Artemisia annua – Importance in Traditional Medicine and Current State of Knowledge on the Chemistry, Biological Activity and Possible Applications

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ABSTRACT

Artemisia annua (annual mugwort) is a species that has long been used in traditional Asian medicine, mainly Chinese and Hindu. The species is widespread and known as a medicinal plant not only in Asia but also in Europe, in both Americas, and Australia. The species has become a subject of particular interest due to the 2015 Nobel Prize awarded for detecting the sesquiterpene lactone artemisinin in it and proving its antimalarial activities. The raw materials obtained from this species are Artemisiae annuae folium and Artemisiae annuae herba. The leaves are a raw material in the Chinese Pharmacopoeia and Vietnamese Pharmacopoeia. Both raw materials are in the International Pharmacopoeia published by the WHO. The main components of these raw materials are mainly specific sesquiterpene lactones, essential oil, flavonoids, coumarins, and phenolic acids. In traditional Asian medicine, the species is used, for example, in the treatment of jaundice and bacterial dysentery, as an antipyretic agent in malaria and tuberculosis, in the treatment of wounds and haemorrhoids, and in viral, bacterial, and autoimmune diseases. Professional pharmacological studies conducted today have confirmed its known traditional applications and explain previously unknown mechanisms of its biological action and have also found evidence of new directions of biological activity, including, among others, anti-inflammatory, analgesic, antioxidant, antitumour, and nephroprotective activities. The species is of growing importance in the cosmetics industry.

Introduction

The purpose of this review is to present the current state of knowledge on the chemistry, biological activity, possible therapeutic applications, and possible uses of *Artemisia annua* L. (annual mugwort), an herbaceous plant of the genus *Artemisia* from the family Asteraceae (Compositae).

The awarding of the 2015 Nobel Prize in Medicine for the discovery of the sesquiterpene lactone artemisinin, found in *A. annua*, and proving the effectiveness of its antimalarial action have resulted in a marked increase in interest in both the chemical

composition and biological activity of various species of the genus *Artemisia* [1, 2]. Among them, *A. annua* has become an object of modern, professional scientific research with a phytochemical and pharmacological profile [3–7].

This species has an important position in traditional Asian medicine (mainly Chinese and Hindu). It is known as a medicinal plant on five continents, not only in Asia but also in Europe, the Americas, and Australia [8–11]. It was used in Asian medicine, for example, in the treatment of jaundice and bacterial dysentery, and fever in the course of malaria and tuberculosis. It was effective in the treatment of wounds and haemorrhoids, various viral and bacterial diseases, and autoimmune diseases [3, 12, 13].

Nowadays, this species has the status of a pharmacopoeial species in China and Vietnam [7, 14–16]. It is also listed in the International Pharmacopoeia published by the WHO. The medicinal raw materials are Artemisiae annuae folium and Artemisiae annuae herba [8].

The performed pharmacological studies explain previously unknown mechanisms of its biological action known from traditional applications. These studies also prove new directions of biological activity, including anti-inflammatory, analgesic, antioxidant, antitumour, and nephroprotective activities. Extracts from *A. annua* act against hepatitis B virus, bovine viral diarrhoea, and Epstein-Barr virus [3, 17–20]. Recently, the possible application of *A. annua* in the treatment of COVID-19 is being scientifically discussed [21–24].

The species has also become an object of growing interest to the cosmetics industry, especially in Europe [25]. In recent years, review articles have been published regarding various *Artemisia* species, with *A. annua* receiving a lot of attention [3, 5, 17, 18].

General Information on the Species

A. annua is widespread in many parts of the world, which is the reason why the plant has numerous synonymous names. The following are 14 Latin synonyms for annual mugwort, with references to their sources: *A. annua* f. *annua, A. annua* f. *genuina* Pamp., *A. annua* f. *macrocephala* Pamp., *A. annua* var. *zelandica* Lam., *Artemisia chamomilla* C.Winkl, *Artemisia exilis* Fisch, *A. exilis* Fisch. ex DC, *Artemisia hyrcana* Spreng, *Artemisia plumosa* Fisch, *A. plumosa* Fisch. ex Bess., *Artemisia stewartii* C. B. Clarke, *Artemisia suaveolens* Fisch, *Artemisia wadei* Edgew., *Omalotheca stewartii* (C. B.Cl.) J.Holub [26–28].

A. annua's English and foreign names are annual mugwort, annual wormwood, Chinese wormwood, sweet Annie, sweet sagewort, sweet wormwood (English); Cao Haozi, Cao Qinghao, Caohao, Chou Qinghao, Chouhao, Haozi, huang hua hao, Jiu Bingcao, Kuhao, San Gengcao, Qinghao, Xiang Sicao, Xianghao, Xiang, Xiyehao (Chinese); Einjähriger Beifuß (German); armoise annuelle (French); sommarmalört (Swedish); Zomeralsem (Danish); Kusoninjin (Japanese); Chui-ho, Hwang-hwa-ho, Gae-tong-sook (Korean); and Thanh cao hoa vàng (Vietnamese) [2, 8, 26, 27, 29, 30].

According to the Chinese Pharmacopoeia and Vietnamese Pharmacopoeia, the raw material is the dried leaves of *A. annua* (Artemisiae annuae folium) [15, 16]. The International Pharmacopoeia published by the WHO also lists dried *A. annua* herb (Artemisiae annuae herba) as a raw material [8].

A. annua is an annual herbaceous plant growing to a height of 30–100 cm [8]. The *A. annua* plant can have stems that are bare or covered with T-shaped hairs. On the leaves and flowers of the plant, in addition to T-shaped hairs, there are also glandular trichomes, which are characteristic of the *Asteraceae* family. The trichomes are composed of 10 cells arranged in four rows. In the upper layers, there are glandular cells filled with essential oil [8, 31]. Unlike other species of the genus *Artemisia, A. annua* has one main vertical violet-brown ribbed stem with smaller alternately growing offshoots [5, 8, 29]. In autumn, the stems take on a red colour [29].

The foliage of the plant has an alternate arrangement [32]. The dark green leaves of the plant are deeply divided [29]. The tripinnatisect lower leaves grow on petioles, the middle leaves are bipinnatisect, while the upper leaves are sessile and have a lanceolate shape [33]. The leaf blades themselves also differ in shape, as they can be ensiform or lanceolate. Often, the edge of the blades is serrated. Smooth bracts can be found at the base of the leaves [29].

The flower heads are collected in raceme-like inflorescences. The heads are small, spherical, and yellow-green. At the base of each head there are 6 bracts [29, 33]. The head contains only tubular flowers. Along its perimeter there are female flowers, while those in the middle are bisexual. The leaves covering the head have two layers. The outer layer consists of short, ensiform leaves, while the inner layer has longer, ovoid leaves [32]. Although the leaves of the plant have a pleasant aroma, *A. annua* flowers are scentless [33]. The fruit of *A. annua* are 0.8 mm long achenes [32].

The species can be propagated from seeds, which germinate easily, and the seedlings grow quickly. The seeds are resistant to harsh weather conditions, both drought and cold winters. *A. annua* is resistant to diseases and pests, which makes it a good plant for cultivation [29]. It is an allopathic plant due to the presence of artemisinin [18].

A. annua occurs naturally in Southeastern Europe and Western Asia in the temperate zone [29, 32]. At the end of the 19th century, it was brought to Western Europe and Southern Europe, and then spread to Russia, Iran, Afghanistan, Pakistan, and China [32, 33]. Nowadays, the plant can be found in different parts of Europe and Asia, North and South America, and Australia. The largest habitats of *A. annua* are in the western United States and Western Europe [27]. The species is not native to Poland, but it can be found in the southern part of the country and in the Silesia and Lublin provinces [32].

The plant grows readily on hillsides, forest edges, and wasteland [29]. It inhabits moderately dry and nutrient-rich sites. In Poland, these are usually areas that have soil with a high humus content, loamy, gravelly, or sandy [34]. Depending on the climate zone, *A. annua* grows at altitudes of 50 to 1500 m a. s. l. [8].

