*-cymene; α-terpinoline; allocimene, camphor; *trans*-caryophyllene; α-humulene, cadinene isomer; (*E*)-farnesene; δ-cadinene; γ-cadinene; and an unknown terpinene. Total phenolics in the flowers was 35.7 mg/g dm and total tartaric esters were 12.9 mg/g dm.

Achillea millefolium L. sensu lato, is a cytogenetically, morphologically and chemically polymorphic aggregate (Benedek et al. 2007a). Besides possessing sesquiterpenes that have chemotaxonomic relevance and mediate the antiphlogistic activity, the plant contains phenolic compounds such as dicaffeoylquinic acids and flavonoids causing choleretic and spasmolytic effects. The investigated species displayed differences in the quantitative and qualitative composition of phenolic acids and flavonoids. The following flavonoids were found in the flower heads of *Achillea* species belonging to the *A. millefolium* group (Trendafilova et al. 2007): *A. collina*, artemetin (1.6 mg), casticin (1.3 mg), centaureidin (7.4 mg), quercetagetin 6,7,3′,4′-tetramethyl ether (1.0 mg), 6-hydroxykaempferol 3,6,7,4′-tetramethyl ether (1.0 mg), santin (4.0 mg), pectolinarigenin (1.5 mg) and diosmetin (1.5 mg); *A. asplenifolia*, artemetin (6.0 mg),

casticin (1.7 mg), centaureidin (1.4 mg), quercetagetin 6,7,3′,4′-tetramethyl ether (1.1 mg), 6-hydroxykaempferol 3,6,7,4′-tetramethyl ether (1.0 mg) and apigenin (3.0 mg); and *A. distans*, centaureidin (2.0 mg), santin (1.5 mg), pectolinarigenin (1.5 mg), ermanin (1.0 mg), acacetin (1.3 mg), mixture of diosmetin and chrysoeriol (1.5 mg) and luteolin (1.5 mg).

Root Phytochemicals

Roots of hydroponic grown plants accumulated higher concentrations (%w/w dw) than those of field-grown plants in apigenin glycosides (1.91 versus 0.49 %) and total flavonoids (apigenin, luteolin and apigenin glycosides) (1.92 versus 0.51 %) but lower amount of aglycone flavonoids of luteolin and apigenin (0.007 versus 0.014 %), respectively (Pedneault et al. 2002).

The various pharmacological activities of *Achillea millefolium* species may be due to the presence of a broad range of secondary active metabolites in the essential oils and extracts of various plant parts such as flavonoids, phenolic acids and dicaffeoylquinic acids, coumarins, proazulenes, monoterpenes, sesquiterpenes, sesquiterpene lactones, diterpenes, triterpenes and sterols (Chandler et al. 1982b; Nemeth and Bernath 2008; Saeidnia et al. 2011). The largest number of data accumulated for antioxidant and antiinflammatory effects, and there are positive results on the analgesic, antiulcer, choleretic, hepatoprotective and wound-healing activities (Nemeth and Bernath 2008). Interesting findings have highlighted antihypertensive, antidiabetic, antitumor and antispermatogenic activities. Recent findings have confirmed several traditional uses. However, human clinical studies are still warranted.

Antioxidant Activity

Achillea millefolium essential oil strongly reduced the diphenylpicrylhydrazyl radical (IC_{50} = 1.56 µg/ml) and exhibited hydroxyl radical scavenging effect in the Fe^{3+}-EDTA-H_2O_2 deoxyribose system (IC_{50} = 2.7 µg/ml) (Candan et al. 2003). It also inhibited the nonenzymatic lipid peroxidation of rat liver homogenate (IC_{50} = 13.5 µg/ml). Eucalyptol, camphor, α-terpineol, β-pinene and borneol were the principal components comprising 60.7 % of the oil. The polar phase of the methanol extract also showed antioxidant activity. Antioxidant activity in terms of TEAC (µM trolox/100 g DW) of *A. millefolium* herb reported was 11.2 µM for ABTS, 200 µM for DPPH and 191 µM for FRAP (ferric reducing antioxidant power) assays (Wojdyło et al. 2007). Total phenolic content was 9.55 mg GAE/100 g DW.

Studies showed that all plant infusions of 15 *Achillea* species were effective on antioxidant enzyme systems of erythrocytes and leucocytes when compared with the hydrogen peroxide-induced group (Konyalioglu and Karamenderes 2005). Among the plant infusions, *Achillea millefolium* subsp. *pannonic*a showed highest activity on superoxide dismutase. The methanol and aqueous extracts of *Achillea millefolium* exhibited DPPH radical scavenging activity with 75 and 50.8 % inhibition, respectively (Eghdami and Sadeghi 2010). The extracts contained 123.9 and 48.4 mg GAL/g total phenolic content and 41.2 and 13.15 mg QE/g flavonoids, respectively. The methanol extract of *A. millefolium* and its flavonol glycosides and chlorogenic acids exhibited significant antioxidant properties as measured by free-radical scavenging activity against 2,2-diphenyl-pycrilhydrazyl, total antioxidant capacity (based on the reduction of Cu^{2+} to Cu^{+}), and ability to inhibit lipid peroxidation as measured by TBARS assay (Vitalini et al. 2011). The results from the TBARS assay showed that among the compounds isolated, only luteolin 7-*O*-glucoside and apigenin 7-*O*-glucoside displayed an activity somewhat comparable to that of chlorogenic acid, even at the lowest concentration tested (1 µM); all the other phenolic compounds were able to inhibit the TBARS formation only at the highest concentration tested (10 µM). Total antioxidant capacity (%) (DPPH

scavenging activity) of yarrow aerial plant parts was 8.29 % and contribution from the main caffeoyl derivatives was as follows: chlorogenic acid 10.01 %, 3,5-DCQA (dicaffeoylquinic acid) 33.17 %, 1,5-DCQA 13.63 %, 4,5-DCQA 4.99 %, total caffeoyl derivatives 61.80 % (Fraisse et al. 2011).

An on-line HPLC-DPPH assay showed that *Achillea millefolium* possessed significant antiradical activity attributable to the presence of active phenolic compounds (Trumbeckaite et al. 2011). Its phenolic compounds had no effect on mitochondrial State 3 respiration rate. The extract at concentrations that had no effect on the State 3 respiration rate significantly decreased H_2O_2 production in mitochondria.

Vahid et al. (2012) conducted a randomized controlled trial involving 31 chronic kidney disease patients; 16 were administered 1.5 g of powdered *A. millefolium* flower 3 days a week for 2 months and 15 received placebo for the same period. They found that countercurrent to the placebo group, plasma nitric oxide metabolites, were marginally decreased after *A. millefolium* administration in chronic kidney disease patients. Nitric oxide-scavenging properties had been reported with some *Achillea* species.

Anticancer Activity

Three sesquiterpenoids, achimillic acids A, B and C, were found to be active against mouse P-388 leukemia cells in vivo (Tozyo et al. 1994). The flavonoid casticin, derived from *Achillea millefolium*, was found to have antitumor activity (Haïdara et al. 2006). Casticin caused cell growth arrest in G2/M and inapoptotic death. As a tubulin-binding agent (TBA), Casticin induced p21, which in turn inhibited Cdk1. Further, casticin appeared to downregulate cyclin A. Following casticin exposure, Bcl-2 depletion occurred in cancer cells, and a sub-G1 accumulation occurred in the cell cycle. A number of features suggested that casticin could be important in cancer therapy as Pgp-overexpressing cells were not resistant to casticin, and its cell killing effect was observed even in p53 mutant or null cell lines.

The chloroform-soluble extract of aerial parts of the *Achillea millefolium* aggregate exerted high tumour cell proliferation inhibitory activities on cervical cancer HeLa and breast cancer MCF-7 cells and a moderate effect on human epithelial carcinoma A431 cells (Csupor-Löffler et al. 2009). In the antiproliferative assay centaureidin was the most effective constituent of the aerial parts of yarrow, exhibiting high cell growth inhibitory activities especially on HeLa (IC_{50} 0.0819 μm) and breast cancer MCF-7 (IC_{50} 0.1250 μm) cells. Casticin and paulitin were also highly effective against all three tumour cell lines (IC_{50} 1.286–4.76 μm), while apigenin, luteolin and isopaulitin proved to be moderately active (IC_{50} 6.95–32.88 μm). Artemetin, psilostachyin C, desacetylmatricarin and sintenin did not display antiproliferative effects against these cell lines.

