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A review on phytochemistry and medicinal properties of the genus *Achillea*.

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ABSTRACT

Achillea L. (Compositae or Asteraceae) is a widely distributed medicinal plant throughout the world and has been used since ancient time. Popular indications of the several species of this genus include treatment of wounds, bleedings, headache, inflammation, pains, spasmodic diseases, flatulence and dyspepsia. Phytochemical investigations of *Achillea* species have revealed that many components from this genus are highly bioactive. There are many reports on the mentioned folk and traditional effects. Although, the medicinal properties of *Achillea* plants are recognized worldwide, there are only one review article mainly about the structures of the phytochemical constituents of *Achillea*. The present paper reviews the medicinal properties of various species of *Achillea*, which have been examined on the basis of the scientific in vitro, in vivo or clinical evaluations. Various effects of these plants may be due to the presence of a broad range of secondary active metabolites such as flavonoids, phenolic acids, coumarins, terpenoids (monoterpenes, sesquiterpenes, diterpenes, triterpenes) and sterols which have been frequently reported from *Achillea* species.

Keywords: *Achillea*, Asteraceae, Bioactive compounds.

INTRODUCTION

The genus *Achillea* L. belongs to Asteraceae (Compositae), the largest family of vascular plants. Asteraceaeous plants are distributed throughout the world and most common in the arid and semi-arid regions of subtropical and lower temperate latitudes. *Achillea* contains around 130 flowering and perennial species and occurs in Europe and temperate areas of Asia and a few grow in North America. These plants typically have hairy and aromatic leaves and flat clusters of small flowers on the top of the stem. Since these flowers have various colors, a number of species are popular garden plants (1-4). The basic chromosome number of this genus is X=9 and most of the species are diploid with great ecological ranges from desert to water-logged habitats (5).

The name of *Achillea* is referred to the Achilles in the literary Trojan War of the Iliad who used yarrow to treat the soldiers' wounds (6). The majority of the *Achillea* species are as the medicinal plants which have therapeutic applications (4). There are few review papers on the different aspects of *Achillea* as a noteworthy and medicinal genus. Recently, Si and co-authors (7) published a review article mainly about the structures of phytochemical constituents and a brief section of biological properties of *Achillea* (7). Literature reviews show that there are many reports on pharmacological, immunological, biological and other therapeutic activities of these valuable herbs which are reviewed in this article.

Traditional usages

Since *Achillea* genus is widespread all over the world, its species have been used by local people as folk or traditional herbal medicines. Bumadaran is a popular name for several species of *Achillea* in Persian language. They are reported as tonic, anti-inflammatory, anti-spasmodic, diaphoretic, diuretic and emmenagogic agents and have been used for treatment of hemorrhage, pneumonia, rheumatic pain and wounds healing in Persian traditional literature (8, 9).

In Spanish-speaking New Mexico and southern Colorado, *A. millefolium* L. is called plumajillo, or "little feather", because of the shape of the leaves. Native Americans and early settlers used yarrow for its astringent qualities that made it effective in wound healing and anti-bleeding (10).

Achillea species are the most important indigenous economic plants of Anatolia. Herbal teas prepared from some *Achillea* species are traditionally used for abdominal pain and flatulence in Turkey (11). Dioscorides also used *Achillea* for dysentery, whether associated with cholera or other causes, which killed

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as many soldiers as did steel and lead. In terms of Chinese medicine, *Achillea* can be said to have three main actions: clear Exterior Wind (diaphoretic), Tonify Deficiency (tonic) and clear Heart Phlegm (anti-hypertention) (12).

Many of these therapeutic usages have been confirmed by new experimental and clinical studies. The consumption of herbal teas from different species of *Achillea*, especially for treatment of the gastrointestinal tract, is common in folk medicine (13). However, there are still several unknown aspects of *Achillea* plants that need more attention.

Phytochemical constituents

Phytochemical investigations of *Achillea* species have revealed that many components from this genus are highly bioactive. The first anti-spasmodic flavonoids, cynaroside I and cosmosiin II (Scheme 1) were isolated from *A. millefolium* L. (14), and the first natural proazulene, achillicin III (Scheme 2) was identified from the genus *Achillea* (15). Literature search shows that the, flavonoids, terpenoids, lignans, amino acid derivatives, fatty acids and alkamides such as *p*-hydroxyphenethylamide IV (Scheme 2) have been identified in *Achillea* species. The main constituents of the most species have been previously reviewed (7). Therefore, in this article some other minor or rare compounds and especially their medicinal or industrial usages which have been less described are reviewed. Among them ,alkamides, the lipophilic and nitrogen containing compounds, are responsible for insecticide, anti-inflammation and some immunological activities of *Achillea* and *Echinacea* plants (16). The genus *Achillea* comprises flavored species which produce intense essential oils. The volatile oils of *Achillea* contain monoterpenes as the most representative metabolites. However, there are reports on high levels of sesquiterpenes compared with monoterpenes (17, 18). There are several pharmacological actions which have been mostly attributed to the presence of azulenogenous sesquiterpene lactones in the essential oil of *Achillea*. Results of studies have indicated that tetraploid species are accumulating proazulenes such as achillicin III (Scheme 2) (19). Except for the essential oil constituents, yarrow (*A. tenuifolia* Lam.) seeds consist of the high oil content which is rich in linoleic acid, an essential polyunsaturated fatty acid. This makes yarrow seed as a potential source of edible oil for human consumption (20). Recently, *A. millefolium* has been introduced as a new source of natural dye for wool dyeing due to the presence of the flavonoids, luteolin V and apigenin VI (Scheme 1). *A. millefolium* was found to have good agronomic potential as a natural dye in Iran (21). In the plant kingdom, hydroxycinnamoyl conjugates of quinic acid represent common end metabolites of the shikimate-phenylpropanoid pathway, and feruloylcaffeoylquinic acid derivates VII have been isolated only from two species of genus *Achillea* so far (22). From the aerial parts of *Achillea* species, proline VIII, stachydrine IX, betonicine X, betaine XI and choline XII have been isolated as the major nitrogen containing compounds (Scheme 2) (23, 24). Betaines, containing the permanent positive charge on the quaternary ammonium moiety, belong to an important class of naturally occurring compounds that function as compatible solutes or osmoprotectants (25). These compounds have shown immunosuppressive activity in the experimental animals (26, 27).