A. annua is a source of artemisinin, which is used to treat malaria, hence, the species has become a cultivated plant [8, 35]. Although the plant comes from the temperate zone, the seeds of various varieties have been successfully adapted for cultivation in many tropical countries, such as Congo, India, and Brazil [36]. Other countries where *A. annua* has become an industrial crop

species are China, Kenya, Tanzania, and Vietnam. For industrial applications, the plant is also harvested from its natural habitats [3, 8, 35].

A. annua is a plant that is relatively easy to grow in a temperate climate [37]. To achieve a high seed germination rate, well-aerated soil and sunlight are needed. When the soil is difficult to drain, the plant should first be grown in a greenhouse [8].

The concentration of artemisinin in the plant is highest during flowering. To maximize the yield of this compound from this species, appropriate duration of light exposure is needed because the plant grows best during long summer days and blooms when the length of the day is reduced. In the drying process, it is best to place the plants in the sun for 1 week, and then transfer them to a shady, airy place [36]. The dried leaves should not be stored for more than 6 months. If, after this time, artemisinin is to be obtained from the raw material, additional tests are required to determine its concentration in the dried product [3, 38]. The time from sowing to harvesting the plant is 4.5 to 5 months [35].

It has been reported that the key factor to achieving a high artemisinin concentration in the plant is the use of the appropriate genetic variety of *A. annua*. One such variety is *A. annua* var. *artemida*. Environmental factors have a lower impact on the yield of this variety [36]. The *A. annua* F1 hybrid called "*Artemis*" (*A. annua* × *F1 Artemis*) is also recommended [39–41]. The cultivation time of the species is quite long, which translates into frequent fluctuations in the supply and prices of the products obtained from *A. annua* [18].

Phytochemical Characteristics

A. annua contains many different classes of compounds and is a plant with a variable chemical composition [42, 43]. The habitat in which it grows affects its chemical composition and thus the medicinal value of the plant [36, 44]. The components that can be distinguished in the chemical composition of the species include specific sesquiterpene lactones, essential oil with mono- and sesquiterpenes, flavonoids, coumarins, phenolic acids [36], tannins, saponins [45], polyalkenes [18], phytosterols, fatty acids [45], and proteins, including enzyme proteins (▶ **Tables 1** and **2**) [45].

The compounds that are of significance for the plant's activity profile are sesquiterpene lactones. The most important compound in this group is artemisinin (▶ **Fig. 1**), which accumulates in its glandular hairs situated on both the leaves and flowers of the plant [31, 36, 45, 70]. Its concentration in *A. annua* leaves ranges from 0.01 to 1.50% dry weight. The discoverer of artemisinin was a Chinese female specialist in pharmaceutical chemistry, Prof. Youyou Tu, who, for this achievement and proving the effectiveness of this compound in the treatment of malaria, was awarded the 2015 Nobel Prize in Medicine [1, 71]. Artemisinin has a characteristic peroxide bridge, which determines its mode of action [38, 45, 72, 73]. After extracting artemisinin, the compound is used to produce the semisynthetic derivatives – artemether, artesunate, dihydroartemisinin, and arteether [18]. Artesunate is obtained by reducing artemisinin. After administration, this compound is transformed into the active form, dihydroartemisinin, which is the most readily soluble in water, and thus translates into its relatively high bioavailability. Artemether is also metabolized to dihydroartemisinin, but to a lesser extent [74]. Apart from artemisinin, other sesquiterpenes are specific components of *A. annua*, including isomers of artemisinin, artemisinic acid, artemisinol, and epoxyartemisinic acid [6, 50].

The concentration of essential oil in the plant varies between 1.4 and 4.0% [18]. The oil is rich in terpenes, and its main components are camphene, *Artemisia* ketone, camphor, *β*-caryophyllene, and *β*-pinene (▶ **Fig. 2**). Germakrene D, borneol, and cuminal are also present in high concentrations [18, 42, 43, 46, 47, 62, 64, 67, 68]

The most frequently listed flavonoids characteristic of the species are artemetin and casticin (▶ **Fig. 3**) [36, 46, 51, 52]. Other flavonoid compounds are derivatives of apigenin, luteolin, quercetin, kaempferol, and isorhamnetin [17]. Quercetin and kaempferol derivatives account for 84.8% of all the polyphenols [53]. Among the coumarins, *cis*- and *trans*-melilotoside, esculetin, isofraxidine, coumarin, tomentin, scopoletin, and scopolin can be distinguished [17, 52, 59].

It has also been proven that *A. annua* is a plant rich in quinic acid and its derivatives, and also in phenolic acids, including chlorogenic acid and its derivatives, as well as caffeic acid and rosmarinic acid [46, 52–54].

Importance in the History of Asian Medicine

Little known in Europe, *A. annua* L. has been used in traditional Chinese medicine (TCM) as a plant-derived antipyretic and antimalarial drug for over 2000 years. Artemisinin, isolated from this plant (in Chinese – Huang hua hao, or Qing Hao) in the 1970s, has become an effective drug in cases of drug-resistant malaria (resistance to quinine and chloroquine) in European pharmacology [75].

The oldest information in the Chinese medical literature regarding the therapeutic use of *A. annua* L. comes from a treatise written about 200 BC on a piece of silk that was excavated in 1973 from the grave of Ma-wang-tui. The treatise, named by Chinese researchers as *Prescriptions for 52 diseases* (Wu Shi Er Bing Fang), is one of the oldest sources of knowledge on the tradition of Chinese pharmaceutical technology. It describes 224 medicines and methods of their preparation [76], with annual mugwort (called qinghao or qui) described as a medicine for haemorrhoids (fumigant) [77]. Among herbal medicines, the plant is also mentioned in later medical works, for example, Shen Nong Ben Cao Jing (Shen Nong's Herbal Classic), Da guan Ben Cao (*Grand Materia Medica*), and Ben Cao Gang Mu (*Compendium of Materia Medica*) [33].

A. annua (in Chinese qinghao or Qing Hao) was first described as an herbal medicine against malaria by Hong Ge (284–363 AD), a physician of the Eastern Jin Dynasty (317–420 AD) in *Zhou Hou Bei Ji Fang* (*A Handbook of Prescriptions for Emergency*). The known recipes included *Qing Hao* pills, *Qing Hao* decoction or drink, *Qing Hao* powder, *Qing Hao* infusion, *Qing Hao* drops, and *Qing Hao* wine. For example, the decoction of *Qing Hao* is also mentioned in *Sheng Ji Zong Lu* (*General Medical Collection of Royal Benevolence*), an encyclopaedic collection of prescriptions written during the Song Dynasty (960–1279 AD), and the pills, *Jie Nue Qing Hao*, in *Dan Xi Xin Fa* (*Danxi' Mastery of Medicine*) during the Yuan Dynasty

▶ **Table 1** Chemical composition of *A. annua*.

