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Review

Achillea spp.: A comprehensive review on its ethnobotany, phytochemistry, phytopharmacology and industrial applications

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Abstract: The genus *Achillea* genus houses more than 100 species, a number of them are popularly used in traditional medicine for spasmodic gastrointestinal, gynecological and hepatobiliary disorders, hemorrhages, pneumonia, rheumatic pain, inflammation, wounds healing etc. Members of the genus contain a wide variety of volatile and non-volatile secondary metabolites, including terpenes, polyphenols, flavonoids and others. Multiple studies have assessed the biological effects and other aspects of *Achillea* spp. In a number of preclinical studies, *Achillea* plants and their essential oils have demonstrated promising antibacterial properties against a number of human and plant pathogens. Besides, the plants have displayed strong antioxidative and potent anti-proliferative and anticancer properties in various cellular and animal models. *Achillea* plants have widely been used as food preservative in food industry. Clinical studies have indicated its potential against multiple sclerosis (MS), irritable bowel syndrome (IBS), ulcerative colitis, episiotomy wound, primary dysmenorrhea, oral mucositis etc. The present work focuses to provide a brief overview on folk knowledge, phytochemistry, biological activity and applications of *Achillea* plants. There is a close relationship between the traditional ethnobotanical usage and pharmacological and clinical data from different *Achillea* spp. The application of *Achillea* plants and their extracts seems to be a promising alternative for antimicrobial and antioxidant purposes in food, pharmaceutical and cosmetic industries.

Key words: *Achillea* plants; *Achillea millefolium*; Biological activity; Bacterial; Food preservatives; Phytopathogens; Antioxidant; Cytotoxicity.

Introduction

Achillea genus comprises more than 100 species, many of them are used in traditional medicine for spasmodic, gastrointestinal and hepatobiliary disorders, hemorrhages, pneumonia, rheumatic pain, wounds healing, and others (1-4). Published reports demonstrated that extracts from *Achillea* spp. have a broad spectrum of biological activity. In fact, various *Achillea* spp. are used in food, pharmaceutical and cosmetic industries, mostly due to their beneficial effects as antibacterial, antifungal and astringent. *A. millefolium* is one of the most economically important *Achillea* sp. Indeed, *A. millefolium* extracts were approved by the German Commission as a bio-additive in cosmetic products, being present at a concentration ranging from 0.5 to 2 % in 65 cosmetic formulations (5). *A. odorata* has also shown a great potential as antinociceptive, anti-

inflammatory and antioxidant, being even proposed as a drug candidate for oxidative and inflammation-related pathological processes (6). The Iranian endemic *Achillea* sp., including *A. pachycephalla, A. aucherii* and *A. kellalensis* have also revealed an acceptable antioxidant activity (7). Increasing evidences have shown that the total phenolic content of *Achillea* sp. is strongly associated with its antioxidant activity (8, 9). When looking at *Achillea* plants' antibacterial activity, *A. biebersteinii, A. fragrantissima, A. santolina* and *A. millefolium* essential oils (EO) and their respective nanoemulsions have shown prominent effects against Gram-positive and Gram-negative bacteria, with EO nanoemulsions being more active than pure EO (10). The content of 1,8-cineole (45.2%), *p*-cymene (20.8%) and *cis*-chrysanthenyl acetate (20.4%) in the EO, and the total phenolic compounds abundance, namely of flavonoids content have been closely associated with the high antimicrobial activity attributed to *Achillea* plants (9, 11-13). Moreover, the antileishmanial and antitrypanosomal effects of *A. fragrantissima* have also been reported. Achillolide A, chrysosplenol-D, chrysosplenetine and pellitorine were identified in the aerial parts of the plant (14). On the other hand, remarkable enzyme inhibitory effects have been also described to *Achillea* spp. *A. wilhelmsii* is able to decrease the activity of lactate dehydrogenase (LDH), creatine kinase (CK) and malondialdehyde (MDA) levels, and to increase the superoxide dismutase (SOD) and catalase (CAT) activities. In summary, it was able to improve the myocardial oxidative stress states on cardiac function during ischemia/reperfusion injury in rat (15). *A. phrygia* ethyl acetate extracts also showed a remarkable enzyme inhibitory potential (16), and the hydroalcoholic extract of *A. millefolium* demonstrated *in vivo* antidiabetic effects, through inhibition of α-glucosidases, insulin secretion and insulin secretagogue activities (17). The Turkish endemic *A. cucullata* also revealed a great ability to inhibit the enzyme activities acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and α-glucosidase (18). Strong *in silico* and *in vitro* inhibitory effects on AChE and BChE have also been attributed to 6-hydroxy-luteolin 7-*O*-β-D-glucoside, isolated from A. *millefolium*, being even more evident than that of *A. cucullata* (19). Specifically, *A. millefolium* hydroethanolic extract exhibited a great potential to inhibit the growth of human tumor HCT-15 and NCI-H460 cell lines by inducing apoptosis and interfering with cell cycle (20). Diuretic (21) and wound healing (22) effects have also been listed to *A. millefolium* and *A. asiatica* extracts. More interestingly, *A. millefolium* aqueous extract showed beneficial effects as an add-on therapy in patients with multiple sclerosis (23). In addition, many clinical studies have been carried out to evaluate the effects of *A. millefolium* extract in acute cutaneous leishmaniasis major, chronic kidney disease, as antihypertensive and antihyperlipidemic, in the relief of primary dysmenorrheal, irritable bowel syndrome, surface rejuvenating, oral mucositis, atopic dermatitis, episiotomy wound healing and as dermatological anti-inflammatory agents. Thus, given the multiple potentialities of *Achillea* species, this review aims to provide a brief overview on botany, traditional knowledge, phytochemistry, biological activity and applications of *Achillea* plants.

Taxonomy, habit, habitat and cultivation

Based on botanical systematics, *Achillea* species belongs to Angiosperms plants, Eudicots clade, Campanulates order, Asteraceae family, Tubuliflorae subfamily and Anthemideae tribe (24). As one of the most important medical groups, *Achillea* with over 130 perennial and flowering species, is classified in Asteraceae family, which is the largest family of vascular plants (25, 26). Plants bring 1 to 4 stems that are clustered and often have rhizomes. The flowers are clustered in groups 3 to 8 which are located upon small disks and usually appear in white to pink. The leaves are seen along the stem, and usually the lower leaves are larger. The leaves are up to 20 cm in length which are covered with hairs. Pollination of *Achillea* is done specially by insects. *Achillea* regenerates through the seeds. Seeds require direct sunlight and temperatures ranging from 18-24 ºC for germination. The morphological diversity is so high, but this variation decreases in the morphology and structure of the flowers.

This genus is found mainly in Europe, Asia, North Africa, Australia, New Zealand and in other parts of the world (27-30). The habitat of this genus is in semi-tropical, temperate, dry or semi-arid regions with temperate climate (27). Mountainous forests and steppes are the main habitats of these plants (31). They prefer well drained soils, but generally tolerate a wide range of soil conditions. For this reason, species of this genus are seen in rangelands, margins of roads and wetlands. Due to low ecological requirements, these plants are used to control wind erosion in degraded lands. *Achillea* spp. are distributed in altitudes from sea level up to 3500 m, which means they are not dependent to a specific altitude. The main growth occurs in the spring and the flowering period is in May to June (24). *Achillea* is resistant to the lack of moisture or direct light, so it is also well settled in degraded grasslands. *Achillea* regeneration occurs through seeds and rhizomes, so it survives in poor soils (32). However, deep, fertile and friable soils with well drained conditions are the most appropriate soils for cultivation. The soil pH could be 6 and 7 in the best conditions for cultivation (33). It was reported that using phosphorus fertilizer increases the growth and root length of these plants and some *Achillea* sp. (*A. millefolium*) tolerate salinity as well (34). Indeed, in lab conditions they tolerated irrigation with up to 4 dS of salinity (35-37). Researches indicate that *A. millefolium* growth is reduced in drought stress, so it needs full irrigation for the maximum amount of growth (38). *Achillea* seeds are cultivated in rows with 60-70 cm distant between rows and 25-30 cm between seeds along rows. The best time for seed cultivation is the first days of fall. *Achillea* is also replicated through the bush. 4-5 year-old plants are removed from the bushes in the fall and each plant is divided into 2-4 plants to be cultivated. Among the different *Achillea* spp., *A. tenuifolia* and *A. filipendulina* show the highest growth rate. Plant irrigation tenure is 5 to 10 days depending on the climate. At flowering, the most ingredients are produced in plants. Therefore, harvesting occurs in the second year before seeding and color change of petals. 2-4 tons per hectare is the amount of dry matter production. The plants oil is 3-5 kg/ha, which is extracted by steam distillation (39).

Achillea spp. are cultivated in agriculture fields, rangelands, forests and gardens, but what matters is the provision of appropriate lighting conditions at the cultivation site. *Achillea* spp. need to be exposed to sunlight directly which should be noted in forests, gardens and under the crown of trees cultivation. *Achillea* spp. are considered as the long day plants that 18-26 ºC is the most suitable temperature for its growth and flowering. *Achillea* grows better in warm and sunny areas and produces more flowers (33).

Some species have been planted extensively in Asia, Europe and the United States, and their hybridization makes it very difficult to identify and categorize them. In *Achillea* genus, the successive cycles of polyploidization, differentiation and hybridization have been done (40). Propagation of plants in the laboratory and transfer them to the main habitats is one of the main methods in cultivation and development of medicinal plants. Micropropagation allows the production of similar plants with the potential for standard secondary compounds production. Since the diagnosis and classification of *Achillea* spp. based upon morphology alone is difficult, there are many genetic studies for its classification (41, 42). Accordingly, the number of chromosomes in different species change significantly in different habitats. Besides the medicinal properties and livestock grazing, *Achillea* species have been used as ground covering plants in urban green spaces (43), and even as an ornamental plant in green space in some parts of the world (44-46).

Phytochemistry

Phytochemistry of *Achillea* spp. is being intensively carried out worldwide. Phenolic acids, flavonoids, terpenes and N-alkylamide compounds have reported as main bioactive substances. The chemical composition of *Achillea* plants is briefly represented in Table 1. As major constituents of the *Achillea* spp. EO were reported to be composed of 1,8-cineole, p-cymene, cis-chrysanthenyl acetate, santolina alcohol, borneol, isoborneol, sabinene, β-caryophyllene, germacrene D, α- and β- pinene, α- and γ- terpinene, limonene, eucalyptol, cis-sabinene hydrate, linalool, carvacrol methyl ether, bornyl acetate, carvacrol, eugenol, neryl acetate, α-copaene, bicyclogermacrene, β-bisabolene, β-sesquiphellandrene, α-calacorene, (E)-nerolidol, dendrolasin, spathulenol, caryophyllene oxide, α-bisabolol, curcunem-15-al, artemisia ketone and chamazulene (9, 47, 48). Fourteen and fifteen N-alkylamide compounds have been found in ethanol extracts of the roots, leaves, stems and flowers of *A. ptarmica* and *A. millefolium*, respectively (49). New sesquiterpene dimers, achillinin B and C were also found in the flowers of *A. millefolium* (50). Two new compounds, (+)-lyoniresinol 4-O-α-L-arabinofuranoside (lignan) and achiterpenoside A (terpenoid) were isolated from *A. millefolium* methanol extract (51). A novel 1,2-seco-guaianolide hemiacetal and crithmifolide have been isolated from the aerial parts of *A. crithmifolia* (52). The chemical structures of achillinin A, crithmifolide and chiterpenoside A are presented in Figure 1.

