Edible Artemisia: Health Effects

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The *Artemisia species*, often known collectively as "wormwood" are herbs and shrubs, which could be perennial, biennial and annual plants, distributed on all continents except Antarctica, mainly on Northern Hemisphere, with only 25 species on the Southern Hemisphere, being the Asian the zone where higher species diversity is concentrated. The use of *Artemisia* species in traditional medicine is well-documented and demonstrates the great ethnopharmacological value of this genus. In addition to the traditional medicine applications, *Artemisia* species exhibit high food value since many of them are species used in culinary as a food, spices, condiments and beverages flavoring.

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1. Introduction

Artemisia genus (Asteraceae family) comprise more than 2290 plant name records in the "The Plant List" database, being only 530 of these taxa with accepted Latin botanical name [1], which shows how challenging the taxonomy of this genus is. The *Artemisia* species are herbs and shrubs, which could be perennial, biennial and annual plants, distributed on all continents except Antarctica, mainly on Northern Hemisphere, with only 25 species on the Southern Hemisphere [2], being the Asian the zone where higher species diversity is concentrated [3][4]. They exhibit a great ability to grow on different ecosystems from the sea level to the mountains and from arid areas to wet regions, but the majority of the species live on temperate zones [2]. Some *Artemisia* species exhibit so high ability to adapt to new habitats that they become invasive species in these environments, posing a significant threat to biodiversity [5][6].

The use of *Artemisia* species in traditional medicine is well-documented [7][8][9][10][11][12][13][14][15][16][17] and demonstrates the great ethnopharmacological value of this genus. *Artemisia annua* L. and *Artemisia absinthium* L. are the best known for their uses in traditional medicine around of the World. For example, *A. annua* is cited in several ancient books as being suitable for the treatment of consumptive fever, jaundice, summer heat wounds, tuberculosis, lice, scabies, dysentery, and hemorrhoids in addition to pain relievers, while in Iran is used as antispasmodic, carminative, or sedative remedy for children [9][16][18]. In turn, *A. absinthium* has been traditionally used to treat mainly gastrointestinal diseases and as anthelmintic although for example in Italy it is also used as an antiparasitic, antihypertensive and anti-inflammatory, while in France it is also used to stimulate appetite, as an antipyretic, and emmenagogue [17][19]. However, many other species are used on each continent. For example, *Artemisia afra* Jacq. ex Willd. is one of the most widely used herbal remedies in South Africa to treat inflammation and pain [20]. It is also used to treat various ailments including coughs, colds, asthma, fever, influenza, diabetes and malaria [20], and by certain South African traditional healers to treat rhinitis [21]. *Artemisia dracunculus* L. is widely used in North America, for example by the Chippewa and Costanoan Indians as abortifacient and medicine to treat chronic dysentery, heart palpitations, wounds, colic in babies, and also to strengthen hair and make it grow [22]. In the Iranian Traditional Medicine *A. vulgaris* is used to treat cervicitis [23], while this species is reported in the ethnobotany of Karok, Kiowa, Miwok Paiute, Pomo and Tlingit areas, as a drug with several applications such as in childbirth, steam bath for pleurisy, gonorrheal sore, cold, rheumatism, headache, a ‘worm’ medicine, pains of afterbirth [24]. The traditional use of *Artemisia* species in Europe is mainly as food, spices and beverages (discussed in more detail below). However, *Artemisia* species are also used in the treatment of various diseases, as for example *Artemisia umbelliformis* Lam. and *Artemisia genipi* Weber ex Stechm. also known as Alpine wormwoods and génépis species, that are used traditionally to fight cold fever, fatigue, dyspepsia and respiratory infections, as wound-healing agents and to treat bruises, while wines aromatized with these species stimulate appetite, promote digestion, and fight the mountain sickness [10].