Group of compounds	Compounds	References
Sesquiterpene lactones	artannuin B	[30, 36, 46]
	artemisinin	[18, 36, 46–49]
	artemisinic acid	[36, 46–48]
Sesquiterpenes	artemisinol, artemisinin I, II, III, IV, V, artemisinin isomers, epoxyartennuic acid	[6, 50]
	dihydroartemisic acid	[46, 48]
Flavonoids	artemetin, casticin	[36, 46, 51, 52]
	3,5-dihydroxy-3′,4′,6,7-tetramethoxyflavone, quercetin 3-glucoside, acacetin, apigenin, astragalin, chrysoeriol, chrysosplenol C, chrysin, cinaroside, 3,4′-dimethyl-quercetagentin ether, 3-methyl-quercetin ether, 7-methyl-luteolin ether, eupatin, 3-methoxy-kaempferol glucoside, marnsetin glucoside, isorhamnetin, kirsiliol, kirsimaritin, quercimeritin, laricitrin, marnsetin, micanine, retina, syringetin, tamarixetine	[36, 46, 51, 52]
	3,5-di-hydroxy-6,3′,4′-tetramethoxyflavone, 3,5-di-hydroxy-6,7,4′-trimethoxyflavone, 3,5-di-methoxyquercetagentin, quercetin 3-O-galactoside, isorhamnetin 3-O-glucoside, 3-O-glucoside of kaempferol, 3-O-glucoside of quercetin, 3-O-hexoside of marnsetin, 3-O-methylquercetagentin, 7-O-glucoside of diosmetin, 8-methoxykaempferol, kaempferol	[53]
	apigenin 6-C-arabinosyl-8-C-glucoside, apigenin 6-C-glucosyl-8-C-arabinoside, patulentin glucoside, jaceidin, chrysoeriol rutinoside, vitexin,	[54]
	luteolin 7-O-glucoside	[53, 54]
	chrysosplenol D	[36, 46, 52, 55, 56]
	chrysosplentin	[36, 46, 52, 57]
	di-hydroartemisinin	[58]
	eupatorine	[36, 46, 52]
	isoquercetin	[59]
	isovitexin	[46, 54]
	kaempferol	[46, 52]
	cirsilineol	[36, 46, 52, 54]
	quercetin	[46, 52, 53]
	luteolin	[46, 52, 53]
	myrcetin	[56]
	myricetin	[46]
	apigenin derivatives, isorhamnetin derivatives, kaempferol derivatives, quercetin derivatives, luteolin derivatives	[60, 61]
	rhamnetine	[31, 56]
	rutoside	[17, 46, 52]
Coumarins	*cis*-melilotoside, *trans*-melilotoside	[17, 52, 59]
	esculetin, isofraxidine, coumarin, tomentin	[52]
	scopoletin	[52, 57]
	scopolin	[17, 52]
Phenolic acids	3,4-diferuloquinic acid, 3,4-di-caffeoylquinic acid, 3,5-diferuloquinic acid, 3,5-di-caffeoylquinic acid, 3,5-di-O-caffeoylquinic acid, 3,5-caffeoyletherquinic acid, 3-feruloquinic acid, 3-caffeoyl-quinic acid, 4,5-diferuloquinic acid, 4,5-di-O-caffeoylquinic acid, 4-feruloquinic acid, 4-caffeoyl-3,5-di-succinylquinic acid, 4-caffeoylquinic acid, 5-feruloquinic acid	[54]
	chlorogenic acid	[46, 52–54]
	diferulcaffeoylquinic acid, ferulic acid	[53]
	caffeic acid	[53, 54]
	coumaric acid	[52]
	rosmarinic acid	[46, 59]
Phenols	syringaldehyde	[53]

continued

▶ **Table 1** *Continued*

Group of compounds	Compounds	References
Saponins	n. d.	[45]
Tannins	n. d.	[45, 62]
Sterols	*β*-sitosterol, stigmasterol	[63]
Polyalkenes	n. d.	[18]
Fatty acids	palmitic acid	[64]
Organic acids	quinic acid	[52, 54]
Polysaccharides	polyuronides	[62]
Enzymes	*β*-glucosidase, *β*-galactosidase	[65]
Proteins	n. d.	[45]
Vitamins	vitamins A and E	[66]

n. d. = no data

(1271–1368 AD). *A. annua* L. was recommended for paroxysmal malarial fever by the physician Shizhen Li (1518–1593) in his book *Ben Cao Gang Mu* (*Compendium of Materia Medica*). This plant, in Chinese medical literature, was given the binominal Latin name *Artemisia annua* only in the 20th century with the publication of the *First Chinese Pharmacopoeia* (*Chung-hua yao-tien*) in 1930 [76, 78]. In herbal medicine of the West, this plant had been given virtually no attention until the early 20th century.

Analysing historical Chinese medical works (from 2000 BC to 640 AD) in search of an effective cure for malaria, Prof. Youyou Tu from the Academy of Traditional Chinese Medicine at the Ministry of Health of China (now China Academy of Chinese Medical Sciences) has collected over 2000 recipes for medicines of plant, animal, and mineral origin, publishing them in the brochure *Antimalarial Collections of Recipes and Prescriptions* (*Kang Nue Dan Mi Yan Fang Ji*). In her research, conducted with her team since 1969, the researcher has relied on the textbook by Hong Ge from the 4th century, *Zhou Hou Bei Ji Fang* (*A Handbook of Prescriptions for Emergencies*), in which he reported that *Qing Hao* relieved the symptoms of malaria [33]. In 1971, the outcome of the experiments conducted by Youyou Tu's team was obtaining a mugwort extract (the extract was called *Qinghaosu*), and a year later the discovery that it contained an organic chemical compound called artemisinin, which has found application in the treatment of malaria. For her discoveries, in 2011, Youyou Tu received the Lasker-DeBakey Clinical Medical Research Award, and in 2015 the Nobel Prize in Physiology or Medicine [79].

Applications in Traditional Asian Medicine

Traditional medicine in China and India makes use of all the parts of the plant, the flowers, leaves, stem, seeds, and essential oil. They are used to treat jaundice, bacterial dysentery, and fever [18, 80].

In China, *A. annua* has been used for over 2000 years as an antipyretic for malarial fever, tuberculosis, and, in TCM, for "fever caused by summer heat" and for "afternoon fever associated with yin deficiency" [8, 29]. *A. annua* is also known as a remedy for bleeding wounds and haemorrhoids [29]. In TCM, it is also recommended to use the plant in the treatment of tumours, to fight infections caused by protozoa from the genera *Plasmodium, Acanthamoeba, Schistosoma, Leishmania,* to fight viral diseases (e. g., AIDS and hepatitis B), and to treat bacterial infections [5, 29]. In TCM, *A. annua* is also recommended for autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis [81]. *A. annua* seed extracts can be used to treat eye diseases [29, 82]. The plant is traditionally used in the form of infusions, aqueous extracts, and tinctures from the dried herb [17, 83].

Applications in Modern Phytotherapy and Position in Official Pan-World Medicine

A. annua has an established position in the treatment of malaria [18]. It is a valuable source of artemisinin [29], which is effective in the early stages of trophozoite malaria. It also inhibits the growth of *Plasmodium* schizonts and has a gametocytocidal effect, which limits the spread of the protozoan to mosquitoes [18]. Its semisynthetic derivatives artemether, artesunate, and dihydroartemisinin are also used in the treatment of malaria [84].

A growing problem in the treatment of malaria is the developing resistance of *Plasmodium* species to antimalarial drugs, including artemisinin [85]. A combined therapy, *Artemisinin Combination Therapy* (ACT), has become a way to reduce resistance. It is based on combining artemisinin with antimalarial drugs with a different mechanism of action that works longer [86]. The most commonly used combinations are artemether with lumefantrine, artesunate with amodiaquine, artesunate with mefloquine, artesunate with sulfadoxine and pyrimethamine, and dihydroartemisinin with piperaquine [84].

The likely causes of the increasing resistance to artemisinin are the uncontrolled use of ACT therapy, the use of subtherapeutic doses of artemisinin, the use of artemisinin derivatives as prophylactic agents, and the use of substandard or counterfeit drugs [85].

Medicines based on *A. annua* constitute standardized extracts in the form of tablets and injections [38, 72]. When preparing

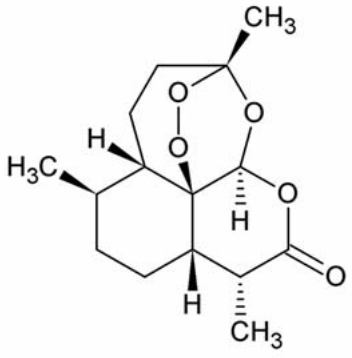
▶ **Table 2** Chemical composition of *A. annua* essential oil.