Ethnobotany

Since Achillea genus is widespread all over the world, its species are used as folk herbal medicines in different regions (2). Achillea pollen was found in a *Homo neanderthalensis* grave at Shanidar, dated to 65,000 B.P. Though it was impossible to know whether its usage had been continuous, there is an opinion it had been persistent, as Achillea genus had been broadly accepted as a medicine by many ancient cultures (53). The oldest surviving texts to record Achillea usage in the European classical medical tradition were documented by Pliny the Elder and Dioscorides (I century C.E.). They described the herb achilleos as being useful to stop bleeding, including from wounds and abnormal menstrual bleeding, to reduce inflammation including earache, and to treat dysentery. This usage of Achillea has recently been supported by marine archaeology. DNA analysis proved the present of this plant in two pressed tablets from a collection of medical supplies in a Roman ship that had sunk off the coast of Tuscany (140-120 B.C.E.) (53). Traditionally, *Achillea* species aerial parts (herb, flowers and leaves) through the form of infusions and decoctions are used for spasmodic gastrointestinal and hepato-biliary disorders, hemorrhages, pneumonia, rheumatic pain and wounds healing (1-3). Nowadays, about 20 species of Achillea genus are used as traditional herbal medicines in different countries and cultures (see Table 2).

Biological activities

Anti-human pathogenic properties

Plant extracts

Achillea spp. and their corresponding extracts have been assessed for antimicrobial effects. Chloroform, n-hexane and methanol extracts of flower heads of 13 *Achillea* spp., *viz. A. multifida*, *A teretifolia, A. schischkinii*, *A. setacea*, *A. crithmifolia*, *A. falcata*, *A. biebersteinii*, *A. coarctata*, *A. millefolium* subsp. *panno-*

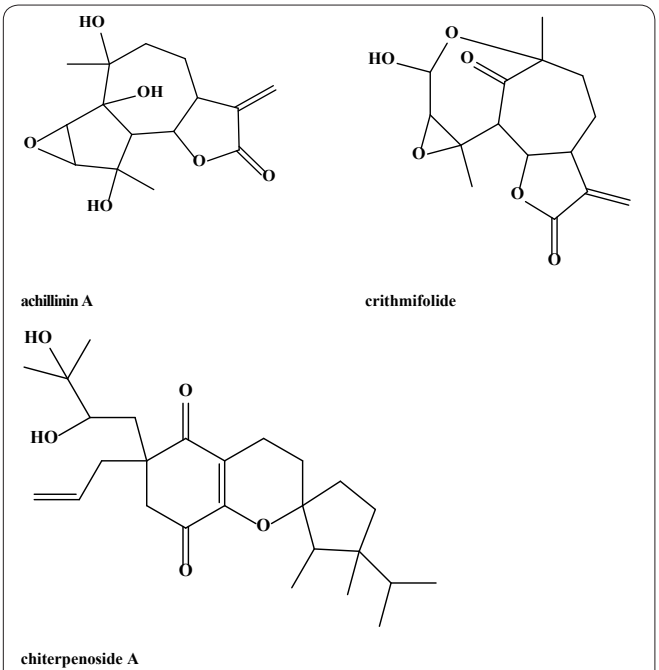

Figure 1. Chemical structures of achillinin A, crithmifolide and chiterpenoside A.

Table 1. Phytochemicals of *Achillea* spp.

Species	Compounds	References
A. aleppica subsp. *zederbaueri*	*p*-coumaric acid, ferulic acid, *o*-coumaric acid, rosmarinic acid	(236)
A. beibrestinii	Gallic acid, *p*-coumaric acid	(237)
A. biserrata	α-thujene, α-pinene, camphene, sabinene, β-pinene α-terpinene, p-cymene, limonene, eucalyptol, γ-terpinene, cis-sabinene hydrate, terpinolene, linalool, cis-menth-2-en-1-ol, chrysanthenone, trans-menth-2-en-1-ol, camphor, borneol, terpinen-4-ol, α-terpineol, myrtenol, trans-piperitol, trans-carveol, cis-carveol, carvacrol methyl ether, bornyl acetate, carvacrol, eugenol, neryl acetate, α-copaene, β-caryophyllene, (E)-β-farnesene, cabreuva oxide B, α-acoradiene (overlapped), D-germacrene, bicyclogermacrene, β-bisabolene, β-sesquiphellandrene, α-calacorene, (E)-nerolidol, dendrolasin, spathulenol, caryophyllene oxide, salvial-4(14)-en-1-one, α-bisabolol, curcunem-15-al	(238)
A. clypeolata	Guaiane, eudesmanes, diterpene, centaureidin, scopoletin	(239)
A. coarctata	Quinic acid, malic acid, chlorogenic acid, tr-caffeic acid, vanillin, 4-OH benzoic acid, salicylic acid, naringenin, luteolin, kaempferol, apigenin	(170)
A. collina	Chlorogenic acid, 3,5 di-O-caffeoylquinic acids, 4,5-di-O-caffeoylquinic acids,	(240)
A. filipendulina	Santolina alcohol, 1,8-cineole, borneol, isoborneol and cischrysanthenyl acetate	(48)
A. fragrantissima	Acerosin, cirsimaritin, cirsiliol, luteolin, apigenin, caffeic acid, santolina triene, α-thujene, α-pinene, α-fenchene, camphene, benzaldehyde, sabinene, β-pinene, 2,3-dehydro-1,8-cineole, yomogi alcohol, α-terpinene, p-cymene, limonene, santolina alcohol, β-phellandrene, 1,8-cineole, γ-terpinene, cis -sabinene hydrate, cis -linalool oxide, linalool, trans -sabinene hydrate, α-thujone, β-thujone, myrcenol, fenchol, chrysanthenone, cis-p-menth-2-en-1-ol, trans-p-menth-2-en-1-ol, camphor, cis –chrysanthenol, borneol, 4-terpineol, p-cymen-8-ol, α-terpineol, methyl chavicol, verbenone, carvone ,isobornyl acetate, thymol, carvacrol, α-terpinyl acetate, β-caryophyllene, germacrene D, bicyclogermacrene, δ-cadinene, caryophyllene oxide, cedrol, β-eudesmol	(241, 242)
A. kotschyi subsp. *kotschyi*	Quinic acid, malic acid, chlorogenic acid, protocatechuic acid, tr-caffeic acid, vanillin, *p*-coumaric acid, rutin, hesperidin, hyperoside, 4-OH benzoic acid, salicylic acid, quercetin, naringenin, luteolin, kaempferol, apigenin	(170)
A. lycaonica	Quinic acid, malic acid, chlorogenic acid, protocatechuic acid, tr-caffeic acid, vanillin, rutin, hesperidin, hyperoside, 4-hydroxy benzoic acid, salicylic acid, fisetin, quercetin, naringenin, luteolin, kaempferol, apigenin	(170)
A. micrantha	Santolina triene, p–cymene, 1,8-cineole, binapacryle, 1,5-heptadien-4-ol, 3,3,6-trimethyl, β–caryophylene, α–eudesmol, α-seline	(243)
A. millefolium	Chlorogenic acid, rutin, apigenin-7-glucoside, luteolin-7-glucoside, 3,5 diCQa, schaftoside, isorhamnetin-3-O-rutinoside, vicenin-2, luteolin, 3-O-caffeoylquinic acid, caffeic acid hexoside, quercetin, ferulic acid, syringic acid, gallic acid, vanillin, trans(3)-hydroxy cinnamic acid, sinapic acid, 4-hydroxybenzoic acid, myrcetin, kaempherol, hyperoside, resveratrol, morin, naringin, naringenin, umbelliferon, α–pinene, camphor, β–terpine, β–pinene, santolina triene, terpineol, p–cymene, 1,8-cineole, binapacryle, 1,5-heptadien-4-ol, 3,3,6-trimethyl, thujene, α–thujene, d–(+)-camphor, 2-nephthalenamine,1,2,4a,5,6,7,8,8aoctahydro-4a-methyl, borneol, terpine-4-ol, α–terpineol, β–caryophylene, α–eudesmol, α-seline, palmitic acid, linoleic acid, linolenic acid, rachidic acid, behenic acid, lignoceric acid	(176, 243-255)
A. millefolium	Undeca-2E,4E-diene-8,10-diynoic acid, isobutylamide, deca-2E,4E-dienoic acid, tyramide, deca-2E,4E,8Z-trienoic acid isobutylamide, deca-2E,6Z,8E-trienoic acid 2-methylbutylamide (homospilanthol), deca-2E,4E,8Z-trienoic acid piperidide, tetradeca-2E,4E-diene-8,10-diynoic acid, isobutylamide (anacycline), deca-2E,4E,8Z-trienoic acid piperideide, deca-2E,4E-dienoic acid 4-methoxyphenylethylamide, deca-2E,4E-dienoic acid piperidide, deca-2E,4E-dienoic acid, piperideide, dodeca-2Z,4E-diene-8,10-diynoic acid isobutylamide, deca-2E,4E,6Z-trienoic acid piperideide, deca-2E,4E,6E-trienoic acid piperideide, Deca-2E,4E,6Z,8Z-tetraenoic acid piperideide, deca-2E,4E,6E,8Z-tetraenoic acid piperideide, tetradeca-2E,4E,12Z-triene-8,10-diynoic acid, isobutylamide	(49)

A. multifida	Chlorogenic acid, quercetin hexoside, luteolin-7-*O*-glucoside, dicaffeoyl quinic acid, luteolin	(75)
A. nobilis subsp. *sipylea*	Protocatechic acid, p-hydroxy benzoic acid, vanillic acid, caffeic acid, chlorogenic acid, syringic acid, ferulic acid, o-cumaric Acid, rosmarinic acid	(256)
A. pacycephalla	Sabinene, δ-3-carene, trans-limonene, 1,8-cineole, trans-pinane, γ-terpinene, α-thujone, β-fenchyl alcohol, β-thujone, trans-p-menth-2,8-dien-1-ol, camphor, borneol, terpine-4-ol, trans-piperitol, pulegone, piperitone, phellandral, bornyl acetate, lavandulyl acetate, carvacrol, decanoic acid, α-copaene, β-elemene, α-gurjunene, caryophyllene, aromadendrene, α-acrodiene, germacrene-D, eremophilene, β-selinene, γ-bisabolene, cis-nerolidol, spathulenol, caryophyllen oxide, 1-hexadecene, geranyl isovalerate, β-eudesmol, tetradecanol, junipene, valerenol, 6,10-dimethyl-2-undecanone, 1,2-benzenedicarboxylic acid, bis(2-methylpropyl) ester, hexadecanoic acid, palmitic acid, eicosane, heneicosene, phytol, docosane, n-tetracosane	(257)
A. ptarmica	Undeca-2E,4E-diene-8,10-diynoic acid isobutylamide, undeca-2E,4E-diene-8,10-diynoic acid piperidide, undeca-2E,4E-diene-8,10-diynoic acid 2-methylbutylamide, undeca-2E,4E-diene-8,10-diynoic acid phenylethylamide, deca-2E,4E,8Ztrienoic acid isobutylamide (8,9-dehydropellitorine), undeca-2E,4E-diene- 8,10-diynoic acid piperideide, deca-2E-ene-4,6,8-triynoic acid isobutylamide, deca-2E,6Z,8E-trienoic acid 2-methylbutylamide (homospilanthol), deca-2E,4E,8Z-trienoic acid piperidide, tetradeca-2E,4E,12Z-triene-8,10-diynoic acid isobutylamide, Deca-2E,4E-dienoic acid isobutylamide (pellitorine), tetradeca-2E,4E-diene-8,10-diynoic acid, sobutylamide (anacycline), tetradeca-2E,4E,12Z-triene-8,10-diynoic acid piperidide, deca-2E,4E-dienoic acid N-methyl isobutylamide	(49)
A. schischkinii	Caffeic acid, luteolin, luteolin glucoside, schaftoside, scutellarein dimethylether, vitexin, vitexin rhamnoside	(258)
A. sieheana	α-pinene, camphene, β-pinene, sabinene, α-terpinene, limonene, 1.8-cineole, γ-terpinene, artemisia ketone, yomogi alcohol, δ-elemene, 3.6-dimethyl 2.3.3a.4.5.7a-hexa hydro furan, artemisia alcohol, camphor, 2(10)-pinene-3-one, terpienole-4, bicyclo[3.1.1] hept-2-ene-2-carboxaldehyde 6.6-dimethyl, trans-pinecarveol, α-terpineol, borneol, germacrene-D, germacrene-B	(131)

Table 2. Traditional and folk medical usage of *Achillea* spp. aerial parts.

