



Achillea fragrantissima: Pharmacology Review

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Abstract

In recent years, there has been a marked increase in the popularity of medicinal plants derived from the traditional sources of knowledge. The desert plant *Achillea fragrantissima* is traditionally used internally in traditional medicine of the Arabian region against hepatobiliary disorders, inflammatory and spasmodic gastrointestinal complaints, against skin inflammations and for wound healing and as an appetite enhancing drug. This plant is characterized by protective antioxidative and anti-inflammatory properties. The main pharmacologically active principles were shown to be polyphenols, flavonoids, terpenes and alkaloids. Aqueous and alcoholic extracts prepared from *A. fragrantissima* were well tolerated in acute and long-term safety studies in rats when administered orally and have a number of significant pharmacological effects, among others beneficially affects astrocytes and downregulates microglial activation.

Keywords: *Achillea fragrantissima*; Neuroprotection; Achillolide

Abbreviations

A549: Lung Cancer Cells; ABAP: 2,2'-azobis (2-amidinopropane); Aβ: β-Amyloid; ACE: Angiotensin Converting Enzyme; ALP: Alkaline Phosphatase; APP: Amyloid Precursor Protein; CML: Chronic Myelogenous Leukemia; ERK½: Extracellular Signal-Regulated Kinases ½; HeLa: Cervical Cancer Cells; HepG2: Liver Hepatocellular Cells; MAPK: Mitogen-Activated Protein Kinase; MCF7: Breast Cancer Cells; MMPs: Matrix Metallo Proteinases; MTT: 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide; NO: Nitric Oxide; PC3: Prostate Cancer Cells; ROS: Reactive Oxygen; SAPK/JNK: Stress-Activated Protein Kinases/Jun Amino-Terminal Kinases; TTF: 3,5,4'-Trihydroxy-6,7,3'-Trimethoxy Flavone

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Introduction

Achillea fragrantissima is a desert plant used in the traditional medicine of Arabian countries to treat many diseases of the liver and kidneys, diseases of the gastrointestinal tract, inflammatory, skin manifestations or wound healing [1,2]. It has antioxidant and anti-inflammatory effects, and the extracts of this plant suppress neuroinflammation, which opens up possibilities for its use in psychiatry [3]. The bioactive compounds isolated from *A. fragrantissima* may be beneficial in the prevention of neurodegenerative diseases in which neuroinflammation is part of a pathophysiology. Bioactive substances present in this plant may have a positive impact on the course of Alzheimer's disease, but there are only studies in laboratory animals, clinical trials are still lacking [4].

Botanical Characteristics

Achillea fragrantissima (Forssk.) Sch. Bip. (Figure 1) is a flowering plant of the genus *Achillea* L. (yarrow) of the Asteraceae family. The genus *Achillea* includes more than 100 species and is chemically characterized by the accumulation of sesquiterpenic lactones and flavonoids. *A. fragrantissima* is a tiny, strongly aromatic white-wooly shrub growing in the height of 30 cm to 60 cm. Plants have numerous upright stalks, alternate hairy serrate leaves and small yellow flowers arranged in capitula. The fruit is an achene. This yarrow comes from northeastern Africa and the Middle East (Egypt, Jordan, Israel, Palestine, Syria, Lebanon, Iraq, Saudi Arabia). It grows mainly in deserts and semi-deserts. In Egypt, it is cultivated for healing purposes [5-7].

Traditional Medicine

A. fragrantissima is one of the most popular and most important medicinal herbs in Arabic traditional medicine for the preparation of medicinal teas for the prevention and treatment of

various health problems [8-12]. *A. fragrantissima* is especially popular in Egyptian folk medicine for the treatment of common health problems such as respiratory disease, eye infections, small pox, fever, gastrointestinal disturbances, diabetes, dysmenorrhea, headache or fatigue [13-16]. In Israel, it is used also in diabetes therapy [8]. Pharmacological studies conducted lately with *A. fragrantissima* confirm the traditional use of this yarrow.

Bioactive Substances

In plants of *Achillea* genus, phenolic acids (protocatechuic, vanilic, chlorogenic, ferulic and quinic acid), flavonoids (apigenin, apigenin-glucoside, apigenin-rutinoside and apigenin-neohesperioside, luteolin, vitexin and vitexin-rhamnoside, cirsiol, diosmetin, chrysoplenetin, chrysophanol D), lignans (sesamin), terpenic lactones (achillolid A) and alkaloids (pellitorin, 8,9-Z-dehydropellitorin, anacyclin) have been found as mainly bioactive compounds [17-20]. In water-alcohol extracts of the above-ground portions of *Achillea fragrantissima*, a varied mixture of water-soluble polyphenols was found in the amount of 56.6 mg of gallic acid equivalent in 1 gram of dry weight of plant [2]. By steam distillation or extraction of the aerial parts of the plant with hexane, chloroform or ethyl acetate, the water-insoluble substances were obtained in the form of yellowish colored essential oil (ca. 0.8%) containing hydrocarbons, monoterpenes and sesquiterpenes. In total, up to 54 compounds were identified in the essential oil [21-23]. Hydrocarbons and different terpenes (n-nonane, 1-dodecene, myrcene, salvene, santolina triene, cis-farnesene, trans-pinane, α -thujone and β -thujone, limonene, sabinene, trans-isolimonene, γ -eudesmol, caryophyllene, cedren, germacrene, α -pinene, β -pinene, thymol, p-cymene, eucalyptol, eugenol, camphor, α -terpineol, geraniol, bergamot, fenchon, isocalamendiol, globulol, α -cubebene, farnesol, spathulenol, δ -elemene, γ -eudesmol, vulgaron B) have been found as important bioactive compounds. Both climatic and seasonal conditions influenced the composition and yield of essential oil [24,25].

