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REVIEW ARTICLE

Traditional uses, Phytochemistry, Pharmacology, and Toxicology of the Genus *Artemisia L.* (*Asteraceae*): A High-value Medicinal Plant

Manzoor Hussain[1,#], Rakesh Kr Thakur[2,#], Jabeena Khazir[3], Sajad Ahmed[4], Mohammad Imtiyaj Khan[5], Praveen Rahi[6], Latif Ahmad Peer[7], Pragadheesh Vppalayam Shanmugam[8], Satwinderjeet Kaur[1], Soom Nath Raina[2], Zafar Ahmad Reshi[7], Deepmala Sehgal[9,*], Vijay Rani Rajpal[10,*] and Bilal Ahmad Mir[7,*]

[1]*Department of Botanical & Environmental Sciences, Guru Nanak Dev University, Amritsar, India;* [2]*Amity Institute of Biotechnology, Amity University, Noida, U.P, 201313, India;* [3]*Department of Chemistry, HKM Govt. Degree College Eidgah, Srinagar, J&K, India;* [4]*Department of Plant Biotechnology, Indian Institute of Integrative Medicine, Canal Road Jammu, 180001, J&K, India;* [5]*Department of Biotechnology, Gauhati University, Guwahati, 781014, Assam, India;* [6]*Biological Resources Center, Institut Pasteur, University de Paris, Paris, 75015, France;* [7]*Department of Botany, University of Kashmir, Srinagar, Jammu & Kashmir, 190006, India;* [8]*Analytical Chemistry, CSIR-CIMAP, Research Centre Bengaluru, 560065, India;* [9]*Syngenta, Jeolett's Hill International Research Centre, Bracknell, Berkshire, UK;* [10]*Department of Botany, HansRaj College, University of Delhi, Delhi, 110007, India*

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Abstract: Biologically active secondary metabolites, essential oils, and volatile compounds derived from medicinal and aromatic plants play a crucial role in promoting human health. Within the large family Asteraceae, the genus *Artemisia* consists of approximately 500 species. *Artemisia* species have a rich history in traditional medicine worldwide, offering remedies for a wide range of ailments, such as malaria, jaundice, toothache, gastrointestinal problems, wounds, inflammatory diseases, diarrhoea, menstrual pains, skin disorders, headache, and intestinal parasites. The therapeutic potential of *Artemisia* species is derived from a multitude of phytoconstituents, including terpenoids, phenols, flavonoids, coumarins, sesquiterpene lactones, lignans, and alkaloids that serve as active pharmaceutical ingredients (API). The remarkable antimalarial, antimicrobial, anthelmintic, antidiabetic, anti-inflammatory, anticancer, antispasmodic, antioxidative and insecticidal properties possessed by the species are attributed to these APIs. Interestingly, several commercially utilized pharmaceutical drugs, including arglabin, artemisinin, artemether, artesunate, santonin, and taralin have also been derived from different *Artemisia* species. However, despite the vast medicinal potential, only a limited number of *Artemisia* species have been exploited commercially. Further, the available literature on traditional and pharmacological uses of *Artemisia* lacks comprehensive reviews. Therefore, there is an urgent need to bridge the existing knowledge gaps and provide a scientific foundation for future *Artemisia* research endeavours. It is in this context, the present review aims to provide a comprehensive account of the traditional uses, phytochemistry, documented biological properties and toxicity of all the species of *Artemisi*a and offers useful insights for practitioners and researchers into underutilized species and their potential applications. This review aims to stimulate further exploration, experimentation and collaboration to fully realize the therapeutic potential of *Artemisia* in augmenting human health and well-being.

Keywords: *Artemisia*, Ethnobotany, Phytochemistry, Pharmacological activity, Toxicology, Phytoconstituents.

1. INTRODUCTION

Since ancient times, phytomedicinal products are used as therapeutic agents in structured (Ayurveda, Unani, Siddha) and unorganized (folk, tribal, native) systems of medicine. According to an estimate by World Health Organization (WHO), about 80% of the global population especially in developing countries still relies on traditional herbal remedies [1] due to their easy affordability and perceived safety. As compared to expensive synthetic drugs, the demand for phytomedicinal drugs is growing expeditiously at a rate of 15-25% annually and projections for global herbal trade are set to reach an astounding value of US$5 trillion by 2050 [2]. In India, Ayurveda alone contributes around US$ 42.28/INR 3, 500 crores annually to the economy [3]. This global trend reflects an increased demand for medicinal plant material driven by industries such as pharmaceuticals, phytochemicals, cosmetics, and nutraceuticals.

*Address correspondence to these authors at the Syngenta, Jeolett's Hill International Research Centre, Bracknell, Berkshire, UK, RG426EY; E-mail: Deepmala.Sehgal@syngenta.com (D. Sehgal); Department of Botany, HansRaj College, University of Delhi, Delhi, 110007, India; E-mails: vijayrani2@gmail.com; vrrajpal@hrc.du.ac.in (V.R. Rajpal); Department of Botany, University of Kashmir, Srinagar, Jammu & Kashmir, 190006, India; E-mails: meerbilal82@gmail.com; bilal.mir@uok.edu.in (B.A. Mir)
[#] *These authors contributed equally to this work.*

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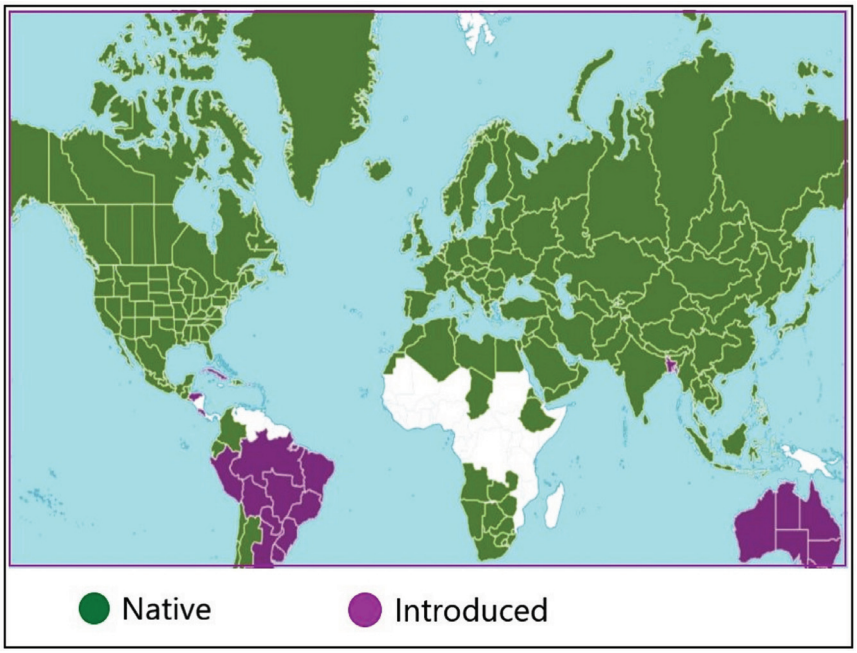


Fig. (1). Distribution of native and introduced species of *Artemisia* L. around the world (POWO 2022). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

The therapeutic potential of medicinal and aromatic plants is due to the presence of many biologically active secondary metabolites. Among the angiosperm families, Asteraceae (Compositae) includes several taxa which yield essential oils, medicinal and aromatic compounds, and possess medicinal importance [4]. One of the largest genera within this family is *Artemisia*, comprising shrubs and herbs with numerous medicinal properties. The name *Artemisia* is derived from Artemis, the Greek goddess associated with the moon and chastity. It is also believed to honour Queen 'Artemisia' of Caria, a Turkish Botanist who lived about 400 BCE [5]. Globally, there are approximately 500 reported species of *Artemisia*, mostly distributed in the temperate zones of Europe, Asia, and North America. Among them, China, Pakistan and India are home to 186, 25 and 45 species, respectively [6]. While *Artemisia* can be found across the globe up to an altitude of 4, 500 meters above sea level (masl), preferably grows in the northern hemisphere as compared to the southern hemisphere [7]. In India, around 20 species inhabit the trans-Himalayan belt, including the cold desert regions of Ladakh Himalayas [8]. *Artemisia* species can exist as native or introduced in many parts of the world [9]. Fig. (**1**) depicts a visual representation of their distribution. As evident, *Artemisia* species have successfully established their presence in different regions contributing to the biodiversity and availability of medicinal resources.

Artemisia species have a rich history of traditional use in treating a wide range of health conditions, including malaria, jaundice, toothache, gastrointestinal problems, wounds, inflammatory diseases, diarrhoea, menstrual pains, skin disorders, headache and intestinal parasites. The species possess diverse therapeutic properties such as antimalarial, antimicrobial, anthelminthic, antidiabetic, anti-inflammatory, anticancer, antispasmodic, antioxidative, and insecticidal potential.

The pharmacological properties of *Artemisia* can be assigned to the presence of a variety of bioactive constituents, including terpenoids, coumarins, sesquiterpene lactones, lignans, and alkaloids. In this context, artemisinin, extracted from *A. annua*, has notably revolutionized malaria treatment, especially against drug-resistant strains of *Plasmodium falciparum* [10]. Artemisinin, a sesquiterpene lactone with an endoperoxide bridge, has also exhibited allelopathic effects on other plants [11]. Additionally, many derivatives of artemisinin, including dihydro-artemisinin, artesunate, artemether, artether, artemisone, and artemiside, have also been found to be quite efficacious as antimalarial drugs.Despite the immense medicinal potential of *Artemisia*, only a small fraction of species have been thoroughly explored for their biological activities. The existing knowledge on traditional and pharmacological uses of *Artemisia* remains fragmented with limited updated comprehensive reviews available. Most of the reviews that were published in the last few years focuses on selected *Artemisia* species such as *A. annua* [12], *A. dracunculus* [13], *A. anomala* [14], *A. absinthium* [15], *A. vulgaris* [16], *A. parviflora* and *A. nilagirica* [17]. The present review, therefore, aims to address these gaps by providing comprehensive information on the traditional uses, phytochemistry, biological properties and toxicity of all the species of *Artemisia*. Consolidated published information in the form of present review will galvanize future research efforts in the genus to unveil the full therapeutic potential of *Artemisia* species for human health and welfare. Google scholar, Pubmed, Web of Science, Science direct, SciFinder and other online databases were used to compile the information detailed in this review.

Table 1. Representative *Artemisia* species and their reported ploidy levels according to the genome size in *asteraceae* database (GSAD) release 3.0 (http://www.asteraceaegenomesize.com.

Species Name	Ploidy Level (n = x = 9)	References
A. absinthium	Diploid (2n = 2x = 18), tetraploid (2n = 4x = 36)	[31, 231, 232]
A. annua	Diploid (2n = 2x = 18)	[232, 233]
A. biennis	Diploid (2n = 2x = 18)	[232, 234]
A. compacta	Diploid (2n = 2x = 18) and tetraploid (2n = 4x = 36)	[232]
A. dracunculus	Diploid (2n = 2x = 18), tetraploid (2n = 4x = 36) and polyploid (2n = 8x = 72, 2n = 10x = 90)	[31, 232]
A. fragrans	Diploid (2n = 2x = 18)	[232, 235]
A. gmelinii	Diploid (2n = 2x = 18), tetraploid (2n = 4x = 36) and polyploid (2n = 6x = 54)	[31, 232]
A. japonica	Tetraploid (2n = 4x = 36)	[232]
A. laciniata	Diploid (2n = 2x = 18)	[31, 232]
A. persica	Diploid (2n = 2x = 18)	[231, 232]
A. santolinifolia	Diploid (2n = 2x = 18) and tetraploid (22n = 4x = 36)	[231, 232]
A. scoparia	Diploid (2n = 2x = 18) and tetraploid (2n = 4x = 36)	[231, 232]
A. sieversiana	Diploid (2n = 2x = 18)	[231, 232, 234]
A. tournefortiana	Diploid (2n = 2x = 18)	[231, 232, 235]

2. BOTANY, CYTOLOGY AND PHENOLOGY

Artemisia species encompass a diverse array of habits ranging from annual, biennial, or even perennial aromatic/non-aromatic herbs and shrubs. The species are characterized by hairy plant bodies and alternately distributed leaves that exhibit a wide range of sizes, textures and shapes [18]. The flowers of *Artemisia* are grouped in small, cylindrical, ovoid or semicircular heads (capitula) arranged in racemose or paniculate synflorescences. Each capitulum is heterogamous, with outer female ray florets and middle hermaphrodite disc florets. The pistillate ray-florets are fertile and have a narrow tubular corolla that tapers upwards and curves, while the bisexual disc-florets can be fertile or sterile, and possess a five-toothed tubular or funnel-shaped corolla. The anthers of the disc florets are oblong and longer than the filaments, with styles that may be exseted or included. One of the characteristic features of the genus is the absence of pappus on the fruits (achene or cypsela) [19]. Pollen grains serve as important identifying markers for *Artemisia* species [18]. They are radially symmetrical, isopolar, tricolporate and often exhibit echinate sculpture or ornamentation [18, 20]. In the equatorial view, they are prolate to perprolate, while in the polar view, they appear three--lobed circular [20]. However, it is important to note that these morphological traits are not diagnostic. The circumscription of the genus remains contentious and has been recently revised and expanded by Jiao *et al.* (2023) to include the genus *Kaschgaria* [21]. The habit of some representative species such as *A. absinthium*, *A. alba, A. vulgaris*, *A. annua*, and others are shown in Fig. (**2**) and exemplifies the diversity within the genus. The species display unique characteristics in terms of growth habit, leaf morphology, and inflorescence. For instance, *A. absinthium* is a perennial herb with silver-grey feathery leaves and small yellowish-green flowers in dense clusters. *A. alba* is a creeping rhizomatous perennial with greyish-green hairy leaves and erect panicles of small yellowish flowers. *A. vulgaris*, a tall perennial, features dark green deeply lobed leaves and dense upright panicles of small greenish flowers. *A. annua*, an annual herb, exhibits finely divided light green leaves and loose panicles of small yellow flowers. These representative species provide a glimpse into the diverse traits observed within the genus *Artemisia.*

Artemisia species show a wide range of somatic chromosome (2n) numbers varying from 2n = 2x = 14 in *A. pattersonii* to 2n = 16x = 144 in *A. medioxima* [22, 23]. The genus encompasses species containing 2n = 14, 16, 17, 18, 25, 26, 27, 32, 34, 36, 45, 48, 50, 51, 52, 53, 54, 56, 58, 63, 64, 65, 72, 78, 87, 88, 89, 90, 108 and 144 chromosomes [7, 24]. The basic chromosome number in *Artemisia* include x = 7, 8, 9, 11, 17, with x = 9 being the most common [19]. Additional basic chromosome numbers (x = 8, 11, 17) occur less frequently and x = 7 reported in a single species needs further validation [19, 25]. The *Artemisia* chromosomes are medium in size (2-10 μm) and are mostly metacentric or submetacentric [7, 19] in morphology. The karyotypes demonstrate symmetry and fall into the 1A, 2A and 2B classes [18]. Supernumerary or accessory B chromosomes have also been reported in a few species of *Artemisia* [26].

Polyploidy has played a significant role in the evolutionary history of genus *Artemisia* [27]. It is widespread in the genus [28-30], with approximately 44% of species reported to be diploid, 30% as tetraploid and 26% exhibiting both diploid and tetraploid levels [31]. Notably, the polyploids based on x = 7 have not been reported, and only tetraploid and hexaploid levels are observed for x = 8. In contrast, ploidy levels from diploids to hexaideacaploids have been reported for x = 9, with some intermediate ploidy levels missing. The genus displays an extensive ploidy series, including 2x, 3x, 4x, 5x, 6x, 7x, 8x, 10x, 12x and 16x [7]. Table **1** rep-

resents some of the *Artemisia* species with their reported ploidy levels. Extensive molecular cytogenetic studies have been undertaken to understand the chromosome evolution in the genus *Artemisia* [31-33] focussing on the chromosomal localization of ribosomal gene families, heterochromatin distribution and AT- and GC-rich chromatin regions using techniques such as banding patterns and fluorescence *in situ* hybridization (FISH) [7, 31-33]. The diverse ploidy series present in *Artemisia* make it an ideal candidate for studying heterochromatin changes, potential variations in rDNA copy numbers, and their relationship with polyploidy [31].

Artemisia species typically flower in late summer, autumn or winter [7, 34]. Their pollination is primarily carried out by wind (anemophily) [19], although some evidence of insect pollination (entomophily) has been reported in certain species such as *A. simplex* [35, 36]. While sexual reproduction predominates in the genus, vegetative reproduction is also observed [37]. Interestingly, *A. tridentata* grows vegetatively under normal conditions but switches to sexual reproduction during harsh climates [38]. Pollination experiments conducted on three *Artemisia* species namely *A. maritima*, *A*. *nilagirica* and *A. scoparia* revealed that cross-pollination is preferred resulting in higher fruit and seed set compared to self-pollination [39].

3. TRADITIONAL USES OF *ARTEMISIA*

The practice of indigenous medicine is age-old across the world. Ayurveda, Unani, Siddha, Chinese, and Sowa-rigpa are among the prominent traditional systems of medicine practiced worldwide. These systems are deeply rooted in beliefs and accumulated knowledge, representing diverse approaches to healthcare and healing. Traditionally, *Artemisia* has been used for centuries to treat numerous human health complications. There are indications that Greeks and Romans used *A. dracunculus* as medicine as early as 500 BC and it is reported to be the most widely used herb in French cuisine to date [5, 13]. Likewise, in Europe, tarragon (*A. dracunculus*) was traditionally utilized to add flavour to sauces, commonly accompanying boiled, baked, or fried fish, meat, and chicken dishes. On the other hand, in the United States, tarragon found its way into various culinary applications. It was commonly used in vinegar, tartar sauce, eggs, as well as in dishes featuring chicken and seafood. The Slovenians used it as a spice for sweet pastry whereas the Russians, Armenians, and Georgians used it to flavour a popular non-alcoholic beverage [40]. The utilization of *A. absinthium* and *A. vulgaris* is believed to amplify the practitioner's psychic abilities during religious practices like Wicca. In Chinese traditional medicine, the aerial parts of *A. annua* (known as sweet wormwood, qinghao, or caohao) have been employed for various treatments, including malaria, fever associated with tuberculosis or summer heat, jaundice, and other ailments [41]. Moreover, in certain African countries, a tea infusion of *A. annua* has been utilized for malaria treatment [42]. Number of *Artemisia* species such as *A. absinthium, A. vulgaris, A. genipi, A. glacialis, A. eriantha, A. umbelliformis*, and others are used in preparation of traditional alcoholic beverages in Italy [43]. *A. herba-alba* is used in Morocco for the preservation of foods particularly meat [44]. In Southern Algeria, infusions of *A. herba-alba* along with *A. campestris* is used for treatment of gastro-intestinal, skin, and blood parasites in humans and animals [45]. Fresh roots of *A. afra* and *A. abyssinica* are used in Ethiopia for the treatment of epilepsy and associated symptoms [46, 47]. Decoction of the aerial parts of *A. calophylla* and *A. japonica* are used in the treatment of rheumatism by the Daman people and Tibetans in the Gyirong town of Tibet [48]. In Mongolia, decoction of leaves or whole plant of *A. argyi* and *A. kanashiroi* are used in treatment of abdominal pain, rheumatism, paediatric fright, prolapsed uterus, menstrual disorders, and others [49].

Artemisia species like *A. dracunculus, A.gmelinii, A. japonica, A. maritima, A. scoparia*are also used in the cold desert regions of Trans-Himalayas ranging from western Nepal's Humla district, Garhwal Himalayas, Western Pakistan, Nanda Devi National Park, Uttarakhand, and Sewa catchment, Kathua (Jammu & Kashmir) to treat multiple ailments ranging from gastrointestinal problems, malaria and skin diseases, diabetes, cough and cold, and abdominal complaints [50-54]. *A. macrocephala* and *A. japonica* are commonly used to treat skin-related problems, which are quite common in people living at high altitudes because of higher exposure to UV radiations. Further, it was noticed that the aerial parts of *Artemisia* are most frequently used for the treatment of digestive system problems, like intestinal disorders, stomach-ache, intestinal worms, and others in the Himalayan populations of India (J&K, Ladakh), Pakistan, Bhutan, Tibet, Nepal, and some regions of China and former Soviet Union, wherein digestive disorders are most prevalent probably due to the harsh environmental conditions [55, 56].

