Matricaria chamomilla

Scientific Name

***Matricaria chamomilla* L.**

Family

Asteraceae

Synonyms

Camomilla deflexa Gilib. (Inval.), *Chamaemelum suaveolens* E.H.L. Krause, *Chamaemelum vulgare* Bubani, *Chamomilla chamomilla* (L.) Rydb. (Illeg.), *Chamomilla courrantiana* (DC.), *Chamomilla officinalis* K. Koch, *Chamomilla patens* Gilib. (Inval.), *Chamomilla recutita* (L.) Rauschert, *Chamomilla recutita* subsp. *bayeri*, *Chamomilla vulgaris* Gray, *Chrysanthemum chamomilla* (L.) Bernh., *Chrysanthemum suaveolens* (L.) Cav., *Courrantia chamomilloides* Sch. Bip., *Matricaria bayeri* Kanitz, *Matricaria capitellata* Batt. & Pit., *Matricaria chamomilla* f. *kochiana* (Sch. Bip.) Fiori & Paol., *Matricaria chamomilla* subsp. *pusilla* (Willd.) Holmboe, *Matricaria chamomilla* var. *recutita* (L.) Grierson, *Matricaria chamomilla* var. *recutita* (L.) Fiori, *Matricaria chamomilla* f. *suaveolens* Fiori & Paol., *Matricaria courrantiana* DC., *Matricaria exigua* Tuntas, *Matricaria kochiana* Sch.Bip., *Matricaria pusilla* Willd., *Matricaria recutita* L., *Matricaria recutita* var. *coronata* (Boiss.) Halácsy, *Matricaria recutita* var. *kochiana* (Sch.Bip.) Greuter, *Matricaria recutita* var. *recutita* L., *Matricaria salina* (Schur) Schur, *Matricaria suaveolens* L.

Common/English Names

Annual Camomile, Blue Chamomile, Camomile, Chamomile, Chamomille, Common Chamomile, German Chamomile, Hungarian Chamomile, Pin-Heads, Scented Mayweed, Sweet Chamomile, Sweet False Chamomile, Sweet Feverfew, True Chamomile, White Chamomile, Wild Camomile, Wild Chamomile

Vernacular Names

Albanian: Maraqi
Arabic: Baabunaj, Babunej
Argentina: Manzanilla
Bolivia: Manzanilla
Brazil: Camomila, Camomila Comum, Camomila Vulgar, Camomilha-Verdadeira. Maçanilha, Matricária
Chinese: Yang Gan Ju
Colombia: Camomilla, Manzanilla Chiquita, Manzanilla Commun, Manzanilla Dulce
Czech: Heománek Pravý, Heřmánek Lékařský, Heřmánek Pravý
Danish: Ægte Kamille, Kamille, Lægekamille, Moderurt, Pigeurt, Velduftende Kamille, Vellugtende Kamille

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Dutch: Echte Kamille, Roomse Kamille Sort
Eastonian: Chamomile, Teekummel
Egypt: Babounag
Esperanto: Kamomilo, Matrikario Refaldita, Vera Kamomilo
Finnish: Kamomillasaunio, Kamelinsaunio
French: Camomille, Camomille Allemande, Camomille Commune, Camomille Commune Ou d'Allemagne, Camomille Sauvage, Camomille Vraie, Herba De La Mera, Kamille, Matricaire, Matricaire Fausse Camomile, Matricaire Odorante, Matricaire Tronquée
Gaelic: Fíogadán Cumhra
German: Apfelblümlein, Apfelkraut, Echte Kamille, Feldkamille, Frauenblume, Ganille, Garnille, German Chamomile, Germeine Kamille, Gramillen, Haugenblume, Helmergen, Helmriegen, Hermel, Hermelin, Herminzel, Johannisköpfchen, Kamelle, Kamille, Kammerblume, Kummerblume, Kühmelle, Laugenblume, Mariamagdalenakraut, Muskatblume, Mutterkraut, Mägdeblume, Ramerian, Remi, Romerei
Guatemala: Manzanilla
Honduras: Manzanilla
Hungarian: Orvosi Székfű, Kamilla
Icelandic: Kryddbaldursbrá
India: Baboanh, Gul-Babunah, Roghan Babunah (Urdu)
Italian: Camomirra, Camomilla, Camomilla Commune, Capomilla
Japanese: Kamitsure, Kamiture
Mexico: Chamomille, Manzanilla
Nicaragua: Chamomille
Norwegian: Ettårig Kamille, Kamille, Kamilleblom, Kamomilleblom, Kannelblom, Kvitblom, Moderurt
Papiamento: Kanelublum
Persian: Baabunah
Polish: Rumianek, Rumianek Pospolity
Portuguese: Camomila, Camomila-Alemã, Camomila-Da-Alemanha, Camomila-Dos-Alemães, Camomila-Vulgar, Camomilla Legítima, Chamomilla, Macela, Macella, Mançanila, Margaça-Das-Boticas, Matricária
Russian: Romaška Aptečnaja
Slovašcina: Kamilica Prava, Prava Kamilica
Slovencina: Rumanček Kamilkový, Rumanček Pravý
Spanish: Amargaza, Bastardilla, Bonina, Camamila, Camamila Del Comercio, Camamilda, Camomilla, Chamomilla, Larrambillo, Magarza, Magarza Común, Magarza Montesina, Magarzuela Manzanilla, Manzanilla Alemana, Manzanilla Basta, Manzanilla Bastarda, Manzallina Blanca, Manzanilla Común, Manzanilla De Alemania, Manzanilla De Aragón, Manzanilla De Castilla, Manzanilla De Los Corrales, Manzanilla De Urgel, Manzanilla Del Huerto, Manzanilla Fina, Manzanilla Hedionda, Manzanilla Loca, Manzanilla Olorosa, Manzanilla Ordinaria, Manzanilla Real, Manzanilla Silvestre, Manzanilla Vera, Mazanilla Vulgar
Swedish: Äkta Kamomill, Kamomill, Sötblomster, Sötblomster Kamomill
Tunisia: Babunj, Matricaire
Turkish: Papatya

Origin/Distribution

Matricaria chamomilla is native to southern and eastern Europe and northern and western Asia. It has been introduced elsewhere and has naturalized in North America and Australia.

Agroecology

German chamomile is a cool climate species, growing in areas with temperatures of 7–26 °C and mean annual rainfall of 400–1,400 mm per season. It is frost tolerant down to −12 °C. It grows best in full sun and requires long summer days and high heat units for optimum essential oil yield (Alberts 2009). Optimum oil yields were found in temperature range of 20–26 °C, but increasing temperature had a negative impact on individual flower-head weight and days from buds to full-opened flowers (Bettray and Vömel 1992). Chamomile is not fastidious of soil types but thrives best on a well-drained, sandy or sandy-loam soils and

tolerates pH from 4.8 to 8.5. It will also grow on clayey lime soils as it has a great tolerance to soil alkalinity.

Edible Plant Parts and Uses

German chamomile is cultivated for its essential oil and dried flowers. The oils are used as agents in alcoholic beverages, confections, desserts, perfumes, aromatherapy and cosmetics. Dried flowers are used for aromatic and soothing herbal teas and blend with other teas, in syrups and fruit jelly (Roberts 2000).

Botany

Chamomile is an erect, aromatic, herbaceous annual, 15–80 cm high with a much branched, light green stem. The leaves are alternate, bipinnate or tripinnate with long and linear pinna, mildy pubescent to glabrous (Plate 1). Flowers are borne in solitary terminal capitula, 10–20 mm across, on 15–25 cm grooved peduncle (Plate 1). The receptacle is 6–10 mm wide; is hollow, swollen and obovoid to subglobose; and lacks involucral scales and paleae. The ray florets are ligulate, white 6–10 mm by 2.5–3.5 mm. The central disc florets are bisexual, tubular with 5-teeth, 1.5–2.5 mm long, yellow. The fruit is a yellowish brown cypsela with 3–5 faint ribs.

Nutritive/Medicinal Properties

Proximate nutrient composition per 100 g of brewed chamomile herbal tea was reported as follows: water 99.70 g, energy 1 kcal (4 kJ), carbohydrate 0.2 g, Ca 2 mg, Fe 0.08 mg, Mg 1 mg, K 9 mg, Na 1 mg, Zn 0.04 mg, Cu 0.015 mg, Mn 0.044 mg, F 13 µg, thiamine 0.010 mg, riboflavin 0.004 mg, pantothenic acid 0.011 mg, total folate 1 µg, total choline 0.4 mg, β-carotene 12 µg, vitamin A 1 µg RAE, vitamin A 20 IU, total saturated fatty acids 0.002 g, total monounsaturated fatty acids 0.001 g and total polyunsaturated fatty acids 0.005 g (USDA 2012).

Plate 1 Chamomile flowers and foliage

Other Flower Phytochemicals

Five organic acids were isolated from chamomile flowers: tartaric acid, citric acid, malic acid, malonic acid and succinic acid (Olennikov and Tankhaeva 2005). Mann and Staba (1986) had listed an extensive range of phytochemicals found in chamomile. The main constituents of chamomile flowers included several phenolic compounds, primarily the flavonoids apigenin, quercetin, patuletin, luteolin and their glucosides (McKay and Blumberg 2006). The principal components of the essential oil extracted from the flowers were the terpenoids α-bisabolol and its oxides and azulenes, including chamazulene.

The following chemicals were reported in chamomile flower heads: ascorbic acid, thiamine, niacin, polyphenols (quercetin, rutin, geraniol, gallic acid, tannin, catechin tannic, caprylic acid, kaempferol, thujone) and fatty acids (oleic, linoleic, palmitic, sinapic) (Mann and Staba 1986).

The terpenoids (−)-α-bisabolol oxides A, B and C were isolated from chamomile extract (Schilcher et al. 1976). Two spirocyclic polyines, the isomeric *cis* (*Z*)-enyne dicycloether *cis*-2-[hexadiyne)-(2,4)-ylidene]-1,6-dioxaspiro-[4,4]-nonene) and *trans* (*Z*)-enyne dicycloether *cis*-2-[hexadiyne)-(2,4)-ylidene]-1,6-dioxaspiro-[4,4]-nonene), were found in chamomile flowers (Bohlmann et al. 1961). The following phenyl carboxylic acids, synergic, vanillic, anisic and caffeic acids, were found in both ligulate and tubular chamomile florets (Reichling et al. 1979). Chamomile flower heads were also reported to contain *cis*/*trans*-en-in-dicycloethers (polyines) (Gasic et al. 1983), anthecotulid (37–120 mg/g) (Hausen et al. 1984) and up to 0.3 % choline (Bayer et al. 1958). In chamomile flowers from different origins, a range of 37.4–98.5 mg/100 g of herniarin and 6–17.8 mg/100 g of umbelliferone were determined (Schilcher and Kamille 1987). The average content in ligulate florets was significantly higher than in the tubular florets. The following coumarins, herniarin, umbelliferone, esculetin, isoscopoletin and scopoletin, were isolated from chamomile flowers (Kotov et al. 1991). A flavone 7-*O*-glucoside-specific glucosidase was purified and characterized from ligulate florets of *Chamomilla recutita*, and salicin, arbutin, naringenin 7-*O*-glucoside, luteolin 5-*O*-glucoside, and various *p*-nitrophenol compounds (-β-D-glucoside, -β-D-galactoside, -β-fucoside and a nitrophenyl-β-D-glucoside) were also isolated from the florets (Maier et al. 1993). The enzyme was confirmed to have a high affinity towards flavone 7-*O*-glucosides. Aqueous alcohol extracts of chamomile flowers were found to contain the following fat soluble compounds: β-farnesene (0.04–0.28 %), bisabolone oxide (<0.01–0.05 %), bisabolol oxide-A (0.15–0.59 %), spiroether (0.3–1.03 %) and pentacosane (0.08–0.11 %) (Kanamori et al. 1992). Two phenylpropanoids and one flavonoid glycosides were isolated from a 1-butanol-soluble portion of chamomile flowers (Kanamori et al. 1993). Their structures were elucidated as *cis*-2-β-D-glucopyranosyloxy-4-methoxy cinnamic acid (1) and *trans*-2-β-D-glucopyranosyloxy-4-methoxy cinnamic acid (2) and cosmosiin (apigenin-7-*O*-β-D-glucopyranoside) (3), respectively. All 3 compounds were found in higher concentration in ligulate flowers (compound (1) 4.32 %, compound (2) 1.32 %, cosmosiin 5.20 %) than tubular flowers (compound (1) 1.07 %, compound (2) 0.52 %, cosmosiin 0.02 %) or involucral scale (compound (1) 2.56 %, compound (2) 1.05 %, cosmosiin 0.17 %). Ahmad and Misra (1997) isolated oleonolic acid, β-sitosterol and β-sitosterol glucoside from the flowers by organic solvent extraction of chamomile flower oil. All three were also found in the capitulum receptacle (compound (1) 0.16 %, compound (2) 0.08 %, cosmosiin <0.01 %), stem (compound (1) 2.45 %, compound (2) 0.69 %, compound (3) 0.02 %) and leaf (compound (1) 1.75 %, compound (2) 0.67 %, cosmosiin 0.02 %). Two polyacylated spermines N1,N5,N10,N14-tetrakis[3-(4-hydroxyphenyl)-2-propenoyl]-1,5,10,14-tetraazatetradecane (tetracoumaroyl spermine) and N1,N5,N10-tris[3-(4-hydroxyphenyl)-2-propenoyl]-1,5,10,l14-tetraazatetradecane were found on chamomile flower extract (Yamamoto et al. 2002). Eleven bioactive phenolic compounds, namely, coumarins, herniarin and umbelliferone; phenylpropanoids, chlorogenic acid and caffeic acid; flavones, apigenin, apigenin-7-*O*-glucoside, luteolin and luteolin-7-*O*-glucoside; flavonols, quercetin and rutin; and flavanone, naringenin, were determined in chamomile extracts (Fonseca et al. 2007). The limits of detection and quantification for apigenin were 35.0 and 150.0 μg/ml, respectively.