Pharmacological Effects

Plants of the genus *Achillea* are known as traditional folk remedies. They are widely prescribed for the treatment of stomach pain, gastrointestinal tract inflammation, bleeding, pneumonia, rheumatism, hemorrhoids, allergic rhinitis and menstrual disorders. It also works well during breast feeding and improves wound healing. They show numerous pharmacological effects, that are also interesting in contemporary medicine [20,26,27] and cosmetics [28]. Among the most well-known and best-researched species is the original yarrow (*A. millefolium*), but many studies confirm the pharmacological effects of *A. fragrantissima*. The structural formulas of some important bioactive compounds of the *Achillea* genus are shown in Figure 2.

Anti-inflammatory effect

The anti-inflammatory activity of *A. fragrantissima* extracts were tested using the animal model of carrageenan-induced paw edema, it was comparable to that of diclofenac [29,30]. The substance responsible for the anti-inflammatory effects of the plant could be a sesquiterpenic lactone called achillolid A. This lactone reduces levels of pro-inflammatory and toxic mediators and levels of intracellular reactive oxygen species in lipopolysaccharide-activated microglial cells [31,32]. Moreover, both non-polar and polar fractions revealed protective effects against rat ulcerative colitis and gastric ulcers [30].



Figure 1: *Achillea fragrantissima* on historical illustration (A. Raffeneau-Delile: Flore d'Egypte, 1813).

Analgesic effect

Extracts of *A. fragrantissima* showed peripheral and central analgesic effects in a number of laboratory tests on rodents [30], as well as *A. millefolium* extracts [33].

Antimicrobial effect

A. fragrantissima essential oil shows antimicrobial activity against gram-positive bacteria *Staphylococcus aureus*, *S. epidermidis* and *Bacillus subtilis* and gram-negative *Escherichia coli*. In general, gram-negative bacteria were less sensitive to the essential oil of *Achillea fragrantissima* than the gram-positive [21,24,34]. It is also effective against *Listeria monocytogenes*, *Pseudomonas aeruginosa*, *Klebsiella sp.* and *Salmonella enteritidis* [35,36]. *A. fragrantissima* also acts against poliovirus, rotavirus Wa, human adenovirus 7 and coxsackievirus B4 [37,38] and two fungal species *Candida albicans* and *Aspergillus niger* [24,39].

Antitrypanosomal effect

Aerial parts of *A. fragrantissima* show considerable antileishmanial and antitrypanosomal activity [40]. It is likely that the sesquiterpenic alkaloids derived from pellitorin to be found in the dichloromethane extract from the aerial parts of the plant [41].

Antidiabetic effect

A. fragrantissima is reputed for its antidiabetic properties in the folk medicine of the Middle East. Ethanolic extract of *A. fragrantissima* and its compounds significantly inhibited α -glucosidase activity *in vitro*, more potent than the positive control acarbose, which is used as an oral anti-diabetic drug [42]. In streptozotocin and high-fat diet induced diabetic rats, elevated blood glucose levels, serum lipid profile, liver functions, and kidney functions were improved after *A. fragrantissima* extract treatment, as well as oxidative-stress and pro-inflammatory markers [43].

Anti-tumor effect

The anti-tumor effects of *A. fragrantissima* leaf extract were studied using human Chronic Myelogenous Leukemia (CML), T-cell lymphoma (Jurkat), hepatocellular carcinoma (HepG2) cell lines [44] and HepG2 by MTT assay [45]. Similarly, cytotoxic effects on melanoma cell lines have been tested [46]. In all tests, the anti-tumor effects of the extract on isolated tumor cells have been demonstrated. Phenolic compounds isolated from *Achillea fragrantissima* displayed

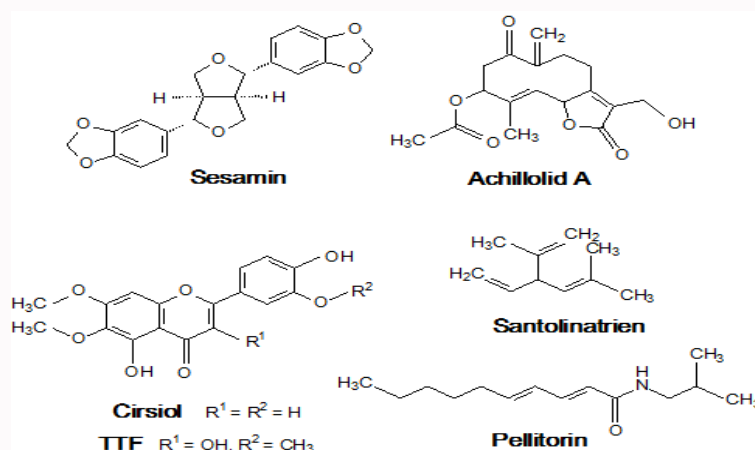


Figure 2: Structural formulas of some important bioactive compounds of the genus *Achillea*.

also cytotoxic activity against MCF7 cell line and moderate cytotoxic activity against A549, HeLa and PC3 cell lines [16].