Group of compounds	References
Monoterpenes	
1,8-Cineole	[18, 42, 43, 46, 47, 62, 64, 67, 68]
4-Terpineol, sabinene	[42, 43, 64, 67, 68]
Artemisinin alcohol	[30, 42, 67, 68]
Santolin alcohol, *cis*-chrysanthenol, dehydro-1,8-cineol, dehydrosabinene, myrtenal, *cis*-pinocarveol acetate, *p*-mentha-2,4 (8) -diene, δ-terpineol	[68]
Yomogi alcohol	[42, 67–69]
Artemisiatrien, *cis*-β-*O*-cymene, bornyl acetate, piperitone, terpinolene, α-felandrene, α-thujone	[43]
Borneol	[18, 42, 43, 47, 62, 64, 68]
cis-Carveol, carvone, myrtenyl acetate, *p*-cymene, *trans*-carveol, *trans*-β-*O*-cymene, thujen, verbenol, verbenone, α-terpinolene	[42]
Dehydrosabinaketone, β-pinene oxide	[67]
Eugenol	[42, 43]
cis-Sabinene hydrate	[43, 67, 68]
trans-Sabinene hydrate, α-campholenal	[42, 68]
Ipsdienol, myrcenol, neryl acetate	[64]
Camphene	[18, 42, 43, 47, 64, 67, 68]
Camphor	[18, 42, 43, 47, 64, 67, 68]
Artemisinin ketone	[18, 30, 42, 67, 68]
Cuminal	[7]
Limonene	[46]
Linalool	[18, 42]
Myrcene	[18, 42, 43, 64, 67]
Myrtenol	[42, 64, 67]
Pinocarvone, *trans*-pinocarveol	[67, 68]
Santolinatriene, α-terpinene	[42, 43, 67, 68]
α-Pinene	[18, 42, 43, 46, 47, 64, 67, 68]
α-Terpineol	[42, 64, 67, 68]
α-Thujene, γ-terpinene	[64, 68]
β-Pinene	[18, 42, 43, 64, 67, 68]
Sescquiterpenes	
(−) – Isolongifolen-9-one, *cis*-β-caryophyllene, epi-α-cadinol, humulene, cubenol, nootkaton, spathulenol, *trans*-β-caryophyllene, β-chamigrene, β-gurjunene, γ-gurjunen, β-cadinene, γ-cadinene	[42]
Aristolon, *cis*-cadin-4-en-7-ol, germacren A, selin-11-en-ol isomer, selin-3,11-dien-6α-ol, α-humulene, β-bourbonene, β-elemen, β-cubeben	[68]
Bicyclogermacrene	[43, 67, 68]
trans-β-Farnesane	[67, 68]
Germacren B, kopaene, α-farnesan, γ-elemen	[64]
Germacren D	[42, 43, 47, 64, 67, 68]
Isoledene, *trans*-beta-kopaene	[62]
Caryophyllene, α-longipinene	[43]
Cubeben	[42, 68]
Nerolidol	[46]
Caryophyllene oxide	[42, 64, 68]
α-Copaene	[42, 43, 67, 68]
β-Caryophyllene	[18, 67, 68]
β-Selinene	[42, 43, 68]

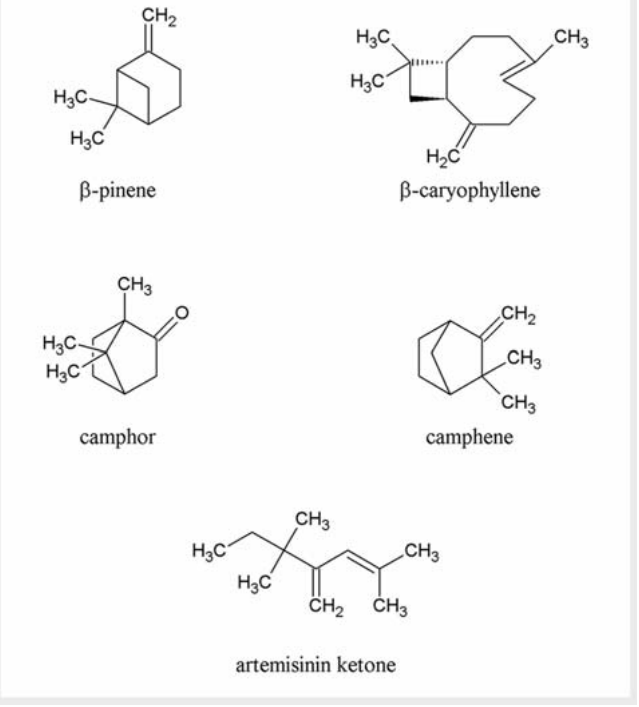
continued

▶ **Table 2** *Continued*

Group of compounds	References
γ-Muurolene	[42,43]
δ-Cadinene	[43,68]
Diterpenes	
Vulgarone	[43]
Other volatile compounds	
Nonanal	[64]
Isovalerate hexanoate	[67]
cis-Jasmon, benzyl benzoate, eudesm-7(11)-en-4-ol, hexanal, arteannuic acid	[42]
Ethyl 2-methylbutanoate, propyl 2-methylbutanoate	[42,68]
1-Dodekene, 2-hexenyl 2-methylbutanoate, *cis*-2-hexenyl 3-methylbutanoate, 2-methyl-2-butenyl 3-methylbutanoate, 3-methyl-3-butenyl 3-methylbutanoate, benzyl 3-methylbutanacetate, nonadecane	[68]
2-H-1-Benzopiranzone	[62]



▶ **Fig. 1** Chemical structure of the sesquiterpene lactone – artemisinin.



▶ **Fig. 2** Chemical structure of volatile compounds characteristic of the essential oil from *A. annua* herb.

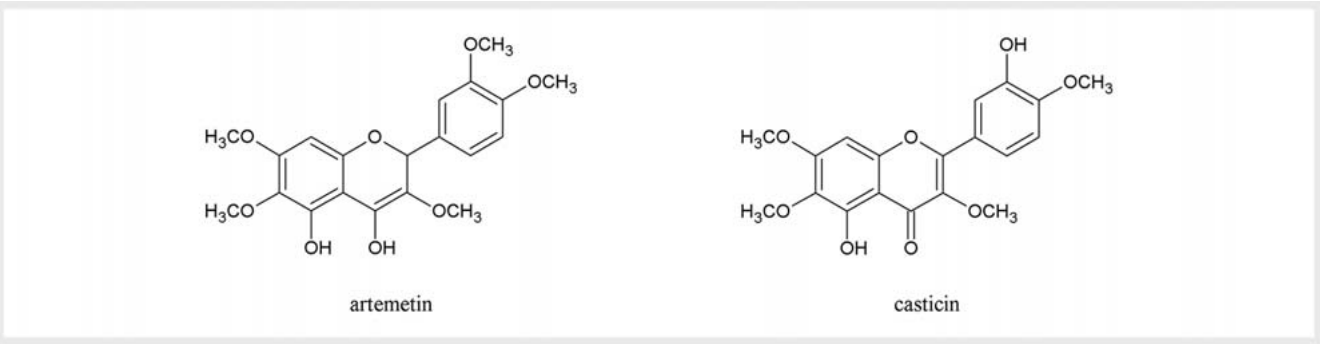
preparations from *A. annua* leaves, or an infusion with artemisinin, one should remember not to use metal objects because artemisinin reacts with iron. In the case of infusion, it has been proven that it is more effective to pour boiling water over the leaves than to add them to boiling water [80].

The raw material is the dried leaves of *A. annua*, Artemisia annuae folium. It has a monograph in the Chinese Pharmacopoeia and the Vietnamese Pharmacopoeia [15,16]. According to these documents, the leaves should be standardized for artemisinin content, which cannot be lower than 0.7% of dry weight. The indications for the use of the raw material given in the Chinese Pharmacopoeia are fever of various origins and malaria [8]. It is also used for gastrointestinal complaints and skin diseases [2]. The International Pharmacopoeia, published by the WHO, also specifies the dried *A. annua*, Artemisiae annuae herba, as a raw material [8]. The species does not have a monograph in European Pharmacopoeia. The most important scientifically proven pharmacological properties of *A. annua* are described below and presented in the ▶ **Table 3**.

Biological Activity Confirmed by Scientific Research

Antimalarial activity

As part of the collaboration of scientists from the German Institute for Medical Mission, the University of Tübingen in Tübingen (Germany) and from Inspection Provinciale de la Santé Publique in Bukavu (Congo), an open, randomized, clinical trial was conducted in which patients with uncomplicated malaria caused by



▶ **Fig. 3** Chemical structure of flavonoids characteristic of *A. annua*.

infection with *Plasmodium falciparum* were administered an infusion of *A. annua* herb in various doses. After 7 days of therapy, the percentage of cured patients was 74% compared to 91% for the control group treated with quinine [87].