4. PHYTOCHEMISTRY OF *ARTEMISIA*

Artemisia phytochemicals largely comprise of essential oil components such as terpenoids, sesquiterpene lactones, and irregular terpenoids; phenolic compounds like phenolic acids, flavonoids, coumarins, caffeoylquinic acids, lignans; and various alkaloids. Table **2** and Fig. (**3**) provide a summary of 152 identified phytochemical compounds from different *Artemisia* species.

4.1. Essential Oils

Medicinal aromatic plants, including *Artemisia* species, produce essential oils as secondary metabolites, which are natural volatile compounds with distinctive aromas. The strong aromatic trait of *Artemisia* plants is attributed to the presence of terpenes, including mono- and sesquiterpenes, in their flowers and leaves [57]. Various extraction methods, such as supercritical carbon dioxide, microwave, and steam or hydro-distillation, have been developed to isolate plant essential oils. As many as 60 different components in the essential oils of different *Artemisia* species have been revealed by Gas Chromatography-Mass Spectrometry (GC-MS) analysis. The composition and concentration of these compounds vary depending on the extraction methods, plant parts used, growth stage, and ecological factors, including

Table 2. Chemical composition of *Artemisia* species.

Plant Name	Phytochemicals Identified	References
A. absinthium	Terpenoids: Bornyl acetate (**8**), Geraniol (**21**), β-myrcene (**10**), (-)-limonene (**11**), γ-terpinene (**14**), Thujyl alcohol (**16**), Phellandrene (**22**), Caryophyllene (**18**), Caryophyllene oxide (**19**), *α*-copaene (**20**), Terpinen-4-ol (**23**), p-cymene (**24**), *β*-thujone (**25**), *cis*-epoxyocimene/(Z)-epoxyocimene (**26**), *β*-pinene (**27**), Chamazulene (**28**), Chrysanthenyl acetate (**29**), Sabinyl acetate (**30**), Lavandulol (**31**), Other essential oil components: Eugenol (**32**), Methyl chavicol/estragole (**33**), Methyl eugenol (**34**)	[65, 91, 236-238]
	Sesquiterpene lactone: Absinthin (**76**)	
	Phenolic compounds: Vanillic acid (**90**), p-coumaric acid (**91**), Syringic acid (**92**), Ferulic acid (**93**), Quercetin (**105**), Kaempferol (**106**), Patuletin (**107**), Fisetin (**108**), Quercitin-3-*O*-*β*-D-glucoside (**109**), Quercetin-3-*O*-rhamnoglucoside (**110**), Isorhamnetin-3-*O*-glucoside (**111**), Salicylic acid (**112**), Chlorogenic acid (**113**)	[15, 237]
A. amygdalina	Sesquiterpene lactone: Ludartin (**74**)	[88]
A. annua	Terpenoids: 1, 8-cineole (**1**), Artemisia ketone (**2**), α-thujone (**3**), α-pinene (**4**), Camphor (**5**), Germacrene D (**6**), Borneol (**7**), Bornyl acetate (**8**), Chrysanthenone (**9**), β-myrcene (**10**), (-)-limonene (**11**), (-)-linalool (**12**), α-terpinene (**13**), γ-terpinene (**14**), Spathulenol (**15**), Thujyl alcohol (**16**), β-selinene (**17**), Caryophyllene (**18**), Caryophyllene oxide (**19**), *α*-copaene (**20**)	[62, 78, 227, 239, 240]
	Sesquiterpene lactones: Artemisinin (**52**), Artemisinic acid (**53**), Arteannuin B (**54**), Arteannuic alcohol (**55**), Arteanniun A (**56**), Annulide (**57**), Isoannulide (**58**), Dihydroartemisinic acid (**59**)	
	Phenolic compounds: Scopoletin (**81**), Scopolin (**82**), Isorhamnetin (**84**), Chrysosplenol D (**85**), Casticin (**86**)	[95]
A. argyi	Sesquiterpene lactone: Arteminolides (**63**)	[82]
A. balchanorum	Terpenoids: Geraniol (**21**)	[241]
A. capillaries (= *A. scoparia*)	Terpenoids: γ-terpinene (**14**), p-cymene (**24**), *β*-pinene (**27**), Other essential oil components: Eugenol (**32**), Methyl eugenol (**34**), Scoparone (**45**), Capillene (**46**), 1-phenyl-2, 4-pentadiyne (**47**), Nonacosane (**48**)	[64, 92, 103, 242-246]
	Sesquiterpene lactone: Achillin (**77**)	
	Phenolic compounds: Quercetin (**105**), Kaempferol (**106**), Chlorogenic acid (**113**), Rutin (**114**), Caffeic acid (**115**), 3, 5-dicaffeoyl-epi-quinic acid (**116**), Aesculetin/esculetin (**79**), Iso-fraxidin (**80**), Scopoletin (**81**), Scopolin (**82**)	[64, 93, 94, 100, 103, 178, 246]
	Others: Capillin (**151**)	[64]
A. diffusa	Sesquiterpene lactone: Tehranolide (**60**)	[79]
A. douglasiana	Terpenoids: Vulgarone B (**37**)	[81, 247]
	Sesquiterpene lactone: Dehydroleucodine (**62**)	
A. dracunculus	Terpenoids: Sabinene (**35**) Other essential oil components: Methyl chavicol/estragole (**33**), Elemicin (**36**)	[104]
	Phenolic compounds: Coumarin (**78**), Herniarin (**87**), Gallic acid (**88**), p-hydroxy benzoic acid (**89**), Vanillic acid (**90**), p-coumaric acid (**91**), Syringic acid (**92**), Ferulic acid (**93**), Sinapic acid (**94**), Estragonoside (**95**), Annagenin (**96**), Pinocembrin 7-O-beta-D-glucopyranoside (**97**), Pinocembrin (**98**), 2-hydroxy-4-methoxy-cinnamic acid (**99**), 3, 5, 4'-triydroxy-7-methoxyflavanone (**100**), Naringenin (**101**), 3, 5, 4'-trihydroxy-7, 3'-dimethoxyflavanone (**102**)	[96, 97, 245]
	Others: Anethole (**150**), Capillin (**151**),	[40, 193, 248, 249]
A. gabella	Sesquiterpene lactone: Arglabin (**61**)	[80]
A. giraldii	Phenolic compounds: 4′, 6, 7-trihydroxy-3′, 5′-dimethoxy flavones (**103**), 5′, 5-dihydroxy-3′, 4′, 8-trimethoxyflavone (**104**)	[99]

(Table 2) contd….

Plant Name	Phytochemicals Identified	References
A. gmelinii	Terpenoids: 1, 8-cineole (**1**), Artemisia ketone (**2**), Chrysanthenyl acetate (**29**), Vulgarone B (**37**), Other essential oil components: *Artemisia* triene (**38**)	[66, 75, 250]
	Phenolic compounds: Coumarin (**78**), Scopoletin (**81**), Scopolin (**82**), Isorhamnetin (**84**), Apigenin (**117**), Luteolin (**118**), Umbelliferone (**119**), 3-hydroxycoumarin (**120**), 4-hydroxycoumarin (**121**), Luteolin-7-O-glucoside (**122**), Apigenin-7-O-glucoside (**123**)	[101, 102]
A. herba alba	Terpenoids: Davanone (**49**), Phellandrene (**22**)	[57, 132]
A. indica	Terpenoids: Davanone (**49**), *β*-pinene (**27**)	[89, 251]
	Sesquiterpen lactone: Ludartin (**74**)	
A. japonica	Terpenoids: Germacrene D (**6**), (-)-linalool (**12**),	[252]
A. judaica	Terpenoids: Piperitone (**51**)	[253]
A. korshinsky	Alkaloids: Artekorine (**147**), 6-ketoartekorine (**148**), Lappaconitine (**149**)	[107]
A. ludovisiana	Sesquiterpene lactone: Achillin (**77**)	[92]
A. maritima	Terpenoids: 1, 8-cineole (**1**), α-thujone (**3**), Camphor (**5**), Borneol (**7**), Bornyl acetate (**8**), Chrysanthenone (**9**), Terpinen-4-ol (**23**)	[63, 69, 85, 254-256]
	Sesquiterpene lactone: Santonin (**71**)	
A. monosperma	Phenolic compounds: Tomentin (**83**)	[257]
A. myriantha	Terpenoids: Germacrene D (**6**)	[80, 258]
	Sesquiterpene lactone: Arglabin (**61**)	
A. nilagirica	Terpenoids: Artemisia ketone (**1**), α-thujone (**3**), Camphor (**5**), Borneol (**7**), (-)-linalool (**12**), Caryophyllene oxide (**19**)	[259, 260]
A. persica	Terpenoids: *Artemisia ketone* (**1**), davanone (**49**)	[132]
A. princeps	Sesquiterpene lactone: Yomogin (**72**), Secotanapartholides A and B (**75**)	[87, 90]
A. roxburghiana	Terpenoids: α-thujone (**3**), Borneol (**7**), Artemisia alcohol (**50**), *β*-thujone (**25**)	[250]
A. rupestra	Alkaloids: Rupestine A (**134**), Rupestine B α-Me (**135**), Rupestine C β-Me (**136**), Rupestine D (**137**), Rupestine E (**138**), Rupestine F (**139**), Rupestine G (**140**), Rupestine H β-Me (**141**), Rupestine I α-Me (**142**), Rupestine J (**143**), Rupestine K (**144**), Rupestine L α-Me (**145**), Rupestine M β-Me (**146**)	[106]
A. sieversiana	Terpenoids: β-myrcene (**10**), Lavandulol (**31**)	[76]
	Lignans: Sesamin (**124**), Sieverlignans A (**125**), Sieverlignans B (**126**), 3, 4, 5'-trimethoxy-3', 4'-methylene dioxy-7, 9':7', 9-diepoxylignan (**127**), Ashantin (**128**), Epiashantin (**129**), Epiyangambin (**130**), Carullignan B (**131**), (1S, 2R, 5S, 6R)2(5 methoxy 3, 4 methylenedioxyphenyl) 6 (4 hydroxy 3, 5 dimethoxyphenyl) 3, 7 dioxabicy-clo[3.3.0]octane (**132**), Diyangambin (**133**)	[104, 105]
	Others: *β*-sitosterol (**152**)	[104]
A. sylvatica	Sesquiterpene lactone: Artemisolide (**64**), Moxartenolide (**65**), 3-methoxytanapartholide (**66**), Deacetyllaurenobiolide (**67**), 3α, 4α-epoxyrupicolins C (**68**), 3α, 4α-epoxyrupicolins D (**69**), 3α, 4α-epoxyrupicolins E (**70**)	[83]
A. tournefortiana	*Terpenoids*: Spathulenol (**15**), Caryophyllene (**18**), Sabinene (**35**), *(Z)*-*β*-farnesene (**39**) Others essential oil components: (*Z*)-nerolidol/cis-nerolidol (**40**), Santolina triene (**41**), Nonadecane (**42**), (E)-nerolidol/trans-nerolidol (**43**), *cis*-spiroether (**44**)	[72-74, 261]
A. vulgaris	Terpenoids: 1, 8-cineole (**1**), Artemisia ketone (**2**), α-thujone (**3**), Camphor (**5**), Chrysanthenone (**9**), Caryophyllene oxide (**19**), *β*-thujone (**25**)	[86, 262, 263]
	Sesqiterpene lactone: Yomogin (**72**), 1, 2, 3, 4-diepoxy-11(**13**)- eudesmen-12, 8-olide (**73**)	

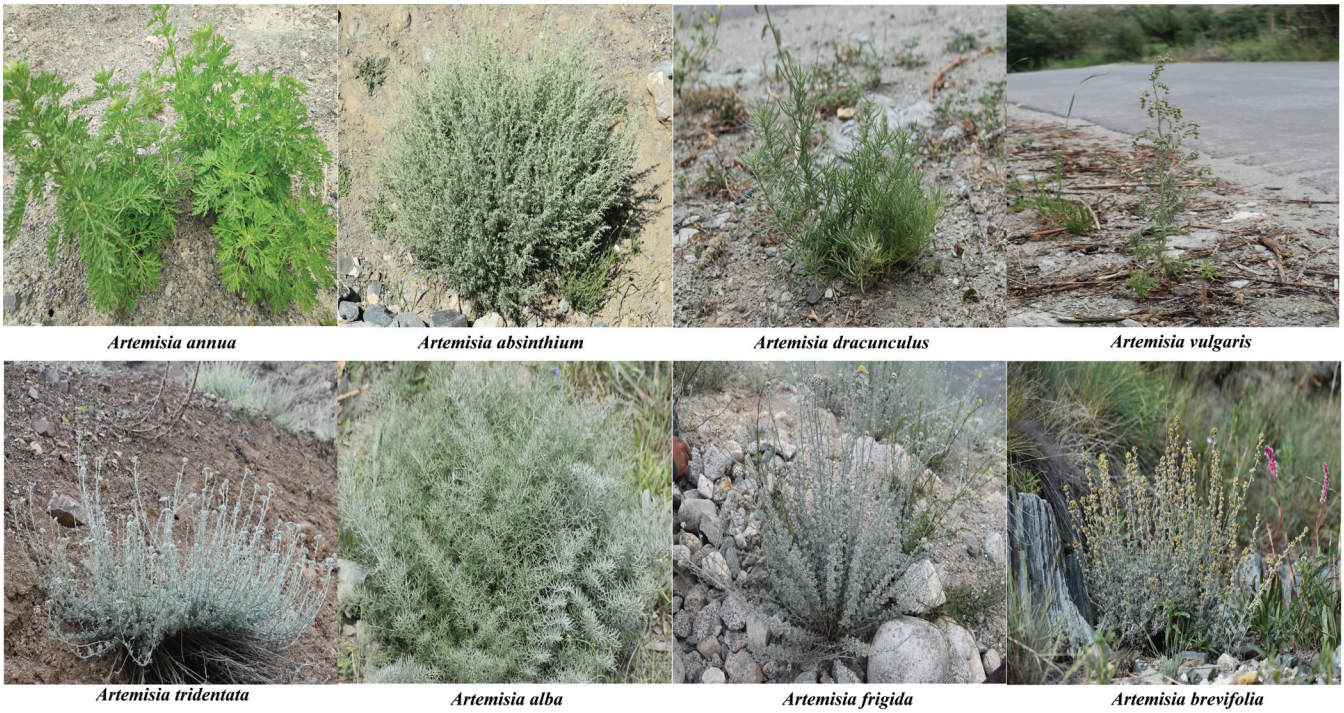


Fig. (2). Some species of *Artemisia* L. of Western Himalaya. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

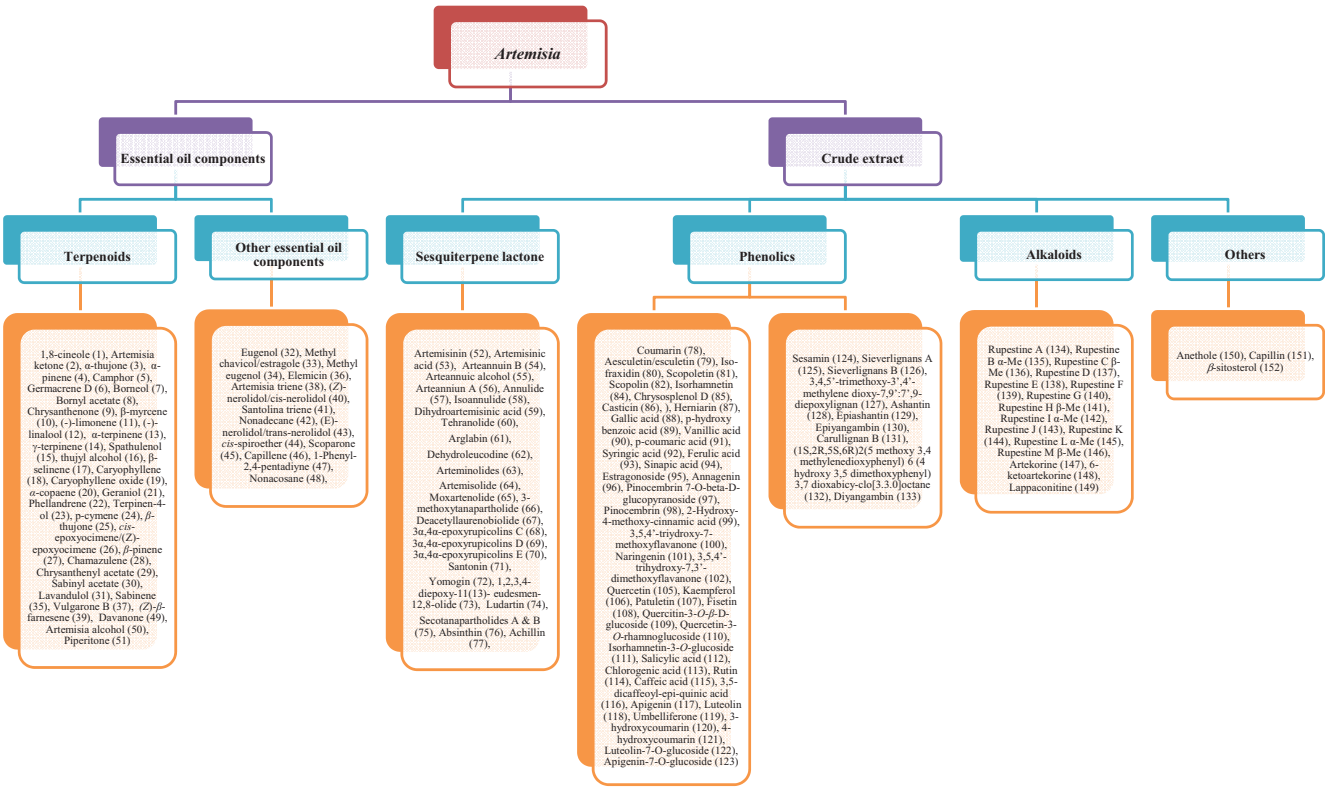


Fig. (3). Phytochemical compounds reported from different *Artemisia* species. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

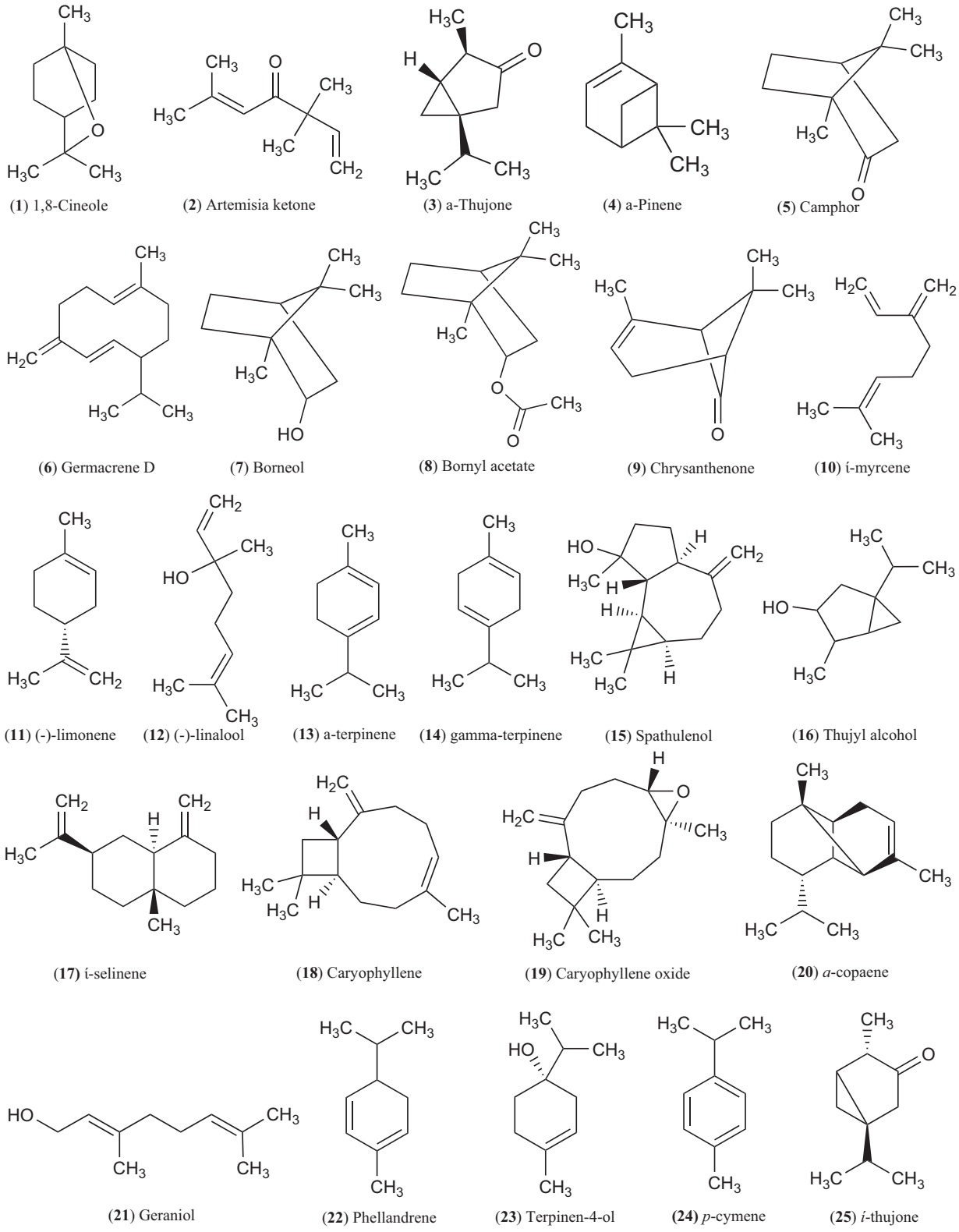
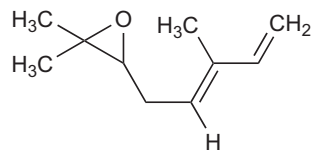
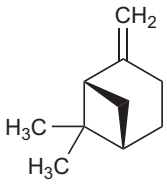

(1) 1,8-Cineole
(2) Artemisia ketone
(3) a-Thujone
(4) a-Pinene
(5) Camphor
(6) Germacrene D
(7) Borneol
(8) Bornyl acetate
(9) Chrysanthenone
(10) í-myrcene
(11) (-)-limonene
(12) (-)-linalool
(13) a-terpinene
(14) gamma-terpinene
(15) Spathulenol
(16) Thujyl alcohol
(17) í-selinene
(18) Caryophyllene
(19) Caryophyllene oxide
(20) *a*-copaene
(21) Geraniol
(22) Phellandrene
(23) Terpinen-4-ol
(24) *p*-cymene
(25) *í*-thujone

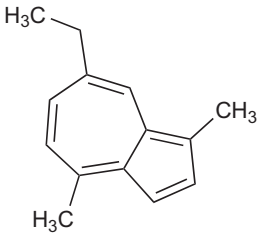
Fig. (4). contd...