Myorelaxant effect

The myorelaxant effect of *A. fragrantissima* is linked to the presence of flavonoid cirsilol [47], which has been shown to effect relaxation of isolated rat ileum, bladder and uterus, and inhibits acetylcholine-induced contractions. Cirsilol is a low affinity competitive ligand of central benzodiazepine receptors and has sedative effects [48].

Neuroinflammatory and neuroprotective effect

The neuroinflammatory process plays a central role in the initiation and progression of neurodegenerative diseases such as Parkinson's and Alzheimer's disease and it is associated with activation of brain microglial cells [49]. During the non-inflammatory process, microglia cells release pro-inflammatory mediators such as cytokines, Matrix Metallo Proteinases (MMPs), Reactive Oxygen (ROS) and Nitric Oxide (NO) [50-52]. Ethanol extract of *A. fragrantissima* has protected rat brain astrocytes culture before cell death induced by H_2O_2 and decreased levels of intracellular ROS produced by treatment with H_2O_2 , $ZnCl_2$ or ABAP (2,2'-azobis (2-amidinopropane)) [53].

Some studies suggest that *A. fragrantissima* contains Amyloid Precursor Protein (APP) metabolism modulators that may have a positive impact on the course of Alzheimer's disease [4]. One of the active substances of this plant is the sesquiterpene lactone, achillolid A, which reduces β -Amyloid cytotoxicity ($A\beta$), reduces the production of Reactive Oxygen Species (ROS) induced by $A\beta$ accumulation and inhibits phosphorylation of Mitogen-Activated Protein Kinase (MAPK) [54]. It has previously been shown that achillolid A protects astrocytes from oxidative stress and inhibits the activation of microglia [32,55] and deserves to evaluate its potential as a potential drug for the prevention or treatment of neurodegenerative diseases or brain injury, where oxidative stress is part of the pathophysiology. Achillolid A also protects nerve cells from the toxic effect of glutamate [56].

Another interesting substance isolated from aerial portions of *A. fragrantissima* is the flavonoid 3,5,4'-Trihydroxy-6,7,3'-Trimethoxy flavone (TTF), which also exhibits neuroprotective effects [57]. TTF protects neurons from $A\beta$ -induced cell death and reduces intracellular ROS accumulation in neurons after $A\beta$. TTF also inhibits the phosphorylation of SAPK/JNK and ERK1/2 signaling proteins belonging to the MAPK family [58] and protects nerve cells

against glutamate toxicity [56]. Flavonoids are among the substances that exhibit a wide range of biological functions including anti-inflammatory, antioxidant and neuroprotective activities [59,60], so that the TTF is also a promising candidate for a potential drug for neurodegenerative diseases.

The substances contained in *A. fragrantissima* essential oil also inhibit both enzymes acetylcholinesterase and butyrylcholinesterase, which was confirmed in *in vitro* experiments [23].

Other effects

The *A. fragrantissima* water-alcohol extract inhibits Angiotensin Converting Enzyme (ACE), which participates in the etiology of hypertension and cardiovascular disorders [61].

Toxic effects

Long-term repeated administration of *A. fragrantissima* extracts revealed no significant changes in body weight, heart rate or other physiological parameters. No abnormal changes in liver and kidney function have been reported. The plant extract caused significant reductions in Alka Line Phosphatase (ALP), urea and creatinine. A significant decrease in blood glucose was found in animals receiving 250 mg/kg of extract. Plant extract did not affect fertility. The males showed comparable data with the control animals at the highest doses (250 mg/kg). These doses did not induce any embryotoxic, teratogenic or other harmful effects on females and their offspring. The litter size, survival and weight gain were comparable to control groups [62].

Conclusions and Perspectives

Achillea fragrantissima L., a plant of the *Asteraceae* family, is used in the traditional medicine of Arab countries for the treatment of gastrointestinal disorders, hepatobiliary and gynecological diseases, inflammatory skin manifestations and wound healing. Literary research of articles published in reviewed journals and scientific databases has revealed that the plant has a number of pharmacological effects and contains a large number of biologically active substances. There are polyphenols, flavonoids, terpenes and alkaloids. All the results so far published with the various extracts of *A. fragrantissima* and essential oil have been obtained from *in vitro* experiments, clinical trials are still lacking. Recent evidence that the bioactive substance of this plant has significant antioxidant, anti-inflammatory and neuroprotective effects represents the untapped potential of a plant in the therapy of neurodegenerative diseases or brain injury.

Current studies show that substances of these plants or substances derived from them will find future use for therapeutic purposes.

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