Other trials confirming the antimalarial action of the compounds contained in *A. annua* leaf extracts were conducted as part of the collaboration between the Université d'Abomey Calavi in Cotonou (Benin), Université Catholique de Louvain in Brussels (Belgium), and Université de Liège in Liège (Belgium). Using aqueous and hydro-ethanolic extracts from *A. annua* leaves, tests were performed *in vivo* against *Plasmodium berghei* and *in vitro* against *P. falciparum*. In the *in vivo* study, extracts from the plant were administered for 4 days to mice infected with *P. berghei*. The *in vitro* study was carried out using the lactate dehydrogenase of the plasmodium, whose activity was tested. In the positive control, artemisinin was used in both experiments. The results of the *in vitro* study proved that the effects of both extracts were similar to those of pure artemisinin at the same dose. In the *in vivo* study, the hydro-ethanolic extract of *A. annua* containing 20 mg/kg of artemisinin was more effective than the aqueous extract and pure artemisinin at a dose of 140 mg/kg. The effectiveness of the aqueous extract containing 20 mg/kg of artemisinin was the same as that of pure artemisinin at a dose of 140 mg/kg. The obtained results indicate the importance of the presence of other *A. annua* components that increase artemisinin activity [88].

The effect of an infusion of *A. annua* leaves on *in vitro* cultures of *P. falciparum* (chloroquine-resistant and chloroquine-sensitive strains) was studied at the University of Salento and Lachifarma in Lecce (Italy). The method used was the lactate dehydrogenase test. The infusion of *A. annua* leaves was also analysed for the concentration of artemisinin. The study showed that infusions from the plant had antimalarial effects. However, the amounts of artemisinin present in the infusions were too low to be responsible for the effect. It was concluded that the effectiveness of infusions against *P. falciparum* was determined by the synergistic effect of artemisinin with other compounds contained in *A. annua* leaves [55].

The likely mechanism of action of *A. annua* is interference of plant components with protein metabolism, and interference with the mitochondrial activity of protozoa of *Plasmodium* spp. [72]. Another more precisely described mechanism of action speaks of artemisinin-assisted inhibition of the calcium pump that is necessary for the synthesis of proteins of the plasmodium cell membrane. Artemisinin connects to the calcium pump, exposing its peroxide bridge. The peroxide bridge opens under the influence of iron present in the mitochondria. The iron attracts an oxygen electron, and the activated oxygen attracts hydrogen atoms nearby. As a result, radicals are created that attack organic carbon-based structures. The whole process leads to the inactivation of the pump and death of the protozoan [89].

P. falciparum requires mitochondrial activity during its life cycle to keep its respiratory chain active. During treatment with artemisinin, after contact with the iron present in mitochondria, this compound was activated. Oxygen atoms disrupt the electron transport chain of the plasmodium and lead to the depolarization of the mitochondrial membrane. This prevents the biosynthesis of pyrimidine, which causes the death of the protozoan [18]. Activated artemisinin also has the ability to inhibit inflammation caused by the presence of protozoa adhering to the endothelium of the capillary vessels [72]. The artemisinin derivatives – artemether, artesunate, and their active metabolite dihydroartemisinin do not affect tissue forms of *Plasmodium* and are not used in the prevention of malaria [74, 86].

Action against other diseases caused by protozoa

A group of Polish researchers from the Poznań University of Medical Sciences in Poznań (Poland) has investigated whether extracts from *A. annua* herb and pure artemisinin can be used against acanthamebiasis, a parasitic disease caused by the protozoan *Acanthamoeba castellanii*. Extracts were obtained using various solvents, such as water, methanol, and chloroform. The *in vivo* study was conducted by giving the prepared extracts to mice infected with *A. castellanii*, while in the *in vitro* study, amoebas were cultured on agar with filter paper saturated with various *A. annua* extracts or artemisinin. The results of the experiments showed that the extracts from *A. annua* had strong lethal properties against *A. castellani* in both the *in vivo* and *in vitro* models. In the experiment on animals, an extension of rodent life was observed, while in the *in vitro* experiment, the use of pure artemisinin was the most effective, followed by extracts with methanol, chloroform, and water [95].

The activity of *A. annua* leaf and seed extracts in the treatment of leishmaniasis has been tested at Indian research centres: Hamdard University and the International Centre for Genetic Engi-

▶ **Table 3** Pharmacological properties of *A. annua*.

Activity	Mechanism of action	References
Antimalarial	Improvement of malaria symptoms after treating patients with infusion of *A. annua* herb. Inactivation of the protozoan calcium pump.	[87]
	Lethal activity of hydro-ethanolic and aqueous extracts from *A. annua* leaves against *P. falciparum* and *P. berghei*.	[88]
	Interference of artemisinin with protein metabolism and mitochondrial activity of *Plasmodium* spp. protozoa.	[72]
	Inhibition of the plasmodium calcium pump.	[89]
	Depolarization of the mitochondrial membrane of *Plasmodium* spp. protozoa and inhibition of pyrimidine biosynthesis.	[38]
	Synergism of action of artemisinin and other compounds contained in *A. annua* leaves against *P. falciparum*.	[55]
Against other diseases caused by protozoa	Lethal activity against *A. castellani* of artemisinin and methanolic, ethanolic, and aqueous extracts from *A. annua* herb.	[34]
	Compounds contained in *A. annua* seed and leaf extracts have lethal activity against *L. donovani*. The mechanism of action is to direct protozoan cells towards apoptosis.	[90]
Antibacterial and antifungal	Lethal activity of *A. annua* leaf extracts against *E. coli*.	[44]
	Lethal activity of essential oil and 1,8-cineol, camphor, and artemisia ketone isolated from *A. annua* herb against *E. coli, S. enteritidis, S. typhi, Y. enterocolitica*, and *L. monocytogenes*. Components of essential oil penetrate through the bacterial cell membrane, causing cellular dysfunction, increasing permeability of bacterial membrane and components.	[67]
	Essential oil inhibits growth of bacteria: *S. aureus, B. subtilis, E. faecalis, P. aeruginosa, E. coli, K. pneumoniae, A. baumannii*, and fungi: *C. famata, C. utilis*, and *C. albicans*, and also inhibits cell adhesion and reduces the expression of virulence factors.	[42]
	Low and moderate inhibition of growth of bacteria: *S. aureus, B. cereus, S. lutea, S. enteritidis, K. pneumoniae, E. coli, Shigella*, and fungi: *C. albicans* and *A. fumigatus*.	[68]
Immuno-suppressive	Inhibition of lymphocyte proliferation and reduction of IgG, IgG1, and IgG2b antibody levels after administration of *A. annua* whole plant extract.	[81]
	Artemisinin obtained from *A. annua* inhibits late-type hypersensitivity response and has a suppressive effect on calmodulin responsible for activation of T lymphocytes.	[91]
Anti-inflammatory	Reduction of pain and stiffness in joints and improvement of mobility after using *A. annua* extract.	[92]
	Use of aqueous extracts from *A. annua* leaves reduces secretion of proinflammatory cytokines, interleukin-8, and interleukin-6. Rosmarinic acid is largely responsible for this effect.	[59]
Analgesic	Giving mice essential oil from *A. annua* herb, camphor, 1,8-cineol, and α-pinene reduces writhing episodes caused by acetic acid.	[68]
Antioxidant	Methanolic extracts from *A. annua* leaves have the highest concentration of phenolic and flavonoid compounds showing a reducing effect.	[93]
	Reducing activity of *A. annua* leaf extracts in DPPH test.	[44]
	Essential oil from *A. annua* herb and its components: 1,8-cineol, artemisia ketone, and α-pinene show weak reducing activity in tests with DPPH, ABTS radical, and hydrogen peroxide.	[68]
Nephroprotective	Administration of *A. annua* essential oil to rats exposed to carbon tetrachloride prevents kidney damage.	[68]
Cytotoxic	Polyphenols contained in *A. annua* inhibit adhesion of cancer cells to endothelial cells and inhibit epithelial-mesenchymal transition.	[53]
	Regression of prostate cancer in patients treated with capsules containing a concentrate with *A. annua* and bicalutamide.	[94]
	Inhibiting proliferation of human osteosarcoma cells and directing them towards apoptosis.	[58]
	Methanolic extract from *A. annua* leaves collected in Egypt showed significant cytotoxic activity against MCF7 human breast adenocarcinoma cell line, human lung cancer cell line, and Chinese hamster ovary CHO cell line.	[44]
Auxiliary action in obesity treatment	Reduction of fat droplet accumulation and inhibition of PPARγ, C/EBPα, SREBP-1c, FAS, and ACC protein expression under the influence of *A. annua* essential oil.	[43]
	Reduction of insulin resistance, reduction of liver steatosis and fibrosis. Lowering the levels of SREBP-1c, ChREBP, COX-2. Inhibition of TGF-β1 and connective tissue growth factor.	[36]
Anthelmintic	Extracts from *A. annua* leaves inhibit growth of larvae and hatching of eggs of *H. contortus* (parasite of sheep and goats).	[17]

neering and Biotechnology in New Delhi, and the Institute of Nuclear Medicine and Allied Sciences in Delhi. The extracts were obtained by extraction with *n*-hexane, ethanol, and water. To evaluate the antiprotozoal activity, the amastigote and promastigote forms of *Leishmania donovani* were treated with the extracts. The researchers demonstrated significant lethal activity against both forms of the protozoan. The authors of the study report that the mechanism of action of the extracts consists in directing protozoan cells towards apoptosis [90].