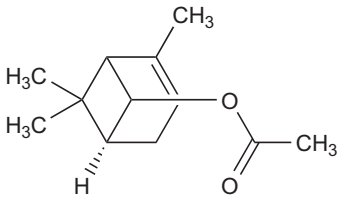
(**26**) *cis*-epoxyocimene



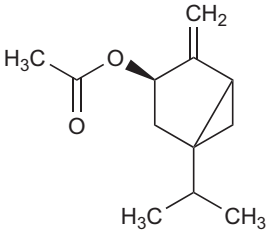
(**27**) *i*-pinene



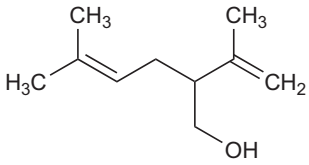
(**28**) Chamazulene



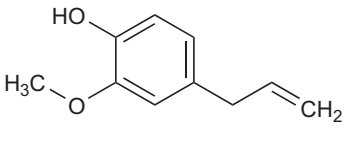
(**29**) Chrysanthenyl acetate



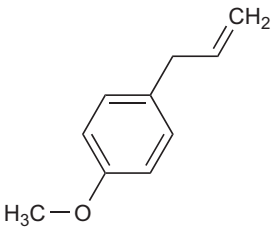
(**30**) Sabinyl acetate



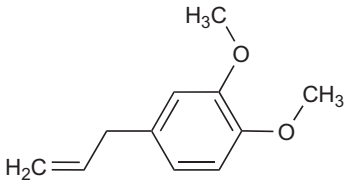
(**31**) Lavandulol



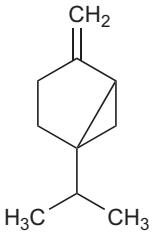
(**32**) Eugenol



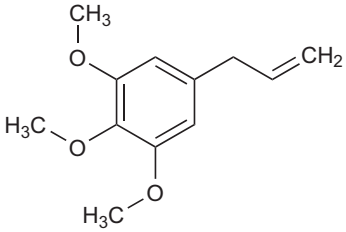
(**33**) Methyl chavicol/Estragole



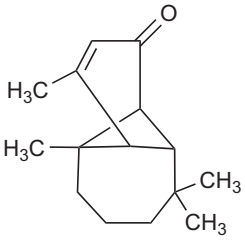
(**34**) Methyl eugenol



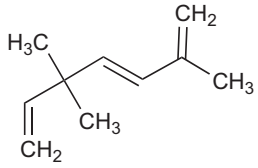
(**35**) Sabinene



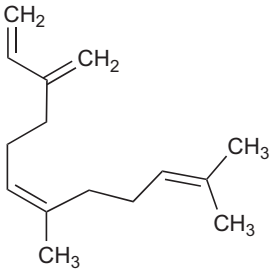
(**36**) Elemicin



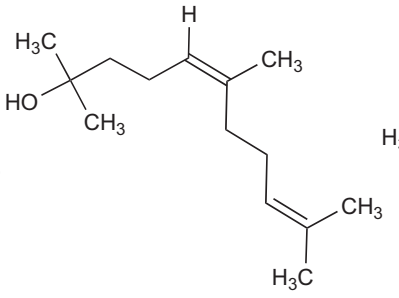
(**37**) Vulgarone B



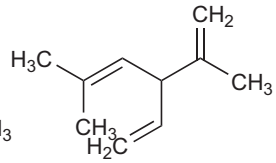
(**38**) Artemisia triene



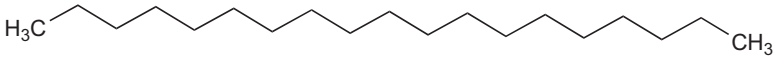
(**39**) (*Z*)-*i*-farnesene



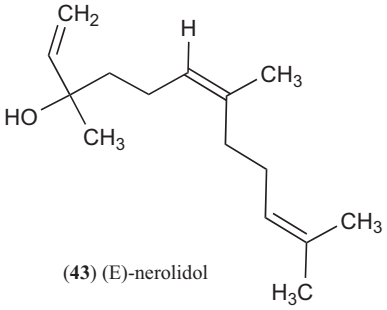
(**40**) (*Z*)-nerolidol



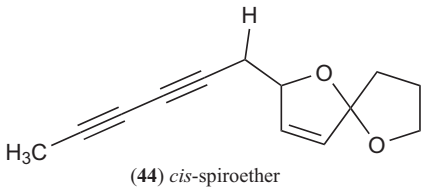
(**41**) Santolina triene



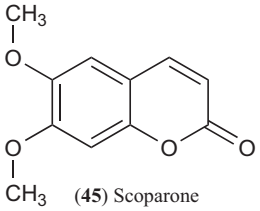
(**42**) Nonadecane



(**43**) (E)-nerolidol

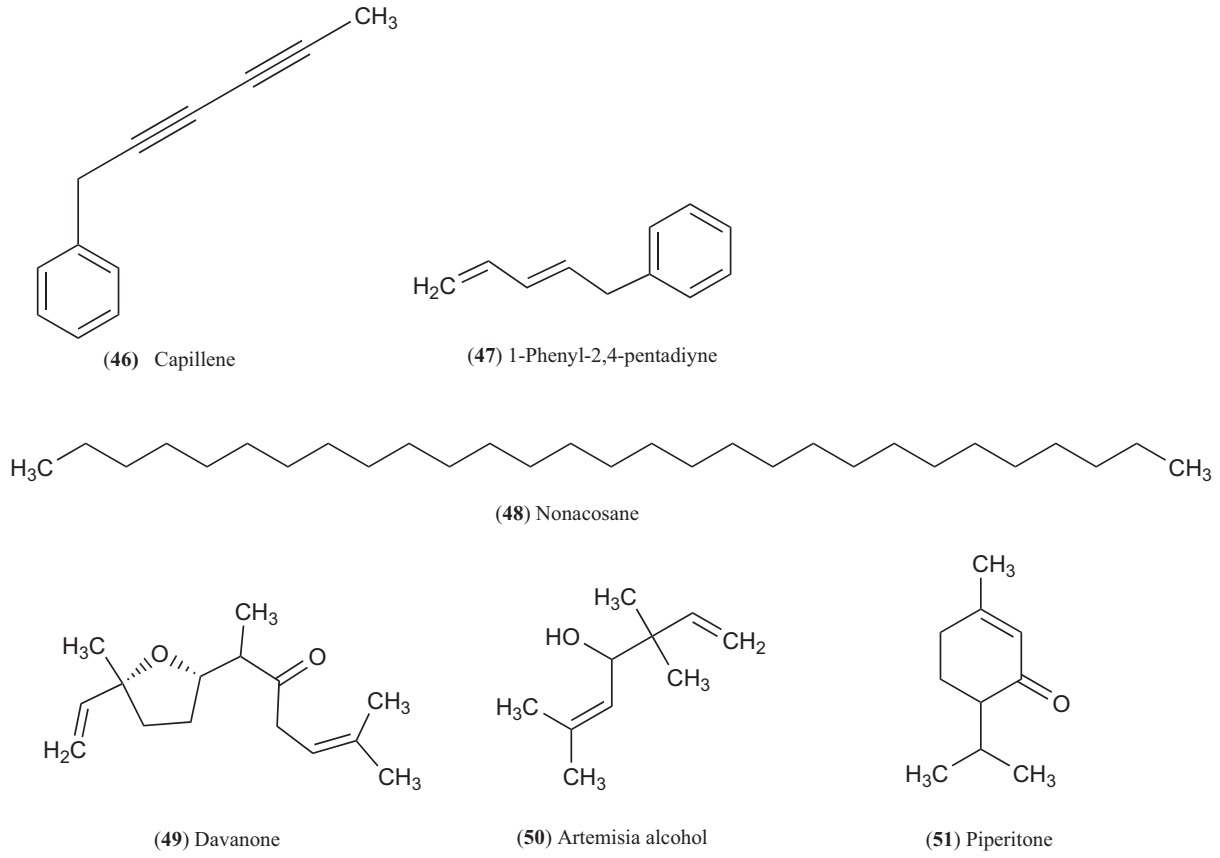


(**44**) *cis*-spiroether



(**45**) Scoparone

Fig. (4). contd...



(**46**) Capillene

(**47**) 1-Phenyl-2,4-pentadiyne

(**48**) Nonacosane

(**49**) Davanone

(**50**) Artemisia alcohol

(**51**) Piperitone

Fig. (4). Chemical structure of various essential oil constituents of *Artemisia* species (**1-51**).

habitat conditions [58]. Fig. **(4)** illustrates the common essential oil components found in major *Artemisia* plant extracts. An understanding of the chemical profile of these essential oils is required for their usage in various industries, including perfumery, cosmetics, and herbal medicine.

Differences in the qualitative and quantitative composition of the phytochemical components of the same species at different locations can be attributed due to the presence of specific heritable chemotypes. Chemotypes are characterized by specific chemical components found in a population of morphologically similar individuals [59]. Chemotypes in *Artemisia* species have been designated with specific nomenclature, for instance, *A. annua* from China and Vietnam are classified as ketone and camphor chemotype with *Artemisia* ketone (**2**) and camphor (**5**) as the major compounds, respectively [60]. While variation in the major essential oil compounds has been reported among the *A. annua* populations, *Artemisia* ketone (**2**) dominates the isolates [61]. Based on the composition of essential oils in their study, Zhigzhitzhapova *et al.*, (2020) categorized the samples of *A. annu* collected from various countries into two primary groups. The first group, referred to as the Asian group consisted of compounds, such as *β*-selinene (**17**), caryophyllene (**18**), caryophyllene oxide (**19**), *Artemisia* ketone (**2**), germacrene-D (**6**), and *α*-copaene (**20**), whereas the European group revealed dominant compounds as camphor (**5**), 1, 8-cineole (**1**), and *Artemisia* alcohol (**50**) [62]. Similar chemotypes have been reported for other *Artemisia* species, such as *A. maritima* [63], *A. scoparia* [64], *A. absinthium* [65], *A. gmelinii* [66], *A. brevifolia* [67] and *A. tournefortiana* [68] from across different geographical regions.

Chemotype diversity is evident within populations of *Artemisia* species, even within specific regions characterized by variations in altitude, temperature, soil type, and other factors. For instance, in the western Himalayan region of India, different chemotypes of *Artemisia* species have been reported (Table **3**). For instance, *A. maritima* collected from Pooh and Lahaul-Spiti, showed 1, 8-cineole (**1**) as the major compound, whereas chrysanthenone (**9**) and *α*-thujone (**3**) dominated in samples from Rhongtong and Garhwal region of Himachal Pradesh, India [63]. Other parts of the Himalayas showed chemotypes of 1, 8-cineole (**1**) with camphor (**5**), and 1, 8-cineole (**1**) with terpinen-4-ol (**23**) and *α*-thujone (**3**) [69, 70]. In Kashmir, *A. dracunculus* showed a chemotype with capillene (**46**) as the major compound [71], whereas the French and Russian chemotypes of the same species contained estragole (**33**) (74%) and elemicin (**36**) (57%) as their major compounds, respectively [40]. Chemotypes variations were also observed in *A. tournefortiana.* In Kashmir, major essential oil compounds included *cis*-spiroether (**44**) (47.66%), (*Z*)-*β*-farnesene (**39**) (22.83%), *trans*-nerolidol (**43**) (3.89%), and camphor (**5**) (3.8%), while in Khorassan, Iran (*Z*)-*β*-farnesene (**39**) (34.2%) and nonadecane (**42**) (8.1%) were prominent [72, 73].

Table 3. List of *Artemisia* species with major essential oil constituents.

Species	Essential Oil Extraction Method, Essential Oil Yield, Colour/Appearance of the Product	Major Essential Oil Constituents (≥ 10%)	Location	References
A. absinthium	Hydro-distillation method, yield from leaves: 0.39%-0.46%; Stem: 0.14%-0.15%; Seeds: 0.06%-0.07%	Bornyl acetate (26.5%-27.1%), terpinen-4-ol (17.0%-18.2%), p-cymene (12.8%-14.8%)	Kashmir, Himalaya	[236]
A. annua	Hydro-distillation method, yield from aerial part: 0.3%-0.7%	Camphor (22.8%-42.6%)	Uttarakhand, Himalaya	[239]
A. capillaris (*A. scoparia*)	Hydro-distillation method, yield from aerial part: 0.60%, yellow coloured	1-phenyl-2, 4-pentadiyne (34.2%), β-pinene (21.3%)	Tajikistan	[243]
	Hydro-distillation method, yield from leaves: 0.40%; Roots: 0.35%	Capillene (60.2%), γ-terpinene (11.1%)	Milam glacier, Utarakhand, Himalaya	[244]
	Hydro-distillation method, yield from flowering twigs: 0.57-0.63%	Capillene (32.5% - 39.6%), γ-terpinene (26.4% -34.3%)	Kumaon Himalaya	[246]
	Hydro-distillation method, yield from inflorescences: 0.4-0.5%	Capillene (27.4-40.1%), γ-terpinene (17-24.6%), eugenol (12.5-15%)	Kumaon Himalaya	[245]
A. dracunculus	Hydro-distillation method, Yield from aerial part: 0.47%-0.55%	Capillene (60.2%), (*Z*)-β-ocimene (12.7%) and methyl chavicol (71.3%)	Kashmir, Himalaya	[71]
	Hydro-distillation method, yield from leaf: 0.1%, stem: 0.5%, root: 0.8%	Acenaphthene (32.6-66.6%), Capillene (12.6-34.7%), (*Z*)-β-ocimene (12.2-17.6%)	Kashmir, Himalaya	[249]
	Hydro-distillation method, yield from aerial part: 0.76 ± 0.04%, yellowish coloured	Capillene (58.38%)	Himachal Pradesh, North-West Himalaya	[248]
	Hydro-distillation method, yield from aerial part: 0.67%	Sabinene (19.19%)	Qinghai-Tibet Plateau	[104]
A. gmelinii	Hydro-distillation method, greenish colour	Artemisia ketone (40.87-53.34%)	Uttarakhand, Himalaya	[75]
	Hydro-distillation method, yield from aerial part: 1.43%	Artemisia ketone (40.7%), cis-Chrysanthenyl acetate (21.3%), 1, 8-Cineole (11%)	North-west Himalaya, Garhwal region	[250]
	Hydro-distillation method	1, 8-cineole (23.8%), chrysanthenone (17.54%) Chrysanthenone (38.1%), 1, 8-cineole (37.3%) and 1, 8-cineole (44.22%), borneol (10.94%)	Pooh, Rhongtong and Lahaul-Spiti, Himalaya	[63]
	Hydro-distillation method, yield from aerial part: 0.5%, pale yellow coloured oil	Chrysanthenone (25.7%), 1, 8-cineole (23.6%)	Garhwal region in north-west Himalaya	[255]
	Hydro-distillation method	1, 8-cineole (41.14%), camphor (20.32%)	Pakistan	[69]
	Hydro-distillation method, yield from leaves 0.25 to 0.45%	1, 8-cineole (38.87%-49.94%), bornyl acetate (8.02%-13.47%), terpinene-4-ol (9.71%-14.2%)	Lahaul and Spiti	[254]
	Hydro-distillation method, yield from aerial part: 1.67%	α-thujone (72.1%)	North-west Himalaya, Garhwal region	[250]
	Hydro-distillation method	1, 8-cineole (25%), chrysanthenone (23.62%)	Uttarakhand Himalaya	[264]
A. indica	Hydro-distillation method, yield from aerial parts: 0.8%	Davanone (30.80%), β-pinene (15.30%)	Uttarakhand, Himalaya	[251]
A. myriantha var. *pleiocephala*	Steam-distillation method, yield from aerial parts: 0.55%	β-eudesmol (12.9%), germacrene D (18.4%)	Uttarakhand, Himalaya	[258]

(Table 3) contd….

Species	Essential Oil Extraction Method, Essential Oil Yield, Colour/Appearance of the Product	Major Essential Oil Constituents (≥ 10%)	Location	References
A. nilagirica	Hydro-distillation method, yield from leaves: 0.25%-1.0%, light yellow coloured	Camphor (46.9%), borneol (35.8%), caryophyllene oxide (28.6%), methanoazulene (14.7%)	Himachal Pradesh	[265]
	Hydro-distillation method, Yield from aerial parts: 0.40%, Pale green coloured	α-thujone (36.35%)	Uttarakhand, Himalaya	[260]
	Hydro-distillation method, yield from aerial parts: 0.2%	*Artemisia* ketone (62.6%)	Uttarakhand, Himalaya	[259]
A. parviflora (*A. japonica*)	Steam-distillation method	Linalool (27.5%), germacrene D (11.2%)	Milam glacier, Uttarakhand, Himalaya	[252]
	Steam-distillation method, yield from aerial part: 0.2%	Germacrene D (41.01%), β-caryo-phyllene (10.58%)	Uttarakhand, Himalaya	[266]
	Hydro-distillation method, yield from aerial part: 0.77-0.9%	Borneol (18.5%), α-thujone (13.1%), *Artemisia* alcohol (11.6%), β-eudesmol (11.6%)	North-west Himalaya, Garhwal region	[250]
A. sieversiana	Hydro-distillation method, yield from Flower: 0.92 %; leaf, stem and root: 0.67%	α-bisabolol (23.5%-45.4%), chamazulene (21.9%-24.1%)	Tibet	[267]
A. tournefortiana	Hydro-distillation method, yield from aerial part: 0.34%, dark yellow colour	*cis*-spiroether (47.66%), (*Z*)-β-farnesene (22.83%)	Kashmir, Himalaya	[73]
A.vulgaris	Hydro-distillation method, yield: 0.19- 1.02%	Chrysanthenone (0.1-26.6%), vulgarole (0.1-20.6%), *Artemisia* ketone (0.01-19.8%), α-thujone (0.01-19.0%), 1, 8-cineole (1.6-13.5%), β-thujone (0.2-13.2%), caryophyllene oxide (1.4-11.2%) and camphor (0.9-11.1%)	Uttarakhand Himalaya	[262]
	Hydro-distillation method, yield from aerial part: 0.4-0.5%	α-thujone (14.4-21.66%), *Artemisia* ketone (29.38%),	Uttarakhand Himalaya	[263]

Interestingly, different extraction protocols yielded varying compound profiles, indicating differences in the solubility or stability of essential oil components. Ardakani and Masoudi (2017) reported different compounds recovered from *A. tournefortiana* using different extraction methods [72]. These findings highlight the influence of extraction technique on the chemical composition of essential oils. Table **3** provides an overview of the variations in chemical profiles, particularly essential oils, when different extraction methods were employed.