Medicinal properties of Achillea species

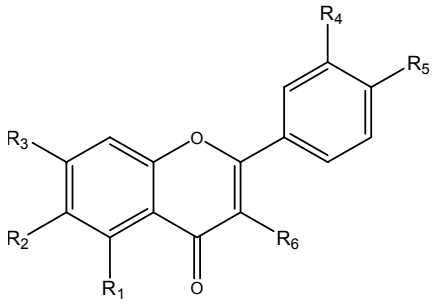
Wound healing activity

Nowadays, the traditional usage of medicinal plants for wound healing has received attention by the scientific community (28). Wound healing is a complex process characterized by homeostasis, re-epithelization, and granulation tissue formation and remodeling of the extracellular matrix. Medicinal plants may affect various phases of the wound healing process, coagulation, inflammation and fibroplasia (29). Aqueous extract of the flowers of *A. kellalensis* Boiss. & Hausskn., applied topically, has shown significant wound healing activity in rats. The wound sizes of the test compared to control groups were reduced faster (30).

Protective activity

The protective activity of natural antioxidants in biological systems has received attention. Some medicinal plants have proved free radical scavenging or antioxidant activities (31). The infusions of *Achillea* species were tested on antioxidant enzyme systems of erythrocytes and *A. falcata* L. was the most effective one against CAT (catalase), GPx (glutathione peroxidase) and SOD (superoxide dismutase) enzyme systems of erythrocytes. Among the plant infusions, highest activities on leucocyte enzymes were by *A. crithmifolia* Waldst. & Kit. and *A. nobilis* L. subsp. *neilrechii* on CAT, by *A. millefolium* subsp. *pannonica* on SOD, by *A. teretifolia* Willd. on GPx and by *A. nobilis* subsp. *sipylea* on LPO (lactoperoxidase). Therefore, *Achillea* species may be of potential sources of natural antioxidants for treatment or prevention of related diseases (32).

The influence of the extracts of *A. alexandri-regis* Bornm. & Rudsky on hydroxyl and superoxide radicals' quantity in different in vitro systems have been determined. The ethyl acetate extract exhibited hydroxyl radical scavenging activity in all tested biological systems (liver homogenate, hemolyzed blood, serum and post mitochondrial liver fraction), whereas butanol extract reduced hydroxyl radicals significantly only in the post mitochondrial liver fraction (a homogenate of liver cells remaining after sedimentation of the mitochondrial fraction by centrifugation). Both extracts affected only



Flavonoid Number	*Names*	R_1	R_2	R_3	R_4	R_5	R_6
I	**Cynaroside**	OH	H	OGlc	OH	OH	H
II	**Cosmosiin**	OH	H	OGlc	H	OH	H
V	**Luteolin**	OH	H	OH	OH	OH	H
VI	**Apigenin**	OH	H	OH	H	OH	H
XX	**Centaureidin**	OH	OCH_3	OH	OH	OCH_3	OCH_3
XXI	**Quercetin**	OH	H	OH	OH	OH	OH
XXIII	**3'-methoxy luteolin**	OH	H	OH	OCH_3	OH	H
XXIV	**Luteolin 7-O-glucoside**	OH	H	OGlc	OH	OH	H
XXV	**Apigenin 7-O-glucoside**	OH	H	OGlc	H	OH	H
XXVII	**5- hydroxy 3', 4', 6, 7- tetra methoxy flavone**	OH	OCH_3	OCH_3	OCH_3	OCH_3	H
XXVIII	**Salvigenin**	OH	OCH_3	OCH_3	H	OCH_3	H
XXXIV	**Galangin**	OH	H	OH	H	H	OH
XXXV	**Eupatilin**	OH	OCH_3	OH	OCH_3	OCH_3	H

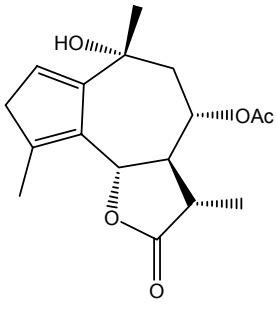
Scheme 1. Structures of the isolated flavonoids from various species of *Achillea*.

hemolysed blood (33).