Even some *Artemisia* species less scientifically known such as *Artemisia ordosica* Krasch, have significant ethnomedicinal applications. This species was recorded on the traditional Mongolian and Chinese medicine books, as having a beneficial effect on the nasal bleeding, rheumatoid arthritis, headache, sore throat and carbuncle [25] and was used by Mongolian "barefoot" doctors for nasosinusitis treatment [26]. *Artemisia tripartita* (Nutt.) Rydb. was reported on

Native American Ethnobotany database [27] as diaphoretic and remedy to treat cold and sore throats, while *Artemisia verlotiorum* Lamotte, distributed in all northern hemisphere, is used in Tuscany folk medicine to treat hypertension [28], and to alleviate stomach problems in Gilgit-Baltistan, Pakistan [29].

Artemisia species, as well as other herbal medicines, with proven pharmacological effects has been incorporated into conventional medicine. This incorporation is supported by the world health organization, which considers that traditional and complementary medicine can make a significant contribution to the goal of achieving universal health coverage by being included in the provision of essential health services [30]. Nevertheless, international research into traditional herbal medicines should be subject to the same ethical and methodological requirements as all research involving humans. Therefore, criteria to promote the safety, quality and effectiveness of the plants used in traditional medicine have been discussed and established [31][32].

Encouraged by this wide application in traditional medicine, the scientific community has dedicated itself to investigating in each *Artemisia* species evidence to support these applications. The result of this vast investigation showed the *Artemisia* species (extracts and essential oils) as exhibiting antiparasitic, anticancer and anti-inflammatory action in addition to antioxidant, wound healing, antinociceptive, immunoregulation, hepatoprotective, neuroprotective, anti-asthmatic, antidiabetic, antihypertensive, anti-adipogenic, anti-ulcerogenic, antiviral, antibacterial, antifungal, and anti-osteoporotic activities [10][11][12][13][18][19][33][34][35][36][37][38][39].

The search for bioactive compounds responsible for these biological activities has led to *Artemisia* species are privileged sources of compounds with highly diversified structures that exhibit a high level and diversity of biological activities, providing the basis for the development of new drugs, some of which are already used in clinical therapeutics [4][8][10][13][40][41][42][43][44][45][46][47].

The *Artemisia* secondary metabolites belong to the several organic compounds families [44][47][48][49] such as terpenoids [14][44], mostly monoterpenes in essential oils [31][44] and sesquiterpene lactones [40][41][50], flavonoids [14][46][51][52], lignans [52][53][54][55], alkaloids [56], steroids [14][57], phenolic acids [37][47][58] and coumarins [14][53][59], all of them well known for their large range of biological activities.

Given the large number of papers published on the theme of health effects of products related to *Artemisia* species all publications related to in vitro studies were excluded from this review.

2. Use of *Artemisia* Species as Food, Spices, Condiments and Beverages

In addition to the traditional medicine applications, *Artemisia* species exhibit high food value since many of them are species used in culinary. The most extensive use of *Artemisia* species as food is found in the countries of Europe, Asia (Japan, Korea, China and India) as well as in North America.

Table 1. Application of *Artemisia* species as food, spices, condiments and beverages.

Species	Common Name	Distribution *	Edible Part	Use	Ref.
Artemisia abrotanum L.	Southernwood	S. Europe	Young shoots	Flavoring cakes, salads and vinegars; herb tea	[60][61][62][63][64][65]
A. absinthium	Mugwort, common wormwood, absinthe	Europe, Asia	Herb	Spice; flavoring beer, wine, vermouth, absinthe, liquors and aperitifs; pelinkovac	[60][61][62][65][66][67][68][69][70][71][72]
A. afra	African wormwood	Africa	Herb	Flavoring; preparation of vermouth; as a tea	[60][61][62][63][64][65][66][67]