The flavonoids quercetin-7-glucoside (quercimeritrin) and apigenin-7-glucoside (apigetrin) were isolated form chamomile florets (Hörhammer et al. 1963). Lipophilic flavonoids isolated from chamomile flowers included eupatoletin, eupalitin, chrysosplenol and chrysosplenitin (3,6,7,3′-tetramethyl-quercetagetin) (Hänsel et al. 1966). A new chamomile flavone apigenin 7-6″-*O*-(acetyl-)-glucoside was isolated from chamomile flowers and florets and the aglyca apigenin, luteolin, patulin, quercetin and isorhamnetin and the glycoside apigenin-7-glucoside, luteolin-7-glucoside, patulitrin and quercimeritrin were identified (Kunde and Isaac 1979). They further reported the presence of flavonoid and postulated a diacetylated apigenin-7-glucoside. They classified

chamomile flavonoids according their polarity into (a) lipophlic aglyca (e.g., methoxylated compounds), (b) hydroxylated flavones aglyca, (c) acetylated flavones monoglycosides and (d) flavones diglycosides. Methylated flavonoid aglycones, eupatoletin, eupalitin and chrysosplenol, were found in the flowers (Exner et al. 1981). From ligulate flowers of *Matricaria chamomilla* were isolated a mixture of apigenin 7-*O*-β-glucoside diacetates, which was shown to be based on (2″, 3″)- and (3″, 4″)-diacetates (Redaelli et al. 1982). The flavones apigenin and its glucosides, apigenin-7-glucoside and apigenin-7-acetylglucoside, were found in ligulate florets but not in the tubular florets of *Matricaria chamomilla* (Redaelli et al. 1981b). Dried ligulate chamomile flowers contained 7–9 % glucosides of apigenin and 0.3–0.5 % free apigenin. Glucosides were identified as apigenin 7-glucoside and a 1:3 mixture of the 2″- and 6″-acetates (Redaelli et al. 1980). The most abundant flavonoid derivatives in chamomile flowers were apigenin 7-glucoside and its acetylated derivatives, as well as luteolin, quercetin and their glycosides (Carle and Isaac 1985). Beside hydroxylated aglyca, methoxylated flavonoids like chrysosplenol, jaceidin, chrysoeriol, patuletin, spinacetin, 6-methoxykaempferol, axillarin, chrysosplenetin, eupatoletin and eupalitin were identified in chamomile flowers (Carle and Isaac 1985).

Accumulation of two phenylpropanoid glycosides, (1) *cis*-2-β-D-glucophyranosyloxy-4-methoxy cinnamic acid and (2) *trans*-2-β-D-glucophyranosyloxy-4-methoxy cinnamic acid and one flavonoid glycoside, (3) cosmosiin (apigenin-7-*O*-β-D-glucopyranoside) glycosides in chamomile flower head, reach a maximum during flowering (Ohe et al. 1995). The content of (1) and (2) reached 2 % and 0.5 % in the head respectively during harvesting, and their content was higher in the ligulate flowers than tubular flowers. Coumarin, umbelliferone and its methoxy analogue herniarin were also found in *M. chamomilla* flowers (Redaelli et al. 1981a). The polyphenolic compounds identified in the methanolic flower-head extract by Mulinacci et al. (2000) included 5-caffeoylquinic acid, 3-caffeoylquinic acid, 4-caffeoylquinic acid, quinic acid, ferulic acid-L-*O*-glycoside, caffeoylquinic acid derivative, ferulic acid-7-*O*-glycoside, quercetin-3-*O*-galactoside, quercetin-7-*O*-galactoside, patuletin-7-*O*-glucoside, dicaffeoylquinic acid derivative, 1,3-dicaffeoylquinic acid, apigenin-7-*O*-glucoside, quercetin derivative, luteolin-4′-*O*-glucoside, quinic acid derivative, apigenin-7-*O*-glucosyl-2″-acetate, apigenin-7-*O*-glucosyl-6″-acetate, apigenin-7-*O*-glucosyl-diacetate, apigenin, luteolin-7-*O*-rutinose and ferulic acid derivative.

Free and total apigenin contents in chamomile extracts were, respectively, determined as 106 and 903 μg/g (methanolic extract), 77 and 817 μg/g (ethanolic extract) and 11.0 and 247 μg/g (glycolic extract) (Fonseca and Tavares 2004). The major flavonoids (apigenin glucosides) identified in the white florets of chamomile were apigenin 7-*O*-glucoside, apigenin-7-(6″-malonyl-glucoside), apigenin-7-(6″-acetyl-glucoside), apigenin-7-(6″-caffeoyl-glucoside), apigenin-7-(4″-acetyl-glucoside), apigenin-7-(4″-acetyl,6″-malonyl-glucoside) and a partially characterized apigenin-7-(mono-acetyl/mono-malonylglucoside) isomer (Svehlikova et al. 2004). The bioactive principles in the ethanol/water extract of chamomile flowers were determined as *cis*-2-β-D-glucopyranosyloxy-4-methoxy-cinnamic acid, *trans*-2-β-D-glucopyranosyloxy-4-methoxy-cinnamic acid, apigenin-7-*O*-β-D-(6″-*O*-rhamnosyl)glucopyranoside (isorhoifolin), apigenin-7-*O*-β-D-glucopyranoside (cosmosiin), apigenin-7-*O*-β-D-(6″-*O*-acetyl) glucopyranoside, 7-Methoxycoumarin (herniarin) and 4′,5,7-trihydroxyflavone (apigenin) (Weber et al. 2008). The following flavonoids, kaempferol, quercetin, myricetin and isorhamnetin, were isolated from the ethanol chamomile flower extract (Mohamed 2010).

The main secondary metabolites of *Matricaria chamomilla* ligulate flowers were apigenin-7-*O*-glucoside derivatives and (*Z*)-2-β-D-glucopyranosyloxy-4-methoxy cinnamic acid and (*E*)-2-β-D-glucopyranosyloxy-4-methoxy cinnamic acid (GMCAs), the precursors of herniarin (Repčák and Krausová 2009). The flavonoids detected were apigenin7-*O*-glucoside,apigenin7-*O*-(6″-malonyl)-glucoside, apigenin 7-*O*-(4″-acetyl)-glucoside,

apigenin 7-*O*-(6″-caffeoyl)-glucoside, apigenin 7-*O*-(6″-acetyl)-glucoside, apigenin 7-*O*-(4″-acetyl, 6″-malonyl)-glucoside, and apigenin. The content of the apigenin glucoside and its main acylated derivatives in ligulate flowers of diploid plants were found to be significantly higher before the start of flowering in comparison with tetraploid plants. During the flowering and post-flowering phase, their content decreased and no difference between diploid and tetraploid plants was observed. The (*E*)-isomer was the dominant form of 2-β-D-glucopyranosyloxy-4-methoxy cinnamic acid. These secondary stress metabolite precursors were accumulated in higher concentrations in young growing ligulate flowers, but during flowering and post-flowering phases, their content decreased. Significantly higher content was found in tetraploid plants in comparison with diploid plants. Aglycones of glycosides were found in low concentrations.

Two new flavonoids quercetin and isorhamnetin besides myricetin and kaempferol were detected in the ethanolic extract of the flower head of *Matricaria chamomilla* growing in Iraq (Mohamed 2010). The most abundant phenolic compounds in both chamomile flowers and chamomile tea extracts were chlorogenic acid, umbelliferone, apigenin and apigenin-7-glucoside (Nováková et al. 2010). In chamomile tea extracts, there was greater abundance of flavonoid glycosides such as rutin or quercitrin, while the aglycone apigenin and its glycoside were present in lower amounts. The total content of polyphenols (in chlorogenic acid equivalents) in chamomile teas showed a significant variability as well as content of total flavonols (0.29–1.21 %) or total phenolic acids (7.7–91.4 mg/200 ml). (Raal et al. 2012). The major phenolic compounds in chamomile tea infusions were chlorogenic acids, ferulic acid glycosides, dicaffeoyl quinic acids and apigenin glycosides. Based on the amounts of essential oil, terpenoids, total flavonols and major phenolic compounds, the quality of the commercial chamomile teas was very variable, and the chamomile teas available in pharmacies should be preferred for the medical purposes. The major polyphenols detected were neochlorogenic acid; chlorogenic acid; cryptochlorogenic acid; ferulic acid glucoside 1; ferulic acid glucoside 2; quercetin galactoside; quercetin glucoside; luteolin glucoside; 3,4-dicaffeoyl quinic acid; 3,5-dicaffeoyl quinic acid; 4,5-dicaffeoyl quinic acid; apigenin glucoside; and apigenin acetylglucoside.

Farnesene, bisabolol, azulene (chamazulene), bisabolol oxide and terpene alcohol (farnesol) were the major constituents of the essential oil from dried chamomile flowers (Mishra et al. 1999). Oil from fresh flowers contained a high amount of terpene alcohol which decreased in shade-dried flowers and was the lowest in sun-dried flowers. The bisabolol content was the highest in sun-dried and minimum in fresh flowers. Farnesene content was higher in shade-dried flowers; bisabolol and azulene were higher in sun-dried flowers. The bisabolol oxide content was comparatively higher in fresh flowers (10.4 %) and was the least (8.4 %) in shade-dried flowers. The essential oil of chamomile inflorescence developed from callus cultures was found to contain chamomillol, gossonorol, cubenol, α-cadinol, (−)-α-bisabolol, 1-azulenethanol acetate and (−)-α-bisabolol acetate (Magiatis et al. 2001).

The Brazilian chamomile flower essential oil contained the following major components: bisabolol oxide B (23 %), bisabolol oxide A (17 %), (*Z*)-β-farnesene (16 %), α-bisabolol (13 %), chamazulene (8 %) and chamo-spiroether (5 %) (Matos et al. 1993). Studies in Yugoslavia found the chamomile essential oil content ranged from 0.24 to 0.50 % (Mimica-Dukic et al. 1993). The main compound in all samples was bisabolol oxide A (33.46–48.48 %); other major compounds were (−)-α-bisabolol, bisabolol oxide B, bisabolon oxide, farnesene, spathulenol, chamazulene, as well as en-in-dicycloether. Thirty-four compounds were identified in chamomile flower essential oil from Cuba, of which α-bisabolol oxide A (23.3 %), chamazulene (14.1 %), α-bisabolone oxide A (13.4 %) and β-caryophyllene (10.4 %) were the main constituents (Pino et al. 2000). Eighty compounds were identified in chamomile essential oil from Iran, of which α-bisabolol oxide A (43.8 %), α-bisabolone oxide A (13.6 %) and β-bisabolene (19.6 %) were predominant (Pino et al. 2002). Thirty-seven

components were found in the essential oil distilled from the flower heads in Eastonia (Orav et al. 2001). Oxygenated sesquiterpenes were the most characteristic chamomile essential oil components comprising 50–70 % of the total oil, among which bisabol oxide A accounted for 20.2 %–33.1 %, bisabolon oxide A 6.7–13.6 %, bisabolol oxide B for 7.9–12.4 % and α-bisabolol 2.9–7.8 %. Chamazulene represented 5.3–7.2 % and en-yn-dicycloether contributed 17.1–21.7 % of the total oil. Sesquiterpenes (5–16 %) mainly comprised (*E*)-β-farnesene (4.3–12.6 %). Monoterpenes and oxygenated monoterpenoid compounds contributed very little (<1 %) to the chamomile oil composition. The minor components included α-pinene trace (tr), sabinene tr 0.1 %,6-methyl-5-hepten-2-one 0.1 %, myrcene tr 0.1 %, 1,2,4-trimethylbenzene tr 0.1 %, 3-octanol 0.1–0.2 %, *p*-cymene tr 0.1 %, 1,8-cineole 0.1 %, limonene 0.1 %, (*E*)-β-ocimene tr 0.1 %, Artemisia ketone 0.2–0.4 %, γ-terpinene tr 0.1 %, terpinolene tr-0.1 %, terpinen-4-ol tr 0.1 %, α-terpineol tr 0.1 %, carvone tr 0.1 %, γ-elemene 0.1–0.3 %, decanoic acid 1.1–2.1 %, β-caryophyllene 0.1 %, germacrene 0.5–1.7 %, γ-muurolene 0.5–1.7 %, α-farnesene 0.3–0.9 %, β-bisabolene tr 0.7 %, γ-cadinene tr 0.1 %, σ-cadinene tr 0.1 %, (*E*)-nerolidol 0.1 %, spathylenol 2.3–3.6 %, caryophyllene oxide tr 0.2 %, T-cadinol 0.2 %, unidentified 0.1 %, and unidentified 0.5–0.9 %. Total oil yield was 1.88–2.09 mg/g. Forty-one components were identified in chamomile grown in the lower region of the Himalayas, representing 97.5 % of the oil (Sashidhara et al. 2006). The main constituents were α-bisabolol oxide A (36.5 %) and B (8.6 %), (*E*)-β-farnesene (14.0 %), α-bisabolol (16 %) and chamazulene (5.6 %). The main constituents, except for α-bisabolol oxide B, were found in higher concentration in oil from the foothills of the Himalayas than in the oil from the northern Indian plain. Eighteen volatile components were identified in the Iranian chamomile flower essential oil (Owlia et al. 2007). The major components were guaiazulene 25.6 %, (*E*)-β-farnesene 20.1 %, chamazulene 12.4 %, α-bisabolol oxide B 7.3 %, α-bisabolol 7.3 %, hexadecanol 5.6 % and germacrene D 3.15 %. Other components included *Z*-γ-bisabolene 2.6 %, -bisabolol oxide A 1.9 %, spathulenol 1.7 %, *n*-nonadecane 1.4 %, caryophyllene oxide 1.2 %, α-muurolene 0.8 %, limonene 0.5 %, γ-terpinene 0.5 %, *n*-pentacosane 0.5 % and sclarene 0.4 %. The main compounds identified in chamomile flower essential oil were α-bisabolol (56.86 %), *trans-trans*-farnesol (15.64 %), *cis*-β-farnesene (7.12 %), guaiazulene (4.24 %), α-cubebene (2.69 %), α-bisabolol oxide A (2.19 %) and chamazulene (2.18 %) (Tolouee et al. 2010). Chamomile essential oil was found to contain 13 compounds, mainly bisabolol and its oxides, chamazulene, farnesene, germacrene and other sesquiterpenes (Hernández-Ceruelos et al. 2002). A total of 39 components were identified, representing over 92 % of the total oil yield of chamomile oils from European countries (Orav et al. 2010). The principal biologically active compounds in chamomile oils were bisabolol oxide A (3.1–56.0 %), α-bisabolol (0.1–44.2 %), bisabolol oxide B (3.9–27.2 %), *cis*-enyne-bicycloether (8.8–26.1 %), bisabolon oxide A (0.5–24.8 %), chamazulene (0.7–15.3 %), spathulenol (1.7–4.8 %) and (*E*)-β-farnesene (2.3–6.6 %). In 8 chamomile samples from 13, bisabolol oxide A (27.5–56.0 %) was predominant (among them in three Estonian samples). α-Bisabolol (23.9–44.2 %) was predominant in the samples from Moldova, Russia and the Czech Republic. The sample from Armenia was rich in bisabolol oxide B (27.2 %) and chamazulene (15.3 %). The oils were obtained in yields of 0.7–6.7 ml/kg and the minimum limit of 4 ml/kg stated by the European Pharmacopoeia was exceeded only in 13 samples from 13 analyzed drugs.