***Achillea* species**	**Country/culture**	**Effect**	**References**
Achillea aleppica	Turkey	diuretic, carminative, emmenagogue	-259
Achillea biebersteinii	Turkey	diuretic, carminative, emmenagogue, anti-asthmatic, cardiotonic, stomachic, tonic, for colds, nephralgia, gynecologic diseases, women' sterility, jaundice, expectorant and abscess, vulnerary, astringent, edema, erythema on skin	-259
	Iran	carminative, sedative (toothache), anti-septic, hemagglutinate, for indigestion, rheumatism, stomachache, fever, hypoglycaemia, hypothermia, food poisoning, inflammation	(260, 261)
Achillea cappadocica	Turkey	astringent, edema, emmenagogue, stomachic	-259
Achillea coarctata	Turkey	diuretic, carminative, menstrual disorders	-259
Achillea collina	Bosnia and Herzegovina	for bedwetting by children, blood purification, skin injuries, skin rash and psoriasis, liver ailments, purulent ulcers, increased diuresis, excretion of urinary stone, regulation of menstruation, bronchitis and asthma, throath ache	(262, 263)
A. damascene	Jordan	carminative, antispasmodic, depurative, for stomachaches and diabetes	-264
Achillea erba-rotta	Italy	digestive, depurative, antibacterial and antiinflammatory for toothache and headaches, mild tranquillizer, emmenagogue	(265, 266)
Achillea falcata	Jordan	carminative, depurative, stomachache, antispasmodic internal hemorrhage, uterine hemorrhoid, stomach aliment, aperitive, gastritis, bladder stonesa	-267
Achillea filipendulina Lam.	Tajikistan	for gastrointestinal disturbances, arthritis, malaria, cardiovascular diseases	(268, 269)
	Egypt	digestive and skin disorders	-270
Achillea fragrantissima	Saudi Arabia	carminative, digestive, for aching joints, fever	-271
	Israel	aching joints, fever, high blood pressure, stomach aches and diabetes	-272
Achillea kellalensis	Iran	carminative, indigestion, anti-bacterial, for gastric ulcer, hemorrhage, dysmenorrhoea, enema and diarrhea, skin infection, edema, burns and wounds	-273

Achillea millefolium	China	stop bleeding and to treat sores, snakebite, wounds, hemorrhoids, varicose veins, dysmenorrhea, and tuberculosis	-53
	India	antipyretic, stimulant and tonic, diaphoretic and diuretic hemorrhoid, for gastric problems and fever, cold, influenza and allergic mucus problems, respiratory phlegm, eczema	(255, 274)
	Indonesia	antimalarial	-53
	Pakistan	stimulant, tonic, diaphoretic and antipyretic, for cough, profuse mucous discharges	(275, 276)
	Turkey	diuretic, carminative, stomachic, urinary antiseptic, antitussive, tonic for, abdominal pain, cnephritis, loosing weight, common colds, migraine, tooth ache, stomach-ache, hemorrhoid pains, menstrual disorders,	(259, 277-280)
	Iran	antidiabetic, anthelmintic, anti-infectious, antihemorrhagic, antiinflammation, dyspepsia, dysmenorrhea, gastritis wounds, stomach ache	(255, 281, 282)
	Israel	high blood pressure, stomach aches and diabetes	-272
	common European folk	gastrointestinal disorders and loss of appetite, for menstrual problems, and as a diaphoretic, and topically as a poultice, wash, or bath for skin inflammations, wounds, and external bleeding	-53
	Eastern-European countries	diaphoretic, astringent, analgesic, for cold, fever, purifies blood, for wounds, cuts and abrasion	-283
	Macedonia	hemostyptic and for wound healing	-284
	Kosovo	anti-diarrhoeal, anti-diabetic, for stomach pain and eczema	-285
	Serbia	for loss of appetite, stomach disorders, menstrual complaints, cough, cramps	-286
	Hungary	internal ailments as well as for burns and wounds treating bronchitis, urinary and kidney problems, and for diarrhea and vomiting	-53
	Britain and Ireland	bleeding wounds, nosebleeds, uterine hemorrhage, and high blood pressure respiratory infections, fevers, and rheumatic complaints	-53
	Italy	haemostatic, diuretic, diaphoretic, anti-haemorrhoidal, gastrointestinal, anti-wound	(53, 265, 266, 287-289)
	Portugal	sudorific; fever; anti-inflammatory; menstruation induction and regulation. anti-inflammatory; antipyretic; antispasmodic; diaphoretic; diuretic; emmenagogue; phlebotonic; stomachic.	-290
	Algeria	tonic digestive	-291
	Sudhan	laxative, diuretic, stimulant, tonic to the brain and female organs of generation	-292
	Botswana	antimalarial	-53
	South Africa	antimalarial	-53
	New York State	analgesic, antidiarrheal, antiemetic, antihelmintic, antipyretic, antirheumatic, gastrointestinal, for venereal disease, menorrhagia; uterine fibroids; “panacea drug”	(66, 293)
	Mexico	diarrhea and colic to calm the nerves	-53
	Brazil	fever, headache, wounds and skin problems, diarrhea and other gastrointestinal problems	(53, 294)
	northern Amazon	antihemorrhoidal, emmenagogue, and stimulant	-53
	Peru	gastritis, diabetes, high cholesterol, skin infections	-53
	Native American tribes	wounds, bruises, skin damage or disorders, and bleeding conditions; colds, fever, and sore throat; digestive problems; and general tonic	-53

Achillea nobilis	Bosnia and Herzegovina	bedwetting by children, blood purification, for skin injuries, skin rash and psoriasis	-262
Achillea odorata	Morocco	hypoglycemic, expectorant	-295
Achillea santolina	Jordan	carminative, antispasmodic, depurative, for stomachaches and diabetes	-264
Achillea schischkinii	Turkey	carminative	-259
Achillea setacea	Turkey	emmenagogue, stomachic	-259
A. sulpherea	Jordan	carminative, antispasmodic, depurative, for stomachaches and diabetes	-264
Achillea tenuifolia	Turkey	hypercholesterolemia, diabetes, asthma, bronchitis, cough	-259
Achillea vermicularis	Turkey	stomachic	-259
	Iraq	helminthiasis, dysentery	-178
	Pakistan	farting, stomach pain, fever and motion of children	-296
Achillea wilhelmsii	Turkey	diuretic, antihemorrhoidal, stomachic, emmenagogues, for abdominal pain, women' sterility	(259, 280)
	Iran	Blood coagulation, diabetes, hypertension, kidney stone, constipation, stomachache, bellyach, backache	(261, 297, 298)

nica, *A. clypeolata*, *A. kotschyi* subsp. *kotschyi*, *A. phyrigia*, and *A. nobilis* subsp. *neilreichii* were evaluated against *Escherichia coli*, MORSA, *S. aureus, Streptococcus epidermidis, Salmonella typhimurium*, *Bacillus cereus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, and *Candida albicans*. Chloroform extracts revealed to be the most active (MIC=50-250 µg/ml) against the tested bacteria. From the hexane extracts, only *A. coarctata* and *A. setacea* exerted remarkable antibacterial activity only against *E. faecalis* (MIC value of 31.25 and 62.5 µg/ml, respectively). The most active species were *A. teretifolia* and *A. multifida,* whereas none of the extracts were active against *C. albicans* (54).

A. clavennae, A. holosericea, A. lingulata and *A. millefolium* hexane-diethyl ether-methanol (1:1:1) extracts were tested against *S. aureus, E. coli, Klebsiella pneumoniae, P. aeruginosa* and *Salmonella enteritidis*) and two fungi (*Aspergillus niger* and *C. albicans*). All species were active against all the tested pathogens, with the weakest activities were attributed to *A. millefolium* (13). *A. millefolium, A. biebersteinii* and *A. teretifolia* water, methanol and ethyl acetate extracts were tested on *E. coli, P. aeruginosa*, *S. typhimurium, Listeria monocytogenes*, *E. faecalis, B. cereus, Micrococcus flavus, S. aureus, Aspergillus fumigatus*, *A. niger*, *Aspergillus versicolor*, *Aspergillus ochraceus*, *Penicillium funiculosum, Penicillium ochrochloron*, *Penicillium verrucosum* and *Trichoderma viride.* Ethyl acetate extracts exhibited the most remarkable effects, followed by methanol and water extracts. *A. biebersteinii* was the most active (MIC=0.015-0.60 mg/ml) and to a lesser extent, antibacterial efficacy was displayed by *A. teretifolia* (MIC=0.03-0.6 mg/ml) and *A. millefolium* (MIC=0.05-0.8 mg/ml). All extracts showed good antifungal effects (MIC=0.006-0.08 mg/ml), of which methanol extracts were found to be the most active ones (55). *A. aleppica* subsp. *aleppica*, *A. aleppica* subsp. *zederbaueri*, *A. biebersteinii* ethanol extracts (56), and *A. cappadocica* acetone and methanol extracts exhibited moderate effects only (57). *A. fragrantissima* methanol extract from Saudi Arabia exerted antibacterial effect against *S. aureus* and *P. aeruginosa* clinical isolates (58). Antimicrobial activities of flavones and sesquiterpenes isolated from *A. atrata*, as well as its crude extract were tested against Gram-positive bacteria *S. aureus*, spore-forming *Bacillus* sp., Gram-negative bacteria *E. coli*, the yeast *C. albicans*, and the fungus *A. niger* by the agar well diffusion method. Bioactivities were detected in case of flavones on *Bacillus, Candida* and *Escherichia* strains. The most active constituent was apigenin with a MIC value of 3.12 µg/ml on *C. albicans* (59).

Ultrasound-assisted extraction of *A. biebersteinii* and *A. wilhelmsii* with 80% methanol significantly increased the antimicrobial effects of the extracts compared to macerates, especially in *S. aureus* (in some cases MIC decreased from 5 mg/ml to 0.04 mg/ml) (60). *A. coarctata* ethanolic extract exhibited antibacterial effect against *E. coli, P. aeruginosa, B. subtilis*, *S. aureus, C. albicans,* and *A. niger* with MICs of 1, 2, 0.5, 0.5, 0.5 and 4 mg/ml, respectively (61). The 80% ethanolic extract of *A. cucullata* (Turkey) displayed moderate antimicrobial activities on two Gram-positive (*S. aureus* and *E. faecalis*), two Gram-negative (*P. aeruginosa* and *E. coli*), and on *C. albicans* (MICs >5 mg/ml) (62).

In a screening assay of plant samples from Lebanon, *A. damascena* methanol extract of whole plants was effective against *Proteus* sp., *P. aeruginosa*, *Shigella dysenteriae*, *S. enteritidis*, *S. typhi*, *S. aureus*, *S. faecalis* and *C. albicans* in a disc diffusion assay (63). *A. grandifolia* and *A. crithmifolia* methanolic extracts exerted weak antimicrobial activities (MIC=12.5-50 mg/ml) (64). *A. hamzaoglui* methanolic extract and EO exhibited moderate antimicrobial activities against bacteria and fungi (*Candida* spp.), where the oil displayed marginally higher antimicrobial activity (65). In a study, where medicinal plants of traditional Haudenosaunee culture were investigated for biological effects, the water extract of *A. millefolium* diplayed antibacterial efficacy against *Salmonella typhimurium* and *S. aureus* (66). In a study, where different plant extracts were tested for their efficacy against pathogens isolated from red deer faeces, the 70% ethanolic extract of *A. millefolium* belonged to the less active extracts, exerting antibacterial activity only against *E. faecalis* strains (MIC 0.78%) (67). The alcohol extract of *A. millefolium* herbs was reported to be effective against different wound pathogens, especially on *S. aureus* and *Stretococcus pneumoniae* (68). Based on its wide use in the West Himalayan region for tongue infections and as mouthwash, *A. millefolium* rhizome was selected for antimicrobial testing. The ethanol extract of the rhizome showed the highest activity against *S. typhi, B. subtilis and S. aureus.* The petroleum ether extract possessed similar activity, whereas the water extract was inactive (69). In a TLC-bioautographic study, the 70% ethanolic extract of *A. millefolium* exerted antimicrobila activity against *S. aureus,* MRSA and *S. epidermidis.* Apigenin was identified as main active component of the extract (70).