Overall, the presence of diverse chemotypes within populations of *Artemisia* species in different regions underscores the impact of environmental factors on the production and composition of phytochemicals. The documentation of chemotype diversity will be helpful in determining the therapeutic potential and efficacy of different chemotypes, and also for identifying most suitable sources of specific compounds required in the pharmaceutical, cosmetic, and food industries.

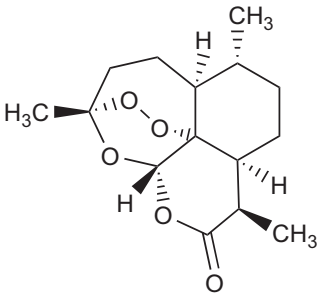
4.2. Irregular Terpenoids

Many *Artemisia* species have revealed irregular terpenoid compounds in their essential oils with structures not congruent with the isoprene rule. Irregular terpenoids like *Artemisia* ketone (**2**) found in *A. annua, A. gmelinii, A. laciniata,* and *A. persica*; *Artemisia* alcohol (**50**) from *A. annua*; chamazulene (**28**) and lavandulol (**31**) from *A. sieversiana*; yomogi alcohol from *A. persica*; *Artemisia* triene (**38**) from *A. gmelinii*; chrysanthenone (**9**) and chrysanthenyl acetate (**29**) from *A. maritima*; and santolina triene (**41**) from *A. tournefortiana* [63, 74-76] have been reported. Furthermore, the irregular terpenoids present in *Artemisia* species belong to different structural scaffolds, such as artemisane, santolinane, chrysanthemane and lavandulane [77]. Additionally, the anti-malarial compound artemisinin (**52**) possesses an unusual peroxide bridge in its structure (Fig. **5**). This demonstrates that the genus *Artemisia* encompasses a wide array of chemically distinct compounds, and holds great potential for further bioprospecting to discover new minor chemical compounds.

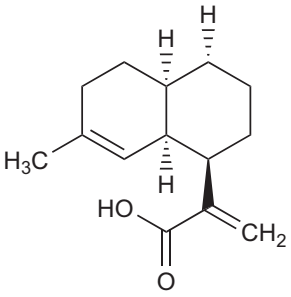
4.3. Sesquiterpene Lactones

The main chemical constituents produced by *A. annua* shown in Fig. (**5**) include artemisinin (**52**), a sesquiterpene lactone and its derivatives [78]. Tehranolide (**60**), another sesquiterpene lactone with an endoperoxide group isolated from *A. diffusa,* is hypothesized to possess effects similar to artemisinin [79]. Arglabin (**61**), belonging to guaianolide class of sesquiterpene lactones and isolated from *A. glabella* and *A. myriantha*, exhibits promising antitumor activity [80]. Dehydroleucodine (**62**), a guaianolide class of sesquiterpene lactone has also been isolated from *A. douglasiana* [81]. Arteminolides A-D (**63**), sesquiterpene lactones isolated from the aerial parts of *A. argyi*, are potent in-

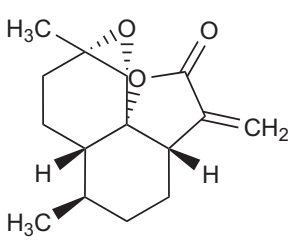
hibitors of farnesyl-protein transferase (FPTase) [82]. From *A. sylvatica,* several sesquiterpene lactones have been isolated, such as arteminolides B and D (**63**), artemisolide (**64**), moxartenolide (**65**), 3-methoxytanapartholide (**66**), deacetyllaurenobiolide (**67**), and 3α, 4α-epoxyrupicolins C-E (**68-70**) [83]. Santonin (**71**), an important sesquiterpene lactone with anticancer and *in vitro* antioxidant activities, has been extracted from the floral buds [84] and aerial parts of *A. maritima* from Kashmir Himalayas [85].



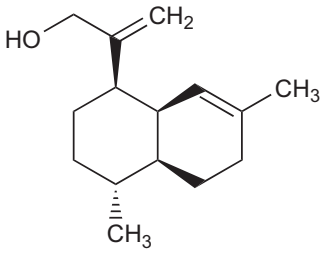
(**52**) Artemisinin



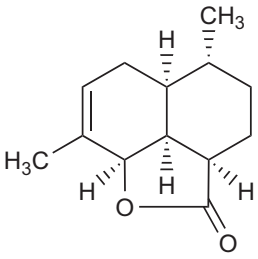
(**53**) Artemisinic acid



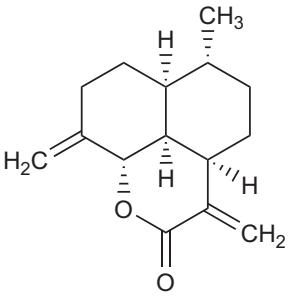
(**54**) Arteanniun B



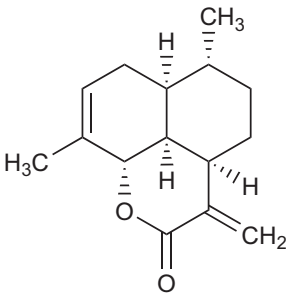
(**55**) Arteannuic alcohol



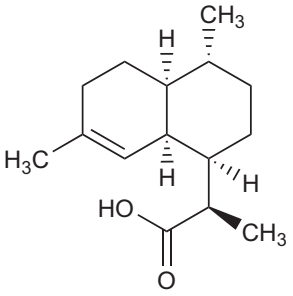
(**56**) Arteanniun A



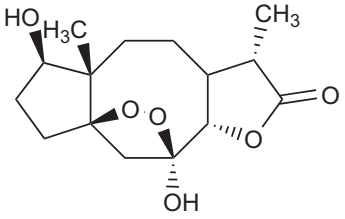
(**57**) Annulide



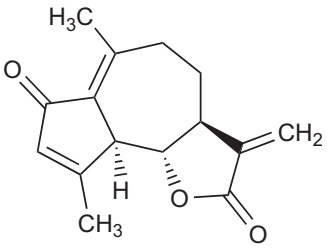
(**58**) Isoannulide



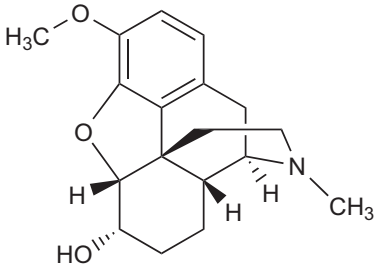
(**59**) Dihydroartemisinic acid



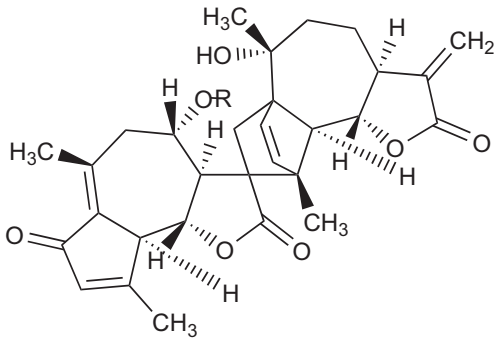
(**60**) Tehranolide



(**61**) Arglabin

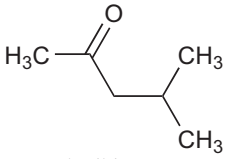


(**62**) Dehydroleucodine

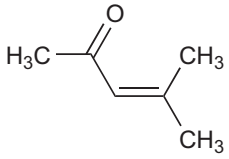


(**63**) Arteminolides

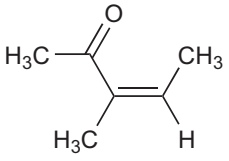
R=



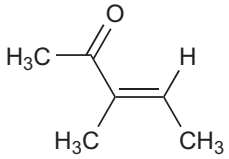
Arteminolide A



Arteminolide B

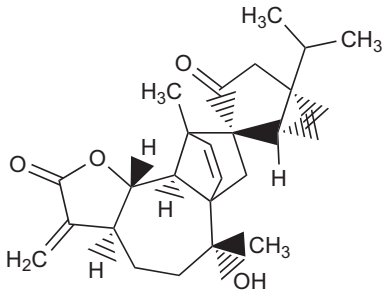


Arteminolide C

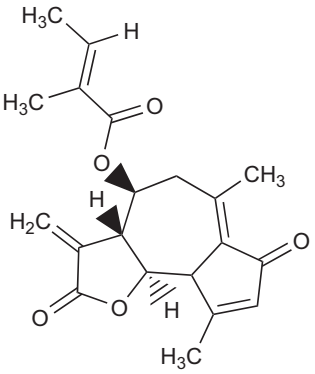


Arteminolide D

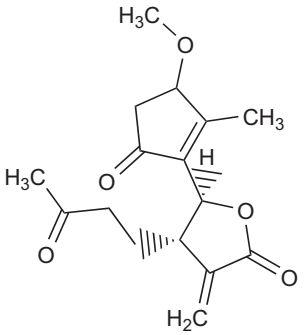
Fig. (5). contd...



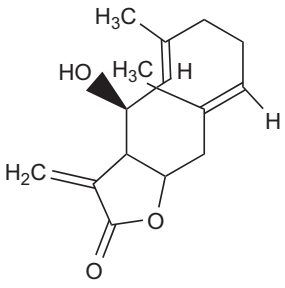
(**64**) Artemisolide



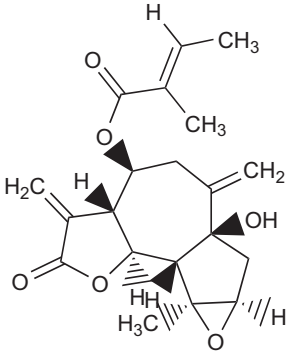
(**65**) Moxartenolide



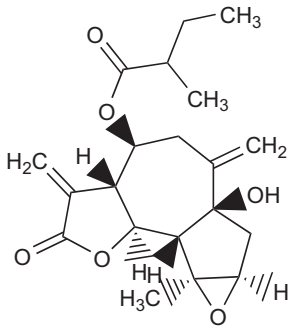
(**66**) 3-methoxytanapartholide



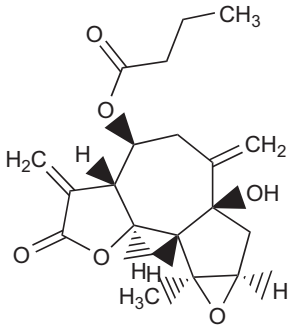
(**67**) Deacetyllaurenobiolide



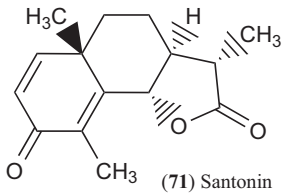
(**68**) 3a,4a-epoxyrupicolins C



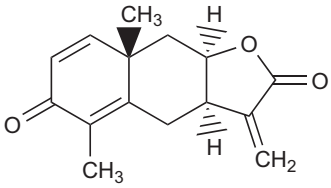
(**69**) 3a,4a-epoxyrupicolins D



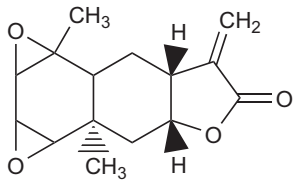
(**70**) 3a,4a-epoxyrupicolins E



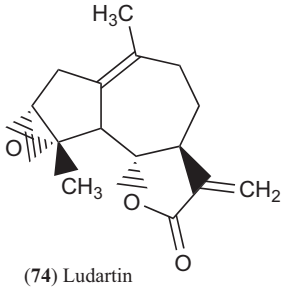
(**71**) Santonin



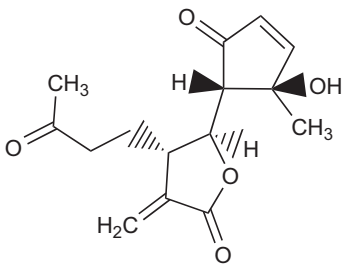
(**72**) Yomogin



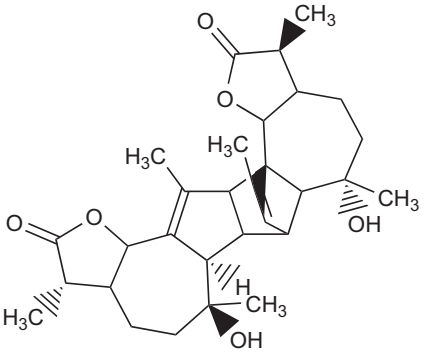
(**73**) 1,2,3,4-diepoxy-11(13)-eudesmen-12,8-olide



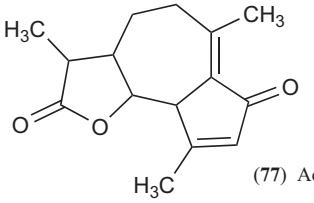
(**74**) Ludartin



(**75**) Secotanapartholides A & B



(**76**) Absinthin



(**77**) Achillin

Fig. (5). Chemical structure of sesquiterpene lactones reported from different *Artemisia* species (**52-77**).

Two eudesmane sesquiterpene lactones, yomogin (**72**) and 1, 2, 3, 4-diepoxy-11(13)-eudesmen-12, 8-olide (**73**) were isolated through bioassay-guided fractionation chloroform extracts of *A. vulgaris* [86] and *A. princeps* [87]. Ludartin (**74**), a cytotoxic guaianolide class of sesquiterpene lactone, has been found in the aerial parts of *A. amygdalina* and shoot and root parts of *A. indica* [88, 89]. Additionally, secotanapartholides A-B (**75**) were isolated from *A. princeps* [90], while absinthin (**76**), a dimeric sesquiterpene lactone, was detected in *A. absinthium* and is responsible for the plant's bitter taste [91]. Furthermore, achillin (**77**), a guaianolide-type sesquiterpene lactone primarily isolated from *Achillea millefolium* was also reported from *A. capillaris* and *A. ludovisiana* [92].

4.4. Phenolic Compounds

A variety of phenolic compounds, including flavones, flavonols, coumarins, and phenolic acids, have been identified in *A. annua*. Notably, coumarin (**78**), aesculetin (**79**), iso-fraxidin (**80**), scopoletin (**81**), scopolin (**82**), and tomentin (**83**) are among the compounds reported so far [93, 94]. Fu *et al.* (2020) observed significant variation in the phenolic compounds of *A. annua* characterized by the presence of isorhamnetin (**84**), scopolin (**82**), scopoletin (**81**), chrysosplenol D (**85**), and casticin (**86**) [95]. *A. dracunculus* has been found to contain a range of intricate polyphenolic compounds, including coumarin (**78**) and its derivative herniarin (**87**), estragonoside (**95**), annagenin (**96**), pinocembrin 7-O-β-D-glucopyranoside (**97**), and pinocembrin (**98**) [96]. These compounds contribute to the complex composition of *A. dracunculus*. Additionally, free phenolic acids, such as gallic acid (**88**), p-hydroxy benzoic acid (**89**), vanillic acid (**90**), p-coumaric acid (**91**), syringic acid (**92**), ferulic acid (**93**), and sinapic acid (**94**) were also identified [97]. (E)-2-Hydroxy-4-methoxy-cinnamic acid (**99**), 3, 5, 4′-triydroxy-7-methoxyflavanone (**100**), naringenin (**101**) and 3, 5, 4′-trihydroxy-7, 3′-dimethoxyflavanone (**102**) were isolated from aerial parts of *A. dracunculus* [98]. Two flavones namely 4′, 6, 7-trihydroxy-3′, 5′-dimethoxy flavones (**103**) and 5′, 5-dihydroxy-3′, 4′, 8-trimethoxyflavone (**104**) were isolated from *A. giraldii* [99].Variations in the occurrence and concentration of flavonoids and phenolic acids have been reported in *A. absinthium*, *A. scoparia* (with 3, 5-dicaffeoyl-epi-quinic (**116**) acid as a major bioactive compound), and *A. gmelinii* [15, 100-103]. The chemical structure of these phenolic compounds from *Artemisia* species are depicted in Fig. (**6**). Recently, sesamin (**124**)-type lignans and flavonoids have also been reported from *A. sieversiana* [104]. In their study, Zhou *et al.* (2021) made noteworthy findings, including the discovery of two new ditetrahydrofuran lignans: Sieverlignan A (**125**) and Sieverlignan B (**126**). They also identified other compounds, such as 4, 50-trimethoxy-30, 40-methylene-dioxy-7, 90:70, 9-diepoxylignan (**127**), ashantin (**128**), epiashantin (**129**), epiyangambin (**130**), carullignan B (**131**), (1S, 2R, 5S, 6R)-2-(5-methoxy-3, 4 methylenedioxyphenyl)-6-(4-hydroxyl-3, 5-dimethoxyphenyl)-3, 7-dioxabicy-clo(3.3.0)octane (**132**), and diyangambin (**133**) (Fig. **7**) [105]. These findings contribute to the expanding knowledge about the diverse compounds present in *A. dracunculus*.

4.5. Alkaloids

In addition to terpenoids and phenolic compounds, various alkaloids and allied nitrogen compounds have been reported from different *Artemisia* species. Rashid *et al.* (2019) characterised these nitrogen-containing compounds and classified them into different groups, such as rupestine derivatives, lycoctonine derivatives, pyrrolizidine alkaloids, purine alkaloids, indole alkaloids, polyamine, alkamides, piperidine, and pyrrolidine derivatives, ceramide and cerebroside, aromatic and nonaromatic amines, benzodiazepine derivatives, flavoalkaloid, and others [106]. Rupestine A-M (**134-146**) (Fig. **8**) belonging to the guaipyridine sesquiterpene alkaloids or rupestine derivatives have been reported from *A. rupestra.* These rupestine derivatives hold chemotaxonomic importance and can be used as biomarkers [106]. Alkaloids of lycoctonine derivatives such as artekorine (**147**), 6-ketoartekorine (**148**), and lappaconitine (**149**) (Fig. **8**) were isolated from the aerial part of *A. korshinskyi* [107].

4.6. Other Bioactive Compounds

Apart from terpenoids, sesquiterpene lactones, phenolic compounds and alkaloids, various other biologically active compounds have been reported form different *Artemisia* species. For instance, *A. dracunculus* contains anethole (**150**), a phenol methyl ether widely used as a flavouring substance and the main bioactive compound of anise oil, fennel, and star anise spices. Another notable compound is capillin (**151**), an aromatic ketone and a ynone, found in *A. capillaris*as the main component of its essential oil [103]. Additionally, *β*-sitosterol (**152**), a phytosterol or a plant sterol, holds commercial significance as a neutraceutical supplement for reducing plasma cholesterol levels [108]. *A. sieversiana* also yields *β*-sitosterol (**152**) with anti-microbial properties [104]. Fig. (**9**) depicts the chemical structure of compounds isolated from *Artemisia* species.

5. PHARMACOLOGICAL PROFILE OF *ARTEMISIA*

Artemisia species, like numerous other medicinal plants, have a long history of traditional use for treating various ailments. The pharmacological profile of the genus *Artemisia* is comprehensively presented in Table **4** and further discussed in the subsequent section. The therapeutic properties of *Artemisia* are attributed to the diverse range of phytoconstituents found within this genus as illustrated in Fig. (**10**).