Both aqueous and methanolic chamomile flower extracts demonstrated the presence of mixture of several apigenin glucosides and parent glycone, apigenin (Srivastava and Gupta 2009). Other apigenin glucosides identified in chamomile extracts were mono-caffeoyl glucoside, mono-acetyl glucoside and mono-malonyl glucoside as well as mono-acetyl/mono-malonyl glucosides. The methanolic chamomile extract had high concentration of apigenin-7-*O*-gluco-

side along with several polyphenolic constituents which include caffeic acid, luteolin and luteolin-7-*O*-glucoside, among common flavonoids. The aqueous chamomile extract was found to contain a small fraction (5–7 % of total essential oil) content of the flower. The essential oil content in the methanolic extract consists of chamazulene, α-bisabolol, bisabolol oxides A and B, a cyclic ether and different hydrocarbons which were insoluble in the aqueous phase. Aqueous extracts obtained from both Lebanese and Egyptian chamomile varieties showed the abundance of apigenin-7-*O*-glucoside. Methanolic chamomile extract prepared from ray florets of Lebanese and Egyptian chamomile showed the presence of apigenin-7-*O*-glucoside (39 %) and the aglycone, apigenin, 6.7 % in the Egyptian and 2.3 % in the Lebanese variety. Disc florets of chamomile from Lebanese origin showed higher content of apigenin-7-*O*-glucoside (38.5 %) compared to Egyptian variety (36.1 %) but had no aglycone. Salamon et al. (2010) characterized Egyptian and Iranian chamomile landraces into 4 basic chemotypes based on the main components (%) in the essential oil:

Type A (South American collection): α-bisabolol oxide B (22.43–58.85 %) > α-bisabolol oxide A (4.74–15.68 %) > α-bisabolol (4.37–15.41 %), (en-yn-dicyloethers 2.61–11.27 %, chamazulene 2.70–17.69 %).

Type B (Egypt and central Europe): α-bisabolol oxide A (31.07–52.25 %) > α-bisabolol oxide B (5.27–18.79 %) > α-bisabolol (8.81–12.92 %), (en-yn-dicyloethers 4.08–9.90 %, chamazulene 5.40–7.95 %).

Type C (Spain/Catalonia, Malta, Crimea): α-bisabolol (24.18–77.21 %) > α-bisabolol oxide B (3.17–34.46 %) > α-bisabolol oxide A(2.13–18.50 %) (en-yn-dicyloethers 1.92–12.00 %, chamazulene 1.91–7.89 %).

Type D (southeast Europe, Turkey): α-bisabolol oxide B (10.43–24.20 %) > α-bisabolol oxide A (9.62–25.83 %) > α-bisabolol (8.49–19.58 %), (en-yn-dicyloethers 5.51–10.68 %, chamazulene 1.91–7.89 %). The highest contents of α-bisabolol oxide A and α-bisabolol oxide B in the flower anthodia were found in the Egyptian chamomile.

The total extract yield of chamomile oil obtained by solvent extraction (4.98 %) was much higher than the oil yield obtained by steam distillation even after 6 hours (0.31 %) (Falzari and Menary 2003). The oil yield increased with increasing duration of steam distillation but after 6 hours distillation the yield of solvent extract is still 16 times greater than the yield of steam distilled oil. The main volatile components of chamomile essential oil were *E*-β-farnesene(42.59 %), germacrene D (2.93 %), bicyclogermacrene (1.99 %), (*E*,*E*)-α-farnesene (8.32 %), α-bisabolol oxide B (4.43 %), α-bisabolone oxide A (4.53 %), chamazulene (1.18 %), α-bisabolol oxide A (21.16 %) and *cis*-ene-yne-dicycloether (5.94 %) (Heuskin et al. 2009). Other minor components included *trans*-ene-yne-dicycloether (0.99), (*E*)-phytol (0.23 %), globulol (0.23 %), spathulenol (0.63 %), dendrolasin (0.21 %), dehydronerolidol (0.09 %), *trans*-nerolidol (0.17 %), unidentified sesquiterpene (0.33 %), sesquirosefuran (0.18 %), δ-cadinene (0.18 %), (*Z*,*E*)-α-farnese (0,83 %), β-selinene (0.22 %), unidentified sesquiterpene (0.10 %), aromadendrene (0.07 %), β-caryophyllene (0.17 %), α-gurjunene (0.04 %), sativene (0.04 %), β-elemene (0.7 %), α-isocomene (0.26 %), β-maaliene (0.07 %), α-copaene (0.04 %), 4,8-dimethylnona-3,8-dien-2-one (0.04 %), isoborneol (0.03 %), artemesia alcohol (0.06 %), artemisia ketone (0.32 %), γ-terpinene (0.17 %), *cis*-β-ocimene (0.69 %), *trans*-β-ocimene (0.11 %), limonene (0.10 %), *p*-cymene (0.11 %), 2-pentylfuran (0.05 %), 6-methyl-5-hepten-2-one (0.03 %), sabinene (0.04 %) and α-pinene (0.03 %). Precocenes and piperitone (Yaguchi et al. 2006) and (*E*)- and (*Z*)-spiroethers (Yoshinari et al. 2008) were isolated from chamomile essential oil.

The constituents of chamomile flower oil comprised oxides (59.42 %), hydrocarbons (5.88 %), ethers (11.98 %), acids/esters (3.87 %), aldehydes/ketones (0.79 %), sesquiterpene lactones (6.18 %), alcohols (2.57 %), coumarins/miscellaneous compounds (0.35 %) and unknowns (5.62 %) (Tschiggerl and Bucar 2012). The major constituents were α-bisabolol oxide A (29.92 %), α-bisabolol oxide B (21.13 %), α-bisabolone oxide A (7.87 %), β-farnesene (3.90 %), *cis*-spiroether

(11.67 %) and chamazulene (6.18 %). The major constituents of the flower infusion extract obtained by hydrodistillation were α-bisabolol oxide A (28.26 %), α-bisabolol oxide B (25.92 %), α-bisabolone oxide A (5.83 %), β-farnesene (1.10 %), *cis*-spiroether (4.69 %), chamazulene (19.11 %) and decanoic acid (1.56 %). The major constituents of the flower infusion extract obtained by solid phase extraction were α-bisabolol oxide A (22.80 %), α-bisabolol oxide B (8.09 %), α-bisabolone oxide A (1.59 %), *cis*-spiroether (25.62 %), *trans*-spiroether (6.40 %), chamazulene (1.77 %), achillin (2.88 %), matricarin/acetoxyachillin (5.20 %) and methylumbelliferone (5.55 %). Two sesquiterpene lactones leucodin (0.53 %) and acetoxyachillin were newly indentified together with achillin and matricarin in the chamomile infusion extract. They found that high amounts of spiroethers (ca. 30% in the infusion as compared to ca. 12 % in the genuine oil) and coumarins (ca. 7 %) and reduced amounts of bisabolol oxides (ca. 32 % in the infusion vs. ca. 60 % in the genuine oil) can be regarded as markers of the volatile fraction of chamomile tea. Their results demonstrated that solid phase extraction or other liquid extraction methods should be preferred over hydrodistillation when characterizing the aromatic composition of infusions.

The highest essential oil content was found in fully developed flowers approximately 1 week after beginning of flowering (Franz 1980). The composition of the essential oil depended on the stage of development. Flower buds contained more hydrocarbons and (−)-α-bisabolol, whereas with development of the flowers, chamazulene and the (−)-α-bisabolol oxides increased. The content of enin-dicycloethers increased in the receptacle. In another study, the quantity of α-bisabolol, α-bisabolol oxides A and B and α-bisabolon oxide A in chamomile flower reached a maximum at full bloom and then declined (Arak et al. 1980). The farnesene content of the flower decreased gradually with flower growth and development. The qualitative composition of essential oil remained stable at all stages of flower development. Accumulation of essential oil in chamomile flowers continued during drying, and its quantitative composition depended on the drying method. Harvesting at the early flowering phase and drying in a shaded place were recommended.

Among 30 compounds detected in dried chamomile flowers at two development stages, (*E*)-β-farnesene (49 %), artemisia ketone (10 %) and germacrene D (9 %) were the predominant volatile components in the HS-SPME (headspace solid-phase microextraction) extract, while α-bisabolol oxide A (42 %), chamazulene (21 %) and (*Z*)-spiroether (8 %) were the main essential oil constituents among the 13 compounds obtained by SDSE (steam distillation-solvent extraction) (Rafieiolhossaini et al. 2012). (*E*)-β-farnesene was the only compound which showed significant differences between the development stages of two flowers: stage I, when ligulate flowers start to develop and tubular flowers were still closed, and stage II, when tubular flowers were partially to completely opened. Eliasová et al. (2012) found that polyamine conjugate 1*N*,5*N*,10*N*,14*N*-tetracoumaroyl spermine (tetracoumaroyl spermine) was present mainly in tubular flowers, reaching its maximal content during the 3rd phase of flowering when the corollae of tubular flowers start to open. The later observed decrease could result from a release of pollen that also contained a considerable amount of tetracoumaroyl spermine. They postulated that tetracoumaroyl spermine may play an important role in pollen development. This polyamine from chamomile flower heads could be used for the treatment of several human disorders such as depression and anxiety.

The purified mucilage from chamomile flowers yielded xylose (21 %), arabinose (10 %), galactose (15 %), glucose (7 %), rhamnose (2 %) and glucuronic acid (45 %) (Janecke and Weisser 1964, 1965). The mucilage had a degree of polymerization of approximately 27 (molecular weight 3,500–4,200) and the linkages of sugars in the mucilage were suggested to be predominantly β-glycosidic. Carle and Isaac (1985) reported that chamomile mucilage consists of fructose, arabinose, xylose, glucose, galactose, rhamnose, galacturonic acid and glucosamine and the main chain the polysaccharide tp consists of α-1 → 4

connected D-galacturone acids. The polysaccharide was later confirmed to be methyl-glucurone oxylane (Füller et al. 1991, 1993). They also identified a neutral fructane of medium molecular mass 3,600 containing 74.3 % fructose, 3.4 % glucose (similar to inulin) and a strongly branched rhamnogalacturonane of medium molecular mass 9,300 consisting of 28 % uronic acid and 3.2 % protein (similar to pectin). These were found to have arabino-3,6-galactane glycoproteins as side chains. In an aqueous alcoholic chamomile extract, only fructanes were found.

Root Phytochemicals

The essential oil of *Matricaria chamomilla* roots contained the sesquiterpenes chamomillol, caryophyllene, caryophyllenepoxide and the polyenes Chamomillaester I and II (Reichling et al. 1984). The essential oil accumulated in schizogenous oil passages and oil cells restricted to the roots. Callus surface cultures of *Matricaria chamomilla* initiated from stems and flower heads produced an essential oil similar to that of the root. It exclusively accumulated in oil cells typical of the roots.

Plant Aerial Parts/Leaf/Cell Culture Phytochemicals

Sesquiterpenes, flavonoids, coumarins and polyacetylenes are considered the most important constituents of the chamomile drug (Schilcher and Kamille 1987). Secondary metabolites found in *M. chamomilla* included isobutyl angelate, 2-methylbutyl angelate, farnesene, β-farnesene, farnesol, (−)-α-bisabolol, bisabolol oxide A, bisabolol oxide B, matricin, chamazulene, guaiazulene, umbelliferone, herniarin, caffeic acid, chlorogenic acid, apigenin, luteolin, apigenin-7-*O*-glucoside, luteolin 7-*O*-glucoside, quercetin and *Z*-enyne dicycloether.

Flavonoids found in chamomile leaves included 7-glucosides of quercetin, isorhamnetin and luteolin together with small amounts of chrysoeriol and apigenin 7-glucoside and their aglyca (Greger 1975).