Achillinin A isolated from the flower exhibited potential antiproliferative activity to adenocarcinomic human alveolar basal epithelial A549, human lung adenocarcinoma RERF-LC-kj and human lung carcinoma QG-90 cells with 50 % inhibitory concentration (IC_{50}) values of 5.8, 10 and 0.31 μM, respectively (Li et al. 2011). Secotanapartholide A isolated from the flower, exhibited moderate cell growth inhibitory activity in vitro against the human cancer cell line MCF7 (IC_{50} = 5.51 μm) (Li et al. 2012a).

Antiinflammatory Activity

A water-soluble protein–carbohydrate complex isolated from the aqueous extract of *Achillea millefolium* flowers, at a dose of 40 mg/kg, exerted antiinflammatory activity as measured by the mouse paw edema test (Goldberg et al. 1969).

The crude plant extract of *A. millefolium* and its flavonoid fraction inhibited human neutrophil elastase (HNE) with IC_{50} values of approximately 20 μg/ml, whereas the dicaffeoylquinic acids fraction was less active (IC_{50} = 72 μg/ml) (Benedek et al. 2007b). The inhibitory activity on matrix metalloproteinases (MMP-2 and -9) was observed at IC_{50} values from 600 to 800 μg/ml, whereas the DCQA fraction showed stronger effects than the

flavonoid fraction and the extract. The scientists concluded that the in-vitro antiphlogistic activity of *Achillea* was at least partly mediated by inhibition of HNE and MMP-2 and MMP-9.

Aqueous extract from *Menyanthes trifoliata* induced a suppressive phenotype of dendritic cells that had reduced capacity to induce Th1 and Th17 stimulation of allogeneic CD4(+) T cells, whereas aqueous extract from *Achillea millefolium* reduced the capacity of dendritic cells to induce a Th17 response (Jonsdottir et al. 2011). Both Th1 and Th17 cells had been implicated in the pathogenesis of inflammatory bowel disease and experimental colitis.

Hepatoprotective Activity

Pretreatment of mice with *Achillea millefolium* crude extract (150–600 mg/kg) significantly prevented D-galactosamine (D-GalN- and lipopolysaccharide (LPS)-induced rise in plasma alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels (Yaeesh et al. 2006). The hepatoprotective effect of the extract was further verified by histopathology of the liver, which showed improved architecture, absence of parenchymal congestion, decreased cellular swelling and apoptotic cells, compared with (d-GalN) and LPS groups of animals. In isolated rabbit jejunum preparations, the extract caused a concentration-dependent (0.3–10 mg/ml) relaxation of both spontaneous and K^+-induced contractions as well as shifting the Ca^{2+} concentration-response curves (CRCs) to the right, similar to that caused by verapamil. These results indicated that the crude extract of *Achillea millefolium* exhibited a hepatoprotective effect, which may be partly attributed to its observed calcium channel blocking activity.

Spasmolytic Activity

The flavonoid fraction of *Achillea millefolium* exhibited spasmolytic activity on isolated terminal guinea pig ilea (Lemmens-Gruber et al. 2006). The aglycones quercetin, luteolin and apigenin exhibited the highest antispasmodic activities with IC_{50} values of 7.8, 9.8 and 12.5 µmol/l, respectively. Rutin and the flavonoid metabolites homoprotocatechuic acid and homovanillic acid showed no significant effects on contractility of the terminal ilea. They concluded that in tea prepared from yarrow, the concentration of the flavonoids was high enough to exert a spasmolytic effect in the gut, which was mainly caused by blockade of the calcium inward current, but additionally also by mediator antagonistic effects. In another study, *Achillea millefolium* hydroalcoholic extract inhibited electrical induced contractions of the isolated guinea pig ileum in a dose-dependent manner with EC_{50} value of 1.5 mg/ml (Babaei et al. 2007).

Choleretic Activity

A fraction of a 20 % methanol yarrow (*Achillea millefolium*) extract enriched in 3,4-, 3,5- and 4,5-DCCA dicaffeoylquinic acids (DCCAs) and luteolin-7-*O*-β-D-glucuronide was found to have choleretic effect in isolated perfused rat liver (IPRL) (Benedek et al. 2006). The fraction caused a dose-dependent increase in bile flow (23–44–47 %). Choleresis was two- to three-fold higher than that of cynarin, the main choleretic compound of *Cynara scolymus*, used as internal standard. The combined effect of DCCAs and luteolin-7-*O*-β-D-glucuronide stimulated bile flow more effectively than the single compound cynarin. Due to their polar structure, these compounds are quantitatively extracted into teas and tinctures.

Estrogenic Activity

A crude extract of the aerial parts of *A. millefolium* exhibited estrogenic activity in-vitro in recombinant MCF-7 cells (Innocenti et al. 2007). After fractionation of the crude extract, nine compounds were isolated and characterized: dihydrodehydrodiconiferyl alcohol 9-*O*-β-D-glucopyranoside, a glycosyl-neolignan; six flavone derivatives, apigenin, apigenin-7-*O*-β-D-glucopyranoside, luteolin, luteolin-7-*O*-β-D-glucopyranoside, luteolin-

4′-*O*-β-D-glucopyranoside, rutin; and two caffeic acid derivatives, 3,5-dicaffeoylquinic acid and chlorogenic acid. Apigenin and luteolin were the most important estrogenic compounds among those tested, for their ability to activate alpha or beta oestrogen receptors (ERalpha, ERbeta) using transiently transfected cells.

Antiulcerogenic Activity

Oral administration of rats with a hydroalcoholic extract of *Achillea millefolium* (30, 100 and 300 mg/kg) inhibited ethanol-induced gastric lesions by 35, 56 and 81 %, respectively (Potrich et al. 2010). Oral treatment with the extract (1 and 10 mg/kg) reduced the chronic gastric ulcers induced by acetic acid by 43 and 65 %, respectively, and promoted significant regeneration of the gastric mucosa after ulcer induction denoting increased cell proliferation, which was confirmed by PCNA (proliferating cell nuclear antigen) immunohistochemistry. The extract prevented the reduction of glutathione levels and superoxide dismutase activity after acetic acid-induced gastric lesions. The results suggested that the antioxidant properties of the hydroalcoholic extract may contribute to its gastroprotective activity.

Aqueous extract of *A. millefolium* aerial parts was found to be effective in protecting the gastric mucosa against acute gastric lesions induced by ethanol and indomethacin and in healing chronic gastric lesions induced by acetic acid with (ED_{50} = 32 mg/kg, p.o.) (Cavalcanti et al. 2006). Safety study showed slight changes in liver weight, cholesterol, HDL-cholesterol and glucose observed in male and female Wistar rats that were not correlated with dose or time of exposure of the animals. The results showed the antiulcer potential of *Achillea millefolium* extract that was accompanied by signs of relevant toxicity even at very long chronic exposure.

Immunomodulatory Activity

Achillea millefolium essential oil and 70 % crude ethanol leaf extract modulated the activation peritoneal macrophages cells from Swiss mice by weakly increasing nitric oxide (NO), at concentrations of 20, 10 and 5 mg/ml, compared to LPS (lipopolysaccharide-potent stimulator of NO production) (Lopes et al. 2003). They also reported *A. millefolium* essential oil was able to stimulate peritoneal macrophages to produce H_2O_2 and TNF-α without causing an overproduction of these compounds in peritoneal macrophages cells from Swiss mice, suggesting that the essential oil could modulate macrophages activation (Lopes et al. 2005).

Three glycosylated phenolic compounds, luteolin 7-*O*-glucoside, apigenin 7-*O*-glucoside and caffeic acid glucoside, were isolated from the methanol extract of aerial parts of *Achillea millefolium* (Yassa et al. 2007), and the immunological properties of different fractions of plant extract were studied on humoral immune system of BALB/c mice using microhaemagglutination test. Only two fractions at 125 and 61.5 mg/kg showed a significant decrease in the anti-SRBC (sheep red blood cell) titer of mice. The immunological properties of the fractions may be attributed to glycosylated derivatives of caffeic acid.