The ethanolic extract of *A. millefoilum* flowerheads did not exhibit any antimicrobial effect on *S. aureus*, *Salmonella choleraesuis, P. aeruginosa*, *B. subtilis, C. albicans, Proteus* spp, *K. pneumoniae*, *Shigella* spp., *Proteus* spp., *Enterobacter aerogenes* and *E. coli* in a disc diffusion assay (71). The extract of *A. millefolium* inhibited specific biofilm formation of *E. coli* and potentiated the effect of streptomycin and cefotaxime in an *in vitro* assay (72). The 50% ethanolic extract of *A. millefolium* exerted moderate activity against the caryogenic *bacteria Streptococcus mutans, Lactobacillus rhamnosus* and *Actinomyces viscosus* (MICs 12.5-50 mg/ml). However, these activities were less remarkable than those of *Salvia officinalis* (73). Different extracts and EO (with camphor as main component) of *A. moschata* of Alpine origin were tested against Gram-positive (*B. cereus, E. faecalis, S. aureus*) and Gram-negative (*E. coli, Proteus mirabilis, P. aeruginosa*) bacterial species using the disk diffusion assay. The dichloromethane and petroleum ether extracts and the EO possessed remarkable antimicrobial activity expressed according to inhibition zone diameter on all tested species, whereas the methanolic extract was less active (74). *A. sieheana* extract exerted moderate antimicrobial activities against *Aeromonas hydrophila*, *Bacillus brevis*, *B. cereus*, *K. pneumoniae*, *Listeria monocytogenes*, *P. aeruginosa*, *S. aureus* and *Yersinia enterocolitica*, whereas no activity was noted against *B. subtilis*, *E. coli*, *Morganella*

morganii, *P. mirabilis*, *S. typhimurium*, *C. albicans* and *Saccharomyces cerevisiae*.

The heptane, chroroform and methanol extracts of *A. multifida* was testred for antimicrobial activity against a series of pathogens. The heptane extract was practically inactive; the methanol extract had weak activities, whereas the chloroform extract inhibited the growth of *S. aureus* and *S. epidermidis* with MICs of 8 mg/ml. None of the tested extracts were active against *K. pleumoniae, P. aeruginosa* and *Candida* spp. (75). The ethanolic extract of *A. schurii* of Romanian origin, characterized by high isoquercitrin and rutin content, was highly active against *Listeria monocytogenes, S. aureus*, and *S. typhimurium* (inhibition zones 16-22), moderately active against *E. coli* and *C. albicans* (76). In a screening assay on Turkish medicinal plants, different extracts of different plant parts of *A. setacea* and *A. biebersteinii* exerted weak to moderate activity in the disk diffusion method against *B. cereus, B. subtilis, S. aureus, S. epidermidis* and *Sarcina lutea*, the former being the more active. No activity was detected against the Gram-negative bacteia and *C. albicans* (77).

Essential oil

Considering the antimicrobial activity of EO, EO from 6 *Achillea* spp. *viz. A. pachycephala*, *A. millefolium*, *A. nobilis*, *A. filipendulina*, *A. santolina* and *A. aucheri* were tested on several Gram-negative and Gram-positive bacterial strains. *A. pachycephala*, *A. millefolium* and *A. filipendulina* exerted the most remarkable effects (MIC 32.5-100 µg/ml) against *S. aureus*, *B. subtilis*, *S. epidermidis, E. coli* and *S. typhimurium*, and no selectivity was detected for the tested bacteria (78). EO from *A. biebersteinii*, *A. fragrantissima*, *A. santolina* and *A. millefolium* were also tested on *S. aureus*, *Listeria monocytogenes*, *E. coli, P. aeruginosa* and *S. enteritidis*, of which *A. biebersteinii* and *A. fragrantissima* demostrated the highest antibacterial activity. These EO and their main components were also tested as nanoemulsions, being stated a marked increase in antibacterial efficacy using nanoformulations (from 60-240 µl/ml to 15-240 µl/ml) (10). *A. ageratum* (79) and *A. schischkinii* (80) EO only exerted moderate antimicrobial effects. *A. ageratum* EO was also chemically characterized, and artemisyl acetate was identified as the main component. Gram-positive bacteria were the most susceptible (MIC=2.55-7.02 mg/ml) than Gram-negative bacteria (MIC=20.40-41.10 mg/ml). In addition, a strong antifungal activity was stated against *C. albicans* (MIC=5.83 mg/ml) (81). *A. atrata* EO, together with its main component 1,8-cineole, were assessed for antifungal effects on *Alternaria alternata*, *Aspergillus* spp., *Cladosporium cladosporioides*, *Fusarium tricinctum*, *Penicillium* spp., *Phomopsis helianthi*, *Trichoderma viride*, *Trichophyton* spp., *Epidermophyton floccosum*, *Microsporum* spp, and positive inhibitory effects were stated (MIC of 2-8 µL/ml and 3-8 µL/ml, respectively) (82). *A. biebersteinii* and *A. teretifolia* oils were tested for antimicrobial activities on 6 different *Candida* and 10 bacteria strains. Piperitoone and 1,8-cineole were identified as the main components, respectively. A remarkable activity was detected only for *A. biebersteinii,* and only on *C. utilis* (MIC 31.25 µg/ml) (83). *A. biebersteinii* and *A. millefolium* EO were also tested on plant pathogems, and both showed only mild effects on tested strains (MIC≥125 µg/ml), whereas their extracts prepared with organic solvents displayed no activities (84). *A. biserrata* and *A. salicifolia* EO (main component: camphor) exerted moderate effects on *E. coli*, *S. aureus*, *P. aeruginosa*, *E. aerogenes*, *P. vulgaris*, *L. monocystogenes*, *S. marcescens* and *C. albicans* (MIC=250-1000 µg/ml) (85). *A. clavennae* EO was characterized, with camphor being the major constituent, and evaluated for antimicrobial effects on Gram-positive, Gram-negative and fungal organisms, but the highest activity was found on Gram-negative and fungal organisms (86). *A. clavennae* EO exhibited antibacterial effects against *K. pneumoniae*, penicillin-susceptible and penicillin-resistant *S. pneumoniae*, *Haemophilus influenzae* and *P. aeruginosa* (87). *A. clypeolata* EO, with the main component (*E*)-γ-bisabolene, showed activity against *E. coli*, *K. pneumoniae, P. aeruginosa* and *S. aureus*, with marginal activity for *E. coli* (88). *A. cuneatiloba* EO from leaves and flowers, both containing artemisia alcohol as main component were active against *E. coli, Klebsiella* spp., *S. aureus, S. epidermidis, Corynebacterium glutamicum* and even against *A. niger, Fusarium solani* and *Alternaria alternata* (MICs 32-256 µg/ml) (89). *A. collina* and *A. pannonica* EO, with β-pinene and 1,8-cineol as major constituents, respectively, were more active on Gram-positive than Gram-negative bacteria. *A. collina* EO in most cases exhibited stronger antibacterial effects than *A. pannonica*. Highest activities were detected for *Streptococcus* and *Staphylococcus* strains, whereas no activity was stated on *P. aeruginosa* (90). *A. cretica* EO from different organs (flowers, vegetative parts and roots) were active against *S. aureus* and *E. faecalis* (MIC=15-39 µg/ml), but not against *E. coli*, *P. aeruginosa* and *Acinetobacter*. The main component of the oils, camphor, displayed only mild effects (91). *A. cretica* EO contained caryophylladienol-II as main component, being bactericidal against *B. cereus* (MIC=62.5 µg/ml) and inactive on *Staphylococcus* spp., *E. coli*, *Shygella flexneri*, *Salmonella* sp. and *C. albicans* (92). *A. eriophora* EO, containing 1,8-cineol as main component, inhibited the growth of a series of pathogenic microorganisms; the most sensitive one was *S. aureus,* followed by *C. albicans*, *C. kefyr*, *A. niger, A. fumigatus,* and *P. aeruginosa* (MIC=0.5-2.5 µL/ml) (93). *A. falcata* EO, containing grandisol as predominant constituent, exerted antibacterial effects on *B. cereus, B. subtilis, S. aureus*, *S. faecalis*, *E. coli, P. mirabilis, P. aeruginosa* and *S. typhi*, with higher activities on Gram-positive than on Gram-negative bacteria (94). *A. formosa* subsp. *amanica* EO, with borneol as main component was highly active against *C. albicans* and *C. tropicalis* (MICs 12.5 µg/ml), but less active against *E. faecalis*, *S.aureus, E. coli* and *P. aeruginosa* (50, 25, 200 and 200 µg/ml, respectively) (95). *A. fragrantissima* EO, with artemisia ketone as the main component in all samples, was revealed to be effective on both Gram-positive and -negative strains (96, 97), and even against Shiga-toxin producing *E. coli* (MIC=5-10 µl/l). This EO, together with others, might be used to control foodborne pathogens (98). *A. frasii, A. holosericea* and *A. taygetea* EO from Greece, the first two with camphor as main componenst and *A. taygetea* with 1,8-cineole were tested for antimicrobial effects. *A.*

holosericea was totally inactive. *A. taygetea* was active on all tested strains (*S. aureus, S. epidermidis, P. aeruginosa, E. cloacae, K. pneumoniae, E. coli, C. albicans, C. tropicalis* and *C. glabrata*, MICs 1.17-4.89 mg/ml), whereas *A. frasii* did not infuence the growth of *Candida* strains (99).

The EO, the water-soluble and -insoluble parts of the methanolic extract of *A. biebersteinii* were tested for antibacterial effect. No activity was observed in the water-soluble fraction whereas the water-insoluble part had moderate activity against *B. cereus*, *C. perfringens* and *C. albicans*. The oil possessed broader and more remarkable activity against *Candida. albicans* in particular, followed by *Clostridium perfringens*, *S. pneumoniae*, *B. cereus*, *E. coli, Mycobacterium smegmatis* and *S. aureus* (MICs 0.15-36 mg/ml). *P. aeruginosa* was resistant to the extracts and the oil (100). The EO of *A. collina* (main component chamazulene) exerted antibacterial effect on *E. coli*, *S. flexneri*, *K. pneumoniae, S. typhimurium* and *S. aureus* using a diffusimetric method (101). EO obtained from *A. coarctata* inflorescences and leaves from Greece, both containing 1,8-cineole as main component, exhibited remarkable antimicrobial effect on *M. flavus, E. faecalis* and *C. albicans* (3.25 µg/ml) and were less active against *S. aureus, S. epidermidis, E. coli, K. pneumoniae* and *P. aeruginosa* (MICs 25-100 µg/ml) (102).

A. holoserica and *A. clavennae* esential oils, with the main components borneol and camphor, respectively, exhibited moderate antibacterial activities on Gram-positive and -negative bacteria and fungi as well (103). Both EOs from *A. ligustica* leaves and flowers contained 4-terpineol as major compound and showed an inhibitory activity on *C. albicans, Hafnia alvei, L. monocytogenes, B. cereus*, *S. aureus*, *P. aeruginosa*, and *E. coli*. The effectiveness of the two oils was comparable in the diffusion assay. In case of *C. albicans* more pronounced activity was detected (104). The antibacterial activity of *A. ligustica* EO was compared to a commercial EO-containing mouthrinse (Listerine) and clove oil. The inhibition efficacy of *A. ligustica* EO alone and in combination with Listerine was evaluated by the micro-dilution method. The most susceptible microorganisms were *B. cereus, Streptococcus pyogenes,* and *C. albicans*. The efficacy was similar to that of the clove oil. *Achillea* oil exhibited MICs of 78-310, 78-155 and 78-155 µg/ml on these three microbes respectively, whereas for the commercial product these walues were 2500, 1250 and 1250 µg/ml respectively. In case of the combination of the *Achillea* oil and the product, MICs decreased to 62.5, 78 and 625 µg/ml, respectively. Based on these data, the use of *A. ligustica* EO seems to be promising in mouth rinses (105). *A. ligustica* EO from Corsica, with the main components camphor and santolina alcohol had antibacterial effect on Gram-positive (*E. faecalis*, *S. aureus*, *Nocardia asteroides* and *Corynebacterium jeikeium*), Gram-negative (*P. aeruginosa* and *E. coli*), and *Streptomyces* (*S. albus*, *S. coelicolor* and *S. avidinii*) bacteria, with most pronounced activities on the latter strains (106). Flowers and stems/leafs of Italian *A. ligustica* contained EO with differenmt compositions, characterized by linalool and virdiflorol as main components, respectively. The oil from the vegetative parts was active on *S. mutans* (MIC 39 µg/ml) whereas both the oils were active on *B. subtilis* (39-78 µg/ml) (107). *A. ligustica* EO showed weak activity against *S. aureus, E. coli, P. aeruginosa* and *C. albicans* and was inactive against a series of agricultural pathogenic fungi (108).