Polyphenolic compounds (g/kg dry matter) in the aerial chamomile plant parts were determined as follows: chlorogenic acid 1.16 g, 3,5-DCQA (dicaffeoylquinic acid) 2.92 g, 4,5, DCQA 1.61 g, total caffeoyl derivatives 5.69 g, total dihydroxycinnamic acid derivatives 15.89 g, total flavonoids 9.48 g, total dihydroxycinnamic acid derivatives + flavonoids 25.37 g and total polyphenolic compounds 36.79 g (Fraisse et al. 2011). The highest amount of phenolic and flavonoid was detected in the methanol extract of chamomile aerial parts with a mean value of 50.7 and 36.7 % and the lowest in the aqueous extract with a mean value of 3.94 and 1.36 %, respectively (Haghi et al. 2013). The apigenin 7-glucoside (0.21–1.23 g/100 g dry samples) in the crude extracts was much higher than the free apigenin (0.04–0.74 23 g/100 g dry samples). The compounds detected were chlorogenic acid, caffeic acid, *p*-coumaric acid, salicylic acid and flavonoids, rutin, apigenin-7-glucoside, quercetin, luteolin, apigenin, kaempferol and isorhamnetin.

Matricaria chamomilla cell suspensions cultured in a two phase system consisting of an aqueous nutrient medium and a nontoxic lipophilic phase (triglyceride) accumulated (Bisson et al. 1983) a great number of lipophilic substances in the triglyceride phase during the first week of culture period. One of these substances was identified as α-bisabolol. The composition of the essential oil of chamomile hairy root cultures on different media, namely, Murashige-Skoog (MS) medium and Gamborg (B5) media, was found to be similar, but differing in proportion (Máday et al. 1999). The main component of the essential oil was *trans*-β-farnesene, as in the intact roots. Chamomile essential oil was found to contain primarily chamazulene, (−)-α-bisabolol, bisabolol oxides, bisabolon oxide A, *trans*-β-farnesene, α-farnesene, spathulenol, β-eudesmol and *cis*/*trans*-en-in-dicycloethers. Formaldehyde was found in intact plants, micropropagated plants and hairy root cultures of chamomile (Máday et al. 2000). HCHO should not be considered as a side product, but a basic and indispensable component, required for various biological processes in chamomile.

Flavonoids, Coumarins, Mucilages, Mono- and Oligosaccharides Also Had Pharmacological Effects

Among the cultivated and wild chamomile species examined, the wild species from the areas of Szeghalom were found to contain the highest quantity of β-eudesmol (9.25 % in the total essential oil) in intact and organized roots of chamomile cultures (Szöke et al. 2004a). A new component α-selinene (Szöke et al. 2004c) and germacrene D, berkheyaradulene, 4-(2′, 4′, 4′-trimethyl-bicyclo[4.1.0]hept-2′-en-3′-yl)-3-buten-2-one, geranyl-isovalerate and cedrol, were found in the hairy roots of sterile chamomile cultures (Szöke et al. 2004d). These cultures generated the most important terpenoid and polyin compounds characteristics of the intact plant. Among wild chamomile populations in Hungary, a population was found in the area of Szabadkigyós containing significant amounts, on average 48 %-of (−)-α-bisabolol in its inflorescence oil. The intact roots of in vitro cultures contained no (−)-α-bisabolol but contained the sesquiterpene alcohol β-eudesmol. The main components of hairy root cultures derived from wild chamomile rich in (−)-α-bisabolol in the inflorescence oil were *trans*-β-farnesene, α-farnesene, geranyl isovalerate and cedrol. β-Selinene was identified as a new component of the genetically transformed cultures (Szöke et al. 2004b).

Effect of Abiotic Factors on Chamomile Oil and Chemical Composition

Optimum chamomile oil yield was found to be strongly influenced by genotype and optimum ecological conditions (Bettray and Vömel 1992). Herb quantity, individual flower-head weight and days from buds to full-opened flowers of genotypes were reduced with increasing temperature, but content of apigenin, (−)-α-bisabolol and essential oil but not chamazulene rose with increasing temperature, optimal yields were obtained from 20 to 26 °C. The content of apigenin-7-glucoside was influenced by genotype and not temperature. The increased content of the coumarin, umbelliferone, was observed in leaves 12 hours after abiotic stress elicitation by $CuCl_2$ (Repcák et al. 2001). In 48 hours, this amount rose approximately ten times. In the same period of time, a decrease of (*Z*)- and (*E*)-2-β-D-glucopyranosyloxy-4-methoxy cinnamic acid and an increase of herniarin were found. The content of herniarin in the $CuCl_2$-treated chamomile plants rose approximately three times, simultaneously with a decline of its precursor (*Z*)- and (*E*)-2-β-D-glucopyranosyloxy-4-methoxycinnamic acid (Eliasová et al. 2004). The highest amounts of umbelliferone in stressed plants exceeded 9 and 20 times those observed in control plants of the tetraploid and diploid cultivar, respectively. Due to stress, the concentration of ene-yne-dicycloether in leaves decreased by more than 40 %. The pattern of quantity changes of the examined compounds in tetraploid and diploid plants was similar. The aerial parts of chamomile were found to synthesize and accumulate(*Z*)- and (*E*)-2-β-D: -glucopyranosyloxy-4-methoxy cinnamic acids (GMCA), the precursors of phytoanticipin herniarin (7-methoxycoumarin), a compound with anticoagulant properties (Repcák et al. 2009).

Studies found that the yield of dry flower and essential oil per pot, essential oil percent and its composition in *Matricaria chamomilla* varied with irrigation regimes (Pirzad et al. 2006). Highest amount of essential oil percent, yield of dry flower and essential oil per pot were obtained from irrigation at 85 % of the field capacity. However, it was not significantly different from irrigation at 70 % of field capacity. Lowest amount of essential oil percent were obtained when the plants irrigated with 100 and 55 % of field capacity. Minimum yield of dry flower and essential oil per pot were observed when the plants irrigated with 55 % of field capacity, but it was not significantly different from irrigation at 100 % of field capacity. Major constituents of the essential oil for all irrigation treatments were azulene-7-ethyl-1,4-dimethyl, limonene, bisabolol oxides A and B, bisabolone oxide, *trans*-β-farnesene and isobornyl isobutyrate <8-isobutyryloxy >.

Nitrogen deficiency was found to induce changes of free amino acids and coumarin contents

in chamomile leaves (Kovacik et al. 2006). Among secondary metabolites, the sum of 2-β-D-glucopyranosyloxy-4-methoxycinnamic acids increased sharply, herniarin increased slowly and the content of umbelliferone was low in N-deficient plants. A decrease in levels of all detected amino acids, besides histidine, was found. Within aromatic amino acids, tyrosine was the most abundant. The content of free phenylalanine was significantly lower in both control and N-deficient plants when compared to the content of tyrosine. The increase of herniarin glucosidic precursors was attributed to enhancing phenylalanine ammonia-lyase activity under nitrogen deficiency and nitrogen-free carbon skeletons were shunted in to the phenylpropanoid metabolism, including biosynthesis of (*Z*)-and (*E*)-2-β-D-glucopyranosyloxy-4-methoxycinnamic acids.

In the 3 years' experiment (2005–2007), Gosztola et al. (2010) found the moderately warm and relatively wet year of 2006 produced the highest contents of essential oil and also that of its alpha-bisabolol component in 28 wild populations of chamomile and 4 registered cultivars. Although bisabolol oxide A also showed a high variability through the years, its direct connection with weather conditions could not be proven. A moderate variability was established for the proportions of chamazulene and the lowest one for bisabolol-oxide B. Considerable genotype–weather interaction was suggested, especially for the essential oil content and for the ratio of bisabolol oxide A. The results of studies suggested that the hexaconazole-induced tolerance to water deficit stress in chamomile was related to the changes in growth variables, antioxidants and the apigenin-7-glucoside content (Hojati et al. 2011). The exogenous application of 15 mg/l provided better protection when compared to the other concentration.

Chamomile had been reported to have antioxidant, antimicrobial antiplatelet activities in vitro and antiinflammatory, antimutagenic, cholesterol-lowering antispasmodic and anxiolytic activities in vivo (McKay and Blumberg 2006). However, human studies had been limited, and clinical trials examining the purported sedative properties of chamomile tea were lacking.

Antioxidant Activity

Chamomile flower essential oil exhibited good antioxidant when evaluated using the β-carotene bleaching assay (Owlia et al. 2007). Total antioxidant capacity (%) (DPPH scavenging activity) of chamomile aerial plant parts was 2.78 % and contribution from the main caffeoyl derivatives was as follows: chlorogenic acid 4.31 %, 3,5-DCQA (dicaffeoylquinic acid) 13.66 %, 4,5-DCQA 7.53 % and total caffeoyl derivatives 25.50 % (Fraisse et al. 2011).

It was found that chamazulene, a bioactive compound of chamomile, inhibited lipid peroxidation in a concentration and time-dependent manner presenting an IC_{50} of 18 μM after 45 minutes incubation (Rekka et al. 1996). It also inhibited the autoxidation of dimethyl sulfoxide (33 mM) by 76 % at 25 mM and had a weak capacity to interact with DPPH radical.

Anticancer Activity

Exposure of chamomile aqueous and methanolic extracts caused minimal growth inhibitory responses in normal cells, whereas a significant decrease in cell viability was observed in various human cancer cell lines (Srivastava and Gupta 2007, 2009). Chamomile exposure resulted in differential apoptosis in cancer cells but not in normal cells at similar doses. The aqueous and methanolic chamomile flower extracts exhibited antiproliferative and apoptosis inducing effects on human prostate cancer PC-3 cells (Srivastava and Gupta 2009). Exposure of PC-3 cells with aqueous chamomile extract for 24 hours resulted in dose-dependent increase in cell growth inhibition varying from 3 to 25 % at concentration ranging from 25 to 800 μg/ml. Similarly, 4–74 % cell growth inhibition was observed after exposure of PC-3 cells to methanolic chamomile extract ranging from 25 to 800 μg/ml. Exposure of PC-3 cells to both aqueous and methanolic chamomile extract at 200 μg/ml concentration for 24 hours caused induction of apoptosis. Similar cell growth inhibitory and apoptotic effects were noted in other human cancer cell lines including breast, colon, fibrosarcoma and cervical

adenocarcinoma. Apigenin glucosides inhibited cancer cell growth but to a lesser extent than the parent aglycone, apigenin. Ex-vivo experiments suggested that deconjugation of glycosides occurred in vivo to produce aglycone, especially in the small intestine. The cytotoxicity of 10 essential oils including chamomile oil on human prostate carcinoma cell (PC-3) was significantly stronger than on human lung carcinoma (A549) and human breast cancer (MCF-7) cell lines (Zu et al. 2010). Studies showed the combination of 5-fluorouracil, an anticancer agent and bisabololoxide A, one of main constituents in German chamomile, inhibited the growth of human leukaemia K562 cells although the additive inhibition of growth by bisabololoxide A became smaller as the concentration of 5-fluorouracil increased (Ogata-Ikeda et al. 2011). The authors suggested that the simultaneous application of German chamomile containing bisabololoxide A may reduce the dose of 5-fluorouracil.

Studies demonstrated that chamomile and Marigold (*Calendula officinalis*) tea exerted selective dose-dependent cytotoxic action against target cancer cells; cytotoxicity of marigold tea was higher than chamomile (Matić et al. 2012). However, the cytotoxic effect of chamomile tea was very weak to healthy peripheral blood mononuclear cells (PBMC), while the effect of marigold tea on PBMC was more pronounced. Chemical analyses showed that dominant phenolic compounds in examined infusions and decoctions were flavonoid glycosides and hydroxycinnamic acid derivatives.

Antigenotoxic Activity

Three phenols (apigenin, bisabolol and protocatechuic acid) from two medicinal plants, *Matricaria chamomilla* and *Uncaria tomentosa*, showed an antigenotoxic effect against the hydrogen peroxide effect in the wing spot test of *Drosophila melanogaster* and also exhibited tumoricidal activity (Anter et al. 2011). Apigenin (2.24–35.96 mM) showed a lower 50 % inhibitory concentration than bisabolol and protocatechuic acid. They did not exhibit any genotoxic effect. These phenolics also induced apoptosis in HL-60 leukaemia cells. The authors suggested that the antioxidant activity of *Chamomilla* and *Uncaria* could be partially responsible of their beneficial activity.

Antiinflammatory Activity

In Vitro Studies

Chamomile treatment inhibited LPS-induced NO production and significantly blocked interleukin IL-1β, IL-6 and TNFα-induced NO levels in RAW 264.7 macrophages (Bhaskaran et al. 2010). Chamomile caused reduction in LPS-induced iNOS mRNA and protein expression. The study found that chamomile inhibited NO production and iNOS gene expression by inhibiting RelA/p65 activation and supported the utilization of chamomile as an effective antiinflammatory agent. Chamomile infusions from both the capitula and sifted flowers exhibited antiinflammatory activity when tested on phorbol 12-myristate 13-acetate-stimulated human adenocarcinoma gastric cells and human neutrophil elastase (Bulgari et al. 2012) This antiinflammatory activity was postulated due to the inhibition of neutrophil elastase and gastric metalloproteinase-9 activity and secretion, the inhibition occurring in a concentration-dependent manner. The promoter activity was also inhibited and the decrease of metalloproteinase-9 expression was found to be associated with the inhibition of NF-kB driven transcription. The results suggested that the flavonoid-7-glycosides, major constituents of chamomile flowers, may be responsible for the antiinflammatory action of the chamomile infusion observed.