5.1. Anti-oxidant Property

The essential oil of *A. annua* exhibited relatively strong radical scavenging potential with IC_{50} values of 29 ± 5.3 μg/mL and 9.218 ± 0.3 μg/mL in DPPH and FRAP assays, respectively, although lower than the positive controls used [109]. A comparison of the DPPH scavenging activity of essential oils from *A. annua* from Buryatian flora and Bosnia revealed higher activity in the former due to differences in chemical composition. The Buryatian flora oil contained

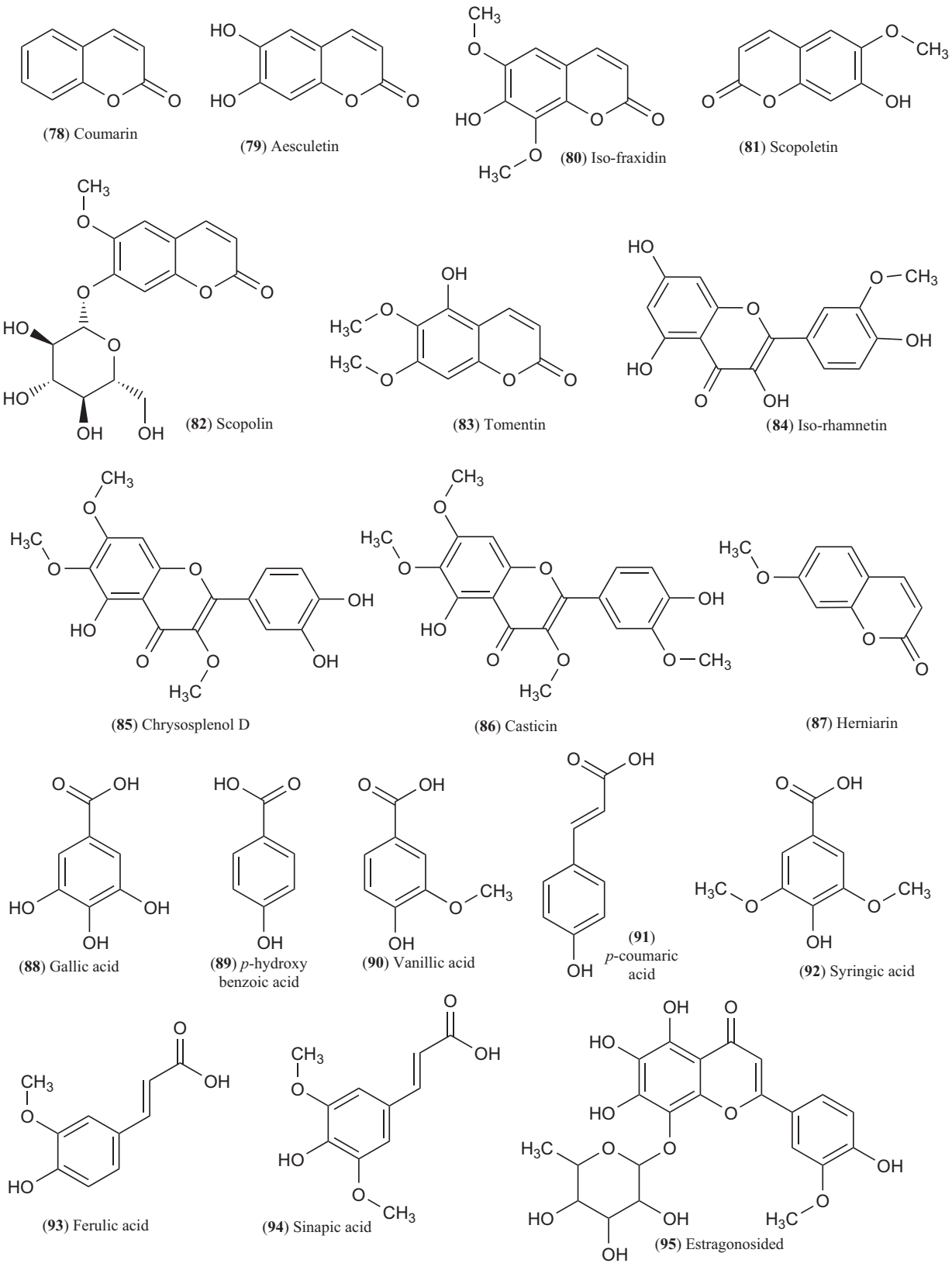
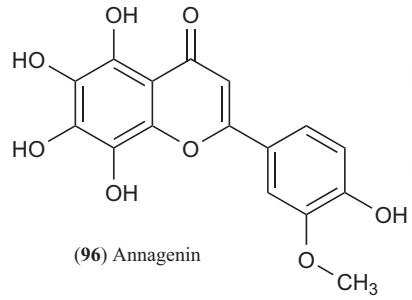
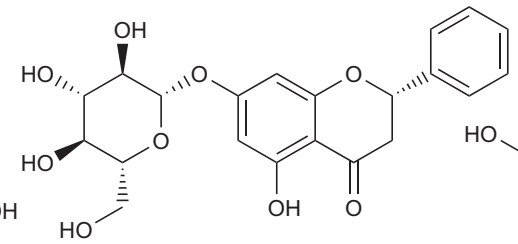

(78) Coumarin
(79) Aesculetin
(80) Iso-fraxidin
(81) Scopoletin
(82) Scopolin
(83) Tomentin
(84) Iso-rhamnetin
(85) Chrysosplenol D
(86) Casticin
(87) Herniarin
(88) Gallic acid
(89) p-hydroxy benzoic acid
(90) Vanillic acid
(91) p-coumaric acid
(92) Syringic acid
(93) Ferulic acid
(94) Sinapic acid
(95) Estragonosided

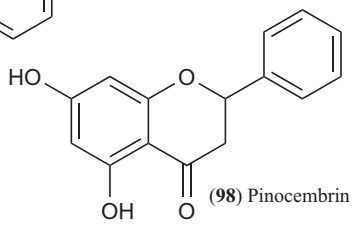
Fig. (6). contd...



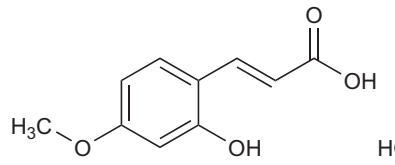
(**96**) Annagenin



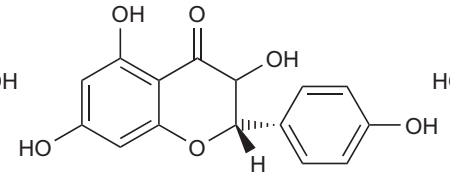
(**97**) Pinocembrin 7-O-beta-D-glucopyranoside



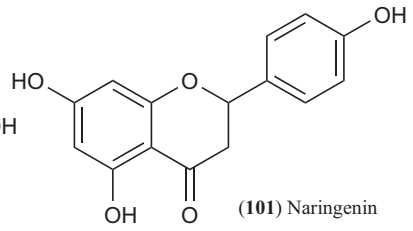
(**98**) Pinocembrin



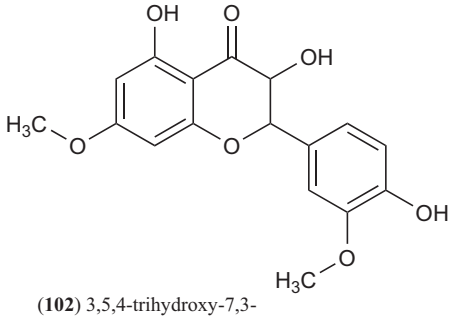
(**99**) 2-Hydroxy-4-methoxy-cinnamic acid



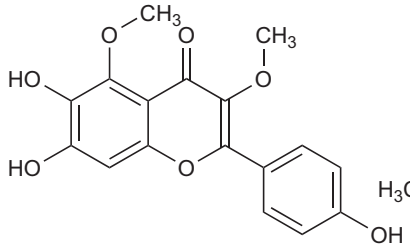
(**100**) 3,5,4-triydroxy-7-methoxyflavanone



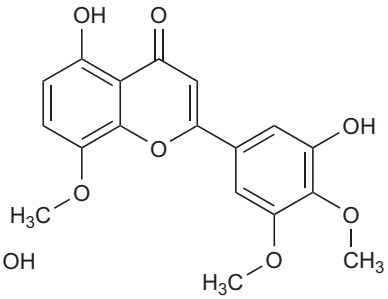
(**101**) Naringenin



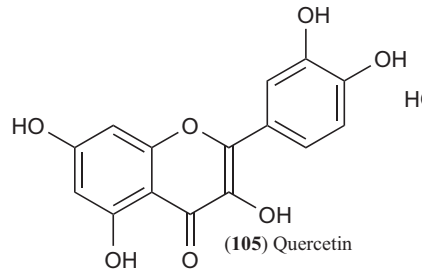
(**102**) 3,5,4-trihydroxy-7,3-dimethoxyflavanone



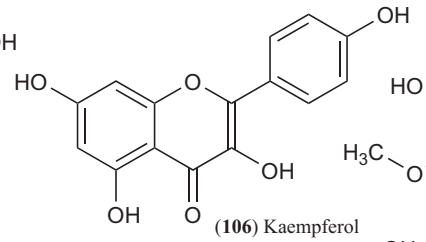
(**103**) 4,6,7-trihydroxy-3,5-dimethoxy flavones



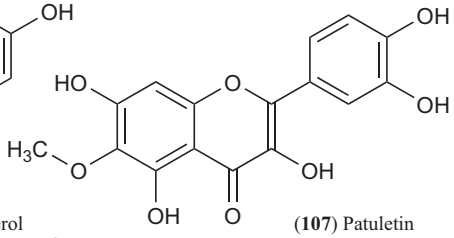
(**104**) 5,5-dihydroxy-3,4,8-trimethoxyflavone



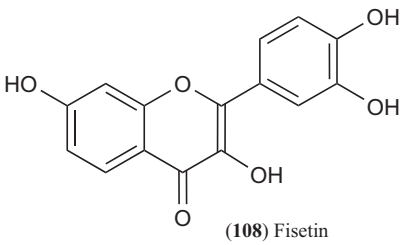
(**105**) Quercetin



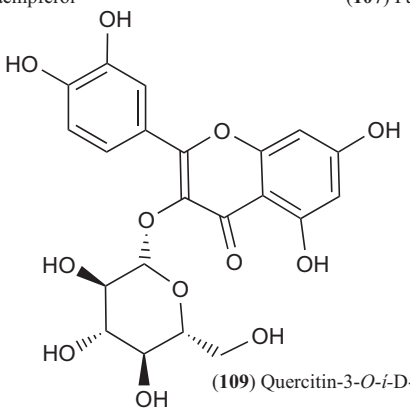
(**106**) Kaempferol



(**107**) Patuletin



(**108**) Fisetin



(**109**) Quercitin-3-*O*-*i*-D-glucoside

Fig. (6). contd...

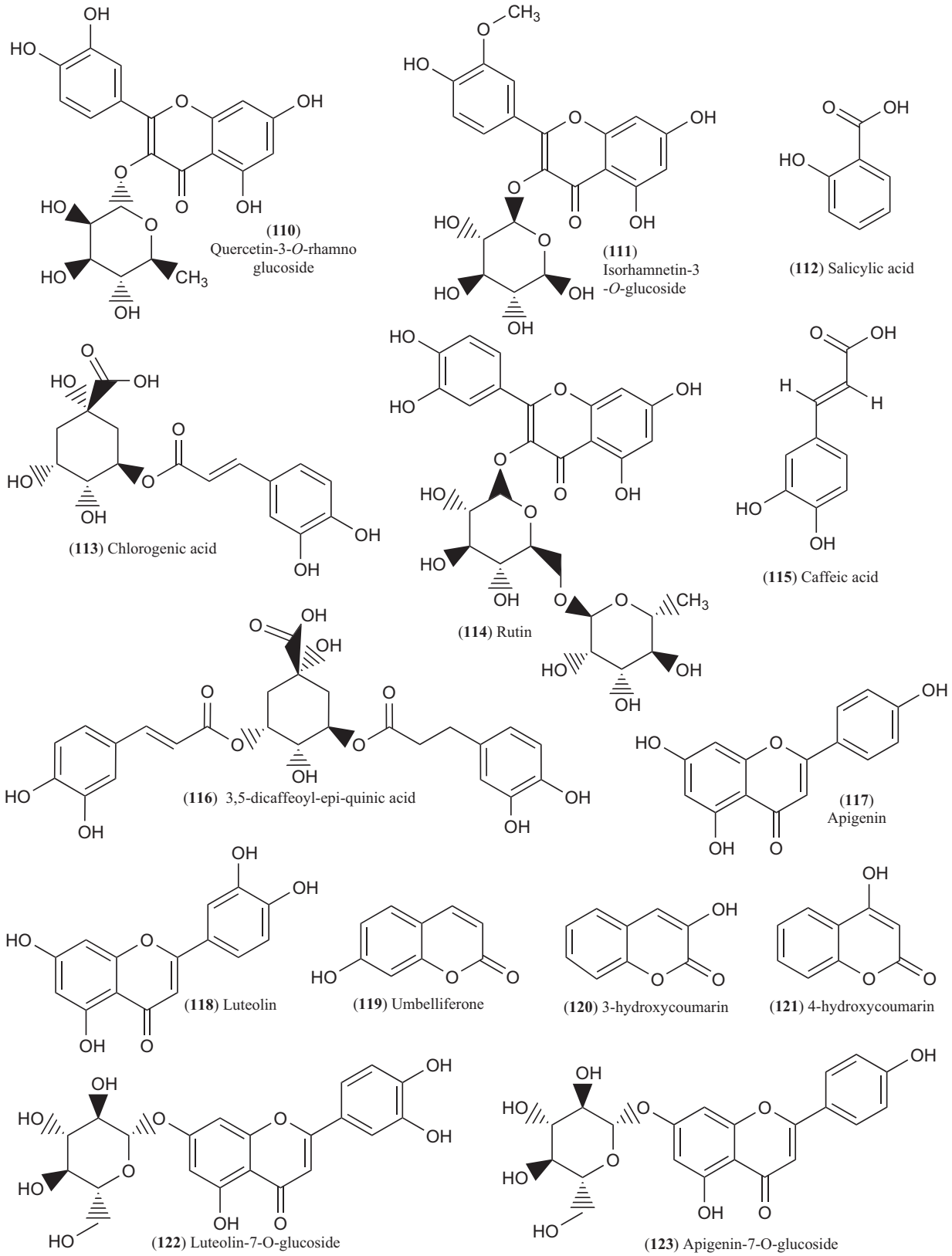
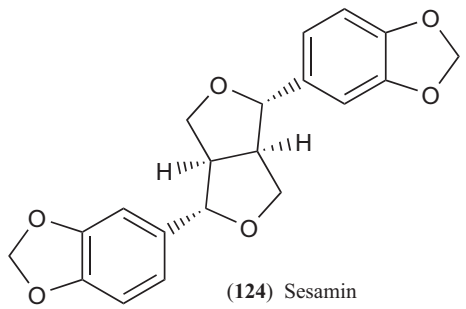
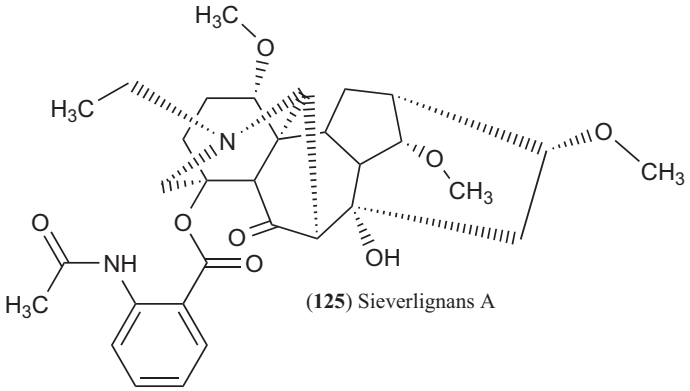


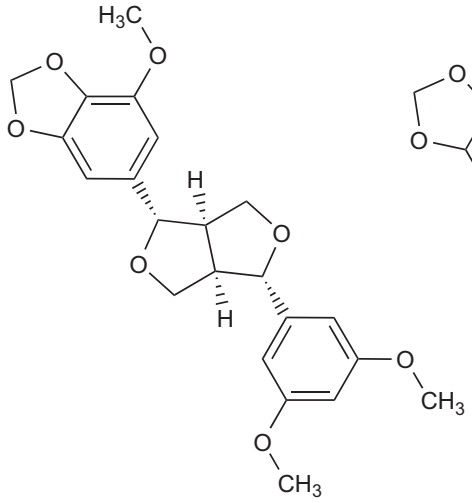
Fig. (6). Chemical structure of phenolic compounds reported in *Artemisia* species (**78-123**).



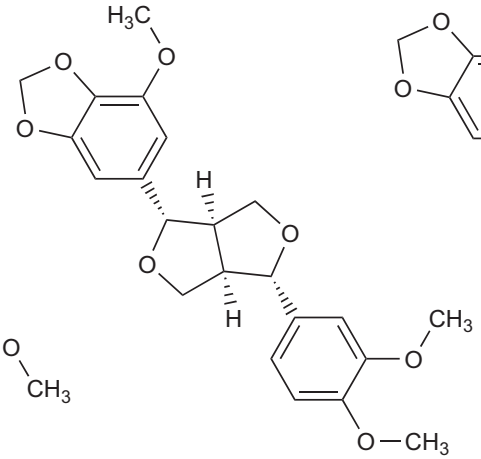
(**124**) Sesamin



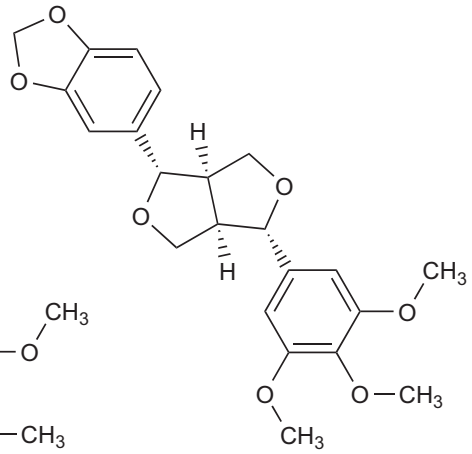
(**125**) Sieverlignans A



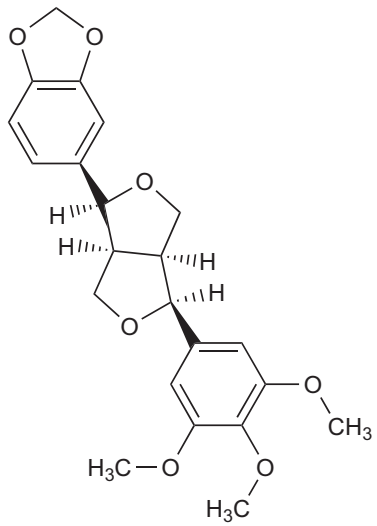
(**126**) Sieverlignans B



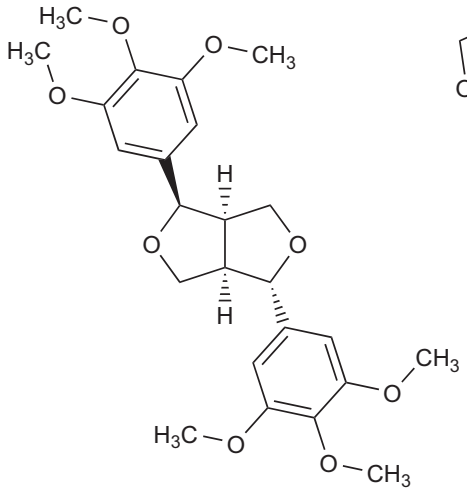
(**127**) 3,4,5-trimethoxy-3,4-methylene-dioxy-7,9:7,9-diepoxylignan



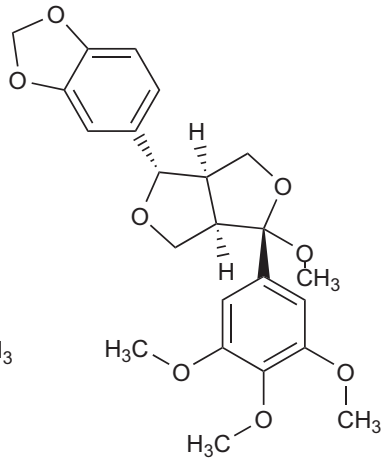
(**128**) Ashantin



(**129**) Epiashantin

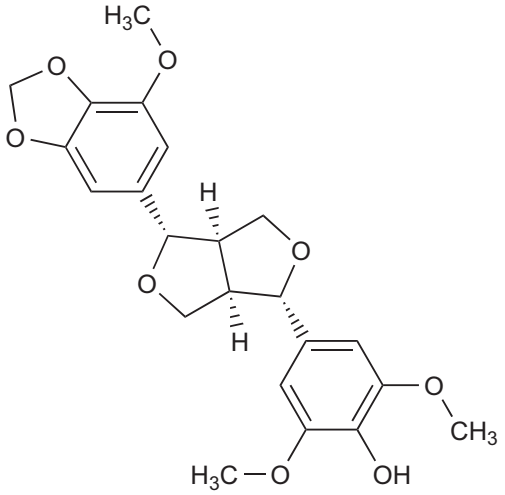


(**130**) Epiyangambin

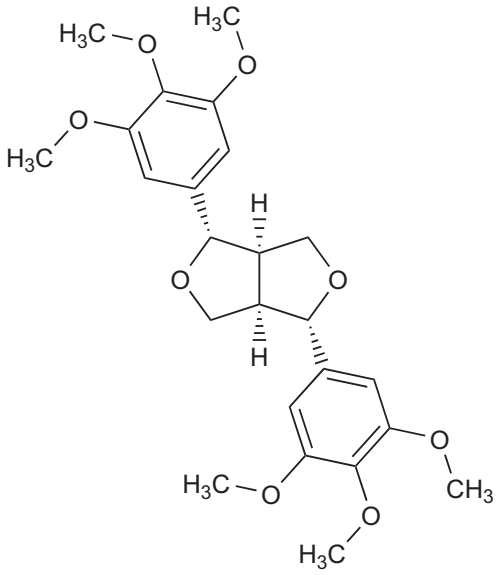


(**131**) Carullignan B

Fig. (7). contd...