Spasmogenic Activity

A water extract of dried flower heads of *A. millefolium* exerted a direct spasmogenic effect on mouse and human gastric antrum (Borrelli et al. 2012). Among its constituents, choline, but not the flavonoids rutin and apigenin, mimicked the spasmogenic action. The authors concluded that the prokinetic effect of *A. millefolium* extract observed in vivo could provide the pharmacological basis underlying its traditional use in the treatment of dyspepsia.

Vasoprotective Activity

Achillea millefolium extract was found to enhance primary rat vascular smooth muscle cells by partly acting through oestrogen receptors and impairing NF-κB signalling in human umbilical vein endothelial cells (HUVECs) (Dall'Acqua et al. 2011). The results suggested that the extract

may have vasoprotective effect against vascular inflammation.

Antiplasmodial Activity

Among the phenolic compounds isolated from *A. millefolium* methanol extract, apigenin 7-*O*-glucoside and luteolin 7-*O*-glucoside were the most active against both strains of *Plasmodium falciparum* (Vitalini et al. 2011). The chlorogenic acids were completely inactive.

Hemostatic Activity

A glycoalkaloid, achilleine, isolated from the leaves was found to reduce clotting time in rabbits by 37 % (Miller and lee 1954).

Antinociceptive Activity

The hydroalcohol extract of *Achillea millefolium* (500 and 1,000 mg/kg) significantly inhibited abdominal contortions by 65 and 23 %, respectively, whereas *Artemisia vulgaris* (500 and 1,000 mg/kg) inhibited them by 48 and 59 %, respectively (Pires et al. 2009). None of the extracts produced differences in the intestinal transit in mice, nor in the response time in the hot plate or in the immediate or late responses in the formalin test. Both hydroalcohol extracts showed the same flavonoid glycoside as a principal constituent, which was identified as rutin. A high content of caffeic acid derivatives were also found in both extracts.

Hypotensive and Vaso- and Bronchodilatory Activities

The oral administration of *A. millefolium* hydroethanol extract (100–300 mg/kg), dichloromethane fractions (20and 10–30 mg/kg), but not ethyl acetate fraction (10 mg/kg) and butanolic fraction (50 mg/kg) fractions significantly reduced the mean arterial pressure (MAP) of normotensive rats (De Souza et al. 2011). The dichloromethane fractions were found to contain high amounts of artemetin which when administered by either oral (1.5 mg/kg) or intravenous (0.15–1.5 mg/kg) to rats was able to dose-dependently reduce the MAP. Intravenous injection of artemetin (0.75 mg/kg) significantly reduced the hypertensive response to angiotensin I while increasing the average length of bradykinin-induced hypotension. Artemetin (1.5 mg/kg, p.o.) was also able to reduce plasma (about 37 %) and vascular (up to 63 %) angiotensin-converting enzyme activity in-vitro, compared to control group.

The crude extract of *Achillea millefolium* caused a dose-dependent (1–100 mg/kg) fall in arterial blood pressure of rats under anaesthesia (Khan and Gilani 2011). In spontaneously beating guinea pig atrial tissues, the extract exerted negative inotropic and chronotropic effects. In isolated rabbit aortic rings, the extract (0.3–10 mg/ml) relaxed phenylephrine and high K^+-induced contractions. In guinea pig tracheal strips, the extract suppressed carbachol and K^+ - induced contractions. The results indicated that *A. millefolium* extract exhibited hypotensive, cardiovascular inhibitory and bronchodilatory effects and thus elucidated its use in hyperactive cardiovascular and airway disorders, such as hypertension and asthma.

Skin-Rejuvenating Activity

Studies showed that *Achillea millefolium* extract improved expression profile of various epidermal differentiation markers: cytokeratin 10, *trans*glutaminase-1 and filaggrin in cultured skin biopsies as well as increased epidermal thickness (Pain et al. 2011). In-vivo, a 2-month treatment with 2 % *A. millefolium* extract significantly improved the appearance of wrinkles and pores compared with placebo. Results were also directionally better than those of glycolic acid that was chosen as reference resurfacing molecule.

Anxiolytic Activity

Studies in mice showed that *Achillea millefolium* exerted anxiolytic-like effects in the

elevated plus-maze and marble-burying test after acute and chronic (25 days) oral administration at doses that did not alter locomotor activity (Baretta et al. 2012). This behavioral profile was similar to diazepam. The effects of *Achillea millefolium* in the elevated plus-maze were not altered by picrotoxin pretreatment but were partially blocked by flumazenil. Further, *Achillea millefolium* did not induce any changes in [(3)H]-flunitrazepam binding to the benzodiazepine (BDZ) site on the GABA(A) receptor indicating that the anxiolytic-like effects were likely not mediated by GABA(A)/BDZ neurotransmission.

Antimicrobial Activity

Achillea millefolium essential oil showed antimicrobial activity against *Streptococcus pneumoniae*, *Clostridium perfringens*, *Candida albicans*, *Mycobacterium smegmatis*, *Acinetobacter lwoffii* and *Candida krusei*, while water-insoluble parts of the methanol extracts exhibited slight or no activity (Candan et al. 2003). *Achillea millefolium* oils exhibited the antifungal activity against *Candida albicans*, *C. tropicalis*, *C. krusei*, *C. guillermondii*, *C. parapsilosis*, *Cryptococcus neoformans*, *Aspergillus niger*, *A. fumigatus*, *A. flavus* and dermatophytes *Trichophyton rubrum*, *T. mentagrophytes*, *T. mentagrophytes* var. *interdigitale*, *T. verrucosum*, *Microsporum canis*, *M. gypseum* and *Epidermophyton floccosum* (Falconieri et al. 2011). The oils showed the highest activity against dermatophyte strains, with MIC values ranging from 0.32 to 1.25 µl/ml.

Cyclophosphamide Toxicity Amelioration Activity

Studies showed that *Achillea millefolium* inflorescence aqueous extract may be partially protective against cyclophosphamide-induced testicular toxicity in male Wistar rats (Jalali et al. 2012). Cyclophosphamide-treated rats showed significant decreases in the body, testes and epididymides weights as well as many histological alterations. Stereological parameters, spermatogenic activities and testicular antioxidant capacity along with epididymal sperm count and serum testosterone concentration were also significantly decreased by cyclophosphamide. Co-treatment with *A. millefolium* extract caused a partial recovery in above-mentioned parameters.

Anticonflict Behaviour Activity

Molina-Hernandez et al. (2004) found that anticonflict-like behaviour actions of aqueous extract of *Achillea millefolium* flowers in female Wistar rats may vary according to the oestrous cycle phase. Doses of 8.0, 10.0, or 12.0 mg/kg of the extract reduced conflict behaviour during late proestrus. Conversely, during diestrus, only the dose of 12.0 mg/kg reduced conflict behaviour. During late proestrus, control rats displayed reduced conflict behaviour compared with diestrus. Diazepam (2.0 mg/kg; i.p.) reduced conflict behaviour both during late proestrus or diestrus.

Anthelmintic Activity

In-vitro studies revealed significant anthelmintic effects of aqueous extracts and ethanol extracts on live *Haemonchus contortus* worms as evident from their paralysis and/or death at 8 hours post-exposure (Tariq et al. 2008). Aqueous extracts of *A. millefolium* resulted in a mean worm motility inhibition of 94.44 %, while ethanol extracts resulted in mean worm motility inhibition of 88.88 %. The mean mortality index of aqueous extracts was 0.95 while for ethanol extracts it was 0.9. The lethal concentration 50 was 0.05 mg/ml for aqueous extracts and 0.11 mg/ml for ethanol extracts. The in-vivo anthelmintic activity of aqueous and ethanol extracts of *A. millefolium* demonstrated a maximum (88.40 %) nematode egg count reduction in sheep treated with aqueous extracts at 2 g/kg body weight on day 15 after treatment and 76.53 % reduction in faecal egg count for the ethanol extract at the same concentration.