Turkish *A. magnifica* and *A. filipendulina* EOs exhibited antimalarial activity against both chloroquine-sensitive D6 (IC_{50} = 1.2 and 0.68 µg/ml) and chloroquine-resistant W2 (IC_{50} = 1.1 and 0.9 µg/ml) strains of *Plasmodium falciparum, however A. tenuifolia was not active*. *A. tenuifolia* and *A. magnifica* oils exerted mild antifungal activity against *Cryptococcus neoformans* (IC_{50} = 20 and 15 µg/ml, respectively) and *A. tenuifolia* oil displayed weak antimycobacterial activity against *Mycobacterium intracellulare* (IC_{50} = 200 µg/ml) (109). *A. micrantha* EO (with the main component 1,8-cineole) did not possess antibacterial (against *S. aureus*, MRSA, *E. coli* and *P. aeruginosa*), anti-tuberculosis, antifungal (against *C. albicans*, *C. glabrata*, *C. krusei*, *A. fumigatus* and *C. neoformans)*, and antimalarial activities (110).

The antimicrobial activity of an EO obtained from *A. millefolium* sample from Iran, and its main constituent, borneol was assessed on Gram-positive bacteria (*B. cereus*, *E. faecalis* and *S. aureus*), Gram-negative bacteria (*E. coli*, *Pseudomonas*, *P. mirabilis*, *S. typhimurium* and *C. freundii*) and fungal strains (*C. albicans* and *A. fumigatus*). Inhibition values ranged between 2.5 µg/ml (*E. coli*) and 25 µg/ml (*P. aeruginosa*) (MIC) and between 2.5 µg/ml (*E. coli*) and 20 µg/ml (*S. aureus*) (MBC) for bacteria, and from 3 µg/ml (*C. albicans*) to 4.5 µg/ml (*A. fumigatus*) (MIC) and from 3.0 µg/ml (*C. albicans*) to 4.5 µg/ml (*A. fumigatus*) (MFC) for fungi. Borneol was more effective in all cases (111). The EO of leaves and flowers of *A. millefolium* from Iran, both with borneol as the major components showed antimicrobial activity against *S. aureus*, *S. enteritidis*, *E. coli*, *Penicillium glaucum* and *S. cerevisiae* (MIC values 0.45-7.20 mg/ml) (112). The EO of a Turkish *A. millefolium* subsp. *millefolium* sample (main component eucalyptol) showed antimicrobial activity (MICs 4.5-18 mg/ml) against *S. pneumoniae, C. perfringens*, *C. albicans*, *M. smegmatis, Acinetobacter lwoffii* and *Candida krusei* while water-insoluble parts of the methanolic extracts exhibited slight or no activity (113). The EO of *A. millefolium* exhibited antibacterial effect on *S. aureus* clinical isolates (12.5-25µl/ml). Moreover, it damaged the biofilm structure of this pathogen at the MIC value by 35.3-94.3% as determined by the reduction of biofilm metabolism (114). In a study, the antifungal effects of *A. millefolium* of Romanian origin was studied. Using the Kirby-Bauer diffusion method, significant antifungal acctivity of the 50% ethanol extract was determined against *A. niger* and *Penicillium hirsutum*. The EO at a concentration of 20 µl/ml significantly inhibited the growth of the fungal strains and induced changes in the macroscopic appearance of fungal colonies (115).

The EO of *A. millefolium,* with chamazulene as main constituent was active against *S. aureus*, *S. typhimurium*, *E. coli*, *K. pneumoniae*, *E. faecalis* and *C. albicans* but not on *P. aeruginosa* as detected using a diffusimetric method (116). On a set of microbes (*B. cereus*, *E. faecalis*, *S. aureus*, *E. coli*, *P. aeruginosa*, *P. mirabilis*, *S. typhimurium*, *Citrobacter freundii*, *C. albicans* and *A. fumigatus*), the EO of *A. millefolium* showed the

strongest activity against bacteria (MICs 2.5–5 µg/ml) and fungi (1-2 µg/ml). Interestingly, this oil was characterized with high thymol content (26.5%, main component) (117). A Croatian *A. millefolium* sample, extracted with 80% ethanol, was active on the Gram-positive *B. cereus*, *Listeria monocytogenes* and *S. aureus,* but inactive on the Gram-negative *E. coli* and *Salmonella infantis*, except *Campylobacter coli* (118). In a study, the EO of *A. millefoilium* did not exert antifungal effect against *C. albicans* (119). The EO from *A. millefolium* (main component cham, azulene) displayed only weak effect against *Trypanosoma cruzi*, exerting a dose-dependent growth inhibition IC_{50}/24 h 145.5 µg/ml (120). The EO of a Turkish *A. millefolium* subsp. *millefolium* sample (main component 1,8-cineole) exhibited antibacterial effect on MRSA, *S. aureus, P. aeruginosa, E. coli* and *B. cereus* by using the disc diffusion method, on MRSA being the most active (121). EO from *A. millefolium* samples (main component germacrene D) from the subtropical regions of India had weak activity against *S. aureus, S. typhimurium* and *C. albicans* (MICs 125 µg/ml) and were less effective on *S. epidermidis, S. mutans, K. pneumoniae, P. aeruginosa* and *E. coli* (47).

Encapsulation of *A. millefolium* EO in hydroxypropyl-beta-cyclodextrin improved the activity significantly against *S. aureus* and *E. coli* (MICs 250 µg/ml and 500 µg/ml, respectively vs. 62.5 µg/ml both) (122). The EO of *A. multifida* with α-thujone as predominant constituent had antimicrobial effect against a series of human pathogenic bacteria (*B. cereus, E. aerogenes, E. coli, P. aeruginosa, S. typhimurium* and *S. aureus*) with MICs of 62.5-250 µg/ml and *C. albicans* (MIC 62.5 µg/ml) (123). EO of *A. nobilis* subsp. *sipylea* (major constituent fragranol) and *A. nobilis* subsp. *neilreichii* (main component 1,8-cineole and piperitone) were active against *E. coli, S. epidermidis, S. aureus, S. typhimurium, E. cloacae*, *E. faecalis, Proteus vulgaris* and *C. albicans*, but inactive against *P. aeruginosa* in a disc diffusion assay (124). The EO of *A. nobilis* (main component 1,8-cineole) was active against *Fusarium* and *Aspergillus* species with MICs of 0.6-1.2 mg/ml (125).

The EO of *A. odorata* subsp. *pectinata* var. *microphylla* from Algeria, containing camphor as major component was tested against nine microorganisms (four bacteria and five fungi). The oil exerted moderate inhibitory effects on *A. alternaria*, *A. fumigatus* and *Cladosporium herbarum*, with MICs of 4 µL/ml and 5 µL/ml. The EO was inactive against *P. aeruginosa, S. aureus* and *E. faecalis* and fairly active against *E. coli* (126).

The EO of a Turkish *A. phrygia* sample, with camphor as predominant constituent showed antimicrobial activity against MRSA, MSSA and *Acinetobacter baumannii* strains in a disc diffusion assay (127). *A. santolina* EO increased the efficacy of standard antobiotics (amoxicillin, chloramphenicol, neomycin, doxycycline, clarithromycin, cephalexin and alidixic acid) on *E. coli* strains, referring to the potential beneficial co-administration of these compounds. This plant has been used traditionally in Jordan for its antibacterial effect, and this study supported the rationale of its use (128). The 95% ethanolic axtract of *A. santolina* flowers had only very mild antibacterial effect on *S. aureus* (129). *A. santolinoides* EO was active against dermatophytes (*Tricophyton* sp., MICs 16–32 µg/ml), moderately active on *S. aureus* and practically inactive on *C. albicans* and *P. aeruginosa* (11). The EO of the endemic Turkish species *A. setacea and A. teretifolia*, both containing 1,8-cineole as major constituent, exhibited inhibitory effects on *C. perfringens, A. lwoffii* and *C. albicans* with MICs of 0.28-2.25 mg/ml and practically inactive on *E. aerogenes, E. coli, K. pneumoniae, P. mirabilis, P. aeruginosa* and *C. perfringens* (130).

The EO, with camphor as main component was moderately active against all strains (131). *A. sintenisii* EO, water-soluble and methanolic extract-insoluble parts were tested for antimicrobial effect. The water-soluble parts exhibited no activity whereas the water-insoluble parts exhibited moderate activity. The oil was active on most of the tested bacteria, with most remarkable activities were noted against *A. lwoffii*, *C. perfringens* and *M. smegmatis* (MIC=0.56-1.12 mg/ml) (132). *A. tenuifolia* methanolic extract had weak-to-moderate effects on *E. facealis* and *B. subtilis*, with no effect on *S. epidermidis* (12).

A. teretifolia and *A. nobilis* subsp. *neilreichii* EO of aerial parts were chemically characterized, with 1,8-cineol and fragranyl acetate being the main components, and were active against *P. vulgaris* (MIC=0.5 mg/ml) and *Candida tropicalis* (MIC=0.5 mg/ml). To *E. coli, S. aureus, P. aeruginosa, E. aerogenes, S. typhimurium* and *B. cereus* only weaker effects were stated (MIC>2 mg/ml) (133). *A. teretifolia* and *A. schischkinii* were also tested on *E. coli*, *S. aureus, B. cereus, P. aeruginosa, K. pneumoniae, E. aerogenes, S. cerevisiae* and *Candida* spp., and *A. teretifolia* exerted moderate effects on all species, while to *A. schischkinii* no positive effects were observed (134). *A. umbellata* EO, with fragranol derivatives tentatively identified as the main constituensts, exerted antimicrobial activity (MIC=0.39-6.25 mg/ml). *S. aureus* was the most susceptible, and *P. aeruginosa* was the most resistant isolated strain (135).

A. wilhelmsii EO, with the main component carvacrol, exhibited remarkable activities on MSSA and MRSA strains (136) and even against 20 *C. albicans* strains (MIC=0.039-0.156%) (137). *A. wilhelmsii* and *A. lycaonica* EO were also tested on *E. coli* ATCC 25292, *S. aureus* ATCC 6538, *P. aeruginosa* ATCC 27853, *E. aerogenes* NRRL 3567, *P. vulgaris* NRLLB 123 and *C. albicans* OGU. Most remarkable efficacy was detected on *C albicans* (MIC=62.50 and 31.25 µg/ml, respectively) (138). *A. wilhelmsii* EO had broad and remarkable (MICs 1-15 µg/ml) antimicrobial effects on *B. cereus, E. cloacea, E. faecalis, L. monocytogenes, S. aureus, A. baumanii, E. coli, K. pneumoniae, P. aeruginosa, P. mirabilis, S. typhimurium, C. freundii, C. albicans, C.tropicalis, C. parapsilosis, A. niger,* and *A. fumigatus*, being thymol and carvacrol the main components (139). *A. wilhelmsii* EO also revealed good antibacterial effects on extended-spectrum beta-lactamase-producing *E. coli* isolates (MIC=0.5-4 mg/ml) (140).