(**132**) (1S,2R,5S,6R)2(5 methoxy 3,4 methylenedioxyphenyl) 6 (4 hydroxy 3,5 dimethoxyphenyl) 3,7 dioxabicyclo[3.3.0]octane



(**133**) diyangambin

Fig. (7). Chemical structutre of lignans from *Artemisia* species (**124-133**).

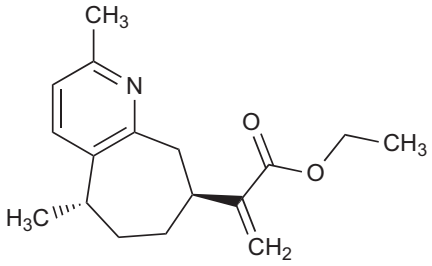
β-selinene and *Artemisia* ketone, while the Bosnian oil had *Artemisia* ketone and camphor as major components [62, 110].

On the other hand, the DPPH radical scavenging potential of *A. rutifolia* essential oils from Buryatian flora was lower compared to Tajikistan, possibly due to high content of monoterpenes in Tajikistan samples [111]. The total antioxidant capacity of *A. dracunculus* essential oil was found to exhibit superior antioxidant activity compared to butylated hydroxytoluene (BHT) when evaluated using the β-carotene method [112]. Similarly, the petroleum ether extract of *A. maritima* displayed greater radical scavenging activity than its methanol extracts. Additionally, santonin, a compound isolated from *A. maritima*, exhibited significant radical scavenging activity in both the DPPH radical scavenging and ferric reducing power assays [85]. According to a study conducted by Qadir *et al.*, in 2021, the essential oil of *A. tournefortiana* demonstrated notable free radical scavenging activity. In the DPPH assay, the essential oil exhibited an IC_{50} value of 56.2 mg/mL, with ascorbic acid serving as the standard reference [73]. When comparing the radical scavenging potential of different extracts of *A. sieversiana, A. wellbyi* and *A. annua*, the dichloromethane extract showed highest activity followed by petroleum ether, n-butanol, and ethyl acetate extracts [113]. Among three wild *Artemisia* species from Algeria, *A. judaica* exhibited the highest antioxidant effect, followed by *A. campestris* and *A. herba-alba* in DPPH and ABTS assay, while the β-carotene assay showed *A. campestris* with the strongest inhibition effect. In the CUPRAC assay, all extracts showed similar activities [114]. Similarly, in Iran, different ecotypes of *A. tournefortiana, A. khorassanica* and *A. haussknechtii* were reported from various provinces with *A. haussknechtii* from Kohgiluyeh and Boyer-Ahmad province exhibiting the highest activity in DPPH assay, and *A. khorassanica* from South Khorasan province in the FRAP assay [115]. *A. brevifolia* from low elevations in the Ladakh region shown much higher antioxidant activities in terms of DPPH and superoxide anion radical scavenging than those from high altitudes [116]. The caffeoylquinic-acid-rich fractions of *A. absinthium and A.ludoviciana* demonstrated strong antioxidant activity compared to other fractions, likely due to the presence of potent functional groups like catechol and their arrangement [117].

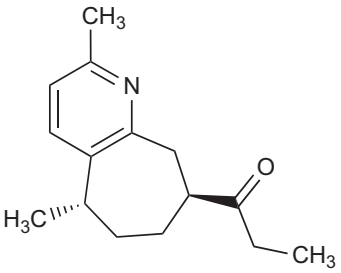
5.2. Antimalarial Property

Since ancient times, Malaria, caused mainly by *Plasmodium falciparum* (Pf), is one of the most widespread parasitic diseases in the world. Over time, several antimalarial drugs including quinine, chloroquinine, mepacrine, mefloquine, azithromycin, and others have been discovered. However, Pf malaria has developed resistance against most of these drugs, posing a major obstacle to eradicating this disease [118]. Artemisinin (ART) is a widely used antimalarial drug particularly effective against *P. falciparum* strains resistant to traditional antimalarials. The discovery of ART as an effective antimalarial drug by Tu Youyou and her team from *A. annua*earned her the Nobel Prize in medicine in 2015 [119], which significantly changed the landscape of malaria treatment and led to a radical shift in antimalarial drug development.

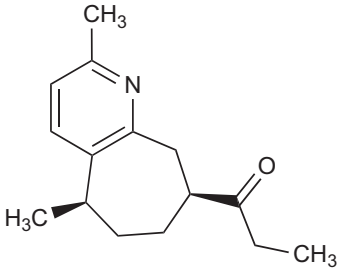
Since the discovery of ART, global malaria incidence rates have decreased by 25%, and the global malaria mortality rate has fallen down by 42% [120]. Many countries are now working towards achieving malaria-free status, replacing quinoline-based antimalarial drugs with ART-based therapies. Various derivatives of artemisinin, including dihydroartemisinin, artemether, arteether, and artesunate, have



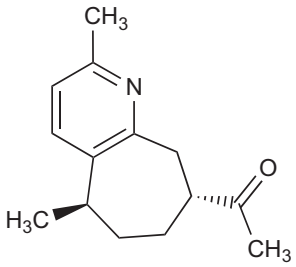
(**134**) Rupestine A



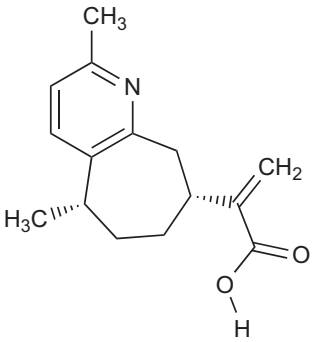
(**135**) Rupestine B



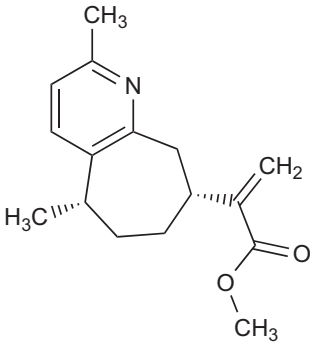
(**136**) Rupestine C



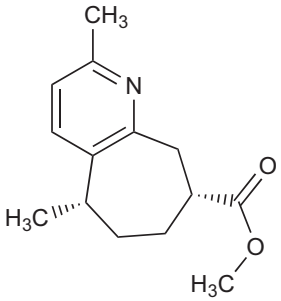
(**137**) Rupestine D



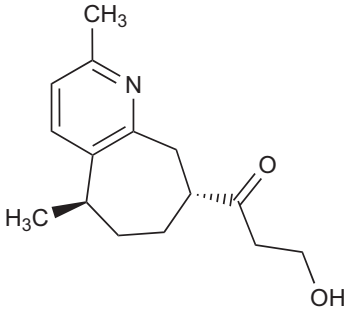
(**138**) Rupestine E



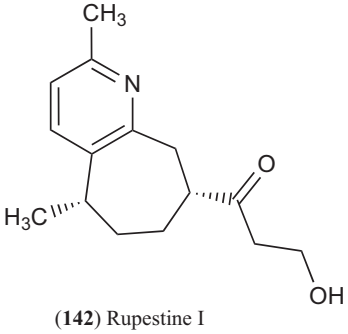
(**139**) Rupestine F



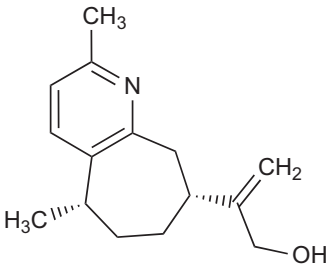
(**140**) Rupestine G



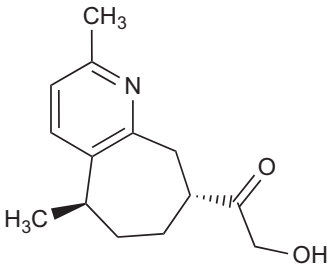
(**141**) Rupestine H



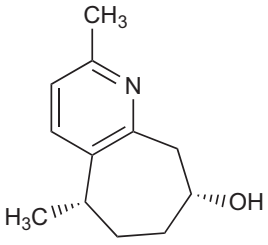
(**142**) Rupestine I



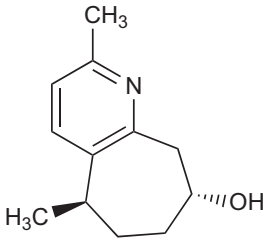
(**143**) Rupestine J



(**144**) Rupestine K

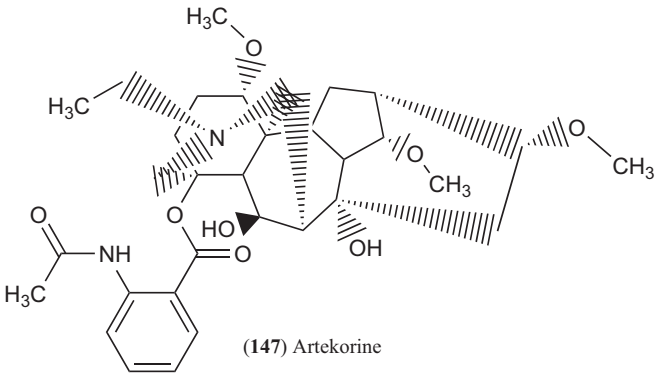


(**145**) Rupestine L

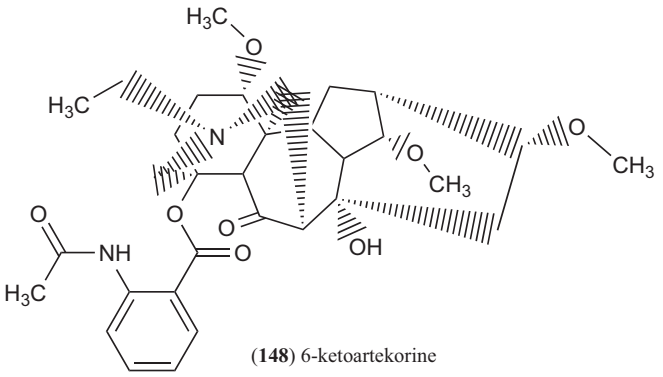


(**146**) Rupestine M

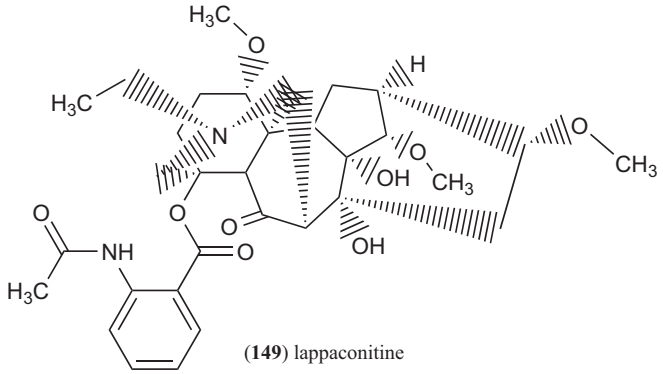
Fig. (8). contd...



(**147**) Artekorine

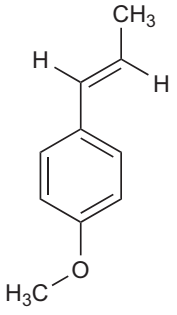


(**148**) 6-ketoartekorine

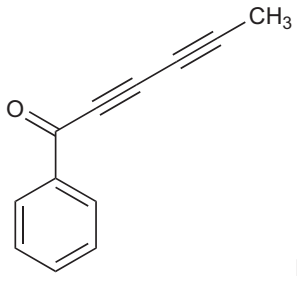


(**149**) lappaconitine

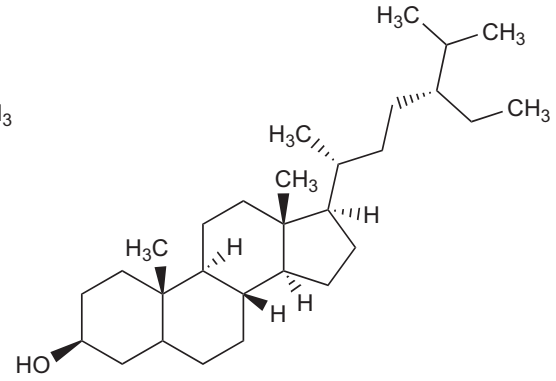
Fig. (8). Chemical structures of alkaloids from *Artemisia* species (**134-149**).



(**150**)Anethole



(**151**) Capilllin



(**152**) *beta*-sitosterol

Fig. (9). Chemical structure of anethole, capillin and *β*-sitosterol from *Artemisia* species (**150-152**).

Table 4. Pharmacological properties of various *Artemisia* species.

Biological Activity	*Artemisia* Species	Region/ Location	Type of Product Used	Mode of Study	Used on the Models/ Microbes/ Insects/Cells	Results	References
Anti-oxidant	*A. absinthium* and *A. ludoviciana*	Lithuania	Fractions of acetone extract	ABTS and FRAP	-	Dicaffeoylquinic-acid-rich fraction > monocaffeoylquinic-acid-rich fraction	[117]
	A. absinthium and *A. scoparia*	Pakistan	Essential oil	DPPH & ABTS	-	*A. scoparia*>*A. absinthium*	[134]
	A. absinthium and *A. annua*	Romania	Ethanolic extracts	DPPH and ABTS	-	*A. absinthium* of second year vegetation showed highest antioxidant activity	[268]
	A. annua	Mediterranean	Essential oil	DPPH and FRAP	-	Significantly high radical scavenging potential than the positive controls used	[109]
	A. herba-alba	High Atlas of Morocco	Essential oil	DPPH and FRAP	-	Significant radical scavenging potential which might be due to essential oil components	[269]
	A. herba-alba, *A. campestris*, and *A. judaica*	Algeria	Hydromethanolic extract	DPPH, ABTS, CUPRAC, and β-carotene assays	-	All the extracts showed significant antioxidant activity	[114]
	A. judaica	Saudi Arabia	Essential oil	FRAP, DPPH, TAC, and MCA	-	Significant free radical scavenging	[270]
	A. dracunculus	Iran	Essential oil and nanoemulsion	DPPH and FRAP	-	Nanoemulsion > free essential oil	[135]
	A. monosperma, A. sieberi, and*A. judaica*	Saudi Arabia	Methanolic extracts	DPPH, H_2O_2 and TAC	-	Significant radical scavenging due to the presence phenolic compounds	[271]
	A. rutifolia	Buryatia (Russia)	Essential oil	DPPH	-	Strong radical scavenging potential with IC_{50} = 17.55 µL/mL	[111]
	A. sieversiana, A. wellbyi and *A. annua*	Tibet	Extracts	DPPH, FRAP, ABTS	-	Dichloromethane > petroleum ether > n-butanol > ethyl acetate	[113]
	A. tournefortiana, A. khorassanica and *A. haussknechtii*	Iran	Methanolic extract	DPPH and FRAP	-	*A.haussknechtii* showed strong DPPH scavenging, whereas, *A. tournefortiana* and *A. khorassanica* showed strong FRAP scavenging	[115]
Anti-bacterial	*A. absinthium* and *A. scoparia*	Pakistan	Essential oil	Agar disc diffusion method	Gram-positive (*Bacillus subtilis*, *S. aureus*) gram-negative (*E. coli*, and *Shigella flexneri*)	Strong against gram-negative compared to gram-positive	[134]
	A. absinthium and *A. annua*	Romania	Ethanolic extracts	MIC and MBC	*E. coli, S. aureus, S. enteritidis, Klebsiella* spp. And *Listeria monocytogenes*	*A. annua* showed the strong inhibitory effect compared to *A. absinthium*	[268]
	A. annua	Mediterranean	Essential oil	Agar diffusion method and MIC	Gram-negative *(E. coli, K. pneumoniae, Salmonella* sp.) gram-positive (*S. aureus, B. subtilis and B. cereus*)	Strong antibacterial activity against gram-negative bacteria compared to gram-positive	[109]
	A. dracunculus	Iran	Essential oil and nanoemulsion	Microdilution method and 96-well microtitre plates	Gram-positive *(S. aureus*, *Listeria monocytogenes*, gram-negative (*Salmonella enteritidis*, *Shigella dysenteriae* and *E. coli)*	Strong inhibitory effect against gram-positive compared to gram-negative	[135]
	A. rutifolia	Buryatia (Russia)	Essential oil	-	Gram-positive bacteria (*S. pyogenes, S. aureus, B. cereus*), gram-negative bacteria (*E. coli, P. aeruginosa, Salmonella enterica*)	Gram-positive strong inhibition compared to gram-negative	[111]
	A. sieversiana, A. wellbyi and *A. annua*	Tibet	Extracts	Agar well diffusion assay	*E. coli*, *Salmonella*, *Streptococcus*, *S. aureus*, *P. mirabilis*, *B. cereus*, and *P. aeruginosa*	Petroleum ether extract showed the strongest inhibitory effect	[113]
	A. vulgaris	North-east India	Essential oil	Agar well diffusion method	*E. coli*, *S. aureus, P. aeruginosa, B. cereus*	Strong inhibitory effect against *S. aureus* compared to *B. Cereus,*no inhibition against the other two	[272]

(Table 4) contd….