Insecticidal Activity

A methanol extract of *Achillea millefolium* exhibited activity against 24-h-old larvae of *Aedes triseriatus* (Lalonde et al. 1980). The active principle was found to be the antilarval *N*-(2-methlpropyl)-(*E,E*)-2,4-decadienamide. Isolated and synthesized amides at 5 ppm resulted in 98 and 100 % mortality of 24-h-old *A. triseriatus* larvae. The *N*-(2-methylpropyl)-amides of decanoic and (*E*)-2-decenoic acids showed the same order of antilarval activity as *N*-(2-methylpropyl)-(*E,E*)-2,4-decadienamide, but *N*-(2-methylpropyl)sorbamide was inactive.

An ethanol extract of *Achillea millefolium* showed repellant activity against the mosquito, *Aedes aegypti* (Tunón et al. 1994). Of 35 compounds isolated from fractions of the extract, the most active were the nitrogen-containing compound stachydrine; the carboxylic acids, caffeic, chlorogenic and salicylic acids; and the phenolic compound pyrocatechol. They showed a distance and contact-repelling activity similar to the well-known repellent *N*,*N*-diethyl-m-toluamide (DEET) at about the same concentrations. Some further substances with lower activity were characterized for the first time in *A. millefolium*, i.e., adenine, ferulic and mandelic acid and the methyl esters of caprylic acid, linolenic acid and undecylenic acid.

Antileishmanial Activity

Studies showed that *Achillea millefolium* hydroalcoholic extract was effective for treatment of cutaneous leishmaniasis in mice (Nilforoushzadeh et al. 2008). Leishmaniasis is a parasitic disease transmitted by sand flies. The extract was more effective than glucantime. Mean of ulcer size reduction was 43.29 %. The essential oil from the leaves and flowers of *Achillea millefolium* was found to have antileishmanial activity in vitro (Santos et al. 2010). The median inhibitory concentration (IC_{50}) against *Leishmania amazonensis* promastigotes was 7.8 μg/ml, whereas the survival of amastigotes of this pathogen, within peritoneal murine macrophages, was halved by treatment with the oil at 6.5 μg/ml. The mean value for the median cytotoxic concentration of the oil, measured against adherent (uninfected) J774G8 macrophages, was 72.0 μg/ml (i.e., 9.2 and 11.0 times higher, respectively, than the IC_{50} against the promastigotes and intracellular amastigotes). Scanning and transmission microscopy studies showed that the oil caused alterations in shape, size and ultrastructural changes.

Trypanocidal activity

Treatment with *A. millefolium* essential oil inhibited the growth of *Trypanosoma cruzi* epimastigote and bloodstream trypomastigote forms (Santoro et al. 2007) but was less effective than clove oil.

Antifertility (Antispermatogenic) Activity

The ethanol extract (200 mg/kg/day, intraperitoneally, for 20 days) and a hydroalcoholic extract (300 mg/kg/day, orally, for 30 days) of *Achillea millefolium* flowers exerted antispermatogeic effect in Swiss mice (Montanari et al. 1998). The alterations observed were exfoliation of immature germ cells, germ cell necrosis and seminiferous tubule vacuolization. Animals treated with the extracts had an increased number of metaphases in the germ epithelium that might be due to cytotoxic substances or substances stimulating cell proliferation. Studies showed that administration *A. millefolium* extract at a dose of 800 mg/kg by intraperitoneal (IP) injection or through gavage to male Wistar rats for 22 days exerted temporary antispermatogenic effect on treated rats (Takzare et al. 2011). IP resulted in thickened seminiferous tubules on basal membrane, decrease in cell accumulation in seminiferous tubule, severe disarrangement, degenerative cells and severe decrease in sperm count. Oral administration caused thickening of basal membrane and cell disarrangement.

Toxicity/Genotoxicity Studies

A. millefolium, 0.35 and 3.5 mg/ml, did not cause statistically significant inhibition of cellular division in the onion root-tip cells (Teixeira et al. 2003). No statistically significant alterations were found, as compared to untreated controls, in either the cell cycle or the number of chromosome alterations, after treatments with *A. millefolium*, in rat cells or in cultured human lymphocytes. These results regarding the cytotoxicity and mutagenicity of *A. millefolium* provide valuable information about the safety of using them as therapeutic agents. Reproductive evaluation of aqueous crude extract of *Achillea millefolium* administered daily (0.3, 0.6 and 1.2 g/kg/day) during 90 days to male Wistar rats revealed no clinical signs of toxicity (in reproductive organ weights, sperm and spermatid numbers) over the treatment period, and body weight gain was similar in all groups (Dalsenter et al. 2004). A significant increase in the percentage of abnormal sperm in the group treated with the highest dose of yarrow extract was detected with no other important changes in the other reproductive endpoints. Additionally, a 3-day treatment of immature female rats with yarrow extract did not show any uterotrophic effects. Animal studies had shown yarrow to be generally safe and well tolerated but more human clinical studies were warranted (Applequist and Moerman 2011). The claim that yarrow had been shown to be specifically contraindicated during pregnancy was based on a single low-quality rat study, the results of which were incorrectly interpreted.

A. millefolium essential oil exhibited genotoxicity in a heterozygous diploid strain of *Aspergillus nidulans*, with green conidia (de Sant'anna et al. 2009). A statistically significant increasing number of yellow and white mitotic recombinants, per colony, of the diploid strain was reported after oil treatment with 0.19 and 0.25 μl/ml concentrations. The genotoxicity of the oil was associated with the induction of mitotic nondisjunction or crossing over.

The Final report on the Safety Assessment of Yarrow (*Achillea millefolium*) concluded that available published data were insufficient to support the safety of yarrow extract for use in cosmetic products (Anonymous 2001b). The following data were still required: (1) ultraviolet (UV) absorption data, if absorption occurs in the UVA or UVB range, photosensitization data are needed; (2) gross pathology and histopathology in skin and other major organ systems associated with repeated exposures; (3) reproductive and developmental toxicity data; (4) two genotoxicity studies, one using a mammalian system, if positive, a 2-year dermal carcinogenicity assay performed using National Toxicology Program (NTP) methods may be needed; and (5) clinical sensitization testing at maximum concentration of use.

Allergy Problems

Alpha-peroxyachifolid, a soluble component of yarrow was found to cause allergic contact dermatitis (Rücker et al. 1991). Alpha-peroxyachifolid was found to be a strong sensitizer in guinea pig sensitization experiments (Hausen et al. 1991). Other minor sesquiterpene lactones also contribute marginally to the sensitizing activity, while other known yarrow constituents like dehydromatricaria ester and pontica epoxide appeared to play no role.

Traditional Medicinal Uses

Yarrow (*Achillea millefolium* L.) is one of the most widely used plants in folk medicine in the world since antiquity. Yarrow is regarded as antiseptic, antispasmodic, mildly aromatic, astringent, carminative, cholagogue, diaphoretic, digestive, emmenagogue, odontalgic, stimulant, bitter tonic, vasodilator and vulnerary (Grieve 1971; Bown 1995; Chopra et al. 1986). It is has been used for treating wounds, inflammation, pain, liver disorders, gastritis disorders, amenorrhea, bowels, bleeding, hypertension, menstrual pains, dyspepsia, eczema, gum ailments, influenza, fevers and colds, catarrh, chicken pox, smallpox, measles, cystitis, diabetes, kidney diseases, menorrhagia, toothache, thrombosis, ulcers, varicose veins, lung haemorrhage, arthritis and poor vision (Grieve 1971; Chandler at el. 1982a, b; Duke and Ayensu

1985; Chopra et al. 1986; Bown 1995; Chevallier 1996). Yarrow is traditionally used against inflammatory and spasmodic gastrointestinal complaints, digestive problems, respiratory infections, hepatobiliary disorders, blood purification, as an appetite enhancing drug, against skin inflammations and for wound healing due to its antiphlogistic, choleretic and spasmolytic properties and, secondarily, among other uses, for liver disease and as a mild sedative (Benedek and Kopp 2007; Benedek et al. 2008; Applequist and Moerman 2011). The main pharmacologically active principles were shown to be the essential oil (antimicrobial), proazulenes and other sesquiterpene lactones (antiphlogistic), dicaffeoylquinic acids (choleretic) and flavonoids (antispasmodic) (Benedek et al. 2008). Yarrow is used in folk medicine as an emmenagogue (Innocenti et al. 2007).