Artemisia alba Turra (syn. *A. camphorata* Vill.)	Camphor absinthe	S. Europe, C. Europe, N.W. Africa	Herb	Spice and flavoring	[60]
A. annua	Qing Hao, Sweet sagewort	S.E. Europe to W. Asia.	Leaves	Essential oil in the leaves is used as a flavoring in spirits such as vermouth; as a vegetable	[67]
Artemisia arborescens (Vaill.) L.	Silver wormwood	N. Africa, S. Europe	Herb	Spice added to the green tea prepared by Moroccans	[60][65][67]
Artemisia argyi H. Lév. & Vaniot	Aicao, Gaiyou, Seomae mugwort	N. Asia, N. Europe, N. America	Leaves, buds, herb	As a tea or other forms of food supplements; dried leaves as a flavoring and colorant for the Chinese dish Qingtua	[46][73]
Artemisia balchanorum Krasch.		Turkmenia	Herb	Spice; potherb	[60]
Artemisia capillaris Thunb.	Yin Chen Hao	E. Asia—China, Japan, Korea	Leaves, stems, shoots	Soaked and boiled eaten as food supplements in times of famine	[67][74]
Artemisia carvifolia Buch.-Ham. ex Roxb.		E. Asia—China, Japan, Himalayas	Leaves	Flavoring for tea and coffee; Young plants—cooked in the spring	[67]
Artemisia dracunculoides Pursh.	Russian Tarragon, Tarragon, French Tarragon	N. America. N. Europe. N. Asia—Siberia	Leaves, seeds	Leaves—raw in salads; The N. American Indians bake the leaves between hot stones and then eat them with salt water; Seed—raw or cooked as an oily texture.	[62][67][68][75]

A. dracunculus	Tarragon, French Tarragon	S. Europe to W. Asia.	Leaves, young shoots	Leaves—raw or used as a flavoring in soups, oily foods, salads, vinegar, etc.; The young shoots can also be cooked and used as a potherb	[60][62][63][66][67][70][76]
Artemisia frigida Willd.	Fringed Wormwood, Prairie sagewort	N. America, N. Asia.	Leaves	The leaves are used by the Hopi Indians as a flavoring for sweet corn	[68][76]
A. genipi.	Genepi, black wormwart, black wormwood, génépi noir	S. Europe	Leaves, flower heads	Spice, flavoring for liqueurs	[10][60][61][66][67]
Artemisia glacialis L.	Glacier wormwood	C. Europe	Herb, flower heads	Flavoring in vermouth and liqueurs	[10][60][61][67]
Artemisia granatensis Boiss.		Spain	Herb	Herb tea	[77]
Artemisia herba-alba Asso		Africa, Mediterranean area	Herb	Herb tea; Flavoring tea and coffee	[78]
Artemisia indica Willd.		E. Asia—China, Japan, India.	Leaves	Young leaves—cooked and eaten with barley; the leaves pounded with steamed rice dumplings to give a flavor and coloring	[60][70]
Artemisia japonica Thunb.		E. Asia—China, Japan, Korea.	Young leaves	Raw as a vegetable or cooked	[70]
Artemisia keiskeana Miq.		E. Asia—China, Japan, Korea, E. Russia.	Leaves, shoot tips	Cooked	[67]
Artemisia ludoviciana Nutt.	White Sage, Louisiana Sage, Prairie Sage, Western Mugwort	N. America	Leaves, flowering heads	Flavoring or garnish for sauces, gravies, etc.; Used like absinthe; herb tea	[60][61][67][75][76]

Artemisia maritima L.	Sea Wormwood	Europe, E. Asia, C. Asia.	Leaves	Spice; flavoring in some Danish schnapps, beer and liqueurs	[60][61][67]
Artemisia montana (Nakai.) Pamp.		E. Asia—China, Japan.	Leaves	Young leaves—cooked; herb tea	[79]
Artemisia pallens Wall. ex DC.	Davana	N.E. India, Thailand	Herb	Spice; flavoring for cakes, pastries, candy, chewing gum, ice cream, beverages, tobacco; for production of essential oil (davana oil)	[60][61][67]
Artemisia pontica L.	Roman wormwood; Small absinthe	S.E. Europe to Siberia, C. Asia	Leaves, herb	Spice, flavoring, like *A. absinthium*	[60][61][66][67]
A. princeps	Mugwort mochi, Yomogi	E. Asia—China, Japan, Korea.	Leaves, young seedlings	Raw or cooked in salads and soups; for flavoring and coloring of rice dumplings (‘mochi’)	[60][67][80]
Artemisia schmidtiana Maxim.	Sagebrush, Silvermound, Wormwood, Mugwort	E. Asia—Japan.	Stems	Cooked; for flavoring and coloring of rice dumplings (‘mochi’)	[78][80]
Artemisia sphaerocephala Krasch.		China	Seed	Seed powder added to noodles and other traditional Chinese foods to improve sensory qualities such as elasticity and chewing quality	[81]
Artemisia tilesii Ledeb.	Wormwood, Tilesius’ wormwood	E. Asia, N.W. America.	Leaves, shoots	The fresh shoots are peeled and eaten, usually with oil; Flavoring rice dumplings	[67]