Antibacterial and antifungal activities

At King Abdullah University of Science and Technology in Thuwal (Saudi Arabia), Research and Development, Qatar Foundation in Doha (Qatar), and at Kuwait University in Kuwait City (Kuwait), tests were conducted on the antibacterial activity of *A. annua* leaf extracts. The experiments were performed by the disk diffusion method against the bacteria *Escherichia coli*. The extraction of *A. annua* leaves collected in Jericho and Egypt was carried out with hexane, chloroform, methanol, and water. It was proven that the origin of the plant material had an influence on the strength of the antibacterial effect. The highest activity was proven for aqueous extracts of the plants collected in Jericho. Other tested extracts showed a lesser effect. None of the extracts of the plants from Egypt showed antibacterial activity [44].

Researchers from the University of Florence in Florence and Sesto Fiorentino and from the University of Pisa in Pisa (Italy) have investigated the activity of *A. annua* components against *E. coli, Salmonella enteritidis, Salmonella typhi, Yersinia enterocolitica*, and *Listeria monocytogenes*. Employing the disc diffusion method, they used essential oil obtained from the blooming *A. annua* herb and selected oil components (1.8-cineol, camphor and artemisia ketone). All the microorganisms tested were found to be sensitive to the essential oil and its components. In addition, *Y. enterocolitica* strains were more sensitive to *A. annua* herb oil than to the positive control – amoxicillin. It was also found that the essential oil was less effective than 1.8-cineol against *S. typhi*. The mechanism of action reported by the authors of the study was the penetration by essential oil components through the cell membrane into the interior of the bacteria, which causes cell dysfunction, increased membrane permeability, and outflow of ions with other components [67].

In 2015, at the University of Bucharest in Bucharest (Romania), the disc diffusion method was used to examine the effect of the essential oil of *A. annua* herb on the bacteria *Staphylococcus aureus, Bacillus subtilis, Enterococcus faecalis, Pseudomonas aeruginosa, E. coli, Klebsiella pneumoniae,* and *Acinetobacter baumannii* and the fungi *Candida famata, Candida utilis*, and *Candida albicans*. The tested strains were found to be sensitive to the essential oil. The measured MIC values ranged from 0.51 mg/mL for *E. faecalis* to 16.3 mg/mL for *E. coli* and *Klebsiella pneumoniae*. The essential oil also inhibited the adhesion of microbial cells to an inert medium and inhibited the expression of hemolysin, gelatinase, deoxyribonuclease, lipases, and lecithinase, which are virulence factors that promote the penetration by microorganisms into the host organism [42].

Another research group from the University of Niš in Niš (Serbia), using the microdilution method on titration plates, also tested the antibacterial and antifungal effects of the essential oil from *A. annua* herb. The tests were performed on the bacteria *S. aureus, Bacillus cereus, Sarina lutea, Salmonella enteritidis, K. pneumoniae, E. coli,* and *Shigella* spp. and the fungi *C. albicans* and *Aspergillus fumigatus*. These microorganisms were found to have low or moderate sensitivity to the essential oil. The highest susceptibility to *A. annua* essential oil was shown by the bacteria *S. lutea*, for which the MIC value was 2.5 mg/mL [68].

Immunosuppressive effect

Researchers at Zhejiang University and The Hospital of Zhejiang University in Hangzhou (China) have investigated an ethanolic extract of *A. annua* herb for immunosuppressive activity. The tests were carried out both *in vitro* and *in vivo*. In the *in vitro* study, they induced proliferation of lymphocytes isolated from mouse spleens with concanavalin A and lipopolysaccharide and assessed immunosuppression after administering the *A. annua* extract. The *in vivo* study involved immunizing mice with ovalbumin and, after administration of the plant extract, examining the suppression of specific antibodies and the suppression of the proliferation of splenic lymphocytes. After administering the *A. annua* extract, inhibition of lymphocyte division in a concentration-dependent manner was observed in both experiments. The study with rodents demonstrated a reduction in the levels of IgG, IgG1, and IgG2b in the serum. The results of the experiments justify the traditional use of *A. annua* in the treatment of autoimmune diseases [81].

Another study confirming the immunosuppressive activity of the species was conducted at Tarbiat Modarres University, Shahed University, and Shahid Beheshti University in Tehran (Iran). Artemisinin obtained from *A. annua* herb was used for the experiment to test whether the administration of the isolated compound to mice would inhibit the delayed-type hypersensitivity (DTH) immune response. Cyclosporin A was used as the control. Significant suppression of the DTH response was demonstrated over the course of the study. With the help of fluorescence spectroscopy, the *in vitro* study also proved the inhibitory effect of artemisinin on calmodulin, a regulatory protein activating T lymphocytes [91].

Anti-inflammatory effect

In 2015, a randomized, double-blind clinical trial was conducted at the University of Otago and Dunedin School of Medicine in Dunedin, and Promisia Integrative Limited in Wellington (New Zealand) that assessed the safety and anti-inflammatory effectiveness of an *A. annua* extract. The study was sponsored by Promisia Ltd., the company producing the preparation "Arthrem" containing 150 mg of *A. annua* extract. The extract is obtained by extracting the herb of the plant using supercritical CO_2. The preparation is recommended for pain and stiffness occurring in the course of osteoarthritis of the hip or knee joints. As part of the experiment, 42 patients were randomly assigned to three groups. Patients in the first group received "Arthrem" at a dose of 150 mg of *A. annua* extract twice a day, those in the second group "Arthrem" at a dose of 300 mg of *A. annua* extract twice a day, while patients in the third group constituted the control and received a placebo twice a day. The study lasted 12 weeks, and the

effectiveness of the extract was assessed using the Western Ontario indicator, McMaster University of Osteoarthritis (WOMAC), and the visual analogue pain scale (VAS). Significant improvement in the WOMAC score was observed among the patients receiving the lower dose (150 mg) of the extract. The patients declared improvement in physical fitness and reduction in joint stiffness, and on the VAS, a reduction in pain. The lower dose was also well tolerated. Using the higher dose of the extract (300 mg), there was no significant improvement in the indicators tested. The authors of the study proved that a 3-month treatment with the *A. annua* extract (150 mg) can reduce inflammation and have an analgesic effect in osteoarthritis [92].

Other studies were conducted at the Institut des Sciences de la Vie & UCLouvain in Louvain-la-Neuve (Belgium) and CPQBA UNICAMP in Paulinia (Brazil). In the first stage, aqueous extracts were prepared from *A. annua* leaves. Then, their effect on Caco-2 cells (human colon adenoma cell line) was investigated [59]. Caco-2 cells are able to form a brush border (microvilli) on the cell surface. They also have the ability to produce enzymes and systems that transport compounds from the intestinal lumen to the bloodstream [96]. In the study, the inflammation of Caco-2 cells was induced with cytokines and lipopolysaccharide. The effect of leaf extracts from the plant on the activity of cytochrome P450, which affects the metabolism of artemisinin, was also investigated. It was proven that the use of aqueous extracts from *A. annua* leaves reduced the secretion of proinflammatory cytokines, interleukin-8, and interleukin-6. This effect was attributed to the presence of rosmarinic acid in the extract. The extracts also inhibited calcitriol-induced activity of CYP3A4 and benz-α-pyrene-induced activity of CYP1A1. The results indicate that extracts from *A. annua* leaves have an anti-inflammatory effect and can increase the bioavailability of artemisinin by inhibiting cytochrome P450 [59].