Anti-phytopathogenic properties

A. micrantha EO, containing 1,8-cineole as the main component, displayed weak antimicrobial activity on phytophatogenic bacteria and fungi, with the most remarkable activity on *Septoria tritici* (MIC 1.3 mg/ml) (141). The composition and effects of *A .gypsicola* and *A. biebersteinii* EO and *n*-hexane extracts were tested

on phytophatogenic fungi by a contact assay. Both oils and extracts of the two species contained camphor and 1,8-cineole. *Alternaria alternata, Botrytis* spp., *Fusarium* spp. (except *F. equiseti* and *F. graminearum*), *Monilinia* spp., *Rhizoctonia solani,* and *Sclerotinia sclerotiorum* were the most susceptible fungi (142). *A. biebersteinii* EO, with 1,8-cineole as main component, was also highly active against 5 phytophatogenic fungi (9), while *A. biebersteinii* and *A. vermiculatus* EO were remarkably active against the phytopathogen *Xanthomonas arboricola* pv. *juglandis* (143).

Anti-fish-pathogenic properties

A. wilhelmsii EO, with 1,8-cineol as main component, exhibited moderate antimicrobial activity against *Yersinia ruckeri* (MIC>250 µg/ml), a common cold-water fish culture pathogen (144). *A. falcata* flowers extract was confirmed to be effective on the fish pathogen *Aeromonas hydrophila*. Moreover, 97% of tested 178 antibiotic-resistant strains were susceptible to treatment with herbal extract (145). *A. millefolium* ethanolic extract was tested against five fish pathogens, and the most remarkable activity was observed against *Photobacterium damselae* subsp. *piscicida* (MIC=8.4 mg/ml), and less pronounced activity was noted on *Listonella anguillarum, Yersinia ruckeri* and *Lactococcus garvieae* (146). *A. kellalensis* EO did not show antimicrobial effects against the aquacultural pathogens *Vibrio harveyi* and *V. parahaemolyticus* (147).

***In vivo* antimicrobial property**

In a burn wound healing study on rabbits, local treatment with *A. millefolium* water extract resulted to a lower number of microbes (*S. aureus, E. coli, Sterptococcus pyogenes* and *C. albicans*) over the 21-days experiment (148).

Antioxidant activities

Medicinal plants are valuable sources of natural antioxidants for consideration on functional ingredients and nutraceuticals formulation as well as feasible and natural alternatives to synthetic antioxidants in food and pharmaceutical industries(149). Several plants containing flavonoids and other phenolic compounds have been proven antioxidant, free radical scavengers and inhibitors of lipid peroxidation (150-157).

Herbal teas prepared from some *Achillea* spp. have been reported traditionally to possess many biological activities. It was already reported that infusions prepared from *Achillea* spp. exhibited antioxidant potential to scavenge stable free DPPH radical (158). Several reports indicate that *Achillea* genus displays a relevant antioxidant activity that is associated or correlated well with its flavonoid and total phenolic and polyphenolic contents (159, 160). The *in vitro* antioxidant activities of different species of *Achillea* including *A. millefolium* (113), *A. ligustica* (161), *A. wilhelmsii* (162) and *A. biebersteinii*. (163) have been previously investigated.

In a vast review, the chemical composition of the EO and extracts of 28 *Achillea* spp. and their biological activities including antioxidant properties were studied (164). In some of these studies, promising IC_{50} values were reported. As DPPH antioxidant activity evaluation was the common assay in all the investigations reviewed, results of this test were taken to compare the antioxidant activity of the *Achillea* spp. It has been reported that *A. millefolium* EO was the most promising, reducing diphenylpicrylhydrazyl radical, with IC_{50} values ranging from 1.56 to 20 µg/ml (113, 164-166).

The isolated *A. millefolium* EO exhibited hydroxyl radical scavenging effect in the Fe^{3+}–EDTA–H_2O_2 deoxyribose system (IC_{50} = 2.7 µg/ml). It also inhibited the non-enzymatic lipid peroxidation of rat liver homogenate (IC_{50} = 13.5 µg/ml) (113). Thymol and carvacrol showed the highest free radical scavenging activity with the IC_{50} value of 12.0 µg/mL and 13.43 µg/mL, respectively and the lowest activity was exhibited by bornyl acetate (IC_{50} = 25 µg/mL). So the results suggested that the antioxidant activity of the EO is mainly due to the action of thymol and carvacrol (167).

The EO of *A. filipendulina* demonstrated antioxidant activity with IC_{50} values of 4.83 µl/mL for DPPH and 2.01 µl/mL for ABTS; and 214.2 µM Fe (II)/mg for FRAP (ferric reducing antioxidant power) assays (168). *A. tenuifolia* EO showed a strong IC_{50} value of 15.12 µg/ml (165). Manayi et al., (2012) established antioxidant activity of the roots of *A. tenuifolia*. The value of IC_{50} for BHA, vitamin E, methanol and ethyl acetate in radical inhibition were calculated in the following order: 7.8, 14.2, 145.5 and 320 µg/mL. The scavenging capacity of methanol extract was higher than ethyl acetate extract (169). According to Mohammadhosseini et al. (2017), the best DPPH IC_{50} value of tested extracts of *A. millefolium*, *A. aleppica* subsp. *aleppica*, *A. aleppica* subsp. *zederbauri*, *A. biebersteinii*, *A. kotschyi*, *A. hamzaoglui* and *A. tenorii* were 45.60 µg/ml, 33.00 µg/ml, 33.00 µg/ml, 32.00 µg/ml, 32.60 µg/ml, 32.09 µg/ml and 31.41 µg/ml respectively (56, 65, 113, 164, 170, 171).

The protective effects of infusions from 15 *Achillea* spp. against H_2O_2-induced oxidative damage in human erythrocytes and leucocytes were investigated. Obtained results indicated that all *Achillea* spp. infusions were found to be protective on glutathione (GSH) and lipid peroxidation (LPO) levels of erythrocytes and leucocytes against H_2O_2-induced oxidative damage. *A. millefolium* subsp. *pannonica* exhibited the highest activity on GSH levels of erythrocytes and leucocytes, which is consistent with its flavonoid and total phenol contents. The most effective one on CAT, GPx and SOD enzyme systems of erythrocytes was *A. falcata*. *A. crithmifolia*. and *A. nobilis* subsp. *neilrechii* exhibited the highest activities on CAT, while *A. millefolium* subsp. *pannonica* exhibited the highest activities on SOD. In addition, *A. teretifolia* and *A. nobilis* subsp. *sipylea* demonstrated the highest activities on GPx and LPO enzyme systems of leucocytes respectively (150).

The *in vitro* antioxidative activities of hydroalcoholic extract of *A. santolina* were also investigated (172). The results revealed that the total phenolic and flavonoid contents of *A. santolina* extract possessed notable inhibitory activity on peroxides formation in linoleic acid emulsion system along with concentration-dependent quenching of DPPH and superoxide radicals. Trumbeckaite and his team have used on-line HPLC-DPPH assay to show the presence of constituents within a complex of the flavonoid and phenolcarbonic acids in *A. millefolium* extract, which were capable of scaven-

ging free radicals. According to the DPPH quenching chromatogram, they found that the main components amongst the identified analytes in the extract, that possessed significant radical-scavenging properties, were flavone luteolin and chlorogenic acid. Minor scavengers such as rutin and luteolin 7-*O*-glucoside were present in low amounts which contributed less to the total antioxidant activity (173). They reported that luteolin and chlorogenic acid (54.96 and 44.84 lmol/g, respectively) were predominant radical scavengers in *A. millefolium* extract and when taken together, these two phytochemicals determine approximately one-third of its total antiradical activity. The obtained results demonstrated the general assumption that the presence of the aromatic B-ring with ortho-arrangement of two hydroxyl groups (catechol group) and 2,3-double bond in conjugation with 4-oxo function in the C-ring are structural features essential for the antiradical scavenging activity of flavonoids (174).

The *in vitro* antioxidant activities of EO of *A. teretifolia* and *A. nobilis* subsp. *neilreichii* were examined. Both EOs showed moderate activity in the DPPH (IC_{50} > 0.5 mg/ml) assay comparing to the positive controls (Vitamin C: 0.008 ± 0.002 mg/ml, Trolox: 0.01 ± 0.01 mg/ml) (132). In a study, the *in vitro* antioxidant and radical scavenging of extracts (methanol, water and chloroform) of *A. schischkinii* and *A. teretifolia* were examined (134). *A. teretifolia* methanol and water extracts (100 µg/ml) exhibited the best ABTS scavenging effect (91.5% and 91.2% respectively), being comparable with controls (BHA: 99.8% and α-tocopherol: 96.9%). The ABTS scavenging activity of methanol and water extracts of *A. schischkinii* were 87.3% and 80.9% respectively. The chloroform extracts of both species showed the lowest activity.

According to Chou et al. the major components isolated from *A. millefolium* EO (artemisia ketone, camphor, linalyl acetate and 1,8-cineole) can suppress the inflammatory responses of lipopolysaccharides (LPS)-stimulated RAW 264.7 macrophages, including decreased levels of cellular nitric oxide (NO) and superoxide anion production, LPO and GSH concentration. This antioxidant activity is a result of the down-regulation of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and heme oxygenase-1 (HO-1) expression, so can reduce the inflammatory response as well (175).

The decoction and microwave *A. millefolium* water extracts was revealed as the most effective with their total polyphenolic content and antioxidant capacities. The highest antioxidant activity value (148.99 ± 1.94 µM TE/g dw) were measured by the CUPRAC assay (176). El-Kalamouni et al. (2017) confirmed that α-pinene, sabinene, camphor, trans-chrysanthenyl acetate, cyclocitral isomers, and germacrene D of *A. millefolium* EO were recorded as the main components with effective antioxidant capacity (177).

Molan and his team reported that the water and ethanol extracts from *A. vermicularis* Trin. showed high total phenolic contents and strong scavenging activity toward DPPH radical. This study demonstrated the scavenging activity towards DPPH radical of the ethanol extract was significantly higher ($P < 0.05$) than the water extract (178). The aqueous-ethanol extracts of *A. vermicularis* showed high flavonoid content and potent free radical scavenging activity (179). The antioxidant activity result obtained from *A. eriophora* DC. and, *A. biebersteinii* extracts revealed that the leaf extract of *A. biebersteinii*, showed the highest antioxidant activity in three selected assays (DPPH, BCB and TBARS). Obtained IC_{50} values for leaf extract of *A. biebersteinii* were 0.27, 0.16 and 13.96 mg/ml, in DPPH, BCB and TBARS tests, respectively. Inflorescence extract of *A. eriophora* showed the lowest DPPH radical scavenging activity. Once again, as results indicated, the higher antioxidant activity could be attributed to their higher phenolic and flavonoid contents (180).

In a recent study conducted by Saeidi et al. the EO compositions and antioxidant activity from Iranian populations of *A. wilhelmsii* were examined. Results showed that the highest activity as a DPPH scavenger was IC_{50} values of 129 mg/ml, whereas the lowest result showed the IC_{50} of 372 mg/ml (181). The results revealed that the EOs of *A. wilhelmsii* displayed moderate to weak antioxidant activity that agrees with previous studies (65, 182) . As established in previous researches (183-185) the antioxidant activities of EOs can be attributed to their phenolic contents. Gharibi et al. illustrated the antioxidant activity of methanol extract evaluated according to DPPH, ferric thiocyanate (FTC) and β-carotene–linoleic acid assay. In DPPH assay, BHT showed the highest radical scavenging ability by showing the lowest IC_{50} (216 g/ml). The IC_{50} values of *A. pachycephala*, *A. kellalensis* and *A. aucherii* were 248 µg/ml, 518 µg/ml and 843 µg/ml, respectively. The data showed that *A. pachycephalla* extract showed higher antioxidant activity in quenching DPPH radical than other analyzed extracts (7).

Albayrak reported that the *A. sieheana* methanolic extract showed an effective DPPH scavenging activity (IC_{50} = 87.04 µg/mL). The extract had also a high reducing effect (71.08%) on the oxidation of β-carotene (131). A comparative study performed on six *Achillea* spp. (*A. pachycephala*, *A. millefolium*, *A. nobilis*, *A. filipendulina*, *A. santolina* and *A. aucheri*) revealed that *A. pachycephala* showed the highest antioxidant activity (IC_{50} = 365.5 µg/ml) which was comparable with butylated BHT (IC_{50} = 359.92 µg/ml). Major phenolic acids and flavonoids variation were identified in tested extracts. HPLC results showed that luteolin and chlorogenic acid were the most common phenolics in *A. pachycephala* (78). The effects of hydroalcoholic extract of *A. millefolium* on the H_2O_2 production in isolated rat heart mitochondria were examined. Extract of *A. millefolium* at concentration of 2.5 and 5 µL/1.5 mL caused a 45% reduction in the rate of H_2O_2 generation as compared to the rate in the absence of *A. millefolium* extract following 14 min incubation. According to this study results, *A. millefolium* extracts have shown to possess 308.8 µmol/g trolox equivalent DPPH radical scavenging activity and inhibition of H_2O_2 generation as 45% in rat heart mitochondria (173).