Artemisia tridentata Nutt.	Sage Brush, Big sagebrush, Bonneville big sagebrush	N. America	Leaves, seeds	Leaves—cooked, as a condiment and to make a tea with sage-like flavor; Seed—can be roasted then ground into a powder and mixed with water or eaten raw	[61][75][76]
A. umbelliformis (syn. *A. mutellina* Vill.)	Alpine Wormwood	Europe—Alps, N. Apennines	Herb, leaves, flower heads	As a condiment; preparation of a tea and a liqueur, often with the addition of absinthe	[10][60][66][67][82]
Artemisia vallesiaca All.	Alpine Wormwood, Valais wormwood	Europe—N. Italy, Switzerland, S. E. France	Herb	Flavoring for liqueurs; product of santonin	[10][60][66]
A. vulgaris	Mugwort, Common wormwood, Felon Herb, Chrysanthemum Weed, Wild Wormwood	Temperate regions of Europe and Asia	Leaves, young shoots, flowering tops	Flavoring fatty foods; to give color and flavor to rice dumplings (‘mochi’); as a potherb; flavoring in beer and liqueurs	[60][61][66][67][70][71][80]
Artemisia wrightii A. Gray.		N. America	Leaves, seeds	Raw or cooked—an oily texture; Seed—ground with water, made into balls and steamed	[75]

The flavoring use of an *Artemisia* species is worldwide and especially of *A. dracunculus* (French tarragon, German tarragon, true tarragon or estragon) and closely related *A. dracunculoides* (Russian tarragon). Additionaly, many *Artemisia* species are applied in the preparation of different non-alcoholic beverages, giving them a bitter taste and alleged tonic properties. Thus, *A. absinthium*, *A. abrotanum*, *A. agryi*, *A. ludoviciana*, *A. montana*, *A. tridentata*, *A. granatensis*, etc. are consumed as herbal tea with digestive properties. Silver wormwood (*A. arborescens*) and *A. herba-alba* are added to the green tea or the coffee in North Africa [67][78] and *A. carvifolia* has the same use in Asia [67]. Tarragon (*A. dracunculus*) is an ingredient of Georgian carbonated soft drink called *Tarkhuna* [75]. *A. maritima*, *A. abrotanum*, *A. absinthium, A. vulgaris*, etc. (Table 1) have been applied as a flavoring ingredient in beer production before the common application of hops.

Undoubtedly, the most famous *Artemisia* species employed in alcoholic drinks is *A. absinthium*, among which two are most noteworthy: vermouth and absinthe. Vermouth is a low alcoholic drink prepared from wine and a cocktail of botanical ingredients with *A. absinthium* as a principal component [83]. There are similar drinks in some countries of the Balkan Peninsula—pelin in Bulgaria [84] and vin pelin in Romania [85]. The spirit drink absinthe was created in French-speaking Switzerland in the late eighteenth century [86] and is produced by macerating *A. absinthium* leaves, anise and fennel seeds in alcohol (85 vol%) [87][88]. Wormwood (*A. absinthium*) is also used for the preparation of a bitter liqueur with lower content of alcohol (28–35 vol%) called pelinkovac (pelinkovec, pelinovec, pelen or pelin) and popular in Croatia, Serbia, Montenegro, Bosnia-Herzegovina, North Macedonia as well as in Slovenia [71].

Another popular herbal liqueurs in which *Artemisia* species present are genepy or génépi (*A. genipi* and related taxa such as *A. glacialis* and *A. umbelliformis*) [10] and ratafia (*A. abrotanum*, *A. absinthium*, *A. arborescens* and *Artemisia chamaemelifolia* Vill. [65].

3. Nutritional Value of *Artemisia* Species

As demonstrated above *Artemisia* species are widely consumed by human as a traditional food, a tea and dietary supplements, owing to the fact that they are rich in fatty acids, carbohydrates, dietary fiber, protein, essential amino acids, vitamins and minerals as demonstrated in Table 2.