Studies showed that matricine, chamazulene, (−)-α-bisabolol and guaiazulene, components of chamomile exhibited varying degree of anti-inflammatory activity in rat paw carrageenan oedema (Jakovlev et al. 1983). Two to four hours after administration, matricine on a molar basis was equally effective as (−)-α-bisabolol. In contrast, chamazulene and guaiazulene showed significantly less activity than (−)-α-bisabolol and matricine. After 4 hours, the pharmacological

effects of guaiazulene decreased significantly, whereas chamazulene showed nearly constant activities over the entire testing period. Safayhi et al. (1994) found that chamazulene inhibited the formation of leukotriene B4 in intact neutrophilic granulocytes, while matricine showed no effect up to 200 μM. Chamazulene (IC_{50}: 2 μM), but not matricine, suppressed the chemical peroxidation of arachidonic acid. Further, matricine (up to 200 μM) had no effects on the cyclooxygenase and 12-lipoxygenase activities in human platelets. Therefore, they concluded that chamazulene, but not matricine, may contribute to the antiinflammatory activity of chamomile extracts by inhibiting the leukotriene synthesis and additional antioxidative effects.

Matricine and chamazulene and (−)-α-bisabolol, components of chamomile essential oil, had no distinct effects on protamine sulphate-provoked degranulation of mast cells from Lewis-1a rats (Miller et al. 1996). The *trans*-enyne-dicycloether partly inhibited the degranulation of rat mast cells in concentrations above 10^{-4} M. Studies in lipopolysaccharide (LPS)-activated RAW 264.7 mouse macrophages suggested that modulation of inducible cyclooxygenase (COX-2) and inducible nitric oxide synthase (iNOS) by apigenin and related flavonoids (genistein, kaempferol) may be important in inflammation and carcinogenesis (Liang et al. 1999). Suppression of transcriptional activation of COX-2 and iNOS by apigenin might mainly be mediated through inhibition of IkB kinase activity induced by LPS or interferon gamma. Chamazulene carboxylic acid, a natural profen and matricin, a degradation product of proazulenic sesquiterpene lactones, both found in chamomile and yarrow, were found to have antiinflammatory activity (Ramadan et al. 2006). Matricin and the yarrow proazulenes were proposed to be antiinflammatory through conversion to chamazulene carboxylic acid.

Aqueous herbal extracts of chamomile (*Matricaria chamomilla*), meadowsweet (*Filipendula ulmaria*) and willow bark (*Salix alba*) and isolated polyphenolic compounds (apigenin, quercetin and salicylic acid, 0–100 μM) were found to have antiinflammatory activity in THP1 macrophages (Drummond et al. 2012). At concentrations of 10 μM, both apigenin and quercetin reduced interleukin IL-6 significantly. Apigenin at 10 μM and quercetin at 25 μM reduced tumour necrosis factor-alpha (TNF-α) significantly. Among the herbal extracts, willow bark had the greatest antiinflammatory activity at reducing IL-6 and TNF-α production. This was followed by meadowsweet and then chamomile.

Animal Studies

Alpha-bisabolol, a component of chamomile oil, suppressed carrageenan-induced paw oedema in rats (Jakolev and Schlichtegroll 1969). In mice, hydroalcoholic extracts of chamomile induced a reduction of oedema similar to the nonsteroidal antiinflammatory agent benzydamine used as reference (Tubaro et al. 1984). Three polysaccharides isolated from chamomile flower heads exhibited remarkable antiinflammatory activity against mouse ear oedema induced by croton oil (Füller et al. 1991, 1993, 2000). Animal studies showed that (−)-α-bisabolol, a bioactive sesquiterpene alcohol obtained from chamomile plant, was found to have peripheral antiinflammatory and antinociceptive activities (Rocha et al. 2011b). In the inflammatory models of paw oedema induced by carrageenan and dextran, the mice treated with (−)-α-bisabolol showed smaller oedemas compared to animals treated only with the vehicle. (−)-α-Bisabolol was capable of reducing paw oedemas induced by 5-HT but not oedemas induced by histamine. (−)-α-Bisabolol exhibited antinociceptive activity in the models of visceral nociception induced by acetic acid and in the second phase of the nociception test induced by the intraplantar administration of formalin. (−)-α-Bisabolol did not have any effect in a thermal nociception model using a hot plate but was able to reduce mechanical inflammatory hypernociception induced by carrageenan. These findings suggested the antinociceptive action of (−)-α-bisabolol was not linked to a central mechanism but instead was related to the inflammatory process. (−)-α-Bisabolol also decreased leukocyte migration, protein extravasations and the amount of TNF-α to the peritoneal cavity in response to carrageenan. Further, (−)-α-bisabolol diminished neutrophil degranulation in response to phorbol myristate acetate.

Clinical Studies

In a phase III double-blind, placebo-controlled study involving 164 patients (men and women), mouthwash containing chamomile flower extract did not decrease 5-fluorouracil-induced stomatitis (Fidler et al. 1996). Mazokopakis et al. (2005) reported a case of methotrexate-induced oral mucositis in a patient with rheumatoid arthritis, who was successfully treated with wild chamomile mouthwashes. Studies showed that hamsters with oral mucositis induced by 5-fluoracil treated with chamomile had a 12-fold greater chance of scoring zero (absence of mucositis) than the control group (Pavesi et al. 2011). Also animals treated with chamomile or the corticoid agent (betamethasone elixir—Celestone®) weighed significantly less than those in the control group. The group treated with the corticoid agent exhibited a more severe clinical condition, whereas the group treated with chamomile exhibited mild mucositis throughout the experiment. Analysis of the histopathological results demonstrated that the group treated with chamomile exhibited a lesser degree of mucositis throughout the evaluation period in comparison to the control and corticoid groups.

In a clinical dose response curve study of 25 patients with phlebitis, peripheral intravenous infusion of chamomile extract elicited an antiinflammatory effect (Reis et al. 2011). The time regression of phlebitis was shorter for groups with 2.5 % concentration (mean = 29.2 hours) and 5 % concentration (mean = 38.8 hours). Local toxicity was almost not observed.

Wound Healing Activity

Studies showed that rats with dead space wounds from excision and incision, treated with chamomile, exhibited a greater reduction in the wound area when compared with the controls (61 % versus 48 %), faster epithelialization and a significantly higher wound-breaking strength after 15 days (Nayak et al. 2007). Additionally, wet and dry granulation tissue weight and hydroxyproline content were significantly higher. In separate studies, male albino rats with induced secondary degree cutaneous burns, treated by rubbing with chamomile extract dissolved in olive oil twice a day, exhibited accelerated wound healing compared to control (Jarrahi 2008). In a subsequent study Jarrahi et al. (2010) demonstrated that chamomile extract dissolved in olive oil administered topically exhibited wound healing potential in linear incisional wound model in male Wistar rats. Studies by Martins et al. (2009) showed that male rats treated with chamomile presented significantly faster wound healing of experimental ulcers in comparison to those treated with corticosteroids, triamcinolone acetonide and clobetasol propionate. Other animal studies showed chamomile to have wound healing effect (Duarte et al. 2011). Rats with inflicted tongue ulcer treated with chamomile showed the best results regarding epithelialization and percentage of collagen fibers after 10 days. As expected, time had a statistically significant effect on fibroblast count, epithelialization, inflammation and wound size; animals sacrificed at 3 days showed the worst results.

In a double-blind trial of 14 patients with weeping wound area after dermabrasion of tattoos, the therapeutic efficacy of chamomile extract was shown by the significant decrease of the weeping wound area as well as the drying tendency (Glowania et al. 1987). In a controlled clinical study of colostomy patients with peristomal skin lesions, the lesions healed significantly faster in the chamomile than in the hydrocortisone group (Charousaei et al. 2011). Stoma patient symptoms (pain and itching) were also resolved more expediently in the chamomile than in the hydrocortisone group. The results suggested that German chamomile could be recommended to relieve itching and inflammation and that twice-daily application facilitated healing of peristomal skin lesions.

Antiviral Activity

Matricaria chamomilla was one of four plants found to inhibit the growth of human herpesvirus 1 and poliovirus 2 in cell culture (Suganda et al. 1983). The hydroalcoholic extract of *Matricaria chamomilla* was found to inhibit poliovirus cellular development and viral RNA synthesis

(Vilaginès et al. 1985). The essential oils anise oil, dwarf-pine oil and chamomile oil exhibited high levels of antiviral activity against acyclovir-sensitive herpes simplex virus type 1 (HSV-1) strain KOS and acyclovir-resistant clinical HSV isolates as well as acyclovir-resistant strain Angelotti (Koch et al. 2008a). At maximum non-cytotoxic concentrations of these plant oils, plaque formation was significantly reduced by 96.6–99.9 %, when herpes viruses were preincubated with drugs before attachment to host cells. No significant effect on viral infectivity could be achieved by adding these compounds during the replication phase. These results indicated that anise oil, dwarf-pine oil and chamomile oil affected the virus by interrupting adsorption of herpes viruses and in a different manner than acyclovir, which was effective after attachment inside the infected cells. Thus, the investigated essential oils were capable of exerting a direct effect on HSV and might be useful in the treatment of drug-resistant viruses. Additionally chamomile oil did not reveal any irritating potential on hen's egg chorioallantoic membrane, demonstrated the highest selectivity index among the oils tested and was highly active against clinically relevant acyclovir-resistant HSV-1 strains. They further found that chamomile oil exhibited a high selectivity index and appeared to be a promising candidate for topical therapeutic application as virucidal agents for treatment of herpes genitalis (Koch et al. 2008b). The inhibitory concentrations (IC_{50}) of chamomile oil against herpes simplex virus type 2 (HSV-2) in-vitro on RC-37 cells was 0.003 %. The results confirmed that essential oils like chamomile affected HSV-2 mainly before adsorption probably by interacting with the viral envelope.

Antimicrobial Activity

Of six matricaria esters (MEs) and two matricaria lactones (MLs), (2*Z*,8*Z*)-ME and (2*E*-8*Z*)-ME gave minimum inhibitory concentrations (MICs) of 50 µg/ml against *Mycobacterium tuberculosis* and respective MICs of 25 and 50 µg/ml against *Mycobacterium avium* (Lu et al. 1998). The (4*Z*,8*Z*)-ML, (2*Z*)-8-dehydro-ME and (2*Z*,8*Z*)-10-angeloyloxy-(2*Z*,8*Z*)-ME showed respective MICs of 12.5, 25, 25 µg/ml against *M. tuberculosis* and MICs of 50, 25, 25 µg/ml against *M. avium*, respectively. The MICs of (2*Z*,8*Z*)-10-tigloyloxy-ME and (2*E*,8*Z*)-10-angeloyloxy-ME and (4*E*,8*Z*)-ML ranged from 50 to >100 µg/ml 1 against both pathogenic mycobacteria.

Chamomile flower essential oil was found to be strongly antimicrobial against *Streptococcus* pathogens in-vitro: *Streptococcus pyogenes*, *S. mutans*, *S. salivarius*, *S. faecalis* and *S. sanguis* with MICs/MBCs values (µg/ml) of 0.1/0.2, 0.5/1.5,0.5/0.8, 4/7 and 0.5/11 respectively (Owlia et al. 2007). Chamomile essential oil was active against three strains of *Staphylococcus aureus*, *Candida albicans* and *Candida krusei* causal agents of acute otitis externa (Nogueira et al. 2008). Gram-positive bacteria were found to be more sensitive to the action of chamomile oil than Gram-negative bacteria (Aggag and Yousef 2009). The oil also showed marked fungicidal activity against *Candida albicans*. The incorporation of the volatile oil in topical preparations for staphylococcal infections was suggested. Chamomile flower oil exhibited antibacterial activity in-vitro against *Helicobacter pylori* (Shikov et al. 2008). The MIC_{90} (minimal inhibitory concentration) and MIC_{50} were 125 and 62.5 mg/ml, respectively. Chamomile oil extract inhibited the production of urease *by H. pylori* and affected the morphological and fermentative properties of *H. pylori*. Studies by Cwikla et al. (2010) found that the herbal extracts showing the highest growth inhibition of *Campylobacter jejuni* were *Calendula officinalis*, *Matricaria recutita*, *Zingiber officinale*, *Salvia officinalis*, *Foeniculum vulgare* and *Silybum marianum*. *C. jejuni* is the most common cause of enteric infections, particularly among children, resulting in severe diarrhoea.

German chamomile essential oil exhibited specific inhibition towards aflatoxin G(1) (AFG(1)) production, and (*E*)- and (*Z*)-spiroethers were isolated as the active compounds from the oil (Yoshinari et al. 2008). The (*E*)- and (*Z*)-spiroethers inhibited AFG(1) production of *Aspergillus parasiticus* with inhibitory concentration 50 %

(IC_{50}) values of 2.8 and 20.8 μM, respectively, without inhibiting fungal growth. The spiroethers were found to inhibit *O*-methylsterigmatocystin conversion to AFG(1) pathway. The (*E*)- and (*Z*)-spiroethers inhibited the enzymatic activity of TRI4 dose-dependently and interfered with 3-ADON (trichothecene 3-acetyldeoxynivalenol) production by *Fusarium graminearum*, with IC_{50} values of 27.1 and 103 μM, respectively. Their results suggested that the spiroethers inhibited AFG(1) and 3-ADON production by inhibiting cytochrome CYPA and TRI4, respectively.

Matricaria chamomilla extract and *Eugenia uniflora* were highly inhibitory against 16 *Staphylococcus aureus* strains (Silva et al. 2012). Studies showed that the antibacterial effect of 50 % aqueous ethanol extract of chamomile flower was attributable to *cis*-spiroether, *trans*-spiroether and the coumarins like herniarin and umbelliferone (Móricz et al. 2012).

In-vitro studies showed that *Aspergillus niger* growth was inhibited dose-dependently with a maximum of approximately 92.50 % at the highest chamomile flower essential oil concentration (Tolouee et al. 2010). A marked retardation in conidial production by the fungus was noticed in relation to the inhibition of hyphal growth. The main changes of hyphae observed by transmission electron microscopy were disruption of cytoplasmic membranes and intracellular organelles, detachment of plasma membrane from the cell wall, cytoplasm depletion and complete disorganization of hyphal compartments. The findings indicated the potential of chamomile essential oil in preventing fungal contamination and subsequent deterioration of stored food and other susceptible materials.