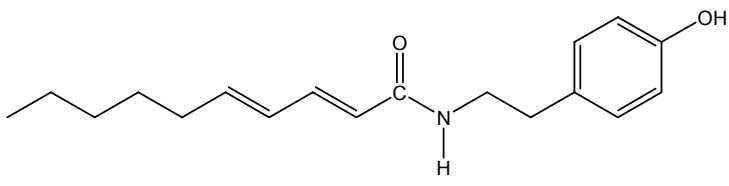
The hydroalcoholic extract of *A. santolina* L. was studied on various in vitro antioxidative systems and it has been reported that the extract prevented formation of thiobarbituric acid reactive substances in Fe^{2+}ascorbate induced lipid peroxidation in rat liver tissue. Free radical induced protein oxidation has also been suppressed significantly by high concentration (1000 µg/ml) of the extract (34). Ethanol extracts of eight wild samples of *A. ligustica* All., and one sample of cultivated *A. millefolium* were evaluated for radical scavenging activites including DPPH test. The TEAC (the concentration of a Trolox solution having an antioxidant capacity equivalent to that of the diluted hydroalcoholic extract) were in the range of 4.18 and 12.3 mM. The ability of the extracts to inhibit non-enzymatic lipid peroxidation using an in vitro system of linoleic acid oxidation has been investigated. Five of the nine extracts had a protective effect at the lowest tested amount (5 µg). Protection on CaCo-2 intestinal cells against TBH-induced toxicity was also investigated and two of the tested ethanolic extracts of *A. ligustica* showed protection against the oxidative stress (35). The antioxidant capacity and cytoprotective activity of *A. collina* Becker ex Rchb. infusions against oxidative stress were investigated by chemical (DPPH and Folin Ciocalteu assay) and biological assays (in vitro model of cytotoxicity and lipid peroxidation in PC_{12} cells line) and it has been shown that the infusions of leaves had the highest antioxidant and cytoprotective activity, where antioxidant capacity was significantly correlated with the total phenolic content but not with the cytoprotective profile (36).

Esterogenic activity

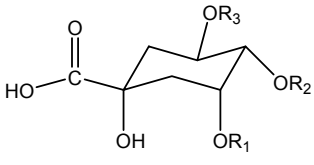
A. millefolium is used in folk medicine as an emmenagogue (8). A crude extract of the aerial parts of *A. millefolium* has shown estrogenic activity based on recombinant MCF-7 cells (37, 38). Evaluation of the isolated and identified compounds from this plant indicated that luteolin V and apigenin VI (Scheme 1) were the most important estrogenic compounds among tested compounds. Apigenin can also stimulate ERs-dependent biological pathways, but less than the endogenous hormone. Both α and β receptors of estrogen could be activated by apigenin. Luteolin seems to have a very slight effect on β and



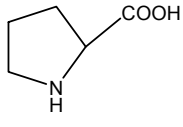
Achillicin III



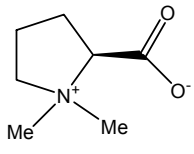
***p*-hydroxy- phenethylamide IV**



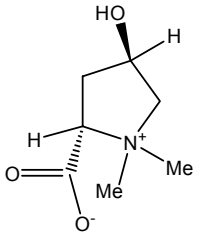
Feruloylcaffeoylquinic acid VII
R_1-R_3 = H or caffeoyl / feruloyl



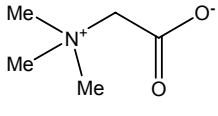
Proline VIII



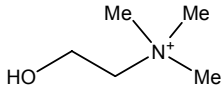
Stachydrine IX



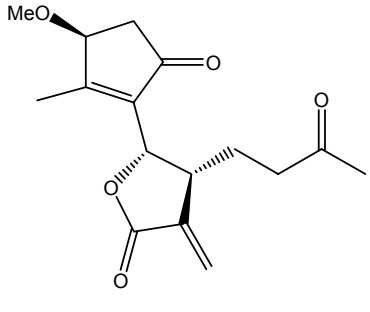
Betonicine X



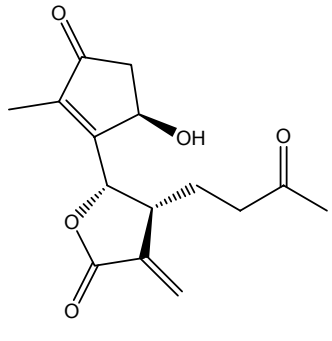
Betaine XI



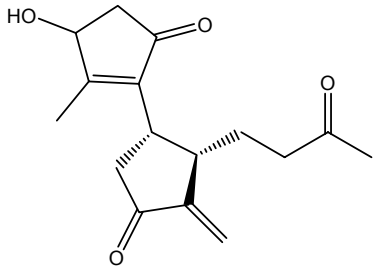
Choline XII



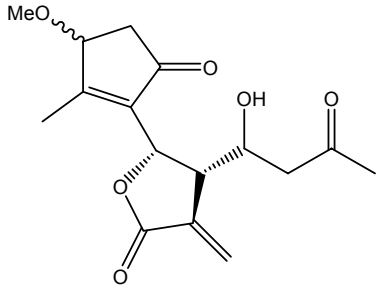
3β- methoxy- iso-seco-tanapartholide XIII



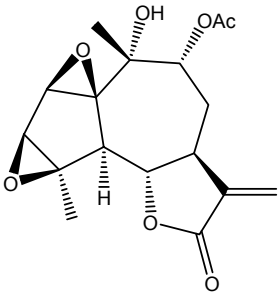
Tanaphillin XIV



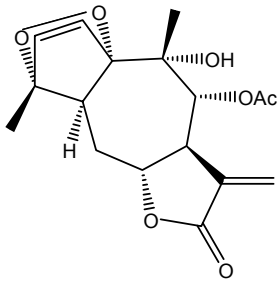
iso-seco-tanapartholide XV



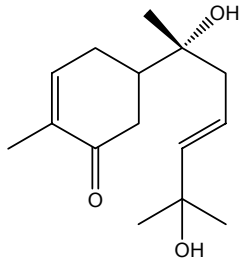
8-hydroxy-3-methoxy-iso- seco-tanaparatholide XVI