Analgesic effect

In 2013, the analgesic activity of essential oil obtained from *A. annua* herb was evaluated at the University of Niš in Niš (Serbia). For this purpose, a writhing test was performed using an animal model (mouse). The essential oil and some of its components (camphor, 1,8-cineol, and α-pinene) were given to rodents separately. The writhing reflex was induced by the administration of acetic acid, which is used in studies of inflammatory peripheral pain. It was proven that all the tested compounds and the essential oil produced an analgesic effect that was dose dependent. At the highest tested dose of 400 mg/kg, a 57% reduction in writhing episodes was recorded after administering the essential oil, a 64% reduction after administering camphor, a 54% reduction after administering 1,8-cineol, and a 39% reduction after administering α-pinene [68].

Antioxidant effect

A study confirming the antioxidant properties of *A. annua* have been conducted at the University of Sargodha in Sargodha, University of Karachi in Karachi (Pakistan) and Universiti Putra Malaysia in Selangor (Malaysia). The extracts used for the experiment were obtained from *A. annua* leaves using hexane, chloroform, ethyl acetate, methanol, and water. The extracts were tested to determine which of them would be the most effective. The oxidation potential of individual extracts was assessed by estimating the total concentrations of phenols and flavonoids by determining the degree of lipid peroxidation, and by conducting the iron (III) reduction potential test (FRAP), DPPH radical scavenging activity test, and a test with vitamin E analogue, trolox, used to measure the total antioxidant potential of a mixture of antioxidant compounds (TEAC). The highest antioxidant activity was proven for the methanolic extract, while the aqueous extract was the weakest. The highest amounts of phenols (134.5 mg/g of extract) and flavonoids (615 mg/100 g of extract) were also extracted using methanol [93].

The DPPH test has also been performed at King Abdullah University of Science and Technology in Thuwal (Saudi Arabia), Research and Development, Qatar Foundation in Doha (Qatar) and at Kuwait University in Kuwait City (Kuwait). Leaves were collected from *A. annua* plants in Jericho and Egypt and extracted with hexane, chloroform, methanol, and water. The results of the study indicate that plants growing in Jericho have higher antioxidant activity, while extracts from plants collected in Egypt do not show any such activity [44].

Researchers at the University of Niš in Niš (Serbia) have also evaluated the antioxidant activity of the essential oil from *A. annua* herb and its components (1,8-cineol, artemisia ketone, and α-pinene). A test involving DPPH and the ABTS radical was carried out, as well as a hydrogen peroxide scavenging test. Artemisia ketone and the essential oil proved to be the most active. The antioxidant potential of the oil and all the tested compounds was, however, significantly lower than the antioxidant potential of the control compounds – butylated hydroxytoluene and quercetin. The authors of the study stated that the *A. annua* essential oil did show antioxidant activity, but it was weak [68].

Nephroprotective effect

The University of Niš in Niš (Serbia) was also the place where the effect of essential oil from *A. annua* herb on kidney damage in rats, caused by carbon tetrachloride, was evaluated. Urea and creatinine levels were the parameters determining the renal function. In the group of rats given carbon tetrachloride and essential oil (test group), the concentration of both urea and creatinine was significantly lower than in the group of rats given carbon tetrachloride alone (control group). The nephroprotective effect was also confirmed by histopathological examination of the rodents' kidneys, which showed a reduction in damage among the rats treated with *A. annua* essential oil [68].

Anticancer effect

Researchers from Gyeongsang National University in Jinju and Dong-eui University in Busan (South Korea) have evaluated the antitumour and, in particular, anti-metastatic activity of polyphenols isolated from *A. annua* herb and roots in an *in vitro* experiment on MDA-MB-231 cells (breast cancer cell line). The study examined the effect of the isolated polyphenols on the adhesion of cancer cells to endothelial cells and on the epithelial-mesenchymal transition (EMT) [53]. EMT is a process in which fixed and polarized epithelial cells transform into cells with a mesenchymal phenotype, which can lead to tissue fibrosis as well as invasion and metastasis of cancer cells [97].

The results of the study proved that the polyphenols contained in *A. annua* inhibited the adhesion of MDA-MB-231 cells to endothelial cells. Invasion of tumour cells activated by tumour necrosis factor was also inhibited by, among others, suppression of the EMT transition. The authors of the study indicated that the polyphenols isolated from *A. annua* could be a good agent for inhibiting tumour metastasis [53].

At the Johannes Gutenberg University in Mainz and the Clinic for General Medicine in Hirzacker (Germany), a study was conducted to determine the effect of an *A. annua* extract on prostate cancer. It was based on the immunohistochemistry of tumour material taken from a patient suffering from prostate cancer who had undergone treatment with a preparation containing a concentrate with the *A. annua* extract and a preparation with bicalutamide. The results obtained were compared with the results of immunohistochemistry on two prostate cancer cell lines (PC-3 and DU-145). The results of the study indicate that long-term treatment with the *A. annua* extract in combination with short-term use of bicalutamide causes significant regression of an advanced stage of metastatic prostate cancer [94].

At the People's Hospital of Zhengzhou University and Henan Province People's Hospital in Zhengzhou (China) tests were performed to determine whether dihydroartemisinin (DHA) influences the development of human osteosarcoma cells (cell lines of various malignancy – MG63, U2OS, 143B, and Saos2). The results of the work showed that all the lines were sensitive to DHA. In addition, the line with the highest malignancy (143B) was found to be the most sensitive to DHA. DHA significantly reduced the proliferation of cells of the 143B line and directed them towards apoptosis [58].

In vitro tests for the evaluation of cytotoxic activity of *A. annua* have also been carried out at King Abdullah University of Science and Technology in Thuwal (Saudi Arabia), Research and Development, Qatar Foundation in Doha (Qatar), and at Kuwait University in Kuwait City (Kuwait). Extraction of *A. annua* leaves collected in Jericho and Egypt was carried out with hexane, chloroform, methanol, and water. The experiment was performed on a human breast adenocarcinoma cell line, human lung cancer line, and on the Chinese hamster ovary cell line using Alamar Blue assay and lactate dehydrogenase test. A significant decrease in cell viability (cytotoxic effect) was exhibited by the methanolic extract from the plants collected in Egypt, in contrast to extracts from *A. annua* leaves from Jericho. The activity of the aqueous extract from the plants from Egypt and the activity of other solvents were not significant [44].

Action in obesity treatment

The potential role of *A. annua* in the treatment of obesity has been investigated by researchers at Hoseo University in Asan and Konkuk University School of Medicine in Chungju (South Korea). They investigated whether the essential oil from the plant had an effect on cell differentiation of the murine 3T3-L1 preadipocyte line. The oil reduced the accumulation of lipid droplets and the expression of obesity-related proteins such as PPARγ (receptor activated by peroxisome proliferators), C/EBPα (proteins that bind to the CCAAT sequence), SREBP-1c (protein that binds to the 1c sterol regulatory element), FAS (fatty acid synthase), and ACC (coenzyme A carboxylase) [43].

In 2016, researchers from the University School of Medicine, Gyeongnam Oriental Medicinal Herb Institute, Gyeongnam National University of Science and Technology, Shinseon F&V Co. in Gyeongam, and from the Ministry of Food and Drug Safety in Busan (South Korea) investigated the activity of an *A. annua* leaf extract in preventing obesity in mice. The leaves of the plant were extracted with 80% ethanol (a hydro-ethanolic extract). The extract from *A. annua* leaves was administered to the study group of mice that were fed a high-fat diet for 12 weeks. The results of the work proved that the hydro-ethanolic extract from the leaves of the plant reduced insulin resistance and limited liver steatosis. The concentrations of SREBP-1c, ChREBP (carbohydrate regulatory element binding protein) and cyclooxygenase-2 (COX-2) involved in inflammatory processes were found to have decreased. Increases in the levels of transforming growth factor β1 (TGF-β1) and connective tissue growth factor were also inhibited, which weakened the liver fibrosis process [56].