Biological Activity	*Artemisia* Species	Region/ Location	Type of Product Used	Mode of Study	Used on the Models/ Microbes/ Insects/Cells	Results	References
Anti-fungal	*A. absinthium* and *A. scoparia*	Pakistan	Essential oil	Agar dilution method	*Aspergillus flavus*, *Aspergillus niger, Candida albicans* and *Trichophyton longifusus*	Both showed strong antifungal against *Aspergillus* species compared to other two	[134]
	A. annua	Mediterranean	Essential oil	Agar diffusion method and MIC	*Fusarium oxysporum, C. albicans* and *A. niger*	Significant antifungal activity compared to antifungal drug fluconazole	[109]
	A. herba-alba	Algeria	Essential oil	Radial growth technique	*Fusarium solani, Penicillium expansum,* and *A. flavus,*	Excellent effect agaitns *P. expansum* and *A. flavus* with 100% inhibition	[273]
	A. rutifolia	Buryatia (Russia)	Essential oil	Agar well diffusion method	*C. albicans* and *A. niger*	*A. niger* >*C. albicans*	[111]
	A. scoparia, A. lavandulaefolia, and*A. annua*	China	Essential oil	Agar diffusion method	*Colletotrichum gloeosporioides*	*A. scoparia,* showed highest inhibitory potential followed by *A. lavandulaefolia,* and *A. annua*	[136]
	A. tournefortiana	India	Extract/isolated compounds	Agar well diffusion assay and MIC	*A. niger*, *Penicilliumchrysogenum,* and *Alternaria alternata*	Chloroform >hexane, tournefortin A lowest MIC against *A. alternata*	[68]
	A. vulgaris	North-east India	Essential oil	Agar well diffusion method	*Sclerotium oryzae* and *F. oxysporum*	Stronger antifungal activity against *S. Oryzae* than *F. oxysporum*	[272]
Antimalarial	*A. absinthium*	Nigeria	Aqueous extract	*In vivo* curative antimalarial activity (Rane's test) and Repository test	Swiss mice experimentally infected with chloroquine resistant *P. berghei* (NK 65)	Showed significant curative and repository antiplasmodial proeprties	[129]
	A. afra	Burundi	Extracts	*In vitro* antimalarial activity	*P. falciparum* (W2 and D6)	Significant antiplasmodial activity	[127]
	A. judaica	Egypt	Extracts	*In-vitro* anti-plasmodial activity and *in vivo* antimalarial efficacy of plant extracts	*Plasmodium falciparum* (3D7 strain) was maintained in O^+ human erythrocytes-*in vitro* and BALB/c mice infected with aprox. 1×10^7*P. yoelii*-infected erythrocytes-*in vivo*	Showed low to moderate *in vitro* antimalarial activity and also suppressed parasite growth *in vivo*	[124]
	A. nilagirica	India	Methanol extract	*In-vitro* anti-plasmodial activity	chloroquine sensitive (3D7) and chloroquine resistant (RKL-9) strains of *P. falciparum*	Showed significant activity against both strains	[125]
Insecticidal	*A. argyi*	China	Essential oil	Larvicidal, fumigant and repellent activity assays	*Anopheles sinensis*	Essential oil from different provinces showed different activities	[156]
	A. dracunculus	Iran	Essential oil/nangel/nanoemulsion	Larvicidal activity	*Anopheles stephensi*	Significant larval mortality was exhibited by both nanogel and nanoemulsion	[155]
	A. herba-alba	Tunisia	Essential oil	Larvicidal activity	*Tribolium castaneum*, *Sitophilus oryzae* and *Lasioderma serricorne*	Significant insecticidal activity against *L. serricorne* and *T. castaneum*	[274]
	A. lavandulaefolia	China	Essential oil	Bioassays and enzymatic assays	*Plutella xylostella*	Showed significant fumigant activity and carboxylesterase (CarE) and glutathione-S-transferase enzyme activities significantly decreased	[148]
	A. maritima	India	Essential oil	Fumigant, repellent, persistence, ovipositional deterrent assays	*Callosobruchus chinensis*and*Callosobruchus maculatus*	Promising fumigant toxicity and significant repellence; more ovipositional deterrence against *C. chinensis* than *C. Maculates*	[150]
	A. vulgaris	Indonesia	Ethanol extract	Larvicidal activity	Aedes aegypti	Significant larvicidal activity wtih 96% of oviposition deterrent effect	[153]
	A. vulgaris	China	Essential oil	Bioassays and enzymatic assays	*Tribolium castaneum*	Inhibits the growth, development, and reproduction; partially inhibited serine protease, cathepsin, and lipase signaling pathways	[146]

(Table 4) contd….

Biological Activity	*Artemisia* Species	Region/ Location	Type of Product Used	Mode of Study	Used on the Models/ Microbes/ Insects/Cells	Results	References
Anti-cancer	*A. argyi*	Taiwan	Aqueous extract	MTT, colony, and spheroid formation assays	Lung cancer cell lines (CL1-0 and CL1-0-GR cells)	Induced apoptosis by regulating PI3K/AKT and MAPK signaling pathways	[275]
	A. annua	Korea	Isolated compounds	CCK-8 assay, Western blot, and flow cytometric analysis	Human colorectal cancer cell line (HCT116-p53$^{+/+}$)	Cell death by upregulation of p53-dependent targets such as p21, bax and DR5	[159]
	A. judaica	Saudi Arabia	Methanol extract/nanoparticles	MTT assay	Prostate cancer cell line (PC3 cells)	Significant cytotoxicity with IC_{50} value of 20.8 µg/mL	[276]
	A. marschalliana	Iran	Essential oil and extracts/fractions	MTT assay, RT-PCR, Western blot, and flow cytometric analysis	Breast cancer cell line (MCF-7) and liposarcoma cell line (SW872)	60% and 80% fractions of dichloromethane extract showed strongest activity against breast and liposarcoma cancer cell lines respectively	[277]
	A. moorcroftiana	India	Isolated compounds	MTT	Lung (A-549), leukemia (THP-1), prostate (PC-3) and colon (HCT-116) cell lines	Few of isolated compounds, like casticin, campesterol, gorgonolide inhibited growth of cancerous cell lines	[130]
	A. sieberi	Saudi Arabia	Essential oil	SRB assay	HCT116, HepG2, A549 and MCF-7 cells	Cytotoxic activity MCF-7 with an IC_{50} value of 38.7 µg/ml	[157]
	A. vulgaris	Nepal	Ethanol extract	MTT assay	Lung cancer cell lines (A549 cells)	Apoptosis by activation of caspase and downregulation of Wnt3 and β-catenin	[278]
	A. vulgaris	Vietnam	Methanol extract	Western blotting, cell viability	Leukemia cell lines (K562, TCCY-T315I, Ba/F3-T315I/Y253H/E279K)	Supressed AKT and MAPK activation by inhibiting the phosphorylation of BCR/ABL	[279]
Anti-inflammatory	*A. annua*	China	Aqueous extract	*In-vivo* animal study	BALB/c mice	Significantly reduced the symptoms of atopic dermatitis	[280]
	A. argyi	Korea	Ethanol extract	*In-vivo* animal study	Mouse leukemia macrophage cell (RAW 264.7 cell line)	Induced Nrf2 and HO-1 and inhibited NF-κB	[180]
	A. dracunculus	USA	Essential oil/compounds	Ca^{2+} mobilization, chemotaxis and cytotoxicity assays	Human THP-1 monocytic cells	Essential oil and farnesene showed promising anti-inflammatory response	[175]
	A. gmelinii	Korea	Ethanol extract	*In-vivo* animal study, cell viability, measurement of cytokines and chemokines	Male BALB/c mice	Reduced the levels of cytokines and chemokines significantly	[177]
	A. judaica	Saudi Arabia	Essential oil	*In-vivo* animal study	3-month-old sprague dawley female rats	Significant decrease in the levels of inflammatory TNF-α and interleukins in the tissue homogenates	[270]
	A. sieberi	Egypt	Essential oil	*In-vivo* animal study	Rats	Reduced oxidative stress and inflammatory responses associated with gastric ulcer	[281]
	A. vulgaris	China	Essential oil	*In-vivo* animal study	Zebrafish	Alleviated zebrafish enteritis effectively	[282]
Anti-spasmodic	*A. campestris*	Morocco	Aqueous extract	*In-vivo* animal study	6-8 week old wistar rats and 4 month old New Zealand rabbits	Significant antispasmodic effect	[194]
Anti-diabetic	*A. abrorescens*	Morocco	Aqueous extract	*In vivo* animal study	STZ-induced diabetic rats	Significantly reduced the blood glucose and plasma triglyceride levels	[282, 283]
	A. absinthium	Morocco	Ethyl acetate and aqueous extracts	Pancreatic α-amylase and intestinal α-glucosidase enzymes test	Wistar rats	Significant inhibitory effect of the enzymes shown by both extracts	[284]
	A. annua	Egypt	Ethanol extract	α-glucosidase and α-amylase inhibition assays	-	Significant anti-diabetic activity	[207]

(Table 4) contd….

Biological Activity	*Artemisia* Species	Region/ Location	Type of Product Used	Mode of Study	Used on the Models/ Microbes/ Insects/Cells	Results	References
	A. campestris	Morocco	Hydro-ethanolic extract	*In vivo* animal study and *in vitro* α-glucosidase and α-amylase inhibition assays	Alloxan induced diabetic wistar rats	Significantly decrease glucose level and reduced α-glucosidase and α-amylase activity	[285]
	A. dracunculus	USA	Ethanol extract	*In-vivo* animal study	Male C57BL/6J mice	PMI-5011 exhibited significant anti-diabetic effect	[200]
	A. gmelinii	China	Essential oil	α -glucosidase inhibition assay and molecular docking study	-	Inhibited the α-glucosidase activity	[203]
	A. judaica	Saudi Arabia	Ethanol extract	*In-vivo* animal study	Streptozotocin (STZ)-induced male diabetic albino Wistar rats	Along with glyburide, *A. judaica* extract controls blood glucose level	[205]
Anthelmintic	*A. absinthium*	Solvakia	Methanol extract	*In vitro* egg hatch test and *in vivo* animal study	*Haemonchus contortus* in sheep (Improved Valachian)	Strong ovicidal effect with ED_{50} value of 1.40 mg/ml	[213]
	A. absinthium	Romania	Aqueous extract	*In vitro* egg hatching and larval development assays	Donkey strongyles	Strong ovicidal effect with LC_{50} value of 0.486 mg/ml	[214]
	A. herba-alba	Ethiopia	Methanol extract	*In vitro* adult motility and egg hatch inhibition assay	*H. contortus*	98.67% egg hatch inhibition by 1 mg/ml extract	[217]

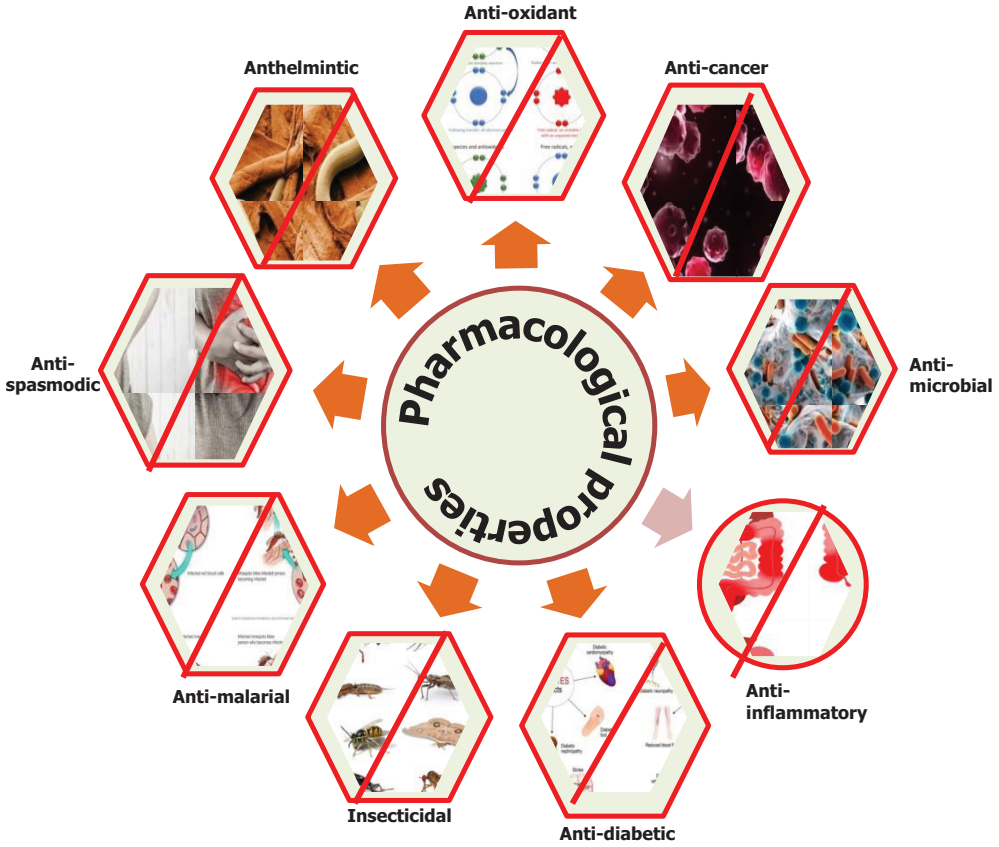


Fig. (10). Various biological activities of genus *Artemisia.* (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

shown efficacy against multidrug-resistant *P. falciparum* and possess antitumor activity [121]. These artemisinin derivatives, along with artemisinin itself, are commonly utilized in combination with other drugs such as lumefantrine, mefloquine, amodiaquine, sulfadoxine/pyrimethamine, piperaquine, and chlorproguanil/dapsone. This combined treatment approach is referred to as artemisinin-based combination therapy (ACT). A few synthetic peroxides with struc-

tures similar to artemisinin, such as OZ277 (arterolane) and OZ439 (artefenomel), are currently under clinical trials as important antimalarial drugs [122, 123].

In addition to *A. annua*, several other *Artemisia* species also contain antimalarial artemisinin in varying concentrations in different plant parts, indicating their potential antimalarial properties [10]. Extract of *A. judaica* demonstrated low-to-moderate antimalarial activity *in vitro* with an IC_{50} value of 20.0 µg/ml and suppressed the growth of *P. yoelii* malarial parasites *in vivo* by about 13.5-60.6% [124]. *A. nilagirica* and *A. afra* exhibited significant antimalarial activity against both chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum* [125, 126]. Furthermore, a recent study conducted by Kane *et al.* (2023), provided insights into the mechanism of action of *A. afra* extracts, revealing their impact on the expression of fatty acid biosynthesis (FAS_II) pathway enzymes such as FAB I and FAB Z which play a crucial role in the survival of the parasite [127]. Another study conducted by Bamunuarachchi *et al.* (2013) reported the potent antimalarial properties of ethanol extract of *A. vulgaris* leaves against a *P. berghei* murine malaria model, which exhibits pathogenesis similar to *P. falciparum* malaria [128]. In a similar study, the antimalarial properties of *A. absinthium* aqueous extracts were evaluated *in vivo* against *P. berghei* (NK 65), revealing repository and curative antimalarial activities of 52.72% and 89.2%, respectively [129]. Compounds isolated from *A. moorcroftiana* such as Casticin also exhibited antimalarial activity with an IC_{50} of 2.4×10 5 M compared to standard artemisinin, which has an IC_{50} of 3.3×10 8 M [130]. Tehranolide, a sesquiterpene lactone compound, was identified as another antimalarial agent from *A. diffusa* [131]. Davanone, the main constituent of several *Artemisia*, is another identified antimalarial agent present in varying concentrations in different species. For instance, *A. persica* contains about 60% davanone followed by 30% in *A. indica,* 21% in *A. abrotanum,* 19.3% in *A. turanica* respectively. Additionally, *A. seibera* and *A. herba-alba* have also been observed to contain davanone [132].

5.3. Anti-microbial and Anti-fungal Activity

The essential oils derived from *Artemisia* species have demonstrated antimicrobial activity against both Gram-positive and Gram-negative bacteria as well as various fungi. For instance, *A. annua* essential oil exhibited strong antimicrobial activity against approximately twenty strains of *Malassezia* species associated with human skin disorders [133]. In the Mediterranean region, *A. annua* essential oil displayed significantly higher antibacterial activity against Gram-negative strains, particularly *E. coli*, compared to Gram-positive strains [109]. Similar findings of strong inhibitory activity against Gram-negative strains in comparison to Gram-positive strains were also reported for *A. absinthium* and *A. scoparia* essential oil when tested against bacterial microbes [134]. However, *A. dracunculus* essential oil and nano-emulsion showed strong antibacterial activity against Gram-positive strains, as opposed to Gram-negative strains [135]. Another study reported a strong inhibition of Gram-positive bacteria compared to Gram-negative bacteria when treated with essential oil of Buryatian *A. rutifolia* [111]. When comparing extracts of *A. sieversiana, A. wellbyi* and *A. annua* prepared in different solvents, petroleum ether demonstrated the most potent inhibitory activity against most of the tested bacteria [113]. *A. annua* essential oil also displayed significant antifungal activity against *Fusarium oxysporum*, *Candida albicans* and almost twenty strains of *Malassezia* species associated with human skin disorders [109, 133]. *A. scoparia* essential oil exhibited highest antifungal activity with EC_{50} value of 9.320 µL/mL, followed by *A. lavandulaefolia* (19.064 µL/mL), and *A. annua* (30.278 µL/mL) against *Colletotrichum gloeosporioides,* the causative agent of Mango anthracnose, a significant fungal disease [136].

Certain compounds isolated from *A. sieversiana*, such as *β*-sitosterol, demonstrated antibacterial activity against *Salmonella typhii* and *Corynebacterium* as well as antifungal activity against *Fusarium* spp. Similarly, epiashantin showed antimicrobial activity against Gram-positive bacteria *Staphylococcus aureus, Bacillus subtilis, Escherichia coli*, and the yeast *C. albicans.* Furthermore, absinthin showed weak anti-HIV activity [104]. Vulgaron B, a sesquiterpene isolated from essential oil of *A. iwayomagi,* was reported to possess significant bactericidal properties against both antibiotic-susceptible and antibiotic-resistant human pathogens [137]. Another study reported strong antimicrobial activity of artemisinin and dehydroleucodine against *Helicobacter pylori,* the causative agent of chronic gastritis and peptic ulcers [138]. Li *et al.* (2005) conducted a study on the antiviral activity of *A. annua* ethanol extract against severe acute respiratory syndrome coronavirus (SARS-CoV) using Vero cell-based CPE/MTS screening [139]. It was speculated that *A. annua* ethanol extract may be effective against coronavirus disease-2019 (COVID-19) [140]. Nair *et al.* (2021) studied the effect of hot water extracts (tea infusions) from seven cultivars of *A. annua,* based on artemisinin, total flavonoids, or dry leaf mass against SARS-CoV-2 and observed anti-viral activity with IC_{50} values of 0.1-8.7 µM, 0.01-0.14 µg, and 23.4-57.4 µg, respectively [141].

Further studies using hot water extracts of four cultivars (A3, BUR, MED, and SAM) were conducted to evaluate their effects against five variants of SARS-CoV-2: alpha, beta, gamma, delta and kappa. These studies revealed a strong anti-viral effect of the extracts against all variants. The IC_{50} values, based on artemisinin and leaf dry weight, ranged from 0.3 to 8.4 µM and 11.0 to 67.7 µg DW respectively [142]. These findings suggest that *A. annua* extracts have the potential to be used in the treatment of COVID-19 caused by new variants of SARS-CoV-2.

5.4. Insecticidal Property

Insects cause significant damage to agricultural food products, particularly during their storage. The use of chemical insecticides results in environmental and health concerns and hence these have been replaced by plant-based essential oils [143]. Many species of *Artemisia* possess strong insecti-

cidal activity. For instance, *A. sieversiana* demonstrated insecticidal activity against *Sitophilus zeamais* adults with LD_{50} (lethal dose) values of 112.7 mg/adult and LC_{50} (lethal concentration) values of 15.0 mg/L air. In comparison, the positive controls exhibited values of 4.29 mg/adult and 0.67 mg/L air respectively [144]. When compared to the positive control DEET, the essential oil of *A. annua* demonstrated comparable or even superior insect repellent activity against two significant pests found in stored products: the cigarette beetle (*Lasioderma serricorne*) and the red flour beetle (*Tribolium castaneum*) [61]. Deb and Kumar (2020) conducted a study where they found that the essential oil of *A. annua* obtained through petroleum ether extraction exhibited enhanced efficacy in fumigant assays against both the adult (0.81 mg/L air) and larval (0.65 mg/L) stages of *T. castaneum* [145].