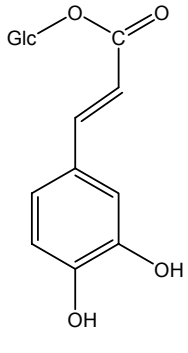
9α-acetoxyartecanin XVII



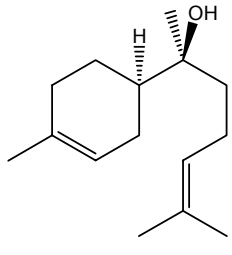
Apressin XVIII



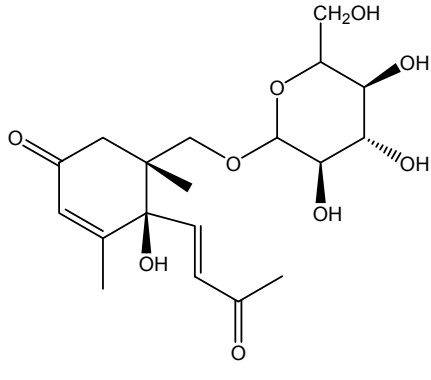
Inducumenone XIX



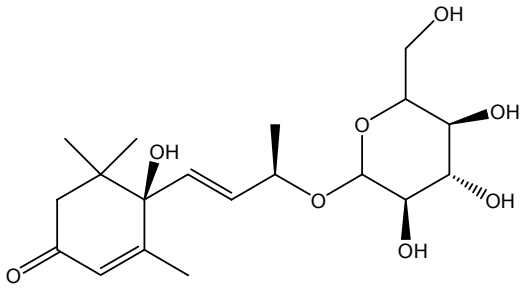
Caffeoyl glucoside XXII



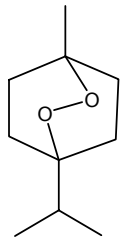
Bisabolol XXVI



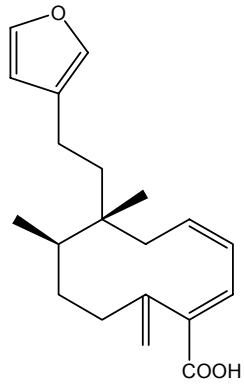
Biebersteiniside XXIX



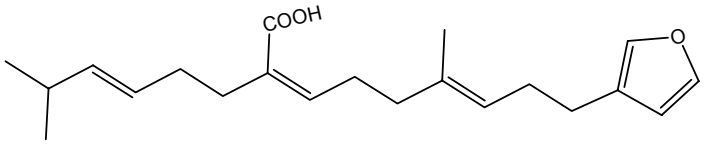
6-epiroseoside XXX



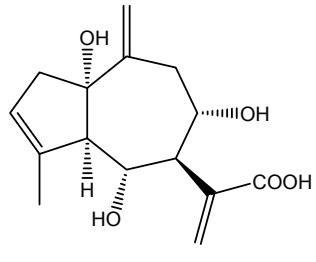
Ascaridole XXXI



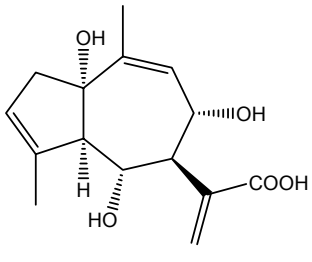
Strictic acid XXXII



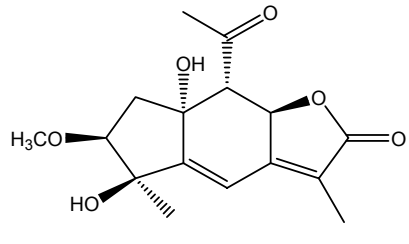
Centipedic acid XXXIII



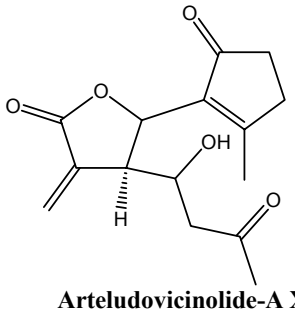
1α,6α,8α-trihydroxy-5α,7βH-guaia-3,10(14),11(13)-trien 12-oic acid XXXVI



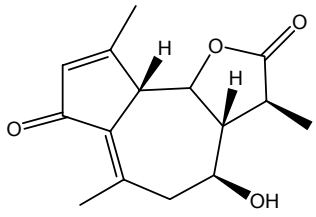
1α,6α,8α-trihydroxy-5α,7βH-guaia-3,9,11(13)-trien-12-oic acid XXXVII