A. millefolium is employed for the treatment of many different ailments in Iran (Kokkini et al. 2004); in West Azerbaijan, Iran, the infusion of dried flowers is recommended for the treatment of haemorrhoids, dyspepsia, dysmenorrhoea and gastritis (Miraldi et al. 2001); in the Parvati valley, west Himalaya, India, leaves and flowers are employed for gastric problems and fever (Sharma et al. 2004). Yarrow (*Achillea millefolium* L. s.l.) *Achillea millefolium* has a long history of use as traditional herb medicine even in veterinary medicine (Eghdami and Sadeghi 2010). Preparations in the form of infusions, decoctions, or fresh juices have been applied against anorexia, stomach cramps, flatulence, gastritis, enteritis, internal and external bleeding (coughing blood, nosebleed, haemorrhoidal and menstrual bleeding, bloody urine), wounds, sores, skin rash, as well as dog and snake bites. Yarrow has been used internally, usually as a tea, and externally as a lotion, ointment or poultice (Grieve 1971; Chandler et al. 1982a).

Yarrow has been used by native American Indians for treating bruises, burns, neck cramps, sprains and swollen tissues; healing wounds; and providing relief from rashes and itching of various causes (Chandler et al. 1982a). The plant was also a popular febrifuge and enjoyed some use in the treatment of the common colds, bloody urine, indigestion, bowel complaints, earache, headache, sore throat, toothache, spitting blood, haemorrhage and haemorrhoids. A number of its minor uses indicate that the plant is capable of imparting an analgesic (local anaesthetic), abortive and/or antiinflammatory effect and as an emmenagogue, laxative, tonic, stimulant, eyewash, sleep aid, liver aid and kidney aid.

Other Uses

Yarrow can be used as ground cover plant to combat soil erosion as it spreads rapidly and is drought resistant. It is also used as a companion plant as it repels bad insect pests and attracts beneficial predatory insects, such as ladybird beetle and parasitic wasps. The plant has been burnt in order to ward off mosquitoes. The plant and leaves can be used as compost and the leaves soaked in water to prepare a liquid leaf fertilizer for plants. The leaves contain essential oil and have been used as a cosmetic cleanser for greasy skin. The dried flowers and fresh foliage make attractive additions to floral arrangements. Yellow and green dyes are extracted from the flowers. The fragrant seeds have been used to impart a pleasant odour indoors.

Comments

In Australia, yarrow (*Achillea millefolium*) is deemed an environmental weed in Victoria, the ACT, and the southern parts of New South Wales. Though this species is naturalized in many parts of southern Australia, it is only considered to be a serious problem in the alpine and highland regions of southeastern Australia.

Selected References

Adekenov SM, Mukhametzhanov MN, Kupriyanov AN (1979) Sesquiterpene lactones of *Achillea noblis* Y. and *A. millefolium* Y. Deposited Doc. VINITI 1394-79 (Chem Abstr 93:3917K)

Afsharypuor S, Asgary S (1996) Volatile constituents of *Achillea millefolium* L. ssp. *millefolium* from Iran. Flavor Fragr J 11:265–267

Agnihotri VK, Lattoo SK, Thappa RK, Kaul P, Qazi GN, Dhar AK, Saraf A, Kapahi BK, Saxena RK, Agarwal SG (2005) Chemical variability in the essential oil components of *Achillea millefolium* agg. from different Himalayan habitats (India). Planta Med 71(3):280–283

Anonymous (2001a) *Achillea millefolium* L. Electronic flora of South Australia. Department for Environment and Heritage, Government of South Australia, Adelaide. http://www.flora.sa.gov.au

Anonymous (2001b) Final report on the safety assessment of yarrow (*Achillea millefolium*) extract. Int J Toxicol 20(Suppl 2):79–84

Anonymous (2001c) Ginini flats wetlands Ramsar site. Plan of management. Environment ACT, Canberra

Anonymous (2002) Australia's virtual herbarium. Australian National Botanic Gardens, Environment Australia, Canberra. http://www.anbg.gov.au/avh.

Applequist WL, Moerman DE (2011) Yarrow (*Achillea millefolium* L.): a neglected panacea? A review of ethnobotany, bioactivity, and biomedical research. Econ Bot 65(2):209–225

Babaei M, Abarghoei ME, Akhavan MM, Ansari R, Vafaei AA, Taherian AA, Mousavi S, Toussy J (2007) Antimotility effect of hydroalcoholic extract of yarrow (*Achillea millefolium*) on the guinea-pig ileum. Pak J Biol Sci 10(20):3673–3677

Baretta IP, Felizardo RA, Bimbato VF, dos Santos MG, Kassuya CA, Gasparotto A Jr, da Silva CR, de Oliveira SM, Ferreira J, Andreatini R (2012) Anxiolytic-like effects of acute and chronic treatment with *Achillea millefolium* L. extract. J Ethnopharmacol 140(1):46–54

Bejnarowicz EA, Smolenski SJ (1968) Gas chromatographic analysis of the essential oil from *Achillea millefolium* L. J Pharm Sci 57:2160–2161

Bélanger A, Dextraze L (1993) Variability of chamazulene within *Achillea millefolium*. Acta Hortic (ISHS) 330:141–146

Benedek B, Kopp B (2007) *Achillea millefolium* L. s.l. revisited: recent findings confirm the traditional use. Wien Med Wochenschr 157(13–14):312–314

Benedek B, Geisz N, Jäger W, Thalhammer T, Kopp B (2006) Choleretic effects of yarrow (*Achillea millefolium* s.l.) in the isolated perfused rat liver. Phytomedicine 13(9–10):702–706

Benedek B, Gjoncaj N, Saukel J, Kopp B (2007a) Distribution of phenolic compounds in middle European taxa of the *Achillea millefolium* L. aggregate. Chem Biodivers 4(5):849–857

Benedek B, Kopp B, Melzig MF (2007b) *Achillea millefolium* L. s.l. – is the anti-inflammatory activity mediated by protease inhibition? J Ethnopharmacol 113(2):312–317

Benedek B, Rothwangl-Wiltschnigg K, Rozema E, Gjoncaj N, Reznicek G, Jurenitsch J, Kopp B, Glasl S (2008) Yarrow (*Achillea millefolium* L. s.l.): pharmaceutical quality of commercial samples. Pharmazie 63(1):23–26

Benetis R, Radušienė J, Janulis V (2008) Variability of phenolic compounds in flowers of *Achillea millefolium* wild populations in Lithuania. Medicina (Kaunas) 44(10):775–781

Borrelli F, Romano B, Fasolino I, Tagliatatela-Scafati O, Aprea G, Capasso R, Capasso F, Coppola Bottazzi E, Izzo AA (2012) Prokinetic effect of a standardized yarrow (*Achillea millefolium*) extract and its constituent choline: studies in the mouse and human stomach. Neurogastroenterol Motil 24(2):164–171

Boskovic Z, Radulovic N, Stojanovic G (2005) Essential oil composition of four *Achillea* species from the Balkans and its chemotaxonomic significance. Chem Nat Compd 41(6):674–678

Bown D (1995) Encyclopaedia of herbs and their uses. Dorling Kindersley, London, 424pp

Candan F, Unlu M, Tepe B, Daferera D, Polissiou M, Sökmen A, Akpulat HA (2003) Antioxidant and antimicrobial activity of the essential oil and methanol extracts of *Achillea millefolium* subsp. *millefolium* Afan. (Asteraceae). J Ethnopharmacol 87(2–3):215–220

Cavalcanti AM, Baggio CH, Freitas CS, Rieck L, de Sousa RS, Da Silva-Santos JE, Mesia-Vela S, Marques MC (2006) Safety and antiulcer efficacy studies of *Achillea millefolium* L. after chronic treatment in Wistar rats. J Ethnopharmacol 107(2):277–284

Chandler RF, Hooper SN, Harvey MJ (1982a) Ethnobotany and phytochemistry of yarrow, *Achillea millefolium*, Compositae. Econ Bot 36:203–223

Chandler RF, Hooper SN, Hooper DL, Jamieson WD, Flinn CG, Safe LM (1982b) Herbal remedies of the Maritime Indians: sterols and triterpenes of *Achillea millefolium* L. (Yarrow). J Pharm Sci 71(6):690–693