Table 2. Nutritional composition of some edible *Artemisia* species.

Plant Species	Plant Part	Nutrient Composition *	Ref.
A. absinthium	Oil cake **	Sugars (9.4%)	[89]

Plant Species	Plant Part	Nutrient Composition *	Ref.
A. annua	Leaves	Protein (27.1%); TAA (27.6%), EAA (16.1%), NEAA (11.5%); Crude fat (8.34%); Minerals: K (26.3 mg/g DM), Ca (11.5 mg/g DM), Mg (7.1 mg/g DM), P (7.1 mg/g DM), S (3.9 mg/g DM), Fe (0.2 mg/g DM), Mn (0.2 mg/g DM), Zn (0.06 mg/g DM); Vitamin A (<0.3 µg/100 g DM); Vitamin E (22.63 mg/kg)	[90]
	Inflorescence	Protein (18.4%); Crude fat (10.5%); TAA (18.3%), EAA (10.14%), NEAA (8.11%); Minerals: K (24.6 mg/g DM), Ca (4.4 mg/g DM), Mg (2.3 mg/g DM), P (3.4 mg/g DM), S (4.6 mg/g DM), Fe (0.2 mg/g DM), Mn (0.3 mg/g DM), Zn (0.06 mg/g DM); Vitamin A (<0.3 µg/100 g DM); Vitamin E (19.38 mg/kg)	
	Stems	Protein (10.7%); Crude fat (2.60%); TAA (10.3%), EAA (5.91%), NEAA (4.38%); Minerals: K (13.3 mg/g DM), Ca (0.9 mg/g DM), Mg (0.9 mg/g DM), P (0.7 mg/g DM), S (0.5 mg/g DM), Fe (0.7 mg/g DM), Mn (0.02 mg/g DM), Zn (0.08 mg/g DM); Vitamin A (<0.3 µg/100 g DM); Vitamin E (1.19 mg/kg)	
	Roots	Protein (8.23%); Crude fat (2.13%); TAA (8.01%), EAA (4.34%), NEAA (3.66%); Minerals: K (11.1 mg/g DM), Ca (11.5 mg/g DM), Mg (7.1 mg/g DM), P (7.1 mg/g DM), S (3.9 mg/g DM), Fe (0.2 mg/g DM), Mn (0.2 mg/g DM), Zn (0.06 mg/g DM) Vitamin A (<0.3 µg/100 g DM); Vitamin E (1.36 mg/kg)	
	Leaves	Protein (24.37 mg/100 g); Crude fat (6.07%); TFA (4.19 mg/g FW), SFA (22.9%), UFA (77.1%), MUFA (8.4%), PUFA (68.7%) Carbohydrates (8%); Fibre (14.2%); Vitamins: Tocopherol (2.74%)	[91] [92]
	Achene	Lipids: SFA (29.21%), UFA (70.87%), MUFA (13.99%), PUFA (56.88%)	[93]
A. arborescens	Leaves	Lipids: TFA (3.31 mg/g FW), SFA (47.4%), UFA (52.6%), MUFA (16.3%), PUFA (36.3%)	[91]