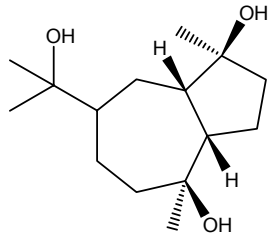
Ligustolide-A XXXVIII



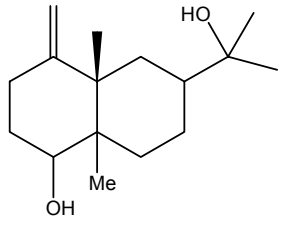
Arteludovicinolide-A XXXIX



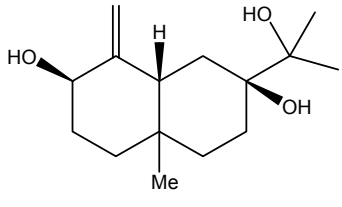
Austricin XL



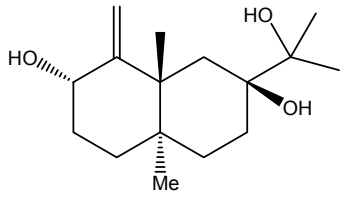
4,10,11-trihydroxyguaiane XLI



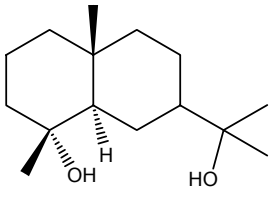
4(15)-eudesmene-1β,11-diol XLII



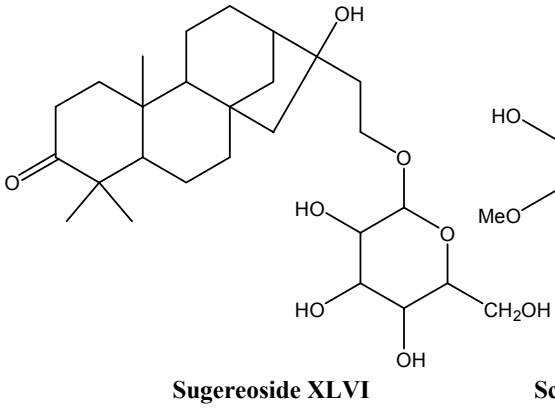
Clypeotriol XLIII



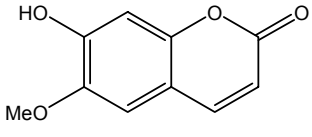
3-epi-clypeotriol XLIV



Cryptomeridiol XLV



Sugereoside XLVI



Scopoletin XLVII

Scheme 2. Structures of the isolated terpenoids amins and phenolic compounds from the various species of *Achillea.*

does not seem to activate α receptor at all, while many phytoestrogens appear to have a stronger binding affinity with β estrogen receptors than estradiol (39).

Anti-diabetic activity

Oxidative stress is produced under diabetic condition and is likely involved in progression of pancreatic damage in diabetes. The effect of *A. santolina* (hydro alcoholic extract) on blood glucose level, serum NO (nitric oxide) concentration and the oxidative stress in rat pancreatic tissue have been evaluated. This herbal treatment could reduce blood glucose level, serum NO, pancreatic MDA (Malondialdehyde), PCO (Protein Carbonyls) and AOPP (Advanced Oxidation Protein Products) levels. In addition, the content of GSH (Reduced Glutathione) was restored to the normal level of the control group. Furthermore, CAT and SOD activities in the treated rats were increased significantly. In conclusion, *A. santolina* have a high hypoglycemic activity which may be due to its antioxidative potential (40).

Antispermatogenic effect

Ethanolic (intraperitoneally) and hydroalcoholic extracts (orally) of *A. millefolium* were administered to Swiss mice to evaluate the effect on spermatogenesis. Observation of morphological characteristics using light and electron microscopes revealed exfoliation of immature germ cells, germ cell necrosis, and seminiferous tubule vacuolization. The extract treated animals had an increased number of metaphases in the germ epithelium which should be due to substances stimulating cell proliferation (41).

Antiulcer activity

A. millefolium is a widespread medicinal plant used in folk medicine to treat inflammation, pain and gastrointestinal disorders. Screening of gastroprotective potential against acute and chronic ulcers has shown positive correlation with its uses in folk medicinal. The aqueous extract of *A. millefolium* showed effectiveness in protecting the gastric mucosa against acute gastric lesions induced by ethanol and indomethacin and in healing chronic gastric lesions induced by acetic acid (ED_{50}= 32 mg/kg, orally). Reviewing literature reveals that the antiulcer potential of *A. millefolium* is not accompanied by any sign of toxicity even by long chronic exposure. Oral administration (30, 100 and 300 mg/kg) of the hydroalcoholic extract inhibited ethanol-induced gastric lesions by 35, 56 and 81%, respectively. Oral treatment with this extract (1 and 10 mg/kg) reduced the chronic gastric ulcers induced by acetic acid by 43 and 65%, respectively, and promoted significant regeneration of the gastric mucosa after ulcer induction denoting increased cell proliferation (42, 43). It has been reported that *A. millefolium* protected rats against ulcers induced by ethanol and restraint-in-cold-stress, but not against indomethacin induced ulcers. When hot water extract was injected into duodenal lumen it could inhibit the basal acid secretion. It seems that the antiulcer activity of *A. millefolium* is related either to inhibition of gastric secretion or increase in protective factors (such as blood flow) in gastric mucosa. Anyhow, further study is required to clarify the mechanism of action (44). There are some reports on gastrointestinal effects of *Achillea*, such as antiulcer, antibacterial, hepatoprotective, choleretic, and antispasmodic. The effects of aqueous ethanol extract of *A. wilhelmsii* on rat's gastric acid output in basal, vagotomized (VX), and vagal-stimulated conditions have been investigated. Result of study showed that introduction of one milliliter of 3 doses (0.5, 1, and 2 mg/kg) *A. wilhelmsii* C. Koch into the stomach of each rat in the test group compared with introduction of the same volume of saline in the control group resulted in an inhibitory effect on acid output in basal condition. The inhibitory effect of the extract (at doses 1 and 2 mg/kg) was exerted via gastric vagal parasympathetic nerve. At VX condition, not only this inhibitory effect on acid output disappeared, but also the acid output significantly increased. The extract showed a reduction in the acid output in vagal-stimulated condition at doses of 1 and 2 mg/kg, which were not statistically significant (45).