In conclusion, the obtained results from most of researches suggest that phenolic compounds are the significant contributors to the antioxidant activity of the medicinal plants studied and the water and ethanol extract of *Achillea* spp. can be used as easily accessible source of natural antioxidants and as a possible food supple-

ment or in the pharmaceutical industry. The concentrations of phenolic compounds in *Achillea* spp. may substantially vary depending not only on the genotype, but also on environmental conditions, the stage of plant development, the ratio of plant parts (flower/leaf/stem) analyzed, drying and storage conditions (173).

All the afore-mentioned reviewed investigations revealed the majority of researches were done on *A. millefolium*. There are many more species which may have valuable antioxidant activity with different mechanism of actions. A large number of the previously published papers on antioxidant activities of *Achillea* spp. have been conducted *in vitro*. Despite the widespread usage of this species in folk medicine, there is a lack of information about *in vivo* investigations to realize the side effects and potential use of these valuable medicinal plants for their therapeutic proposes (164). Based on the investigations and obtained results there is a close relationship between pharmacological and traditional ethno-botanical usage of different *Achillea* spp.

Anticancer activities

The antiproliferative and cytotoxic activities of the extracts and isolated compounds from selected members of genus *Achillea* have been reported in previous literature. Compounds including vitexicarpin, centaureidin, and quercetagetin 3,3-dimethyl ether isolated from the flowers of *A. millefolium,* exhibited antiproliferative activity against MCF7WT cell line with IC_{50} values of 0.59, 0.91, and 1.19 μM, respectively. Moreover, vitexicarpin and centaureidin showed antiproliferative activity against PC-3 cell lines (IC_{50} = 1.24 and 1.74 μM, respectively) (186). Achillinin A isolated from the flowers of *A. millefolium* demonstrated promising cytotoxic activity against A549, RERF-LC-KJ, and QG-90 cancer cell lines (IC_{50} = 5.8, 10, and 0.31 μM, respectively) (187). Another study was performed on the aerial parts of *A. millefolium* to study the antiproliferative activities of different fractions and compounds on three human cancer cell lines. Results revealed that the most active compound was the flavonol centaureidin with IC_{50} values ranging from 0.0819 to 0.3540 μM. Surprisingly, artemetin a close analogue of centaureidin was inactive, and casticin (IC_{50} = 1.286–3.582 μM) with 3′-hydroxy and 3-methoxy groups were less active than centaureidin. The authors concluded that the hydroxy substituents on C-3′ and C-5, and methoxy groups on C-3 and C-4′ were essential for the maximum cytotoxic activity (188). Secotanapartholide A isolated from *A. millefolium* flower extract demonstrated moderate cytotoxic activity against the human cancer cell line MCF7WT (IC_{50} = 5.51 μM) (189).

A. millefolium leaves and flowers' ethanolic extracts were investigated for their cytotoxic activity on human breast cancer (SK-Br-3 and MDA-MB-435) and leukemia (U937 and K562) cell lines. The extracts showed a dose-dependent inhibition of proliferation on the studied cell lines (190). Bhat et al. 2014 studied the cytotoxic activity of the methanol and the chloroform extracts of *A. millefolium* aerial part against MCF-7, THP-1, PC-3, and OVCAR-5 cancer cell lines. Results revealed that the chloroform extracts exhibited broad spectrum cytotoxic activity against all investigated cancer cell lines with growth inhibition of 99%, 98% and 99% against THP, MCF-7 and OVCAR-5 cell lines at 50 μg/ml, respectively (191). In addition, the effect of methanol extract of *A. millefolium* on the antiproliferative activity of bleomycin on human prostate cancer (DU-145) and human nonmalignant fibroblast (HFFF2) cell lines were studied. Results revealed a significant enhancement of bleomycin induced cytotoxicity in DU-145 cell lines. Furthermore, the extract did not show cytotoxicity on HFFF2 normal cells (192).

Trifunović et al. 2006 studied the antiproliferative activity of compounds isolated from *A. clavennae* against HeLa, K562 and Fem-X cancer cell lines. 9a-Acetoxyartecanin and apressin exhibited noticeable cytotoxic effects against all tested cancer cells with IC_{50} values ranging from 4.44 to 16.96 μM (193). Phytochemical investigation of the aerial parts resulted in the isolation of three new sesquiterpene lactones. The new isosecoguaianolide exhibited cytotoxicity equivalent to that of cisplatin by the induction of the apoptotic cell death in human U251 and rat C6 glioma cell lines (IC_{50} = 36.6 and 41.6 μM) (194).

The cytotoxic activity of *A. biebersteinii* extract was investigated against various cancer lines. Results suggested that *A. biebersteinii* could be used to fight MDR cancer cells. Remarkably, normal hepatocytes (AML12) were resistant to the extract than HepG2 cancer cell lines (195). Baharara et al. 2015 investigation the anti-apoptotic effect of silver synthesized nanoparticles using *A. biebersteinii* flower extract on MCF-7 cell lines. Results showed that Ag-NPs produced a dose-dependent reduction in cell viability, fragmented the nucleic acid, suppressed the specific cell cycle genes and thus resulted in inhibition of the proliferation and induction of apoptosis on MCF-7 (196).

Tohme et al. 2013 investigated the cytotoxic and growth inhibitory effects of the extract and isolated sesquiterpene lactones from *A. falcata* aerial parts against HCT-116 cell lines. Rupin A showed the highest activity with an IC_{50} value of 15.2 μg/ml while chrysartemin B showed the lowest activity (IC_{50} = 67.0 μg/ml); this might be attributed to the extra hydroxy group at C-8 next to the α-methylene-γ-lactone moiety, which significantly increased the activity of rupin A (197). The sesquiterpene lactones (3β-methoxy-iso-seco-tanaparatholide, tanaphillin, iso-seco-tanaparatholide, and 8-hydroxy-3-methoxy-iso-seco-tanaparatholide) isolated from *A. falcata*, showed a significant cytotoxic activity against HaCaT cell lines (198). The dichloromethane fraction obtained from *A. fragrantissima* displayed the highest cytotoxic activity against HePG-2 cell lines (IC_{50} = 38.7 μg/ml). This activity might be attributed to the flavone acerosin isolated in high concentration from this fraction (IC_{50} = 24.69 μg/ml) (199). Piceol, veratric acid, eupatilin 7-methyl ether, chrysosplenol D, cirsiliol, and cirsimaritin isolated from *A. fragrantissima* methanol extract displayed a promising cytotoxic activity against MCF7 (IC_{50} = of 18.2, 15.7, 9.5, 8.33, 3.23, and 3.83 μg/ml, respectively), and against HepG2 with IC_{50} values of 19.4, 41.2, 28.3, 20.8, 23.8, and 23.8 μg/ml, respectively. In addition, they demonstrated a cytotoxic activity against A549 cell lines (IC_{50} = 17.8, 13.6, 3.98, and 10.3 μg/ml respectively) (200). Phytochemical investigation of *A. cretica* resulted in the isolation of two new

sesquiterpene lactones, achicretin 1 and achicretin 2. Cytotoxic activity was tested for both compounds on four human cancer cell lines, IGROV-1, OVCAR-3, MCF-7, and HCT-116. Results showed that achicretin 2 displayed more potent cytotoxic activity against OVCAR-3 and HCT-116 cell lines with IC_{50} = values of 14.0 and 16.0 µM, respectively (201). Agar et al. 2015, reported that from the three studied species growing in Turkey, *A. kotschyi* subsp. *kotschyi* was the most active regarding their anticancer properties. (170).

The hydroalcoholic extract of *A. wilhelmsii* demonstrated a potent antiproliferative and apoptotic effects on PC3 cell line, which might be attributed to the inhibition of prominent oncogene hTERT expression in PCa (202). The cytotoxic and pro-apoptotic effects of *A. teretifolia* extracts were investigated. The methanol extract displayed a significant cytotoxic activity on prostate cancer cells by up regulation of bax and caspase-3 genes expression and down regulation of bcl-2 expression. In contrary, no cytotoxic activity was observed in HGF cells (203). Haidara et al. 2006, studied the mechanism of action of the flavonoid casticin isolated from *A. millefolium* as an antitumor agent. Casticin arrested cell growth in G2/M phase. It acted as a tubulin-binding agent, induced p21, which resulted in Cdk1 inhibition and down regulation of cyclin A (204).

The EO obtained from *A. ligustica* flowers and vegetative parts exhibited a moderate cytotoxic activity against T98G, A431, PC3, and B16-F1 cancer cell lines, with the highest activity observed for the flowers EO on B16-F1 cell lines (IC_{50} = 0.220) (107). The EO prepared by hydro distillation obtained from *A. fragrantissima* revealed an IC_{50} value of 0.51 µg/ml for MCF-7 and 0.62 µg/ml for HCT116, whereas the oil obtained by volatile solvent extraction showed an IC_{50} value of 0.80 µg/ml against MCF-7 and 0.91 µg/ml for HCT116 (205).

The EO of *A. filipendulina* exhibited cytotoxicity against five human tumour cell lines, HeLa, CaCo-2, MCF-7, and CCRF-CEM with IC_{50} values 209.9, 551.5, 223.7, 29.9, and 45.1 µg /ml, respectively (206).

The *in vivo* antitumor activity of sesquiterpenes isolated from *A. millefolium* flower extract was examined against mouse P-388 leukemia cells. The compounds achimillic acids A, B and C methyl esters were administered at a dose of 1, 2, 5, 20, and 50 mg/kg. Results showed a dose dependent anticancer activity of the compounds (207). In addition, the anticancer activity of the hydroalcoholic extract of *A. millefolium* flowers on bleomycin-induced lung fibrosis in Sprague Dawley rat was investigated *in vivo*. Rats were treated for two weeks using different doses of *A. millefolium* extract (400, 800, 1600 mg/kg/day P.O.) Results showed that lungs strips isolated from bleomycin-treated fibrotic lungs generated more contractions when compared to the group receiving *A. millefolium* extract after bleomycin (208).

Applications of *Achillea* spp. as food preservative

Food safety and quality issues are the highest concerns of food industry and consumers. The role of food industry is to provide natural, healthy and safe food products with high quality and extended shelf-life during storage. In order to meet the consumer needs of the rapidly growing human population in the future, waste and product loss should be reduced, and the sustainability of both agricultural and food manufacturing sector should be maintained. Due to the undesirable and harmful effects of synthetic additives and preservatives in the environment and human health, natural preservatives have gained considerable attention by consumers, agricultural and food sector as alternative pesticides, antimicrobials, antioxidants and insecticides (209). Moreover, using natural active compounds in novel functional food products is also a great interest to the consumers (210, 211).

Many natural plant extracts and EOs are Generally Recognized as Safe (GRAS) by the Food and Drug Administration (FDA) (212, 213). Natural active agents with antimicrobial and antioxidant properties have been used as preservatives to protect food products against deterioration caused by microorganisms and oxidation (214, 215). Many researchers have extensively studied naturally active compounds, especially derived from plant extracts and EOs for multiple applications in food industry (216-220).

Many researches mentioned *Achillea* spp. for potential applications in food systems to enhance both quality and safety of food products. For instance, *A. pachycephalla, A. nobilis, A. filipendulina, A. santolina, A. aucheri* and *A. millefolium* were assessed for their antibacterial, antioxidant, and anti-advanced glycation end-products (AGE) effects (78). AGEs compounds are formed by Maillard reaction when foods prepared by standard cooking methods, such as roasted almonds, broiled beef (15 min) and chicken breast (15 min), homemade pancake and fried eggs (221, 222). Among the studied species, *A. pachycephala* and *A. nobilis* were those with highest activities.