Plant Species	Plant Part	Nutrient Composition *	Ref.
A. argyi	Leaves	Protein (22.0 mg/g FW); Free amino acids: EAA (3.71 mg/g DW), NEAA (2.42 mg/g DW), FAA (6.13 mg/g DW); Total lipid (24.7 mg/g FW); SFA (40.8%), MUFA (7.1%), PUFA (52.1%); Total carbohydrates (52.3 mg/g FW); Dietary fiber (39.9 mg/g FW); Minerals: K (74.22 mg/100 g FW), Ca (14.74 mg/100 g FW), Mg (36.64 mg/100 g FW), Zn (0.89 mg/100 g FW), Cu (0.13 mg/100 g FW), Mn (0.76 mg/100 g FW), Fe (3.15 mg/100 g FW); Vitamin C (total ascorbic acid) 2.09 mg/g DW	[46] [73]
A. austriaca Jacq.	Achene	Lipids: SFA (47.43%), UFA (49.02%), MUFA (9.65%), PUFA (39.37%)	[93]
A. campestris L.	Leaves	Lipids: TFA (10.22 mg/g FW), SFA (21.0%), UFA (79.0%), MUFA (3.6%), PUFA (75.3%)	[91]
	Aerial	Crude protein (115 mg/g DM)	[94]
A. camphorata Vill.	Leaves	Lipids: TFA (14.82 mg/g FW), SFA (37.4%), UFA (62.6%), MUFA (8.3%), PUFA (54.3%)	[91]
A capilaris	Leaves	Lipids: TFA (6.01 mg/g FW), SFA (16.0%), UFA (84.0%), MUFA (4.7%), PUFA (79.4%)	[91]
A. frigida	Aerial	Crude protein (17.9%); Minerals: K (18.34 mg/g DM), Ca (7.46 mg/g DM),P (2.54 mg/g DM), Mg (2.17 mg/g DM), Cu (1.1 mg/100 g DM), Mn (24 mg/100 g DM), Fe (20.0 mg/100 g DM) Zn (1.9 mg/100 g DM); Na (5 mg/100 g DM)	[95]
A. glacialis	Leaves	Lipids: TFA (8.95 mg/g FW), SFA (21.6%), UFA (78.4%), MUFA (6.8%), PUFA (71.6%)	[91]
A. gmellini Weber ex Stechm.	Leaves	Lipids: TFA (14.11 mg/g FW), SFA (25.5%), UFA (74.5%), MUFA (4.5%), PUFA (70.0%)	[91]
A. herba-alba	Aerial	Crude protein (103.4–153.6 mg/g DM); Crude fibre (407.9 mg/g DM)	[94] [96] [97]
A. jacutica Drobow	Leaves	Lipids: SFA (61.21–68.12%), UFA (31.88–38.79%)	[98]
A. ludoviciana	Leaves	Lipids: TFA (14.28 mg/g FW), SFA (19.6%), UFA (80.4%), MUFA (5.3%), PUFA (75.1%)	[91]

Plant Species	Plant Part	Nutrient Composition *	Ref.
A. macrocephala Jaq. ex Bess	Leaves	Lipids: UFA (50.80–65.22%), SFA (34.78–49.20%).	[98]
A. oleandica (Besser) Krasch	Leaves	Lipids: TFA (9.84 mg/g FW), SFA (17.6%), UFA (82.4%), MUFA (4.7%), PUFA (77.7%)	[91]
A. princeps	Leaves	Lipids: TFA (6.49 mg/g FW), SFA (20.2%), UFA (79.8%), MUFA (5.7%), PUFA (74.1%)	[91]
	Leaves	Lipids: SFA (27.5%), MUFA (35.1%), PUFA (37.4%); Free amino acids: EAA (3.19 mg/g DW), NEAA (2.42 mg/g DW), FAA (5.61 mg/g DW); Vitamin C (total ascorbic acid) 1.01 mg/g DW;	[73]
A. santolinifolia Turcz. ex Bess	Leaves	Lipids: SFA (51.8–65.02%), PFA (9.74–44.14%), MFA (4.06–30.85%)	[99]
A. santonicum L.	Achene	Lipids: SFA (43.70%), UFA (56.33%), MUFA (8.26%), PUFA (48.07%)	[93]
A. sieberi Besser	Aerial	Crude protein (55 mg/g DM); Crude fiber (484 mg/g DM); Minerals: K (13.1 mg/g DM), Ca (15.9 mg/g DM),P (2.5 mg/g DM), Mg (1.8 mg/g DM), Cu (1.37 mg/100 g DM), Mn (2.26 mg/100 g DM), Fe (20.0 mg/100 g DM) Zn (21.2 mg/100 g DM)	[100]
A. sieversiana Ehrh. ex Willd	Leaves	Lipids: UFA (64.11–73.23%), SFA (26.77–35.89%)	[98]
A. sphaerocephala	Seed	Carbohydrate (73%)	[101]
A. stelleriana Bess	Leaves	Lipids: TFA (17.78 mg/g FW), SFA (70.2%), UFA (29.8%), MUFA (1.3%), PUFA (28.4%)	[91]
A. tridentata subsp. *wyomingensis* Beetle & A.L.Young	Leaves	Crude protein (15.7%)	[102]
A. vallesiaca	Leaves	Lipids: TFA (5.27 mg/g FW), SFA (17.1%), UFA (82.9%), MUFA (9.3%), PUFA (73.6%)	[91]
A. vulgaris	Leaves	Lipids: TFA (13.32 mg/g FW), SFA (15.2%), UFA (84.8%), MUFA (3.7%), PUFA (81.1%)	[91]