Cytotoxicity effect

There are some reports about the anti-proliferative activity of the isolated constituents from *A. falcata* and *A. clavennae*. L.Four sesquiterpene lactones have been isolated from *A. falcata*, which had significant ability to inhibit HaCaT-cell growth and identified as 3β-methoxy-iso-seco-tanapartholide XIII, tanaphillin XIV, iso-seco-tanapartholide XV, and 8-hydroxy-3-methoxy-iso-seco-tanaparatholide XVI. These compounds have been found to decrease keratinocyte cell viability significantly (Scheme 2). Statistical analyses confirmed an enhanced potency of the β-OH iso-seco-tanapartholide over the α,β-OH diastereoisomeric mixture. The enhancement of the lipophilicity of the molecule resulted in the highest potency (46). The aerial part of *A. clavennae* was used for isolation of the phytoconstituents and the antiproliferative activity of the compounds was tested to HeLa, K562 and Fem-X human cancer cell lines. Guaianolides, 9α-acetoxyartecanin XVII and apressin XVIII showed significant cytotoxic effects in all tested cell lines. A bisabolene, inducumenone XIX exhibited a moderate activity (Scheme 2). The most active compound was a flavonol, centaureidin XX (Scheme 1), which was already known as cytotoxic agent (47).

Immunosuppressive activity

The aqueous extract of *A. talagonica* Bioss. was studied on humoral antibody responses in BALB/c mice and albino rabbits. Intraperitoneal administration of the extract to mice, prior to immunization with sheep red blood cells, resulted in a significant dose dependent decrease in haemagglutinating antibody (HA) titer. In rabbits after intrascapular injection of the extract, a significant decrease in typhoid-H antibody (anti-HD) titer was found, but no change was observed in secondary response (48).

Methanol and aqueous methanol (80% and 50% v: v) extracts of *A. talagonica* have been examined to find its immunosuppressive components. Guided by anti-SRBC (sheep red blood cells) assay, active principles were isolated by chromatographic methods and identified as choline XII (Scheme 2), quercetin XXI (Scheme 1) and caffeoyl glucoside XXII (Scheme 2). These compounds compared to the control groups decreased anti-SRBC titer significantly. Alongside these compounds, 3'-methoxy luteolin XXIII (Scheme 1) and proline VIII (Scheme 2) has been also reported from this plant (49).

Methanol extract and some other fractions of *A. millefolium* were studied on humoral immunity in BALB/c mice by microhaemagglutination test. Only two fractions showed a significant decrease in the anti- SRBC titer of mice. The immunological properties may be related to presence of glycosylated derivatives of caffeic acid, because caffeic acid glucoside XXII (Scheme 2) was isolated and identified from the active fractions. Some known compounds including, luteolin 7-O-glucoside XXIV and apigenin 7-O-glucoside XXV (Scheme 1) have also been reported from this species (50).

Effects of the essential oils of *A. talagonica* and *A. millefolium* have been studied on humoral immune responses in BALB/c mice. The oil isolated from *A. millefolium* ssp. *millefolium* possessed a high percentage of sesquiterpenes (55.4%) in which bisabolol XXVI (Scheme 2) was the main compound. The volatile oil of *A. millefolium* decreased the anti-SRBC antibody titer, but the oil of *A. talagonica* was not effective. High percentage of sesquiterpenes and presence of proazulene in *A. millefolium* together with the lack of these compounds in *A. talagonica* could account for the different immunological effects of these plants (51).

Biological effects

Ethyl acetate extract of *A. talagonica* showed toxicity in BST (brine shrimp lethality test) and on the basis of results only 5- hydroxy 3', 4', 6, 7- tetra methoxy flavone XXVII (Scheme 1) showed toxicity (LC_{50}=15 µg/ml) against *Artemia salina* larvae. Another separated flavonoid named salvigenin XXVIII (Scheme 1) showed no activity (52).

It is reported that the essential oil of *A. biebersteinii* Afan. exhibited antimicrobial activity against 8 bacteria, 14 fungi and one yeast namely *C. albicans*, whereas methanolic extract was inactive (53). The antimicrobial activity of the essential oil of *A. ligustica* was evaluated by the broth micro-dilution method on 6 microbial strains and it showed to be effective against *Streptococcus mutans* (54). In another report, antibacterial activity of the extracts (hexane: ether: methanol = 1:1:1) of the aerial parts of *A. clavennae, A. holosericea* Sm., *A. lingulata* and *A. millefolium* were evaluated against five bacteria (*S. aureus, E. coli, K. pneumoniae, P. aeruginosa* and *Salmonella enteritidis*) and two fungi (*A. niger* and *C. albicans*) and it was found that the extracts of all four species possessed a broad spectrum of antimicrobial activity against all tested strains (55). Recently, the oil of *A. millefolium* was evaluated on heterozygous diploid strain of *Aspergillus nidulans*, with green conidia and a significant increase in the number of yellow and white mitotic recombinants (per colony) of the diploid strain was observed when it was treated with 0.19 and 0.25 µl/ml of the oil. The induction of mitotic non-disjunction may cause the genotoxicity (56).