On the other hand, *A. aleppica* and *A. biebersteinii* have shown greater or similar antimicrobial activity compared to standard antibiotics (Imipenem, Amoxycillin, Ampicillin/Sulbactam) on tested food spoilage microorganisms and foodborne pathogens; also, these plants have high antioxidant activity (56). The antimicrobial properties of *Achillea* spp. against spoilage and pathogenic bacteria and also antioxidant properties have been well documented (47, 86, 100, 106, 108, 113, 177), while limited research has been conducted on *Achillea* plants extracts and EOs as food preservatives.

Some researchers focused on these properties for food preservation (98), and investigated the potential antimicrobial effect of some *Achillea* plants EOs, including *A. fragrantissima*, against Shiga toxin producing *E. coli* (STEC) serotypes for row cold-pressed raw juice (the cold press of kale, spinach, cucumber, celery, green apple, ginger, and lemon which may have *E. coli*-associated contamination). All selected EOs revealed antibacterial activity against the STEC serotypes. *S. officinalis* was the less effective, while *A. fragrantissima* seemed to be a candidate for the design of new antimicrobial agents for increasing the microbial safety of unpasteurized cold-pressed juices.

A comprehensive study reported *A. fragrantissima* EOs as a natural food preservative for different food model matrix (cheese, meat, milk, and tomato) (223). Both antibacterial (*B. cereus*, *S. aureus*, *E. coli,* and

P. aeruginosa) and antifungal (*A. niger*, *Penicillium* and *Rhizopus* spp.) effects were assessed, and compared with the standards drugs Cefaclor and fluconazole. The EO exhibited significant antibacterial and antifungal effects compared to the standard controls. The maximum antibacterial effect was observed on tomato matrix against *S. aureus*, while the minimum antibacterial effect was noted on meat matrix against *P. aeruginosa*. With regards to antifungal efficiency, the highest antifungal effect was observed on meat matrix against *Penicillium* sp., while the lowest antifungal effect was observed on cheese matrix against *Rhizopus* sp. These results demonstrated that *A. fragrantissima* EO has a great utility for new formulations for food preservation. Recently, *A. millefolium* has been used in functional food formulations, namely in kombucha beverages production (224). All *A. millefolium* produced kombucha beverages possessed antimicrobial activity against *E. coli, S. aureus, B. subtilis, K. pneumonia, P. vulgaris, P. mirabilis* and even *A. niger* and *C. albicans*. Moreover, kombucha beverages from *A. millefolium* had good antioxidant and antiproliferative activities, and had the potential to be consumed as novel functional foods.

Looking at the use of *Achillea* spp. EOs, due to EOs hydrophobicity, volatility, and high degradation rates in environmental conditions, these disadvantages limit their use as antimicrobials on food products. However, encapsulation techniques may overcome these critical aspects, at same time that enhance their bioavailability, efficacy and stability; therefore, provide possible solutions for the above cited limitations (213). Food industries have close attention on the use of nanotechnology to put EOs in food matrix to extend foodstuffs' shelf-life and increase the efficacy at low doses. Nanoemulsions, microemulsions, solid-lipid nanoparticles, cyclodextrin inclusion complexes, and liposomes are amongst the most frequenly used in this regard (225). Ahmadi and co-authors encapsulated *A. millefolium* EO in chitosan nanoparticles using ionic gelation method against *Tetranychus urticae* (226), which cause yield losses in many food products (227, 228). In another study, the antibacterial activity of *A. millefolium, A. fragrantissima, A. biebersteinii* and *A. santolina* EOs and nanoemulsions prepared from *Achillea* oils against foodborne bacteria was reported (10). Nanoemulsions were formulated with EOs and Tween 20 using High-Pressure Homogenization technique. All tested EOs, and their nanoemulsions showed significant antibacterial effects on S. *aureus, L. monocytogenes, E. coli, P. aeruginosa*, and *S. enteretidis*. Moreover, *A. millefolium* and some other medicinal plant extracts were encapsulated in alginate-chitosan microbeads through electrostatic extrusion technique to improve their antioxidant activity (229). A high encapsulation efficiency (82.4%) was obtained for yarrow extract. Similarly, yarrow EO encapsulated with hydroxypropyl-β-cyclodextrin (HPβCD) using freeze-drying technique with an encapsulation value of 45% revealed higher antimicrobial activity and stability compared to free one, while lower antioxidant activity was noted (122). Thus, EO nanoemulsions seem to markedly enhance the antibacterial activity when compared to the non-encapsulated EOs. In another work, the bioactive compounds from *A. millefolium* EO were encapsulated microbeads with alginate and chitosan and incorporated in chocolate formulations, and textural, sensorial and physical quality were reviewed (210).

On the other hand, the use of *Achillea* EOs in bacterial disinfection applications, and food packaging containing these EOs seems to be a promising approach for reducing the risk of foodborne pathogens in food industry. Plant pathogens are threats to food processing, agricultural sustainability and food security (230). Therefore, the control of agricultural plant pathogens is a major challenge in agriculture. *Achillea* plants have the potential to control these pathogens. Different kinds of EOs, including *Achillea* plants EOs, were assessed for its antibacterial effect on 25 agricultural plant pathogens (84). *A. biebersteinii* and *A. millefolium* EOs were those with more prominent effects against most of the tested agricultural plant pathogens. Moreover, food borne pathogens are able to form biofilms, causing food borne diseases. *L. monocytogens* is a foodborne pathogen and capable to form biofilms on food matrixes or manufacturing equipment. Lack of preventive controls for the proliferation of food borne pathogens is a food safety challenge in food industry, especially in ready-to-eat products manufacturer (231). Yarrow EO have revealed inhibitory effects on both biofilms and planktonic cells of *L. monocytogens* and *L.innocua* (232). Strong bactericidal effects on planktonic cells were stated, meaning that it could be a new approach for the biofilm prevention of *L. monocytogens* and *L. innocua*. Given this data, *Achillea* EOs have the potential to be used in bacterial disinfection and sanitizer formulation applications in food field to minimize the public health risk.

The extract of yarrow (*A. millefolium*) and different plants were tested against fish pathogens, *Listonella anguillarum***,** *Yersinia ruckeri***,** *Photobacterium damselae* subsp. *piscicida, and Lactococcus garvieae* (146). Yarrow ethanol extract showed antibacterial activity against fish pathogens. Yarrow extract may be used to reduce the food safety risk associated with aquaculture. The potential use of *A. millefolium* ethanol extract with poly(lactic acid) (PLA) film in active packaging applications was also highlighted (227). *A. millefolium* crude extract exhibited antimicrobial activity against both *E. coli* and *S. aureus*. Although extract loaded PLA films possessed antibacterial activity against *S. aureus* but not observed against *E. coli*.

On the other side, pest control is a major problem in agriculture, especially for stored food grains. Pests can cause losses in stored agricultural commodities which are the main source of foods. Synthetic pesticides and fumigants are available for insect control of stored foods, but because of their toxic effects to the environment and human health, usage of most of them have been restricted from the authorities (209). Some studies have proposed safe control methods with plants extracts and EOs. *Achillea* plants have been proposed for insects disinfection, being highly effective in triggering mortality and inhibiting progeny production (233). The inhibitory activity of *A. biebersteinii, A. santolina and A. mellifolium* EOs and their nanoemulsions were also confirmed against red flour beetle, *Tribolium castaneum* (234); thus, they can be proposed as great fumigants. But, other studies have also reported the insecticidal and herbicidal activity of some *Achillea* spp. EOs, specifically *A. millefolium* against the stored food

insect *Sitophilus zeamais* (209) and *A. biserrata*, *A. wilhelmsii*, *A. coarctata*, and *A. biebersteinii* on Colorado potato beetle *(L. decemlineata)* (235). *A. gypsicola* and *A. biebersteinii* have also revealed a great herbicidal and antifungal activity against phytopathogenic fungi in Turkish cultivated areas of the Erzurum region. Thus, these findings point *Achillea* plants as being helpful in the development of natural compounds for innovative prevention and control strategies to reduce both insects- and pests-associated infections. In real, food model application of active compounds from the extract and EO can be different. Microbial resistance to active compounds, bioactive properties and action mechanism of active compounds, food matrix complexity etc. are the main factors that affect the efficiency of the compound in real food models.

Many studies have investigated the bioactive compounds of natural products for food preservation. Regarding the performed research, the use of *Achillea* plant extracts and their EOs appears to be a promising antibacterial, antioxidant, and antifungal agent to preserve both the quality and safety of foodstuffs. Moreover, due to their insecticidal and herbicidal potential, it may also be a good strategy for pest management.

Clinical effectiveness of *Achillea* spp. in humans

Health benefits of *Achillea* spp. have been investigated in a number of clinical trials against various human conditions such as multiple sclerosis (MS), irritable bowel syndrome (IBS), ulcerative colitis, episiotomy wound, primary dysmenorrhea, oral mucositis etc. The neurological disorder MS has no cure and the present disease-modifying drugs just only decrease the rate of disease progression. In a triple-blind randomized placebo-controlled parallel group trial on 75 patients, aqueous extract of *A. millefolium* (500 mg) reduced the rate of annual relapse and mean volume change of lesions in MS patients as an add-on therapy (22). In a double-blind clinical trial study involving 140 primiparous women, *A. millefolium* and *Hypericum perforatum* ointments reduced pain, edema, redness and ecchymosis of episiotomy wound and it was suggested as a promising treatment against episiotomy wound in human (294). About 50% of postmenarche women suffer from primary dysmenorrhea characterized by intense pain and a double-blind randomized clinical trial has proven its clinical efficacy in reducing the severe pain in the patients treated with *A. millefolium* (295). Functional gastrointestinal disorders (FGIDs) includes an array of diseases of which the most prevalent one is IBS (296). In another randomized, placebo-controlled clinical trial, IBS was ameliorated by *A. wilhelmsii* capsules via reducing the symptom severity and enhancing the quality of life in IBS patients (297). Moreover, a mixture of *Boswellia carterii*, *Zingiber officinale*, and *A. millefolium* was found to be significantly beneficial in 60 IBS patients since it reduced the symptom severity, anxiety, and depression in the patients (296). In addition, *A. wilhelmsii* has been used as a common Persian traditional medicine and dietary supplement for gastrointestinal disorders. In a randomized, double-blinded, placebo-controlled clinical trial, *A. wilhelmsii* powder was mentioned as safe and efficacious following 4 weeks of treatment in 40 ulcerative colitis patients who have completed the study (298). In another double-blind randomized controlled trial, addition of *A. millefolium* on mouthwash was found to be beneficial in cancer patients with chemotherapy induced oral mucositis (299).

Conclusions and future perspectives

Many *Achillea* species are considered for having immense potential for food and pharmaceutic industries. Since ancient times, *Achillea spp*. have been used in traditional medicine of many cultures and countries for spasmodic, gastro-intestinal and hepatobiliary disorders, hemorrhages, pneumonia, rheumatic pain and wound healing as infusions and decoctions. The therapeutic benefits of *Achillea spp.* are attributed to the presence of secondary metabolites such as phenolic acids, flavonoids and EOs. Both *Achillea* plants phytochemistry and bioactivity have been intensively studied, and possess a great interest for the discovery of new pharmacologically active compounds. Most of the research suggest that phenolic compounds are the significant contributors to the antioxidant activity of the *Achillea* plants studied, and both water and ethanol extracts can be used as an easily accessible source of natural antioxidants and as a possible food supplement in pharmaceutical industry. Multiple studies have also assessed the bioactive compounds of *Achillea* plants and their EOs for food preservation. Given the current data, its use appears to be a promising strategy for antibacterial, antioxidant, and antifungal purposes to preserve the quality and safety of food products. Additionally, many other clinical studies have been performed to improve knowledge on their multiple potentialities. Anyway, it has been increasingly stated that there is a close relationship between traditional ethnobotanical usage and pharmacological and clinical data from *Achillea spp.* So, the application of *Achillea* plants and their extracts seems to be a promising alternative for antimicrobial and antioxidant purposes in food, pharmaceutical and cosmetic industries.

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