Antidiabetic Activity

In streptozotocin-induced diabetic rats, treatment with different doses of chamomile ethanol extract significantly reduced postprandial hyperglycaemia and oxidative stress, and augmented the antioxidant system (Cemek et al. 2008). In histological investigations, chamomile treatment protected the majority of the pancreatic islet cells, with respect to the control group. As a result, chamomile exhibited significant antihyperglycemic effect and protected beta cells in streptozotocin-induced diabetic rats, in a dose-dependent manner, and diminished the hyperglycaemia-related oxidative stress. In another study, hot water chamomile extract and its major components esculetin (3) and quercetin (7) exhibited moderate inhibition of sucrase with IC_{50} values of 0.9 mg/ml and 72 and 71 μM, respectively (Kato et al. 2008). In a sucrose-loading test, the administration of esculetin (50 mg/kg body weight) fully suppressed hyperglycaemia after 15 and 30 minutes, but the extract (500 mg/kg body weight) and quercetin (50 mg/kg body weight) were less effective. In contrast, a long-term feed test (21 days) using a streptozotocin-induced rat diabetes model revealed that the same doses of chamomile extract and quercetin showed significant suppression of blood glucose levels. It was also found that these samples increased the liver glycogen levels. Further, chamomile extract exhibited potent inhibition against aldose reductase (ALR2), with an IC_{50} value of 16.9 μg/ml, and its components, umbelliferone (1), esculetin (3), luteolin (6) and quercetin (7), could significantly inhibit the accumulation of sorbitol in human erythrocytes. These results clearly suggested that daily consumption of chamomile tea with meals could contribute to the prevention of the progress of hyperglycaemia and diabetic complications. Chamomile extract exhibited antidiabetic potential in alloxan-induced diabetic rats (Estakhr and Javdan 2011). The extract significantly reduced the level of glucose, total cholesterol and triglycerides with an increase in insulin and glycogen concentration to near normal levels in a dose-dependent manner. In another study, administration of chamomile leaf extract 200 mg/kg body weight once daily for 21 days reduced the elevated fasted blood glucose (FBG) by 62.2 %, and the levels of urea, creatinine, uric acid, aspartate transaminase, alanine transaminase, alkaline phosphatase, total cholesterol, triglyceride and LDL-cholesterol were also reduced in streptozotocin-induced diabetic rats (Najla et al. 2012). There was also improvement in the histological changes in the liver. The results

demonstrated that the water extract of *Matricaria chamomilla* possessed a strong hypoglycemic effect in streptozotocin-induced diabetic rats.

Nephroprotective Activity

M. chamomilla injection of rats corrected the hypocalcaemia that resulted from cisplatin nephrotoxicity, normalized the kidney functions, improved the apoptotic markers, reduced the oxidative stress markers and significantly increased the body weight (Salama 2012). Its nephroprotective activity was probably attributed to its antioxidant activities and inhibition of gamma glutamyl transferase activity.

Neuroprotective Activity

Studies showed that the methanolic chamomile extract elicited potent dose-dependent neuroprotective activity against global cerebral ischaemia/reperfusion injury-induced oxidative stress in rats (Chandrashekhar et al. 2010). The extract decreased in lipid peroxidation and increase in the superoxide dismutase, catalase, glutathione and total thiol levels in extract treated groups as compared to ischaemia/reperfusion group. Cerebral infarction area was significantly reduced in extract treated groups as compared to ischaemia/reperfusion group. Another study showed that the methanol extract of German chamomile elicited potent neuroprotective activity against aluminium fluoride-induced oxidative stress in rats (Ranpariya et al. 2011). Chamomile significantly decreased lipid peroxidation and increased superoxide dismutase (SOD), catalase (CAT), glutathione (GSH) and total thiol levels in extract-treated animals as compared with negative control group. The histopathological studies also revealed the potent neuroprotective action of German chamomile against oxidative brain damage.

Immunomodulatory Activity

The heteroglycan polysaccharide was chamomile flower was found to enhance phagocytosis in mice in the chemoluminescence model (Wagner et al. 1985). Maximum activity of 64 % was observed at a concentration of 10–3 mg/ml. Intragastric and parenteral administration of chamomile heteropolysaccharides chamomile was found to normalize the immune response upon air cooling and enhanced (but do not normalize) this process upon immersion cooling (Uteshev et al. 1999). The immunomodulating effect of the heteropolysaccharides upon cooling was attributed to initiation of immunostimulating properties of heavy erythrocytes (macrocytes), activation of immunoregulation cells of peripheral blood, and increased sensitivity of effector cells to helper signals.

Analgesic Activity

Administration of chamomile hydroalcoholic extract before formalin injection showed significant decrease of pain responses in vincristine-induced neuropathy in both phases in mice (Nouri and Abad 2012). Administration of vincristine produced significant increase in pain response in the second phase of the formalin test. Injection of chamomile and vincristine together showed that chamomile was able to decrease the vincristine induced pain significantly.

Anxiolytic/Antidepressant/Sedative Activities

Animal Studies

Lyophilized infusion of chamomile flower administered intraperitoneally in mice displayed a depressive effect on the central nervous system (Della Loggia et al. 1981, 1982). A sedative effect of chamomile flower extract was demonstrated via prolongation of hexobarbital-induced sleep, reduction of spontaneous mobility and reduction of explorative activity in mice. In contrast to diazepam, chrysin and apigenin do not cause reductions in memory. Restriction stress-induced increases in plasma ACTH (adrenocorticotropic hormone) levels in normal and ovariectomized rats were decreased by inhalation of chamomile flower oil vapour and administration

of diazepam (Yamada et al. 1996). Inhaling chamomile vapour induced greater decreases in plasma ACTH levels in ovariectomized rats then treatment with diazepam; this difference was not observed in normal rats. The plasma ACTH level decreased further when diazepam was administered along with inhaling chamomile oil vapour. Flumazenil was found to block the decrease in plasma ACTH level induced by inhaled chamomile oil vapour.

Apigenin, from chamomile flower head, exhibited clear anxiolytic activity in mice in the elevated plus maze without evidencing sedation or muscle relaxant effects at doses similar to those used for classical benzodiazepines, and no anticonvulsant action was detected (Viola et al. 1995). Apigenin competitively inhibited the binding of flunitrazepam and had no effect on muscarinic receptors, alpha 1-adrenoceptors and on the binding of muscimol to GABAA receptors. However, a tenfold increase in dosage produced a mild sedative effect since a 26 % reduction in ambulatory locomotor activity and a 35 % decrement in hole-board parameters were evident. The results indicated apigenin to be a ligand for the central benzodiazepine receptors exerting anxiolytic and slight sedative effects but not being anticonvulsant or myorelaxant. Electrophysiological studies performed on cultured cerebellar granule cells showed that apigenin, from methanol chamomile flower extract, reduced GABA (gamma-aminobutyric acid)-activated Cl^- currents in a dose-dependent fashion (Avallone et al. 2000). Apigenin reduced the latency in the onset of picrotoxin-induced convulsions. Further, apigenin injected i.p. in rats reduced locomotor activity, but did not demonstrate anxiolytic, myorelaxant or anticonvulsant activities. The results suggested that the inhibitory activity of apigenin on locomotor behaviour in rats could not be ascribed to an interaction with GABA(A)-benzodiazepine receptor but to other neurotransmission systems, since it was not blocked by Ro 15-1788. Of two flavonoids, apigenin and chrysin, contained in *Matricaria chamomilla*, chrysin exhibited a clear anxiolytic effect when injected at the dose of 1 mg/kg in rats, apigenin failed to exert this activity (Zanoli et al. 2000). The anxiolytic effect of chrysin, which was blocked by the injection of Flumazenil, could be linked to an activation of the GABA(A) receptor unit.

Studies suggest that treatment with Chamomilla 6cH was found to be related to the recovery of basal behavioural conditions in mice subjected to stressful conditions (Pinto et al. 2008). Mice who cohabitated with a sick cagemate showed a decrease in their general activity, but those treated with Chamomilla 6cH were less severely affected. In the open field area model, only the amitriptyline and ethanol treated mice showed significant excitatory behaviour; chamomilla 6cH-treated animals scored intermediate between water control and ethanol or amitriptyline.

Studies found that *M. recutita* exhibited benzodiazepine-like effects of *Matricaria recutita* on morphine withdrawal syndrome in adult male Wistar rats (Kesmati et al. 2008). Chamomile decreased significantly the number of climbing in comparison to control group, but it had no significant effect on other signs. Flumazenil increased significantly the signs of jumping and face washing in comparison to control group. Chamomile in the presence of flumazenil exhibited no sedative effect and the climbing behaviour increased significantly. The sedative effect of *M. recutita* on morphine withdrawal syndrome was suggested to be related to its benzodiazepine-like components that acted on benzodiazepine receptors. Studies showed that pretreatment of male mice with different doses of chamomile hydro-methanolic extract increased the latency of the beginning time of seizure induced by picrotoxin (Heidari et al. 2009). The most effective dose was 200 mg/kg. In addition, this dose delayed the time of death in mice but had no effect on the death rate.

Matricaria recutita essential oil at 50 and 100 mg/kg significantly increased the numbers of spontaneous locomotor activities, exhibited anxiogenic effect in the open field, elevated plus-maze and social interaction tests and decreased the immobility times of mice in tail suspension tests (Can et al. 2012). The falling latencies in rotarod tests did not change. This activity profile of the essential oil was similar to the typical psychostimulant caffeine.

Clinical Studies

In a small observation study of three 14–16-year-old male psychiatric outpatients, diagnosed with attention-deficit disorder (ADHD), administration of chamomile was found to improve patients' mean score for Conners's hyperactivity, inattention and immaturity factors (Niederhofer 2009). The small study indicated that chamomile might be a slightly effective treatment also for ADHD.

In a randomized, double-blind, placebo-controlled efficacy trial involving 57 patients with mild to moderate generalized anxiety disorder (GAD) Amsterdam et al. (2009) observed a significantly greater reduction in mean total Hamilton Anxiety Rating (HAM-A) score during chamomile versus placebo therapy. They found that chamomile may have modest anxiolytic activity in patients with mild to moderate GAD. They conducted another randomized, double-blind, placebo-controlled study, to examine the antianxiety and antidepressant action of oral chamomile extract in participants with symptoms of comorbid anxiety and depression (Amsterdam et al. 2012). Of the 57 participants in the 2009 trial, 19 had anxiety with comorbid depression; 16 had anxiety with a past history of depression; and 22 had anxiety with no current or past depression. They observed a significantly greater reduction over time in total Hamilton Depression Rating (HAM-D) scores for chamomile versus placebo in all participants. They also observed a clinically meaningful but nonsignificant trend for a greater reduction in total HAM-D scores for chamomile versus placebo in participants with current comorbid depression. They found a significantly greater reduction over time for chamomile versus placebo in all participants in the HAM-D core mood item scores and a clinically meaningful but nonsignificant trend for a greater reduction over time for chamomile versus placebo in participants without current or past depression. Their findings suggested that chamomile may provide clinically meaningful antidepressant activity that occurs in addition to its previously observed anxiolytic activity. In a double-blind, randomized, placebo-controlled of subjects suffering generalized anxiety disorder, chamomile showed potential for use in treating such disorder (Faustino et al. 2010).

Inhibition of Morphine Dependence

Animal studies showed that the withdrawal behavioural manifestations and weight loss were inhibited significantly by chronic co-administration of *M. chamomilla* extract with morphine (Gomaa et al. 2003). Administration of a single dose of *M. chamomilla* before the naloxone challenge in morphine-dependent rats abolished the withdrawal behavioural manifestations. The dramatic increase of plasma cAMP induced by naloxone-precipitated abstinence was prevented by chronic co-administration of *M. chamomilla* extract with morphine. The results suggested that *M. chamomilla* extract inhibited the development of morphine dependence and expression of abstinence syndrome.

Sleep Enhancing Activity

A significant decrease in sleep latency in rats was observed with chamomile extract at a dose of 300 mg/kg, but no significant effects were observed on total times of wakefulness, non-rapid eye movement (non-REM) sleep, REM sleep and delta activity during non-REM sleep (Shinomiya et al. 2005). Chamomile extract was found to have benzodiazepine-like hypnotic activity.

In a randomized, double-blind, placebo-controlled pilot trial in 34 patients aged 18–65 years with DSM-IV (*D*iagnostic and Statistical Manual of Mental Disorders) primary insomnia for ≥6-months, chamomile, 270 mg twice daily for 28 days, was found to provide modest benefits of daytime functioning and mixed benefits on sleep diary measures relative to placebo (Zick et al. 2011).

Oral Hygiene Activity

Chamomile hydroalcoholic extract was found to be significantly more effective than distilled water and tea tree oil (*Melaleuca alternifolia*) as an intracanal irrigant for the removal of the smear layer (Sadr Lahijani et al. 2006). The most effective removal of smear layer occurred with the use

of NaOCl with a final rinse of 17 % ethylenediaminetetraacetic acid (EDTA) (negative control) followed by the use of a chamomile extract. The use of a 2.5 % NaOCl solution alone, without EDTA and that of tea tree oil, was found to have only minor effects.

Gastroprotective/Antiulcerogenic Activities

Torrado et al. (1995) reported significant protective effect against gastric toxicity induced by 200 mg/kg acetylsalicylic acid was achieved after oral administration of chamomile oil to rats at doses ranging from 0.8 to 80 mg/kg (−)-α-bisabolol. Earlier, studies found that oral administration of chamomile flower extract and (−)-α-bisabolol inhibited the development of ulcers induced in rats by indomethacin, stress or ethanol (Szelenyi et al. 1979). They also reduced healing time for ulcers induced by chemical stress (acetic acid) or heat coagulation.