* Free (FAA), essential (EAA) and non-essential (NEAA) amino acids; total (TFA), saturated (SFA), unsaturated (UFA), monounsaturated (MUFA) and polyunsaturated (PUFA) fatty acids; DW—dry weight; FW—fresh weight; DM—dry matter. ** Oil cake remaining after the extraction of essential oil.

4. Therapeutic Uses of *Artemisia* Species Based on Clinical Trials

Encouraged by long traditional use of many *Artemisia* species for treatment of various ailments, research into their pharmacological effects has been carried out and seem to support the traditional applications [5][12][15][16][17]. In this regard, *Artemisia* species and their biologically active compounds have already been introduced as antimalarial, antioxidant, cytotoxic, antispasmodic, anthelmintic, antinociceptive, neuroprotective, anti-inflammatory, and antimicrobial agents, among others [16][44]. It is noteworthy that although *Artemisia* species have been intensively studied in vitro as cytotoxic agents, there are no reports on their clinical evaluation for cancer therapy in humans [4]. However, one report by Saeed et al. showed that supplementing pet food with an *A. annua* formulation (Luparte®) clearly improved survival prognosis in veterinary treatment of small tumors [103].

Nevertheless, clinical evaluations of *Artemisia* species for a range of other diseases have been carried out [4]. The effect of *A. annua* in traditional medicine in China for treating fever, inflammation and malaria [9] have been evaluated in clinical trials for stiffness and functional limitation associated with osteoarthritis of the hip and knee, pain management, experimental heterophyid infection and treatment of malaria [104][105][106].

Artemisia dracunculus has been used for glycemic control, insulin sensitivity, and insulin secretion [107] and likewise, *A. princeps* was evaluated for the same effects in subjects with impaired fasting glucose and mild-type 2 diabetes [108] and *A. absinthium* in the control of diabetes type 2 [109].

Ointments and liniments of *A. absinthium* can be effective in the treatment of knee osteoarthritis [110]. Based on the suppressor activity of *A. absinthium* compounds on tumor necrosis factor alpha (TNF-α) and other interleukins [111], Krebs et al. [112] established the curative effect of this *Artemisia* species in patients with Crohn's disease. There was improvement in symptoms after treatment with dried powder of the plant together with a conventional therapy, and a cardamonin present in the plant was considered responsible for the anti-inflammatory activity.

In addition to being widely used clinically to treat itching in icteric and dialytic patients, owing to its anti-histaminic and anti-allergenic effects, *A. vulgaris* (mugwort) lotion has also provided good results in patients with post-burn hypertrophic scars [113].

Recently, the preventive effect on hepatitis B cirrhosis of *A. capillaris* decoction combined with the entecavir has been evaluate by a randomized, double-blind and placebo controlled clinical trial (Chinese Clinical Trial Registry: ChiCTR1900021521), to assess its efficacy and safety [114].

Artemisia annua and *A. vulgaris* are the species of the genus that produce the highest levels of allergens in their pollen, being one of the main causes of seasonal allergic rhinitis ("hayfever"). Lou et al. [115] carried out a phase III clinical trial (ClinicalTrials.gov identifier: NCT03990272) from March 2017 (approximately 4 months before the local natural *Artemisia* pollen season) to October 2017, involving patients from 13 centres across Northern China. The aim was to test the efficacy and safety of sublingual immunotherapy (SLI) with drops of *A. annua* for allergic rhinitis related to this plant. Results indicated that *A. annua* was a safe and significantly effective therapy. However, longer term follow-up is required, particularly to determine the mechanism of action.