E. coli contains certain strains that can cause resistant infections to antibiotics. Multidrug-resistant *E.coli* produces extended-spectrum β lactamases (ESBLs) and is an important cause of urinary tract (UTIs) and bloodstream infections. Activity of nineteen Jordanian plants against multidrug-resistant *E.coli* has been reported. The methanolic extract of *A. santolina* (one of 19 species) was combined with antibiotics of different classes (chloramphenicol, neomycin, doxycycline, cephalexin and nalidixic acid) and tested against both the standard and resistant strain of *E. coli*. The results showed that the activity of all tested antibiotics especially doxycycline on the resistant strain was enhanced when it was used in combination with plant material. The enhanced activity of cephalexin against the standard strain has been reported to be higher than resistant strain (57) Also, the extracts of 13 Brazilian medicinal plants were screened for their antimicrobial activity against bacteria (*E. coli, P. aeruginosa, B. subtilis* and *S. aureus*) and yeasts (*Candida albicans, C. krusei, C. parapsilosis,* and *C. tropicalis*) and the ethanol-water extract (90% v/v) of *A. millefolium* was considered inactive (58). The in vitro antimicrobial efficacy of 39 water and 39 methanol extracts of 27 indigenous wild plant species that have been commonly used in Lebanese folk medicine has been reported on nine test microorganisms (*E. coli, Proteus sp., P. aeruginosa, S. dysenteria, S. enteritidis, S. typhi, S. aureus, S. faecalis,* and *C. albicans*) by the single disk diffusion method. The percentage of test organisms, which were susceptible (20 µl /disc) to methanol extract of *A. damascena* DC., was 88.8%. The methanol extract of *A. damascena* showed different efficacy against the tested microorganisms when harvested from two different locations. The MIC of *A. damascena* range

for *S. aureus*, *Proteus* sp., and *S. dysenteriae* were 1-3.5 and for *C. albicans*, *S. enteritidis*, and *S. faecalis* were 1-2.5. These differences were explained by the nature and level of the antimicrobial agents present in the extracts and their modes of actions on the different test microorganisms (59).

In a recent investigation, the in vitro susceptibility of 15 *H. pylori* strains to botanical extracts was evaluated. The minimum inhibitory concentration (MIC) of the methanol extract of *A. millefolium* is reported as 50 µg/ml (60).

Besides the antimicrobial effects of *Achillea* plants, the in vitro anti-epimastigote activity of some extracts of *A. biebersteinii* and *A. millefolium* have been reported. Diethyl ether extracts of the above *Achillea* species showed activity (MLC=12.5 µg/ml) against the epimastigotes of *Trypanosoma cruzi,* the etiological agent of Chagas disease. Aqueous and methanol extracts were not so effective (61). In another study, the ethyl acetate extracts of *A. talagonica* and *A. tenuifolia* showed a moderate activity against the epimastigotes of *T. cruzi* (62).

Forty-two Egyptian medicinal plant species were subjected to antiviral screening bioassay to evaluate their biological activities. Hydro-alcoholic extracts of each species were prepared and tested against three viruses, herpes simplex-1 virus (HSV), poliomyelitis-1 virus (POLIO) and vesicular stomatitis virus (VSV). The antiviral activity were determined by means of the end point titration technique (EPTT) that depends on the ability of diluted plant extract to inhibit the produced cytopathogenic effect (CPE) and was expressed as reduction factor (Rf) of the viral titer. *A. fragrantissima* (Forssk) Sch. Bip. showed the highest antiviral activity (among these species) against POLIO in a concentration dependent manner at complete non-toxic concentration range (10–100 µg/ml) and the highest detected antiviral activity was recorded at Rf of 10^{6}. It seems that the interesting antiviral activity of *A. fragrantissima* against POLIO may be attributed to of essential oil content which has been traditionally used as an antiseptic agent (63). Furthermore, a new ionone glucoside, biebersteiniside XXIX, together with four known compounds 6-epiroseoside XXX, ascaridole XXXI, strictic acid XXXII and centipedic acid XXXIII (Scheme 2) were reported from the aerial parts of *A. biebersteinii*. The compounds XXX-XXXIII were reported for the first time from *A. biebersteinii*. Also, antifungal activity was observed from the compounds XXIX and XXXI-XXXIII (64).

Antispasmodic activity

The use of herbal teas from different species of the *A. millefolium* group against the gastrointestinal disorders, especially as an antispasmodic and anti-inflammatory, is quite common in folk medicine. The antispasmodic effect of *A. nobilis* subsp. *sipylea* on rat duodenum has been reported recently. The total herb extract (70% ethanol) exhibited an inhibitory effect on the dose-response curves induced by acetylcholine and $CaCl_2$ on rat duodenum. This effect was similar to that of papaverine, but not to that of atropine on the dose-response curves. The extract also reduced the maximal response in curves induced by $CaCl_2$ (in a similar manner to verapamil) (65). The antispasmodic effects of *Achillea* species might be due to the flavonoid constituents of the plant. Galangin XXXIV, quercetin XXI and eupatilin XXXV (Scheme 1), which are found commonly in *Achillea*, are reported to cause a potent relaxation of the ileum (66, 67).

The effect of *A. millefolium* hydro-alcoholic extract on the contractile responses of the isolated guinea-pig ileum at five concentrations ranging from 0.05 to 5 mg/ml has been reported. Changes in contraction of tissues were monitored using force displacement transducer amplifier connected to physiograph. Each segment served as its own control. Results showed that the contractile response was inhibited by extract in a dose-dependent manner (EC_{50} = 1.5 mg/ml). Those results demonstrated that in vitro evaluation of *A. millefolium* extract resulted in inhibition of electrical induced contractions of the guinea-pig ileum (68).