Extracts from the plants *Iberis amara*, *Melissa officinalis*, *Matricaria recutita*, *Carum carvi*, *Mentha x piperita*, *Glycyrrhiza glabra*, *Angelica archangelica*, *Silybum marianum* and *Chelidonium majus*, singly and combined in the form of a commercial preparation, STW 5 (Iberogast) and a modified formulation, STW 5-II, lacking the last 3 constituents, were found to have antiulcerogenic activity against indomethacin-induced gastric ulcers of rats (Khayyal et al. 2001). All extracts produced a dose-dependent antiulcerogenic activity associated with a reduced acid output and an increased mucin secretion, an increase in prostaglandin E2 release and a decrease in leukotrienes. The most beneficial effects were observed with the combined formulations STW 5 and STW 5-II in a dose of 10 ml/kg b.w., comparable with cimetidine in a dose of 100 mg/kg b.w. The antiulcerogenic activity of the extracts was also confirmed histologically. The cytoprotective effect of the extracts could be partly due to their flavonoid content and to their free radical scavenging properties.

Oral administration of chamomile extract at 400 mg/kg was found to be effective in preventing HCl-ethanol-induced gastric ulceration in mice and did not produce toxic effects in doses up to 5,000 mg/kg (Karbalay-Doust and Noorafshan 2009). In another study, chamomile extract was found to reduce gastric damage in rats at all doses tested (Bezerra et al. 2009). α-bisabolol and its bioactive component at oral doses of 50 and 100 mg/kg markedly attenuated the gastric lesions induced by ethanol by 87 and 96 %, respectively. Further, the α-bisabolol effect was significantly reduced in rats pretreated with glibenclamide, an inhibitor of K ATP⁻ channel activation. The results suggested that α-bisabolol reduced the gastric damage induced by ethanol, at least in part, by the mechanism of activation of K ATP⁻ channels. In another study, oral administration of (−)-α-bisabolol (bioactive sesquiterpene from chamomile) 100 and 200 mg/kg was able to protect the gastric mucosa from ethanol (0.2 ml/animal p.o.) and indomethacin-induced ulcer (20 mg/kg p.o.) in mice (Moura Rocha et al. 2010). Administration of L-NAME (10 mg/kg i.p.), glibenclamide (10 mg/kg i.p.) or indomethacin (10 mg/kg p.o.) was not able to revert the gastroprotection promoted by (−)-α-bisabolol 200 mg/kg on the ethanol-induced ulcer. Dosage of gastric reduced glutathione (GSH) levels showed that ethanol and indomethacin reduced the content of nonprotein sulfhydryl (NP-SH) groups, while (−)-α-bisabolol significantly decreased the reduction of these levels on ulcer-induced mice, but not in mice without ulcer. The data indicated that the gastroprotective effect on ethanol and indomethacin-induced ulcer promoted by (−)-α-bisabolol may be associated with an increase of gastric sulfhydryl groups bioavailability leading to a reduction of gastric oxidative injury induced by ethanol and indomethacin. Using ethanol-induced gastric lesions model, Rocha et al. (2011a) found that (−)-α-bisabolol-induced gastroprotection was associated with reduction in oxidative stress caused by lipid peroxidation, increase in superoxide dismutase activity and reduction in inflammatory neutrophil migration in the gastric mucosa.

Pretreatment with chamomile hydroalcoholic extract significantly reduced ethanol-induced gastric lesions in rats (Cemek et al. 2010).

Chamomile significantly reduced malonaldehyde, and significantly increased GSH (reduced glutathione) levels in gastric tissue or whole blood. Serum beta-carotene and retinol levels were significantly higher in the 200 mg/kg chamomile-administered group with respect to control. The gastroprotective effect of chamomile was attributed, at least in part, upon the reduction in lipid peroxidation and augmentation in antioxidant activity. Studies showed that treatment with aqueous chamomile extract significantly and dose-dependently reduced gastric ulcer index induced by ethanol in albino rats (Al-Hashem 2010). Chamomile treatment prevented the fall in glutathione (GSH) level induced by ethanol and increased GSH level. Chamomile treatment alleviated, or completely resolved ethanol-induced degenerative alterations, including disorganization of cell nuclei and gland morphology with erosion in the gastric mucosa and interrupted muscularis mucosa.

Chamomile flowers have been traditionally used in the treatment of gastrointestinal disorders such as dyspepsia, gastritis and peptic ulcer disease. In a study of in-vitro susceptibility of 15 *Helicobacter pylori* strains to botanical extracts, Mahady et al. (2005) found that the methanol extracts of *Myristica fragrans* (seed) had a MIC of 12.5 μg/ml; *Zingiber officinale* (ginger rhizome/root) and *Rosmarinus officinalis* (rosemary leaf) had an MIC of 25 μg/ml. In comparison methanol extracts of *Matricaria recutita* (flowers) and *Ginkgo biloba* (leaves) were less potent with a MIC>100 μg/ml.

In double-blind, randomized, placebo-controlled, multicenter trial of 120 patients with functional dyspepsia, the herbal preparation (bitter candy tuft, matricaria flower, peppermint leaves, caraway, licorice root and lemon balm) tested improved dyspeptic symptoms significantly better than placebo after 8 weeks treatment (Madisch et al. 2004).

Hepatoprotective Activity

The methanol extract of chamomile capitula (300 mg/kg) exhibited significant antioxidant activity against CCl4 induced liver injury in rats (Gupta et al. 2006). The extract exhibited significant antioxidant activity by showing increased levels of glutathione peroxidase, glutathione-s-transferase, glutathione reductase, superoxide dismutase, catalase and glutathione. It decreased lipid peroxidation and halted hepatic damage. The aqueous ethanolic extract of chamomile capitula exhibited hepatoprotective activity against paracetamol-induced hepatic damage in albino rats (Gupta and Misra 2006). Chamomile extract protected against decreases in the levels of GSH, blood glutathione, serum marker enzymes, liver Na K -ATPase activity, abnormal high level of serum alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP) bilirubin and increased liver thiobarbutiric acid-reactive substance resulting from hepatocellular damage and hepatic dysfunction induced by paracetamol.

Antipruritic/Antiallergic Activity

In a study 161 patients suffering from inflammatory dermatoses on hands, forearms and lower legs, 3–4 weeks application of Kamillosan cream (containing chamomile extracts) was found to be as effective as hydrocortisone for eczema and more effective than 0.75 % fluocortin butyl ester and 5 % bufexamac (Aertgeerts et al. 1985). A controlled and physician-blind randomized trial found no major differences in skin reactions after acute radiation between areas treated with Kamillosan cream (chamomile) and almond ointment (Maiche et al. 1991). None of these agents could prevent the skin reaction and all patients got grade 1 erythema. A lesser number and a later appearance of grade 2 reactions suggested an advantage for Kamillosan cream, although the difference between the results achieved was not statistically significant. The patients, however, preferred Kamillosan cream because of its rapid absorption and stainlessness. In a partially double-blind, randomized study carried out as a half-side comparison, 2 weeks application of Kamillosan(R) cream showed a mild superiority towards 0.5 % hydrocortisone and a marginal difference as compared to placebo in atopic eczema (Patzelt-Wenczler and Ponce-Pöschl 2000).

Intradermal application of liposomal apigenin-7-glucoside inhibited in a dose-dependent manner skin inflammation caused by xanthine oxidase and cumene hydroperoxide in rats (Fuchs and Milbradt 1993). Glucose-oxidase (hydrogen peroxide)-induced dermatitis was not significantly inhibited. The results are in good agreement with the in-vitro superoxide anion radical and peroxyl radical scavenging properties of apigenin and indicated that its antioxidant properties may have contributed to the antiinflammatory effect in this model system. The ethyl acetate extract of German chamomile dose-dependently suppressed compound 48/80-induced scratching without affecting body weight increase in ddY mice (Kobayashi et al. 2003). The ethyl acetate fraction of the ethanol extract and the ethanol extract of hot water extraction residue of German chamomile flower also showed strong inhibition on the compound 48/80-induced scratching. The inhibitory effects of the dietary intake of the German chamomile extracts on compound 48/80-induced itch-scratch response were comparable to oxatomide (10 mg/kg, p.o.), an antiallergic agent. The combined administration of the ethyl acetate extract of German chamomile (300 mg/kg) and antihistamine H1 antagonists, oxatomide (10 mg/kg) and fexofenadine (10 mg/kg), remarkably enhanced the antipruritic effects of these agents mice (Kobayashi et al. 2005). They found that the co-medication with the ethyl acetate extract or essential oil of German chamomile and antihistamines might be effective for the pruritus which could not be perfectly resolved alone by conventional antihistamines.

The methanol chamomile extract exhibited inhibitory effects on anaphylaxis induced by compound 48/80 and significant dose-dependent antipruritic property by inhibiting mast cell degranulation in rats (Chandrashekhar et al. 2011). Dose-dependent reduction in the histamine release, along with decreased release of serum, rat peritoneal and bronchoalveolar lavage fluid nitric oxide (NO) levels was observed. The results suggested the methanol chamomile extract exhibited potent antiallergic activity by inhibition of histamine release from mast cells.

Spasmolytic Activity

Alcoholic chamomile extracts obtained from ligulate flowers appeared to exert stronger spasmolytic activity than from tubular florets (Achterrath-Tuckermann et al. 1980; Carle and Gomaa 1992). Beside flavonoids, components of the essential oil were assumed to contribute to the spasmolytic effects. (−)-α-bisabolol, (+)-α-bisabolol and, to a lower extent their oxides, the chamomile oil itself, *cis*-spiroether, a standardized hydroalcoholic extract (Kamillosan®) and the coumarin derivatives umbelliferone and herniarin, exhibited spasmolytic activity in isolated guinea pig ileum. The hydrophilic (flavonoids) and the lipophilic components (essential oil) of chamomile were found to contribute to the musculotropic antispasmodic effect.

The extract of dried chamomile flowers was found to contain a potent tachykinin the extract of dried. The structure of the antagonist was identifiedasN1,N5,N10,N14-tetrakis[3-(4-hydroxyphenyl)-2-propenoyl]-1,5,10,14-tetraazatetradecane (tetracoumaroyl spermine, 1a) (Yamamoto et al. 2002). The Ki values of 1a, estimated from the inhibitory action on the substance P (SP)-induced contraction of the guinea pig ileum and the inhibition of the binding of [3H][Sar9, Met(O2)11] SP to human NK1 receptors, were 21.9 and 3.3 nM, respectively. The antagonist was concentrated in chamomile pollen. Another new compound found in the flower, N1,N5,N10-tris[3-(4-hydroxyphenyl)-2-propenoyl]-1,5,10,14-tetraazatetradecane, exhibited no tachykinin antagonist activity.

Inhibition of human cAMP-phosphodiesterase was found to be a mechanism for the spasmolytic effect of *Matricaria recutita* (Maschi et al. 2008). Chamomile flower/capitula infusion inhibited human platelet cAMP- and cGMP-phosphodiesterases (PDE) activity (IC_{50} = 17.9–40.5 µg/ml), while cGMP-PDE5 was less affected (−15 % at 50 µg/ml). Among the individual compounds tested, only flavonoids showed an inhibitory effect (IC_{50} = 1.3–14.9 µM), contributing to around 39 % of the infusion inhibition; other compounds responsible for cAMP-PDE inhibition still remain unknown.

Antidiarrhoeal Activity

The results obtained in the study by Calzada et al. (2010) provided some scientific support to the popular use of 23 of the plants including *M. recutita*, tested for the treatment of gastrointestinal disorders such as diarrhoea in Mexican traditional medicine. These plants showed moderate inhibitory activity (30–100 %) against charcoal-gum acacia-induced hyperperistalsis in rats. Their activities were greater than that of or equal to loperamide (34 % of inhibition at doses of 10 mg/kg) drug used as control.

Antimutagenic Activity

Studies found chamomile essential oil exhibited a dose-dependent inhibitory effect on the sister chromatid exchanges formed by both mutagens, daunorubicin and methyl methanesulfonate (Hernández-Ceruelos et al. 2002). In the case of daunorubicin, a statistically significant result was observed in the three tested doses: from the lowest to the highest dose, the inhibitory values corresponded to 25.7, 63.1 and 75.5 %. No alterations were found with respect to the cellular proliferation kinetics, but a reduction in the mitotic index was detected. In the case of methanesulfonate, the inhibitory values were 24.8, 45.8 and 60.6 %; no alterations were found in either the cellular proliferation kinetics or in the mitotic indices. Their results suggested chamomile oil may be an effective antimutagen. Alpha-bisabolol (BISA), a sesquiterpene alcohol found in chamomile oil, markedly and dose-dependently reduced the mutagenic effects of aflatoxin B1, 2-aminoanthracene and 2-aminofluorene, cyclophosphamide and benzo[a]pyrene, B[a]P mutgens using TA100, TA98, TA97a and TA1535 *Salmonella typhimurium* strains, without and with addition of S9 mixture microsome assay (Gomes-Carneiro et al. 2005). Gomes-Carneiro showed weak inhibitory effect on 4-nitroquinoline-*N*-oxide and 2-nitrofluorene and did not alter the mutagenicity of sodium azide and 4-nitroquinoline-*N*-oxide mutagens. It was also found that BISA inhibited pentoxyresorufin-o-depentylase and ethoxyresorufin-*o*-deethylase, markers for cytochromes CYP2B1 and 1A1 in rat liver microsomes. The results suggested that BISA-induced antimutagenicity could be mediated by an inhibitory effect on the metabolic activation of these promutagens.

Antiarthritic Activity

In a placebo-controlled double-blind crossover trial of 42 patients (40–76 years old) with painful knee osteoarthritis, administration of the herbal pomade Marhame-Mafasel (comprising a mixture of medicinal herbs including *Arnebia euchroma* and *Matricaria chamomilla*) elicited positive analgesic (pain reduction) effect in primary knee osteoarthritis (Soltanian et al. 2010) The herbal joint pomade Marhame-Mafasel had a significantly greater mean change in score compared to the placebo group for osteoarthritis severity.