Chatzopoulou P, Katsiotis ST, Svendsen AB (1992) An ascaridole containing essential oil of the *Achillea millefolium* L. complex growing wild in northern Greece. J Essent Oil Res 4(5):457–459

Chevallier A (1996) The encyclopedia of medicinal plants. Dorling Kindersley, London, 336pp

Chopra RN, Nayar SL, Chopra IC (1986) Glossary of Indian medicinal plants (Including the supplement). Council Scientific Industrial Research, New Delhi, 330pp

Csupor-Löffler B, Hajdú Z, Zupkó I, Réthy B, Falkay G, Forgo P, Hohmann J (2009) Antiproliferative effect of flavonoids and sesquiterpenoids from *Achillea millefolium* s.l. on cultured human tumour cell lines. Phytother Res 23(5):672–676

Cuong BH, Gács-Baitz E, Radics L, Tamás J, Ujszászy K, Verzár-Petri G (1979a) Achillicin, the first proazulene from *Achillea millefolium*. Phytochemistry 18(2):331–332

Cuong BH, Verzár-Petri G, Tamás J (1979b) Mass spectrographic and proton NMR structural data of chamazulene carboxylic acid. Arch Pharm 312:626–628

Dall'Acqua S, Bolego C, Cignarella A, Gaion RM, Innocenti G (2011) Vasoprotective activity of standardized *Achillea millefolium* extract. Phytomedicine 18(12):1031–1036

Dalsenter PR, Cavalcanti AM, Andrade AJ, Araújo SL, Marques MC (2004) Reproductive evaluation of aque-

ous crude extract of *Achillea millefolium* L. (Asteraceae) in Wistar rats. Reprod Toxicol 18(6):819–823

de Sant'anna JR, Franco CC, Miyamoto CT, Cunico MM, Miguel OG, Côcco LC, Yamamoto CI, Junior CC, de Castro-Prado MA (2009) Genotoxicity of *Achillea millefolium* essential oil in diploid cells of *Aspergillus nidulans*. Phytother Res 23(2):231–235

de Souza P, Gasparotto A Jr, Crestani S, Stefanello MÉ, Marques MC, da Silva-Santos JE, Kassuya CA (2011) Hypotensive mechanism of the extracts and artemetin isolated from *Achillea millefolium* L. (Asteraceae) in rats. Phytomedicine 18(10):819–825

Dokhani S, Cottrell T, Khajeddin J, Mazza G (2005) Analysis of aroma and phenolic components of selected *Achillea* species. Plant Food Hum Nutr 60(2):55–62

Duke JA, Ayensu ES (1985) Medicinal plants of China, vols. 1 and 2. Reference Publications, Inc. Algonac, 705pp

Eghdami A, Sadeghi F (2010) Determination of total phenolic and flavonoids contents in methanolic and aqueous extract of *Achillea millefolium*. Org Chem J 2:81–84

Facciola S (1990) Cornucopia: a source book of edible plants. Kampong Publications, Vista, 677pp

Falconieri D, Piras A, Porcedda S, Marongiu B, Gonçalves MJ, Cabral C, Cavaleiro C, Salgueiro L (2011) Chemical composition and biological activity of the volatile extracts of *Achillea millefolium*. Nat Prod Commun 6(10):1527–1530

Falk AJ, Smolenski SJ, Bauer L, Bell CL (1975) Isolation and identification of three new flavones from *Achillea millefolium* L. J Pharm Sci 64(11):1838–1842

Farooq U, Khan A, Khan SS, Iqbal S, Sarwar R, Khan SB, Ahmad VU (2012) Isolation and structure determination of three new sesquiterpenoids from *Achillea millefolium*. Z Naturforsch B Chem Sci 67(5):421–425

Figueiredo AC, Barroso JG, Pais MSS, Scheffer JJC (1992a) Composition of the essential oil from leaves and flowers of *Achillea millefolium* ssp. *millefolium*. Flavor Fragr J 7:219–222

Figueiredo AC, Barroso JG, Pais MSS, Scheffer JJC (1992b) Composition of the essential oils from two populations of *Achillea millefolium* L. ssp. *millefolium*. J Chromatogr Sci 30:392–395

Fraisse D, Felgines C, Texier O, Lamison J-L (2011) Caffeoyl derivatives: major antioxidant compounds of some wild herbs of the Asteraceae family. Food Nutr Sci 2:181–192

Gherase F, Miron A, Zagnat M, Hancianu M, Stanescu U, Grigorescu E (2004) Phytochemical investigations regarding the flavonoidic compounds of some species belonging to the *Achillea millefolium* L. group. Rev Med Chir Soc Med Nat Iasi 108(1):177–180 (In Romanian)

Glasl S, Kastner U, Jurenitsch J, Kubelka W (1999) Qualitative and quantitative determination of sesquiterpenoids in *Achillea* species by reversed-phase high-performance liquid chromatography, mass-spectrometry and thin-layer chromatography. J Chromatogr B Biomed Sci Appl 729(1–2):361–368

Glasl S, Mucaji P, Werner I, Presser A, Jurenitsch J (2002) Sesquiterpenes and flavonoid aglycones from a Hungarian taxon of the *Achillea millefolium* group. Z Naturforsch C 57(11–12):976–982

Glasl S, Mucaji P, Werner I, Jurenitsch J (2003) TLC and HPLC characteristics of desacetylmatricarin, leucodin, achillin and their 8alpha-angeloxy-derivatives. Pharmazie 58(7):487–490

Goldberg AS, Mueller EC, Eigen E, Desalva SJ (1969) Isolation of the anti-inflammatory principles from *Achillea millefolium* (Compositae). J Pharm Sci 58(8):938–941

Greger H, Hofer O (1989) Polyenoic acid piperideides and other alkamides from *Achillea millefolium*. Phytochemistry 28(9):1363–1368

Greger H, Werner A (1990) Comparative HPLC analyses of alkamides within the *Achillea millefolium* group. Planta Med 56(5):482–486

Grieve M (1971) A modern herbal, 2 vols. Penguin/Dover Publications, New York, 919pp

Guédon D, Abbe P, Lamaison JL (1993) Leaf and flower head flavonoids of *Achillea millefolium* L. subspecies. Biochem Syst Ecol 21(5):607–611

Hachey JM, Collin GJ, Gagnon MJ, Simard S, Dufour S, Jean FI, Vernin G, Fraisse D (1990) Extraction and GC/MS analysis of the essential oil of *Achillea millefolium* L. complex (Compositae). J Essent Oil Res 2(6):317–326

Haggag MY, Shalaby AS, Verzár Petri G (1975) Thin layer and gas-chromatographic studies on the essential oil from *Achillea millefolium*. Planta Med 27(4):361–366

Haïdara K, Zamir L, Shi QW, Batist G (2006) The flavonoid casticin has multiple mechanisms of tumor cytotoxicity action. Cancer Lett 242(2):180–190

Hausen BM, Breuer J, Weglewski J, Rücker G (1991) Alpha-Peroxyachifolid and other new sensitizing sesquiterpene lactones from yarrow (*Achillea millefolium* L., Compositae). Contact Dermatitis 24(4):274–280

Heinrich M (1996) Ethnobotany of Mexican Compositae: an analysis of historical and modern sources (pp. 475–503). In: Caligari PDS, Hind DJN (eds) Compositae: biology and utilization. Proceedings of the international Compositae conference, Kew, 1994, 2 Royal Botanic Gardens, Kew, 689pp

Hochmannová J, Herout V, Sorm F (1961) Isolation and structures of [three crystalline] sesquiterpenic lactones from yarrow (*Achillea millefolium*). Collect Czechoslov Chem Commun 26:1826–1831 (Chem Abstr 55:27400a)

Innocenti G, Vegeto E, Dall'acqua S, Ciana P, Giorgetti M, Agradi E, Sozzi A, Fico G, Tomè F (2007) In vitro estrogenic activity of *Achillea millefolium* L. Phytomedicine 14(2–3):147–152