Importance in Veterinary Medicine

Researchers from the Instituto de Investigação Agrária de Moçambique in Maputo (Mozambique), the Appalachian Farming Systems Research Center in Beaver, the National Soil Erosion Research Laboratory in West Lafayette, the US Salinity Laboratory in Riverside (United States), and the Brazilian Agricultural Research Corporation in São Carlos (Brazil) have tested extracts from *A. annua* against *Haemonchus contortus* (a parasite of mainly in sheep and goats). The scientists extracted *A. annua* leaves with water, 0.1% sodium bicarbonate solution, dichloromethane, and methanol. Artemisinin was then isolated from the extracts obtained. The highest amount of it was confirmed in the dichloromethane extract (9.8%). *In vitro* tests included the egg hatching test (EHT), in which all the extracts were used, and the larval development test, in which only the bicarbonate extract was used. The results of both studies showed that extracts from *A. annua* inhibit the development of parasites, as they reduce the number of hatched eggs and inhibit the development of larvae. The EHT study demonstrated higher activity of the bicarbonate extract. In a subsequent stage of the study, *H. contortus*-infected sheep were orally given the bicarbonate extract from *A. annua* leaves and pure artemisinin. The number of parasite eggs per gram of animal faeces was then counted. Both the extract and artemisinin proved ineffective. The authors of the study concluded that poor bioavailability of artemisinin and the compounds contained in the extract could have contributed to this outcome [48].

Applications in Cosmetology

A. annua is used not only by the pharmaceutical industry but also by the cosmetics industry. The European CosIng (Cosmetic Ingredients) database [98] informs that *A. annua* is a species authorized for use in 12 forms. These are agents for the protection and care of the skin and hair, and antibacterial, antioxidant, masking, fragrant, anti-dandruff, moisturizing, and softening substances (▶ **Table 4**). For their production, mainly *A. annua* herb extract or essential oil is used, as well as the filtrate obtained after fermenta-

▶ **Table 4** Applications of *A. annua* in cosmetology as recommended by the CosIng database.

Name in CosIng	Description	Application profile
Artemisia annua (leaf/stem)/*Ficus carica* fruit/*Ginkgo biloba* leaf extract	extract of leaves and stems of annual mugwort, fig fruit, and ginkgo biloba leaves	skin care agent
Artemisia annua callus extract	extract from annual mugwort callus cultures	antibacterial agent, antioxidant substance, skin care agent, hair care agent, skin protection agent
Artemisia annua extract	mugwort herb extract	masking agent
Artemisia annua herb oil	essential oil of *A. annua* herb	fragrance
Artemisia annua leaf extract	mugwort leaf extract	anti-dandruff agent, antibacterial agent, fragrance, skin care agent
Artemisia annua leaf/stem extract	extract of leaves and stems of annual mugwort	skin care agent
Artemisia annua meristem cell extract	extract from meristematic cells of annual mugwort	antioxidant
Artemisia annua oil	essential oil obtained from annual mugwort herb	antioxidant, emollient, humectant, hair care agent
Artemisia annua seed extract	extract of annual mugwort seeds	antioxidant
Artemisia annua/*Citrus junos* fruit/*Pinus densiflora* leaf extract	extract from annual mugwort, *C. junos* (yuzu) fruit and *P. densiflora* pine leaves	skin protection agent
Aspergillus/apricot kernel/*Artemisia annua*/*Aquilaria agallocha* stem/*Elettaria cardamomum* seed/*Cordyceps sinensis*/*Hericium erinaceum*/*Polyporus umbellatus*/wheat flour/*Xanthium strumarium* fruit ferment extract filtrate	filtrate of product obtained by fermentation of apricot kernels, annual mugwort herb, *A. agallocha* stalks, *E. cardamomum* seeds, *C. sinensis* fungus, *H. erinaceum* fungus, whole *P. umbellatus*, wheat flour, and turnip fruit by fungi of the genus *Aspergillus*	emollient
Bacillus/apricot seed/*Artemisia annua* extract/*Phaseolus angularis* seed/soybean seed/wheat bran/*Xanthium strumarium* fruit extract ferment extract	extract of product obtained by fermentation of apricot seeds, annual mugwort extract, azuki bean seeds, soybean oil, wheat bran and turnip fruit by *Bacillus* bacteria	skin care agent
Lactobacillus/*Leuconostoc*/*Artemisia annua* extract/polysorbate 80 ferment lysate filtrate	lysate filtrate of product obtained by fermentation of extract from annual mugwort and polysorbate 80 by *Lactobacillus* and *Leuconostoc* bacteria	skin care agent

tion of the leaves by microorganisms such as *Lactobacillus* spp., *Aspergillus* spp., *Bacillus* spp., and *Leuconostoc* spp.

The *A. annua* species is used as an ingredient in skincare cosmetics such as shampoos, essences, serums, hand and eye creams, masks, lotions, and tonics. These products are effective in moisturizing the skin of the hands, head, face, and the whole body. They also have a protective and cleansing effect.

Cosmetics that have *A. annua* in their composition can be found in the offers of many foreign companies operating in Europe, Asia, and North America. In Europe, they are German (e.g., *Curamisia*) and Swiss (e.g., *Kingnature*) companies, while in North America they are American companies (*Aromahealth* and *Celvos*). Products containing *A. annua* are also offered by South Korean producers (*Farmgrain, Missha, Neogen, KB Cosmetics*, and *d'Alba Piedmont*, among others).

Applications in the Food Industry

The green parts of *A. annua* are consumed as a vegetable. The species is also used as a source of green dye and as an ingredient in vermouths [8, 29].

Safety of Use

A. annua can cause inflammation of the skin, and due to its highly allergenic pollen, allergies may develop in susceptible people. Documented side effects experienced after using extracts of the herb are abdominal pain, bradycardia, diarrhoea, nausea, vomiting, decreased appetite, flu-like symptoms, reticulocytopenia, and fever. Consumption of preparations with *A. annua*, such as antimalarial drugs, taken in small doses for a short time should not cause side effects. The use of preparations based on this species is contraindicated in patients with ulcers and gastrointestinal disorders [29, 99, 100].

Artemisinin and its derivatives used in malaria are well tolerated, however, they can cause gastrointestinal disorders, dizziness, tinnitus, and bradycardia. The most serious side effect are type 1 hypersensitivity reactions [101, 102]. The EFSA (European Food Safety Authority) lists *A. annua* leaves as a raw material that is not health-neutral due to the high concentration of camphor (2.58–37.5%) in the composition of the oil [103].

Summary

A. annua, a species that has become famous around the world in connection with the 2015 Nobel Prize for discovering artemisinin

in its composition and proving its antimalarial activity, having the status of a pharmacopoeial species in China and Vietnam and having a monograph published by WHO, is currently still a subject of phytochemical and pharmacological research.

Research on the chemical composition has proved the presence in the species (in the leaves and herb) of mainly a number of specific sesquiterpene lactones, essential oil, flavonoids, coumarins, and phenolic acids.

Modern pharmacological studies of the herb and/or leaf extracts and/or the essential oil have proven their antiprotozoal (not only against *Plasmodium* spp.), antibacterial, antifungal, immunosuppressive, anti-inflammatory, analgesic, antioxidant, anticancer, and nephroprotective activities. Some of these professionally proven activities confirm the medicinal properties of this species that have been known for a long time. The novelty is primarily the proven antioxidant, anti-inflammatory, analgesic, and nephroprotective activities.

Interestingly, this species has become an object of special interest of the cosmetics industry in Europe, North America, and East Asia. In the European CosIng (Cosmetic Ingredients) database, this species appears in as many as 12 forms that are possible for cosmetic applications.

The food industry treats the species as a vegetable, an ingredient of vermouths, and a source of dye.

A review of the scientific literature on the species shows that this seemingly well-known and tested medicinal plant can, thanks to the use of modern research methodology in the fields of phytochemistry and pharmacology, be a source of new discoveries regarding its chemical composition and can be used in previously unknown areas of medicinal and paramedicinal applications.

Contributors' Statement

Data collection: H. E., J. Ś., P. K., A. R., and A. S.; design of the study: H. E.; analysis and interpretation of the data: H. E., J. Ś., P. K., A. R., and A. S.; drafting the manuscript: H. E., J. Ś., P. K., A. R., and A. S.; critical revision of the manuscript: H. E. and A. S. All authors read and approved the manuscript in its final form.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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