Based in previous study where Xiao et al. [25] demonstrated using in vivo models, the ability of *A. ordosica* Krasch. extracts to control the allergic inflammatory response in rhinitis, clinical trials using nasal spray preparations of *A. abrotanum* containing its essential oils and flavonols have been performed with good results [116].

Munyangi et al. [117] published a randomized controlled clinical trial reporting far superior cure rates of *A. afra* and *A. annua* infusions than with artemisinin combination therapy (artesunate—amodiaquine), in the treatment of malaria. Contrastingly, a recent review by Toit and van der Kooy [15] concluded that tea infusions do not have in vitro activity, and in fact contain no artemisinin. Another randomized large-scale double-blind controlled trial on *A. annua* and *A. afra* tea vs. praziquantel for the treatment of schistosomiasis was documented by Munyangi et al. [118]. Controversially, Gillibert found scientific and ethical issues such as the article on schistosomiasis referring to the same ethics committee registration number as the malaria article [119].

Sensitive skin was initially believed to be an unusual reaction occurring in only a small subset of individuals. However, during recent decades, it has been shown to affect half the population of the world [120]. Accordingly, extensive in vitro, preclinical, and clinical research with artemisinin and its derivatives has been undertaken, notably into their anti-inflammatory, immunomodulatory and antioxidant properties [121]. Yu et al. [122] tested the effectiveness of cosmetics containing *A. annua* extract in repairing sensitive skin. In this study, the xylene-induced ear swelling and human clinical efficacy tests were used, and the authors found that applications containing *A. annua* extract can inhibit inflammation,

repair the skin barrier, improve damaged skin, and reduce redness and other sensitive skin symptoms. Aside from this, its leaves are eaten in salads in some Asian countries and in the United States, and several companies currently sell ground leaves and their extracts as dietary supplements [123].

5. Some Sesquiterpene Lactones Constituents of *Artemisia* Species with High Clinical Relevance

The pharmaceutical industry has always been interested in the secondary metabolites produced by plants, for the treatment of diseases, in cosmetics, dyes, fragrances and flavorings [124]. The *Artemisia* species are well known by its content of sesquiterpene lactones [40][41][43][50]. These family of compounds have been studied and reveal high therapeutic potential [125][126]. Here are presented some of the most studied and promise sesquiterpene lactones constituents of edible *Artemisia* species (does not intent to be an exhaustive list) which, due to its medicinal properties discussed above, could contributes to the benefits effects of the *Artemisia* species. Sesquiterpene lactones such as arglabin parthenolide, cynaropicrin, helenalin, costunolide and thapsigargin identified in species of the genus *Artemisia* [40][41][50][125] and other genera, exhibit high pharmacological potential, including in in vivo studies and clinical trials, as demonstrated and discussed very recently [126]. So, they will not be considered in this work. The most recent and relevant experimental evidence of other sesquiterpene lactones medical potential will be highlighted discussed below. In this selection, was considerate mainly the in vivo and clinical studies, once they are the last steps of new drugs development and their results are the most significant to drug development.

The chemical structures of the selected sesquiterpene lactones discussed below are indicated in the Figure 1.

Figure 1. Chemical structures of some sesquiterpene lactones constituents of edible *Artemisia* sp. and derivatives with pharmacological relevance.

Concerning the *Artemisia* constituents, clinical and in vivo studies involving artemisinin and its derivatives show them as efficient antimalarial and anticancer agents. Additionally, the additive or synergistic interactions of artemisinin and derivatives in combination with a wide array of clinically established drugs to combat different cancer are highlighted. The high therapeutic potential is evident in the WHO proposal to investigate artemisinin and derivatives as well as *A. annua* to the treatment of Covid-19 infection. In addition to artemisinin and its derivatives, other sesquiterpene lactones isolated from different species of *Artemisia*, such as santonin, achillin and tehranolide, have been the target of further studies with a view to the development of new derivatives and their application as medicines. These compounds exhibit very interesting activities, in in vivo models, such as immunosuppressant and anti-inflammatory and potent antinociceptive effect. Achillin acts as a meiotic inhibitor and smooth muscle cell relaxant, properties very relevant to improve human embryonic development in-vitro fertilization procedures and to treat asthma and chronic obstructive pulmonary disease, respectively.

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