Ivancheva S, Tomas-Barberan F, Tsvetkova R (2002) Comparative analysis of flavonoids in *Achillea* sp. sect. *millefolium* and sect. *ptarmica*. Compt Rend L'Acad Bulgare Sci 55:43–46

Jalali AS, Hasanzadeh S, Malekinejad H (2012) *Achillea millefolium* inflorescence aqueous extract ameliorates cyclophosphamide-induced toxicity in rat testis: stereological evidences. Chin J Nat Med 10(4):247–254

Jonsdottir G, Omarsdottir S, Vikingsson A, Hardardottir I, Freysdottir J (2011) Aqueous extracts from *Menyanthes trifoliata* and *Achillea millefolium* affect maturation of human dendritic cells and their activation of allogeneic CD4+ T cells in vitro. J Ethnopharmacol 136(1):88–93

Judzentiene A, Mockute D (2010) Essential oil composition of two yarrow taxonomic forms. Cent Eur J Biol 5(3):346–352

Kaloshina NA, Neshta ID (1973) Flavonoids of *Achillea millefolium*. Chem Nat Compd 9(2):261

Kasymov SZ, Sidyakin GP (1972) Lactones of *Achillea millefolium*. Chem Nat Compd 8(2):246–247

Khan AU, Gilani AH (2011) Blood pressure lowering, cardiovascular inhibitory and bronchodilatory actions of *Achillea millefolium*. Phytother Res 25(4):577–583

Kokkalou E, Kokkini S, Handidou E (1992) Volatile constituents of *Achillea millefolium* in relation to their infraspecific variation. Biochem Syst Ecol 20(7):664–670

Kokkini S, Kleftoyanni V, Hanlidou E, Karousou R (2004) The herbal market of Thessaloniki (N Greece) and its relation to the ethnobotanical tradition. J Ethnopharmacol 91:281–299

Konovalov DA, Chelombit'ko VA (1991) Sesquiterpene lactones from *Achillea millefolium*. Chem Nat Compd 27(5):640–641

Konyalioglu S, Karamenderes C (2005) The protective effects of *Achillea* L. species native in Turkey against H_2O_2-induced oxidative damage in human erythrocytes and leucocytes. J Ethnopharmacol 102:221–227

Lalonde RT, Wong CF, Hofstead SJ, Morris CD, Gardner LC (1980) N-(2-methylpropyl)-(E, E)-2,4-decadienamide a mosquito larvicide from *Achillea millefolium* L. J Chem Ecol 6(1):35–48

Lemmens-Gruber R, Marchart E, Rawnduzi P, Engel N, Benedek B, Kopp B (2006) Investigation of the spasmolytic activity of the flavonoid fraction of *Achillea millefolium* s.l. on isolated guinea-pig ilea. Arzneimittelforschung 56(8):582–588

Li Y, Zhang ML, Cong B, Wang SM, Dong M, Sauriol F, Huo CH, Shi QW, Gu YC, Kiyota H (2011) Achillinin A, a cytotoxic guaianolide from the flower of yarrow, *Achillea millefolium*. Biosci Biotechnol Biochem 75(8):1554–1556

Li Y, Ni ZY, Zhu MC, Zhang K, Wu YB, Dong M, Shi QW, Huo CH, Sauriol F, Kiyota H, Gu YC, Cong B (2012a) Millifolides A–C. New 1,10-seco-guaianolides from the flowers of *Achillea millefolium*. Z Naturforsch 67b(5):438–446

Li Y, Zhu MC, Zhang ML, Wang YF, Dong M, Huo CH, Shi QW, Sauriol F, Gu YC, Kiyota H, Cong B (2012b) Achillinin B and C, new sesquiterpene dimers isolated from *Achilliea millefolium*. Tetrahedron Lett 53(21):2601–2603

Lopes FCM, Placeres MP, Moreira RRD, Santos LE, Carlos IZ (2003) Avaliação de atividade imunológica de *Achillea millefolium* L. ("mil-folhas"). Rev Bras Farmacogn 13(2):11–13 (In Portuguese)

Lopes FCM, Benzatti FP, Junior CMJ, Moreira RRD, Carlos IZ (2005) Effect of the essential oil of *Achillea millefolium* L. in the production of hydrogen peroxide and tumor necrosis factor-α in murine macrophages. Rev Bras Cienc Farm 41(3):401–405

Lyakina MN (2002) Study of the total terpenoid composition in *Millefolium* homeopathic tinctures prepared from fresh and dry material. Pharm Chem J 36(8):437–439

Mehlführer M, Troll K, Jurenitsch J, Auer H, Kubelka W (1997) Betaines and free proline within the *Achillea millefolium* group. Phytochemistry 44(6):1067–1069

Miller FM, Lee MC (1954) Alkaloids of *Achillea millefolium* L. I. Isolation and characterization of achilleine. J Am Chem Soc 6(5):1353–1354

Miraldi E, Ferri S, Mostaghimi V (2001) Botanical drugs and preparations in the traditional medicine of West Azerbaijan (Iran). J Ethnopharmacol 75:77–87

Molina-Hernandez M, Tellez-Alcantara NP, Diaz MA, Perez Garcia J, Olivera Lopez JI, Jaramillo MT (2004) Anticonflict actions of aqueous extracts of flowers of *Achillea millefolium* L. vary according to the estrous cycle phases in Wistar rats. Phytother Res 18(11):915–920

Montanari T, de Carvalho JE, Dolder H (1998) Antispermatogenic effect of *Achillea millefolium* L. in mice. Contraception 58(5):309–313

Montsko G, Boros B, Takatsy A, Ohmacht R, Glasl S, Krenn L, Mark L, Reznicek G (2008) Separation of sesquiterpenes from yarrow (*Achillea millefolium* L. s. l.) by LC-MS on non-porous columns. Chromatographia 67(5–6):467–470

Nadim MM, Malik AA, Ahmad J, Bakshi SK (2011) The essential oil composition of *Achillea millefolium* L. cultivated under tropical condition in India. World J Agric Sci 7(5):561–565

Nemeth E, Bernath J (2008) Biological activities of yarrow species (*Achillea* spp.). Curr Pharm Des 14(29):3151–3167

Neshta ID, Kaloshina NA, Zapesochnaya GG, Ban'kovskii AI (1972) Rutin from *Achillea millefolium*. Chem Nat Compd 8(5):664

Nilforoushzadeh MA, Shirani-Bidabadi L, Zolfaghari-Baghbaderani A, Saberi S, Siadat AH, Mahmoudi M (2008) Comparison of *Thymus vulgaris* (Thyme), *Achillea millefolium* (Yarrow) and propolis hydroalcoholic extracts versus systemic glucantime in the treatment of cutaneous leishmaniasis in balb/c mice. J Vector Borne Dis 45(4):301–306

Ohir G, Budešínský M, Motl O (1991) 3-Oxa-guaianolides from *Achillea millefolium*. Phytochemistry 30(12):4163–4165

Orav A, Arak E, Raal A (2006) Phytochemical analysis of the essential oil of *Achillea millefolium* L. from various European Countries. Nat Prod Res 20(12):1082–1088

Pain S, Altobelli C, Boher A, Cittadini L, Favre-Mercuret M, Gaillard C, Sohm B, Vogelgesang B, André-Frei V (2011) Surface rejuvenating effect of *Achillea millefolium* extract. Int J Cosmet Sci 33(6):535–542

Pedneault K, Léonhart S, Gosselin A, Papadopoulos AP, Dorais M, Angers P (2002) Variations in concentration of active compounds in four hydroponically-and field-grown medicinal plant species. Acta Hortic (ISHS) 580:255–262

Pino JA, Rosado A, Fuentes V (1998) Chemical composition of the leaf oil of *Achillea millefolium* L. grown in Cuba. J Essent Oil Res 10(4):427–428

Pires JM, Mendes FR, Negri G, Duarte-Almeida JM, Carlini EA (2009) Antinociceptive peripheral effect of *Achillea millefolium* L. and *Artemisia vulgaris* L.: both plants known popularly by brand names of analgesic drugs. Phytother Res 23(2):212–219

Popescu H, Pop-Hakkel I (1980) Volatile oils extracted from the inflorescences of *Achillea-millefolium* from Sibiu district Romania. Clujul Med 53:74–78