Cardiovascular Activity

Haemodynamic measurements were obtained prior to and 30 minutes after the oral ingestion of chamomile tea on 12 patients with cardiac disease who underwent cardiac catheterization (Gould et al. 1973). With chamomile tea, the patients demonstrated a small but significant increase in the mean brachial artery pressure. No other significant haemodynamic changes were observed.

All the test beverages containing different polyphenol structures and being rich in either phenolic acids (chlorogenic acid in coffee), monomeric flavonoids (herb teas), chamomile (*Matricaria recutita*), vervain (*Verbena officinalis*), lime flower (*Tilia cordata*), pennyroyal (*Mentha pulegium*) and peppermint (*Mentha piperita*) or complex polyphenol polymerization products (black tea and cocoa) were found to be potent inhibitors of Fe absorption and reduced absorption in a dose-dependent fashion depending on the content of total polyphenols (Hurrell et al. 1999). Compared with a water control meal, beverages containing 20–50 mg total polyphenols/serving

reduced Fe absorption from the bread meal by 50–70 %, whereas beverages containing 100–400 mg total polyphenols/serving reduced Fe absorption by 60–90 %. Inhibition by black tea was 79–94 %, peppermint tea 84 %, pennyroyal 73 %, cocoa 71 %, vervain 59 %, lime flower 52 % and chamomile 47 %. At an identical concentration of total polyphenols, black tea was more inhibitory than cocoa, and more inhibitory than herb teas chamomile, vervain, lime flower and pennyroyal, but was of equal inhibition to peppermint tea.

Menopause Treatment Activity

In a placebo-controlled experiment on 55 postmenopausal women who complained of hot flushes and refused hormonal therapy, 12-week treatment with Climex (*Angelica sinensis* and *Matricaria chamomilla* plant extracts) appeared to be effective for menopausal symptoms without apparent major adverse effects (Kupfersztain et al. 2003). This hormone-free preparation may be used as an important modality for menopausal women with contraindications for hormone replacement therapy.

Antiosteoporotic Activity

Studies demonstrated that all the plant extracts (*Sideritis euboea*, *Sideritis clandestina*, *Matricaria chamomilla* and *Pimpinella anisum*) studied at a concentration range 10–100 μg/ml stimulated osteoblastic cell differentiation and exhibited antiestrogenic effect on breast cancer cells without proliferative effects on cervical adenocarcinoma (HeLa) ells (Kassi et al. 2004). The presence of estradiol inhibited the antiestrogenic effect induced by the extracts on MCF-7 breast cancer cells, suggesting an estrogen receptor-related mechanism. The authors concluded that the aqueous extracts derived from *Sideritis euboea*, *Sideritis clandestina*, *Matricaria chamomilla* and *Pimpinella anisum* may form the basis to design 'functional foods' for the prevention of osteoporosis.

Antifertility Activity

Chamomile hydroalcoholic extract was found to decrease spermatozoa count and motility, spermatozoon tail length and serum testosterone level and increase serum estradiol level in male adult rat (Karbalay-Doust et al. 2010). The body weight and weight and volume of the testis in the control and treated rats did not change significantly.

Antileishmanial Activity

Chamomile essential oil was found to be active against *Leishmania infantum* promastigotes, the main species responsible for human leishmaniasis in Spain (Morales-Yuste et al. 2010). At the two highest concentrations tested (1,000 and 500 μg/ml), (−)α-bisabolol (a principal chamomile oil component) and pentamidine (control agent) achieved 100 % inhibition of *L. infantum* promastigote. 80 % ethanol chamomile extract inhibited *Leishmania mexicana* growth by 100 % at protein concentration of 0.8 mg/ml (Shnitzler et al. 1996). Chamomile also inhibited human cell lines HeLa growth by 78 % and T_4 growth 100 %.

Anthelminthic Activity

Studies found *Matricaria chamomilla* essential oil and two of its main components (chamazulene and α-bisabolol) to have larvicidal activity against the L(3) larvae of the nematode Anisakis type I in in vitro and in vivo assays (Romero et al. 2012). The essential oil (125 μg/ml) caused the death of all nematodes, which showed cuticle changes and intestinal wall rupture. In the in-vivo assays, only 2.2 % of infected rats treated with the essential oil showed gastric wall lesions in comparison to 93.3 % of control. Chamazulene was ineffective, while α-bisabolol showed high activity to that of the essential oil in in vitro tests but proved less active in vivo. These findings suggested that the larvicidal activity may result from the synergistic action of different compounds of

M. chamomilla essential oil. Neither of the tested products induced irritative damage in the intestinal tissues.

Herb/Drug Interaction Activity

The crude chamomile essential oil demonstrated inhibition of four selected human cytochrome P450 enzymes (CYP1A2, CYP2C9, CYP2D6 and CYP3A4), with CYP1A2 being more sensitive than the other isoforms (Ganzera et al. 2006). Three constituents of the oil, namely, chamazulene (IC_{50} = 4.41 μM), *cis*-spiroether (IC_{50} = 2 μM) and *trans*-spiroether (IC_{50} = 0.47 μM), showed to be potent inhibitors of this enzyme, also being active towards CYP3A4. CYP2C9 and CYP2D6 were less inhibited; only chamazulene (IC_{50} = 1.06 μM) and α-bisabolol (IC_{50} = 2.18 μM) revealed a significant inhibition of the latter. These in-vitro data suggested that chamomile preparations containing constituents that inhibited the activities of major human drug metabolizing enzymes may interact with drugs whose route of elimination is mainly via cytochromes (especially CYP1A2). Sega and Pilote (2006) reported a case of a 70-year-old woman who, while being treated with warfarin, was admitted to hospital with multiple internal haemorrhages after having used chamomile products (tea and body lotion) to soothe upper respiratory tract symptoms. This case highlighted a theoretical risk for potentiation, since chamomile contained coumarins.

Inhibition of Mycotoxin Production

Precocenes and piperitone isolated from chamomile essential oil inhibited deoxynivalenol production by *Fusarium graminearum* and may be useful for protecting crops from deoxynivalenol contamination (Yaguchi et al. 2006). Precocenes I and II and piperitone inhibited the production of 3-acetyldeoxynivalenol, a biosynthetic precursor of deoxynivalenol produced by *F. graminearum* in a liquid and solid cultures. Precocene II and piperitone decreased the mRNA levels of *Tri4*, *Tri5*, *Tri6* and *Tri10* encoding proteins required for deoxynivalenol biosynthesis. The (*E*)-spiroether and (*Z*)-spiroether isolated from chamomile essential oil showed specific inhibition towards aflatoxin G(1)(AFG(1)) production by the fungus *Aspergillus parasiticus* without inhibiting fungal growth (Yoshinari et al. 2008). (*E*)- and (*Z*)-spiroethers inhibited the enzymatic activity of TRI4 dose-dependently and interfered with 3-acetyldeoxynivalenol production by *Fusarium graminearum.*

Insecticidal Activity

Treatment with the volatile oils of chamomile flowers (LD_{50} 76 μg/fly) and *Clerodendron inerme* leaf (LD_{50} 64 μg/fly) induced serious effects on the biology and biotic potential of the adult house fly *Musca domestica* (Shoukry 1997). Treatment significantly increased the acidic and the aromatic amino acids during oogenesis and significantly decreased content of aliphatic amino acids. The concentration of basic and the sulphur amino acids was varied with the two treatments, and the amino acid was completely disappeared in the ovaries of the treated flies.

Pharmacokinetic Studies

After oral ingestion of 40 ml of a hydroethanolic chamomile flower extract (containing 225.5 mg of apigenin 7-glucoside, 22.5 mg of apigenin and 15.1 mg of herniarin per 100 ml), no flavones could be detected in blood plasma nor in 24-hours urine of the female volunteer, while herniarin was found in both (maximum plasma concentration of 35 ng/ml; 0.324 mg in 24-hours-urine) (Tschirsch and Hölzl 1993).

Allergy Problem

Subiza et al. (1990) reported seven hay fever patients that suffered from conjunctivitis, two of them also had lid angioedema after eye washing with chamomile tea. All seven patients had positive

skin prick tests to the chamomile tea extract, *Matricaria chamomilla* pollen and *Artemisia vulgaris* pollen extracts. Positive conjunctival provocations were also observed in all the patients with the chamomile tea extract. They found that chamomile tea eye washing could induce allergic conjunctivitis and attributed this to pollens contained in these infusions as the allergens responsible for these reactions. German chamomile, a common and well-known allergen, had been reported to elicit type-IV allergic reactions such as allergic and systemic contact dermatitis in some people consuming chamomile tea (Pereira et al. 1997; Rodríguez-Serna et al. 1998).

In a clinical study conducted between 1991 and 2009, 36 selected patients with known or suspected Compositae contact allergy were patch tested with herniarin (from chamomile) 1 % petrolatum (Paulsen et al. 2010). Among 36 patients tested, there was 1 positive and 3 doubtful positive reactions to herniarin. All 4 patients had a relevant contact allergy to German chamomile, whereas the majority of the remaining 32 patients had chamomile allergy of unknown relevance. Sensitization may occur through, for example, external use of chamomile tea or use of chamomile-containing topical herbal remedies. Andres et al. (2009) reported a case of a 38-year-old Caucasian man who developed an episode of severe anaphylaxis with generalized urticaria, angioedema and severe dyspnoea 1 hour after consuming chamomile tea. Laboratory examination demonstrated a total serum IgE of 123 kU/l with specific IgE against chamomile (4.94 kU/l, class 3). Skin prick test and labial provocation test with chamomile elicited a strong positive reaction. Their case confirmed the presence of a type-I allergy to orally ingested chamomile. Contact dermatitis from bisabolol, a primary component in German chamomile, had been reported in Europe and in the United States (Russell and Jacob 2010). Patch testing with bisabolol-containing products or bisabolol may be useful in the work-up of patients with presumptive allergic contact dermatitis or potentially worsening atopic dermatitis. Patients sensitized to bisabolol should be counselled to avoid any bisabolol-containing products.

Toxicity/Safety Studies

Bisabololoxide A (BSBO), a principal constituent in German chamomile, was found to induce apoptosis and cellular changes of rat thymocytes when incubated with BSBO at concentrations of 30 μM for 24 hours (Ogata et al. 2010). The significant changes in cellular parameters of rat thymocytes by BSBO were not observed when the concentration was 10 μM or less. Furthermore, the short incubation (3 hours) of cells even with 30–100 μM BSBO did not significantly affect the cells. Therefore, the authors suggested BSBO to be practically safe when German chamomile is conventionally used.

Traditional Medicinal Uses

Chamomile has been used as herbal folk medicine since antiquity in ancient Egypt, Greece and Rome (Mann and Staba 1986). The herb is considered antispasmodic, carminative, diaphoretic, sedative, stomachic and emmenagogue (Grieve 1971; Mann and Staba 1986; Martens 1995; Alberts 2009). The herb has been used as bitter, tonic, insect repellent, antiseptic, antispasmodic, sudorific and anthelminthic and as a folk remedies against asthma, colic, fevers, inflammations and cancer. It is used as a digestive aid to treat gastrointestinal disturbances including flatulence, motion sickness, indigestion, nausea and vomiting and as a liver stimulant (Mann and Staba 1986). It is used to treat hysteria, nightmares and other sleep problems (Martens 1995). Eye washing with chamomile tea is a folk remedy used by the general public to treat conjunctivitis and other ocular reactions (Subiza et al. 1990). Chamomile has long been used in traditional medicine for the treatment of inflammation-related disorders (Bhaskaran et al. 2010). In a 3-year study of ethnopharmacology and folk-medicine use among the population of the Atlantic Coast of Colombia, 39 plant species were identified to be of traditional medical importance, among which was *M. chamomilla* for colic ailments (Gómez-Estrada et al. 2011).

Other Uses

Chamomile (dried flower heads and extracts) is used in medicine, tinting hair and in cosmetics. Dried chamomile leaves are used in potpourri and herb pillows for their aromatic apple-like smell. The leaves are burnt in aromatherapy for their soothing scent to relax the mind and body. In Egypt, chamomile is steep in religion as the plant was consecrated to the god of the sun.

Chamomile flowers also have insecticidal properties. Studies showed that chamomile flower-head extracts elicited highly significant acaricidal activity against the mite *Psoroptes cuniculi*, responsible for otoacariasis in domestic animals (Macchioni et al. 2004). The decoction of 10 % was the only formulation which gave 100 % activity at all the three observations times of 24, 48 or 72 hours. Chamomile flower extract was found to have acaricidal activity against engorged *Rhipicephalus annulatus* tick in-vitro (Pirali-Kheirabadi and Razzaghi-Abyaneh 2007). The mortality rate caused by different dilutions of chamomile flower extract ranged from 6.67 to 26.7 %, whereas no mortality was recorded for non-treated control group. The mass of produced eggs varied form 0.23 g (in 8.0 % solutions) to 0.58 g (in control), with no statistical differences between the treatments and control. In the highest concentration used (8.0 %) chamomile extract caused 46.67 % failure in egg laying in engorged females while non-failure was observed for non-treated control group. Macroscopic observations indicated that in effective concentrations of the extract (4.0 and 8.0 %), patchy haemorrhagic swelling appeared on the skin of treated ticks.

Comments

Chamomile is cultivated commercially in Europe, Belarus, Ukraine, Moldova, North Caucasus to South Siberia, North Africa (Egypt, Ethiopia), Middle Asia (Turkey, Afghanistan), Asia (Pakistan, North India and Japan), North and South America (Eastern USA, Cuba, Argentina and Brazil), and New Zealand (Alberts 2009).

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