Anti-inflammatory activity

As shown in traditional usage, *Achillea* species are well known as the anti-inflammatory plants. Besides the alkamides, as the noteworthy active anti-inflammatory compounds (16), sesquiterpenes are introduced as another effective group of the secondary metabolites. After the last review (7) on photochemistry of *Achillea*, isolation of some other sesquiterpenes have been reported as follows:

The methylene chloride - methanol extract of aerial parts of *A. coarctata* was investigated by chromatographic analysis and resulted in isolation of two new guaiane acid derivatives, 1α,6α,8α-trihydroxy-5α,7βH-guaia-3,10(14),11(13)-trien-12-oic acid XXXVI and 1α,6α,8α-trihydroxy-5α,7βH-guaia-3,9,11(13)-trien-12-oic acid XXXVII, in addition to three known compounds, ligustolide-A XXXVIII, arteludovicinolide-A XXXIX and austricin XL (Scheme 2) (69). They also reported that the compounds XXXVI and XXXVII enhanced the proliferation of beneficial macrophages significantly and compounds XXXVII and XXXIX exhibited anti-inflammatory properties (69). Another article has reported that chromatographic separation on dichloromethane extract of *A. clypeolata* resulted in one guaiane 4,10,11-trihydroxyguaiane XLI, four eudesmanes 4(15)-eudesmene-1β,11-diol XLII, clypeotriol XLIII, 3-epi-clypeotriol XLIV, cryptomeridiol XLV, one diterpene sugereoside XLVI (Scheme 2) and two phenolics centaureidin XX (Scheme 1) and scopoletin XLVII (Scheme 2). The compounds XLI and XLVI have been reported

for the first time (70).

Adverse effects and safety

Adverse reaction of herbal medicines is an important point which needs further systematic investigation. Adverse drug reactions (in association with complementary and alternative medicine substances) have been spontaneously reported therefore, such a data could be used in monitoring the safety of these products. By analyzing such data (in Sweden), it has been found that *A. millefolium* (in combination with hawthorn, peppermint, and paprika, seed of pumpkin, rosemary and vitamins) showed urticarial and skin reactions which have been poorly documented (71). Because *A. millefolium* is effective in protection of gastric mucosa against acute gastric lesions (ED_{50} = 32 mg/kg, p.o.), safety studies were performed in female and male Wistar rats by daily treatment with aqueous extract of *A. millefolium* (0.3-1.2 g/kg, p.o./day) or vehicle (water, 10 ml/kg/day) for 28 or 90 consecutive days. Slight changes in liver weight, cholesterol, HDL-cholesterol and glucose were observed in male and female animals which were not correlated with dose or time of exposure of the animals to the plant (72).

Ethnomedicinal and pharmaceutical usage

There are many botanical remedies, consisting powdered plant material or extracts of *Achillea* species, which are used for the treatment of skin and soft tissue infections, visceral pain, gastrointestinal disorders and inflammations. Literature review indicated that there is a patent for treatment of dermatose, by topical application of botanical medicinal compounds (from *Achillea*), eczema, atopic dermatitis, non-allergic dermatitis, psoriasis and rosacea, or any inflammation of the skin (73). A medicinal combination, named Sedospasmil®, for the treatment of chronic colitis was prepared from medicinal plants including *A. millefolium, Matricaria chamomillae, Hypericum perforatum* and *Valeriana officinalis*. Normalization of the intestinal functions, tranquilization, spasmolytic and analgesic activity of a combination made with *A. millefolium* and some other medicinal plants has been reported for this medicine (74). Also, a Chinese medicinal preparation for relieve of pain and inflammation of some medicinal plants including *Achillea* with gelatin, in the form of ointment, pellicle, or powder for external use is reported. The formulation is suggested to be used for treatment of soft tissue injury, fracture, dislocation, carbuncle furuncle, and gout (75). In addition, a medicine for treatment of hysteromyoma, prepared from *A. millefolium* together with *Inula, Calami, Urtica, Arnica*, *Capsella* and some other medicinal plants, has been reported. The medicine is suggested to be useful for treatment of hysteromyoma, particularly hormone-dependent tumor (76).

CONCLUSION

Achillea has been used in popular medicine for its anti-hemorrhagic, healing, and analgesic properties in the various regions throughout the world. It was used by northern European and North American native people as a contraceptive, abortifacient, and emmenagogue. Some of these traditional and folk usages have been evaluated showing the potential medicinal use of the plant. The medicinal properties of *A. millefolium* are worldwide recognized and the plant is included in the national *Pharmacopoeias* of countries such as Germany, Czech Republic, France and Switzerland. As it is reviewed in this paper, antioxidant and protective activity is of various species of *Achillea* is reported frequently. This might be due to high content of flavonoids and phenolics in these plants. It is noteworthy that oxidative stress is produced under diabetic condition and *Achillea* plants are considered for high hypoglycemic activity. Among the medicinal properties of *Achillea*, their cytotoxic and antiulcer effects are important especially when the species contain immunomodulatory constituents. The activity of these plants against different bacteria, fungi and parasites might be due to the presence of a broad range of secondary active metabolites such as flavonoids, phenolic acids, coumarins, terpenoids (monoterpenes, sesquiterpenes, diterpenes, triterpenes) and sterols which have been isolated. Finally, presence of anti-inflammatory compounds such as sesquiterpenes and alkamides is another reason for importance of these plants as the potential source of medicinal compounds and drugs in future.

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