Potrich FB, Allemand A, da Silva LM, Dos Santos AC, Baggio CH, Freitas CS, Mendes DA, Andre E, Werner MF, Marques MC (2010) Antiulcerogenic activity of hydroalcoholic extract of *Achillea millefolium* L.: involvement of the antioxidant system. J Ethnopharmacol 130(1):85–92

Roberts MJ (2000) Edible and medicinal flowers. New Africa Publishers, Claremont, 160pp

Rohloff J, Skagen EB, Steen AH, Iversen TH (2000) Production of yarrow (*Achillea millefolium* L.) in Norway: essential oil content and quality. J Agric Food Chem 48(12):6205–6209

Romo de Vivar A, Olmos F (1968) Chemical study of *Achillea millefolium*. Rev Soc Quim Mex 12:212A–213A (Chem. Abstr. 71: 3493q)

Rücker G, Manns D, Breuer J (1991) Peroxides as plant constituents. 8. Guaianolide-peroxides from yarrow, *Achillea millefolium* L., a soluble component causing yarrow dermatitis. Arch Pharm (Weinheim) 324(12):979–981 (In German)

Rücker G, Kiefer A, Breuer J (1992) Isoachifolidiene, a precursor of guaianolide peroxides from *Achillea millefolium* L. Planta Med 58(3):293–295

Saeidnia S, Yassa N, Rezaeipoor R (2004) Comparative investigation of the essential oils of *Achillea talagonica* Boiss. and *A. millefolium* L. chemical composition and immunological studies. J Essent Oil Res 16:262–265

Saeidnia S, Gohari A, Mokhber-Dezfuli N, Kiuchi F (2011) A review on phytochemistry and medicinal properties of the genus *Achillea*. Daru 19(3):173–186

Santoro GF, Cardoso MG, Guimarães LG, Mendonça LZ, Soares MJ (2007) *Trypanosoma cruzi*: activity of essential oils from *Achillea millefolium* L., *Syzygium aromaticum* L. and *Ocimum basilicum* L. on epimastigotes and trypomastigotes. Exp Parasitol 116(3):283–290

Santos AO, Santin AC, Yamaguchi MU, Cortez LE, Ueda-Nakamura T, Dias-Filho BP, Nakamura CV (2010) Antileishmanial activity of an essential oil from the leaves and flowers of *Achillea millefolium*. Ann Trop Med Parasitol 104(6):475–483

Schofield J (2003) Discovering wild plants: Alaska, Western Canada, The Northwest, 1st edn. Alaska Northwest Books, Anchorage, 353pp

Schröder H, Kastner U, Gargula K, Budešínský M, Haslinger E, Jurenitsch J, Kubelka W (1994) Artabsin and 3-oxa-artabsin derivatives from *Achillea millefolium* species. Phytochemistry 36(6):1449–1451

Sharma PK, Chauhan NS, Lal B (2004) Observations on the traditional phytotherapy among the inhabitants of Parvati valley in western Himalaya, India. J Ethnopharmacol 92:167–176

Shi Z, Humphries CJ, Gilbert MG (2011) *Achillea* Linnaeus. In: Wu ZY, Raven PH (eds) Flora of China, vols. 20–21 (Asteraceae). Science Press/Missouri Botanical Garden Press, Beijing/St. Louis

Smelcerovic A, Lamshoeft M, Radulovic N, Ilic D, Palic R (2010) LC–MS analysis of the essential oils of *Achillea millefolium* and *Achillea crithmifolia*. Chromatographia 71(1–2):113–116

Srabi RS, Meshkatalsadat MH (2010) The bioactive and volatile compositions of *Achilliea millefolium* using GC/MS and nano scale injection technique. Dig J Nanomater Biostruct 5(3):735–738

Suleimenov YE, Atazhanova GA, Ozek T, Demirci B, Kulyjasov AT, Adekenov SM, Baser KHC (2001) Essential oil composition of three species of *Achillea* from Kazakhstan. Chem Nat Compd 37(5):447–450

Takzare N, Hosseini MJ, Hamideh Mortazavi S, Safaie S, Moradi R (2011) The effect of *Achillea millefolium* extract on spermatogenesis of male Wistar rats. Hum Exp Toxicol 30(4):328–334

Tariq KA, Chishti MZ, Ahmad F, Shawl AS (2008) Anthelmintic efficacy of *Achillea millefolium* against gastrointestinal nematodes of sheep: in vitro and in vivo studies. J Helminthol 82(3):227–233

Teixeira RO, Camparoto ML, Mantovani MS, Vicentini VEP (2003) Assessment of two medicinal plants, *Psidium guajava* L. and *Achillea millefolium* L., in in vitro and in vivo assays. Genet Mol Biol 26(4):551–555

The Plant List (2012) http://www.theplantlist.org/

Tozyo T, Yoshimura Y, Sakurai K, Uchida N, Takeda Y, Nakai H, Ishii H (1994) Novel antitumor sesquiterpenoids in *Achillea millefolium*. Chem Pharm Bull(Tokyo) 42(5):1096–1100

Trendafilova A, Todorova M, Mikhova B, Duddeck H (2007) Flavonoids in flower heads of three *Achillea* species belonging to *Achillea millefolium* group. Chem Nat Compd 43(2):212–213

Trumbeckaite S, Benetis R, Bumblauskiene L, Burdulis D, Janulis V, Toleikis A, Viškelis P, Jakštas V (2011) *Achillea millefolium* L. s.l. herb extract: antioxidant activity and effect on the rat heart mitochondrial functions. Food Chem 127(4):1540–1548

Tunón H, Thorsell W, Bohlin L (1994) Mosquito repelling activity of compounds occurring in *Achillea millefolium* L. (Asteraceae). Econ Bot 48(2):111–120

Ulubelen A, Öksüz S, Schuster A (1990) A sesquiterpene lactone from *Achillea millefolium* subsp. *millefolium*. Phytochemistry 29(12):3948–3949

Uphof JCT (1968) Dictionary of economic plants, 2nd edn. (1st edn. 1959). Cramer, Lehre, 591pp

Vahid S, Dashti-Khavidaki S, Ahmadi F, Amini M, Salehi Surmaghi MH (2012) Effect of herbal medicine

Achillea millefolium on plasma nitrite and nitrate levels in patients with chronic kidney disease: a preliminary study. Iran J Kidney Dis 6(5):350–354

Valant-Vetschera KM, Wollenweber E (1988) Leaf flavonoids of the *Achillea millefolium* group. II. Distribution patterns of free aglycones in leaf exudates. Biochem Syst Ecol 16(7/8):605–614

Verzár-Petri G, Cuong BH, Tamás J, Radics L, Ujszászy K (1979a) The main azulenogenous sesquiterpene lactones of *Achillea millefolium* L. ssp. *collina* as compounds in the plant kingdom. Planta Med 36:273–274

Verzár-Petri G, Cuong BH, Radics L, Ujszászy K (1979b) Isolation of azulene from yarrow oil (*Achillea millefolium* L. species complex) and its identification. Herba Hung 18:83–95 (Chem Abstr 93:53745y)

Verzár-Petri G, Tamás J, Radics L, Ujszászi K (1980) Separation and identification of prochamazulenes of *Achillea millefolium* L. ssp. *collina* Becker. Acta Hortic (ISHS) 96:105–112

Vitalini S, Beretta G, Iriti M, Orsenigo S, Basilico N, Dall'Acqua S, Iorizzi M, Fico G (2011) Phenolic compounds from *Achillea millefolium* L. and their bioactivity. Acta Biochim Pol 58(2):203–209

Wojdyło A, Oszmian'ski J, Czemerys R (2007) Antioxidant activity and phenolic compounds in 32 selected herbs. Food Chem 105:940–949

Yaeesh S, Jamal Q, Khan AU, Gilani AH (2006) Studies on hepatoprotective, antispasmodic and calcium antagonist activities of the aqueous-methanol extract of *Achillea millefolium*. Phytother Res 20(7):546–551

Yassa N, Saeidnia S, Pirouzi R, Akbaripour M, Shafiee A (2007) Three phenolic glycosides and immunological properties of *Achillea millefolium* from Iran, population of Golestan. DARU 15(1):49–52