A. vulgaris essential oil inhibited the growth, development and reproduction of *T. castaneum,* by partially inhibiting the activity of serine protease, cathepsin, and lipase signalling pathway enzymes [146]. The authors also discovered that the essential oil induced the expression of detoxification enzyme uridine diphosphate glucosyltransferases, which could be one of the possible mechanisms of resistance [147]. Essential oil components of *A. lavandulaefolia* were tested against *P. xylostella*, one of the most significant pests of cruciferous crops. Among numerous essential oil components, eucalyptol and caryophyllene oxide showed strong toxicity [148]. Further studiesrevealed that (-)-4-terpinol also reduced the growth of *P. xylostella* by decreasing the activity of glutathione S-transferase, catalase, acetylcholinesterase and Na+/K+-ATPase [149]. The essential oil of *A. maritima* also demonstrated promising fumigant toxicity, repellence and ovipositional deterrence of pulse beetle (*C. chinensis* and *C. maculatus*) by inhibiting the activity of glutathione-S-transferase enzyme [150]. The LC_{50} values estimated for essential oil of *A. sieberi* were 1.45 µL/L against *Callosobruchus maculatus*, 3.86 µL/L against *Sitophilus oryzae* and 16.76 µL/L against *T. castaneum* [151]. *A. herba-alba* and *A. absinthium* essential oils showed LC_{50} and LD_{50} of 30.22 and 0.209 µL/L against *Oryzaephilus surinamensis*, respectively [152].

In addition to their insecticidal activity against pests, essential oils derived from various *Artemisia* species have also demonstrated effectiveness against vectors of some harmful diseases such as dengue and malaria (Table **4**). *A. vulgaris* essential oil was tested against the vector of dengue fever *A. aegypti*, and significant larvicidal, adulticidal and ovicidal activities were observed [153]. Furthermore, a nano-ointment prepared from *A. vulgaris* leaf extract exhibited excellent and prolonged repellent effect against *A. aegypti* [154]. Nanogel and nano-emulsion of *A. dracunculus* bark essential oil showed significant larvicidal activity with LC_{50} values of 6.68 (2-19 µg/mL) and 13.53 (7-25 µg/mL), respectively, against the malaria vector *Anopheles stephensi* larvae [155]. *A. argyi* essential oils from different geographical provinces of China exhibited very strong larvicidal, fumigant and repellent effects on both larvae and adults of *Anopheles sinensis* [156].

5.5. Anti-cancer Property

Essential oil and extracts derived from various *Artemisia* species have demonstrated significant cytotoxic activity against different cancer cell lines. A study showed that *A. sieberi* essential oil showed significant anti-cancer activity against MCF-7 cells and inhibited the activation of the extracellular signal-regulated kinase (ERK) signalling pathway [157]. Hydro-alcoholic extracts of *A. argyi*, *A. vulgaris,* and *A. judaica* also exhibited significant cytotoxic potential against various cancer cell lines by inhibiting or down-regulating various signalling pathways (Table **4**). The anti-proliferative and cytotoxic effects of these plant extracts are assigned to the bioactive compounds such as alkaloids, phenols, flavonoids, terpenes, sesquiterpene lactones [158].

Polyphenols isolated from *A. annua* showed anti-cancer properties against colorectal cancer cell lines by activating phospho-c-Jun N-terminal kinase (JNK) and up-regulating tumor suppressor p53-dependent targets such as p21, Bax and DR5. These compounds also induced cleavage of PARP1 and lamin A/C [159, 160]. A study found that *A. carvifolia* plants with the rol A gene exhibited significantly higher cytotoxic potential compared to wild plants due to elevated polyphenol levels [161]. Chlorogenic acid (5-*O*-caffeoylquinic acid), a phenolic acid, isolated from *A. absinthium* extract showed anticancer activity in the liver, large intestine and tongue. It also exhibited an ameliorative effect on oxidative stress [15].

Flavonols chrysosplenol D and casticin, isolated from *A. annua* were tested against various cancer cell lines including breast, prostate, pancreas and non-small-cell lung cancer (NSCLC). Both compounds showed promising cytotoxic activity against the cancer cells, albeit with varied intensity [162]. Further studies on NSCLC, analysing RNA-sequences and screening differentially expressed genes, indicated that these flavonols induce DNA damage and apoptosis by down-regulating the expression of topoisomerase IIα [163]. Chrysosplenol D also induces apoptosis in oral squamous cell carcinoma by suppressing the mitogen-activated protein kinase pathway and activating heme oxygenase-1 [164]. Apart from their recognized anti-malarial properties, artemisinin and its derivatives also hold significant therapeutic value in the treatment of various cancer types. These compounds exert their effects by generating reactive oxygen species (ROS) that induce apoptosis in cancer cells. Notable cancer types that have exhibited responsiveness to artemisinin treatment include leukemia, glioblastoma, T-cell lymphoma, neuroblastoma, and breast cancer [165]. In specific cases, such as salivary gland cancer cell lines like A-253, artemisinin treatment triggers the activation of pro-apoptotic proteins like PARP1 and caspase-3, thereby initiating apoptosis [166]. Arglabin, a sesquiterpeniod lactone isolated from *Artemisia glabella*, an endemic wormwood species in Kazakhstan, was approved as an anticancer drug in that country in 1996. Arglabin inhibits the phosphorylation of EF-

GR-RTK and downstream signalling pathways, mTORC1 and mTORC2. It also induces autophagy and apoptosis in human prostate cancer cell lines [167]. Another sesquiterpeniod lactone called ludartin, produced in the aerial parts of *A. amygdalina* displays potent anticancer activity (6.6 μM to 19.0 μM) against mouse melanoma and human epidermoid carcinoma in MTT assay [88, 89]. Yomogin, a sesquiterpeniod lactone isolated from *A. princeps*, has been identified to synergistically increase the differentiation of human promyelocytic leukemia HL-60 cells when combined with 1, 25-dihydroxyvitamin D [168]. Furthermore, yomogin induces apoptosis in human promyelocytic leukemia HL-60 cells by activating caspase-8, cleaving Bid, and translocating Bax to mitochondria, followed by the release of cytochrome *c* into the cytoplasm [87].

Tehranolide, a newly discovered antitumour sesquiterpeniod lactone isolated from *A. diffusa,* selectively inhibits the proliferation of breast cancer cell lines. It achieves this by arresting the cell cycle, decreasing PMA-induced COX-2 expression and PGE 2 production, as well as COX-2 promoter-driven luciferase activity in a dose dependent manner [169]. Analogues of santonin, a sequiterpeniod lactone found in the aerial parts of *A. maritima,* have also been reported as potent anticancer molecules with IC_{50} value of 0.01 μM on prostate cancer cell lines. They function by down regulating NF-κB [170]. Sesquiterpeniod lactones, artemisolide and arteminolides A-D, isolated from the aerial parts of *A.argyi*, exhibited *in vitro* cytotoxic activity against numerous cancer cells and inhibited tumour growth in a mouse xenograft model and human tumour xenograft, respectively [82, 171].

Casticin inhibits the growth of various cancer cell lines such as leukemia (THP-1), lung (A549), prostrate (PC-3) and colon (HCT-116), with IC_{50} values of 2.3, 4.6, 7.6 and 8.3 μM respectively. Additionally, campesterol showed significant anticancer activity against THP-1 and A549 cell lines with an IC_{50} of 11.4 and 8.5 μM [130]. Two compounds, absinthin and achillin, isolated from *A. absinthium*, demonstrated inhibitory effects on SMMC-7721 cell lines *in vitro*, indicating anticancer activities [172].

5.6. Anti-inflammatory Property

In a study conducted by Eidi *et al.*, in 2016, notable analgesic and anti-inflammatory properties of *A. dracunculus* were identified [173]. The ethanolic extract derived from *A. dracunculus* demonstrated significant alleviation of stress-induced social avoidance and self-neglect behaviours in a mouse model of depression [174]. Farnesene, an essential oil component of *A. dracunculus*, down-regulated the human neutrophil chemotaxis induced by *f*MLF (IC_{50} = 1.2 μM), WKYMVM (IC_{50} = 1.4 μM), or interleukin 8 (IC_{50} = 2.6 μM) [175]. Phenylpropanoids and flavonoids from the methanolic extract of *A. gmelinii* showed free radical anti-inflammatory activity, which might be helpful to cure inflammatory liver conditions [176]. By blocking the mitogen-activated protein kinases (MAPK)/nuclear factor kappa- light-chain B cells (NF-B) signalling pathway, the ethanolic extract of *A. gmelinii* reduced the levels of cytokines, chemokines, inducible nitric oxide synthase, and cyclooxygenase-2 in alveolar macrophages [177]. *A. gmelinii* extract enhanced the level of cytokines and suppressed the transcription factor of TH1 and TH2 thereby reducing inflammation in lung and nasal tissues of allergic and asthmatic mouse models. The extract of *A. scoparia* extract and 3, 5-dicaffeoyl-epi-quinic acid significantly decreased inflammatory mediators, such as TSLP, TNF-α, IL-1β and IL-6 *via* blockade of caspase-1/NF-kB signalling pathway. Furthermore, they exhibited the ability to reduce serum levels of histamine, IgE, TSLP, and IL-4 in mice with DNFB-induced atopic dermatitis. This effect is thought to be mediated through the regulation of caspase-1 signalling pathways [178, 179]. *A. argyi* extract also exhibited anti-inflammatory activity by suppressing the expression of cytokines and other pro-inflammatory proteins in various tested tissues and cells [180-182].

Many sesquiterpenoid molecules isolated from *Artemisia* species have been reported to exhibit anti-inflammatory and immunomodulatory effects. Sesquiterpenes isolated from *A. princeps, A. sieversiana* and *A. vulgaris* exhibited promising anti-inflammatory activity by suppressing the expression of pro-inflammatory cytokines and nitric oxide (NO) in lipopolysaccharide (LPS) induced RAW 264.7 macrophages [183-185]. Sesquiterpene lactones isolated from *Artemisia* species are also effective anti-inflammatory agents. Among 22 sesquiterpene lactones isolated from *A. vulgaris*, most of them inhibited NO production in LPS-activated RAW 264.7 macrophages [186]. Artemisinin has also been observed to produce anti-inflammatory effects by inhibiting the secretion of tumour necrosis factor (TNF)-α, interleukin-(IL) 1*β*, and IL-6 in a dose-dependent manner [187]. Furthermore, its derivatives like dihydroartemisinin, artesunate also produce anti-inflammatory effects by inhibiting the production of IL-1*β*, IL-6 and IL-8 in human rheumatoid arthritis through NF-κB inhibition [188]. Artemisolide isolated from *A. asiatica*, and other bioactive sesquiterpenoid lactones like arteminolides B and D, moxartenolide, deacetyllaurebiolide, 3α-4α-epoxyrupicolins C-E, and 3-methoxytanapartholide isolated from *A. sylvatica* produce anti-inflammatory response by inhibiting NO and TNF-α production [83].

Dehydroleucodine, a sesquiterpenoid lactone isolated from *A. douglasiana* exerts an anti-inflammatory response by interfering with transcription factors, such as NF-κB and cytokines [189]. *A. sieversiana* compounds including sesamin, absinthin, achillin and several flavonoid compounds, demonstrate anti-inflammatory effects [104]. Additional sesquiterpenoid lactones derived from *Artemisia* species and known for their anti-inflammatory and immunomodulatory properties include arglabin, yomogin [190, 191]. One study proposed arglabin as a promising new drug to treat inflammation and atherosclerosis, based on its pharmacological actions including reduction in inflammation and plasma lipids, increased autophagy, and induction of an anti-inflammatory phenotype in tissue macrophages in ApoE2. Ki mice fed a high-fat diet [192].

5.7. Anti-spasmodic Property

The essential oil of *A. maritima* displayed spasmolytic activity by suppressing spontaneous contractions, with an EC_{50} value of 0.24 mg/mL (range: 0.11-0.39). This activity is comparable to that of anti-spasmodic drugs like verapamil and papaverine, which are known anti-spasmodic drugs. The mechanism of action involves dual inhibition of Ca^{++} influx and phosphodiesterase inhibitors [69]. *A. dracunculus* essential oil exhibits sedative effects and motor deficits at certain anticonvulsant doses. These effects can be attributed to the terpene compounds present in the oil such as eugenol and anethole, which possess anaesthetic, sedative and muscle relaxant properties [193].

In vivo evaluation of the aqueous extract of *A. campestris* on Wistar rats and rabbits demonstrated significant myorelaxant and anti-spasmodic effects. The extracts exhibited an IC_{50} of 1.52 ± 0.12 mg/ml and acted on both muscarinic and nicotinic receptors, as well as guanylate cyclase pathway [194]. Furthermore, the authors' investigation of the impact of essential oils revealed significant effects on cholinergic receptors, likely attributed to the presence of major compounds such as m-Cymene, Spathulenol, α and β-Pinene, and α-Campholenal, as supported by a docking study [195].

5.8. Antidiabetic Property

Several reports have highlighted the anti-diabetic activity of the ethanol extract from *A. dracunculus* known as PMI-5011. This extract enhances insulin signalling [196, 197], down-regulates PEPCK gene expression and reduces glucose production [96]. It also regulates gluconeogenesis [198]. Tarralin™, an ethanolic extract of *A. dracunculus* (tarragon), has been used as a medicinal herb for centuries without any reported side effects. Itexhibitsanti-hyperglycemic activity against both chemically induced and genetically prone diabetic conditions [199]. Tarralin™ has been shown to significantly decrease mRNA expression phosphoenolpyruvate carboxykinase (an essential player in gluconeogenesis and glucose homeostasis) by 28% and increase the binding of glucagon-like peptide (which enhances insulin secretion, stimulates pro-insulin gene expression and suppresses glucagon secretion) to its receptor [198]. In skeletal muscles and muscle cells, PMI-5011 enhances the phosphorylation of AMPK's at Thr172, activating it. Activated AMPK coordinates the actions of crucial metabolic pathways involved in lipid and glucose metabolism, as well as protein synthesis, thereby controlling the levels of these metabolites [200]. The ethanolic extract of the aerial part of *A. herba-alba* effectively decreases serum glucose levels in alloxan-induced diabetic rats without producing any visible undesirable clinical side effects [201]. Ethanol extracts of the whole part of *A. absinthium* exhibits significant anti-hyperglycemic activity compared to the diabetic control group of rats [202].The antidiabetic activity of these extracts may be attributed to essential oils containing thujone, myrcene, sabinene, and others [202]. Essential oil from *A. gmelinii* also significantly inhibits α-glucosidase activity with an IC_{50} value of 63.2 µg/mL which can be attributed to eucalyptol and germacrene D [203].

In streptozotocin-induced diabetes, *A. judaica*, shows anti-diabetic effects by improving insulin levels, serum glucose, glycosylated haemoglobin, serum lipid profile, and male sex hormone (testosterone, FSH and LH) level in Wistar rats [204, 205]. These effects may be attributed to anti-diabetic compounds such as vulgarin, which was isolated from *A. judaica* and used in conjunction with glibenclamide to restore insulin content and decrease levels of glucagon and somatostatin in pancreatic islets [206]. However, the main anti-diabetic components present in most of these herbs, which contribute to the reduction of blood glucose levels, are likely thujones. Thujone has been found to increase free insulin-stimulated glucose transporter through the activation of adenosine monophosphate-activated protein kinase [202]. Phenolic compounds such as dicaffeoylquinic acids, isolated from *A. annua* and *A. argyi* showed potent anti-diabetic potential by inhibiting the activities of α-glucosidase and α-amylase in both *in vitro* and *in vivo* experiments conducted [207, 208].

5.9. Anthelmintic Property

Haemonchus contortus, a gastrointestinal nematode that affects the abomasums, causes significant losses in animals and is rapidly developing resistance to multiple drugs in various regions worldwide [209]. Santonin, isolated from *Artemisia* species, was previously used as an anthelmintic agent before the introduction of synthetic anthelmintics. Notably, Pfizer, a renowned pharmaceutical corporation, produced Santonin as their first product, serving as a potent anthelmintic drug against *H. contortus.* While Santonin was present in *A. cina*, it has also been reported from *A. maritima* [73, 210]. Due to its toxic effects, Santonin is no longer used in humans, but the plant is still utilized for veterinary purposes in certain regions [84]. In studies conducted on gerbils and periparturient goats infected with *H. contortus*, the n-hexane extract of *A. cina* significantly reduced the worm count by approximately 81-87% at concentrations of 2-4 mg/ml [211]. Artemisinin, another compound found in *A. annua,* has shown anthelmintic activity against trematodes, such as *Schistosoma* sp. in mice, *Coccidia* (*Eimeria*) in chicken, *Fasciola* in sheep, and *Chlonorchis* in rats [212]. Both aqueous and ethanol extracts of *A. absinthium* exhibited strong ovicidal effect and reduced the mortality of *H. Contortus* and donkey strongyles. Their IC_{50} values were 1.4 mg/ml and 0.486 mg/ml, respectively, in both *in vitro* and *in vivo* conditions [213, 214]. Methanolic extracts of *A.indica, A. roxburghiana* and *A. brevifolia* also demonstrated significant *in vitro* anthelmintic activity against gastrointestinal nematodes [215, 216]. Additionally, extracts of *A. herba-alba* and *A. maritima* exhibited ovicidal effects against *H. contortus* in goats and cattle [217].

6. TOXICOLOGY OF *ARTEMISIA*

Extracts of certain *Artemisia* species have been reported to exhibit some levels of toxicity in dose dependant manner.

The toxicological impact of essential oils derived from *A. herba-alba* and *A. monosperma* was investigated on insects, revealing a significant reduction (83 to 90%) in the population of tested insects, including *Bemisiatabaci*, *Aphis gossypii*, and *Thripstabaci* [218]. *In vivo* studies on rats showed that the aqueous extract of *A. herba-alba* had a toxic effect in rats primarily on kidney tissues at a dosage of up to 2g/kg body weight [219]. During an 8-week period, the administration of SPB-201 (an aqueous extract powder of *A. annua*) at a dosage of 686 mg/2 tablets/day resulted in a remarkable improvement in liver function in 174 patients with borderline and mild liver dysfunction. The levels of AST and ALT decreased from 271% and 334% to 199% and 216%, respectively, demonstrating outstanding efficacy [220].

Absinthe, a popular alcoholic beverage containing *A. absinthium,* gained popularity in France during 19th and early 20th centuries but was later banned due to its reported toxic effects. The toxicity was attributed to the presence of thujone, a monoterpene ketone commonly found in the essential oil of *A. absinthium*. Later on studies showed that the exact reason behind the toxic effects was high consumption of alcohol and not due to thujone content. Absinthe has been reinstated as beverage, however the content of thujone consumption in absinthe should not more than 3.0 mg thujone/-day/person according to European Medicines Agency (EMA) [221]. Actually thujone exhibits neurotoxic properties in animals, likely due to its modulation of GABA type A receptors [222]. While a toxicological study of Tarralin™, an ethanolic extract of Russian tarragon *A. dracunculus*, showed no adverse effects in rats [223], another study revealed that the genotoxic compound methyl chavicol increases the risk of cancer [224]. Genotoxicity of methylchavicol (estragole) has been confirmed in both *in vitro* and *in vivo* urine drug screen (UDS) tests conducted on rat hepatocytes. However, the consumption of tarragon was deemed safe as methylchavicol showed no genotoxicity when administered orally [225]. The aqueous extract of *A. capillaris* also showed no significant toxicity or genotoxicity in both *in vitro* and *in vivo* studies, indicating its safe use in traditional medicines [226]. The essential oil derived from the ketone/α-pinene/1, 8-cineole chemotypes of *A. annua* showed relatively low acute toxicity compared to other chemotypes of the same species [227].

A toxicological study on pregnant Wistar rats revealed that artemisinin isolated from *A. annua* caused post-implantation losses at the dosage of 35 or 75 mg/kg, which correlated with lower progesterone level and a significant decrease in maternal testosterone [228]. In mammals (rats, dogs, primates) intramuscular injection of artemether and arteether resulted in selective damage to the brain stem centres. Different doses of artemether and arteether ranging from 20 to 100 mg/kg/day on Swiss albino mice showed no abnormalities at 30 mg/kg/day. However, abnormalities were observed in six out of 12 artemether and two out of 12 artesunate recipients at 50 mg/kg/day. At a dosage of 100 mg/kg/day, two mice died out of 36 artemether recipients and two out of 36 artesunate recipients. The study concluded that intramuscular artemether is significantly more neurotoxic than intramuscular artesunate in this mice model [229]. Although parts of *A.annua* are used for the treatment of malaria in the form of *A. annua* herbal tea, a case study reportedsevere acute cholestatic liver injury with lymphocytic infiltration of the bile ducts, intra-canalicular and intra-cytoplasmic bilirubinostasis in a patient who took *A. annua* tea for chemoprophylaxis of malaria [230]. The major ingredients in the tea were arteannuin b, deoxyartemisin, camphor, and scopoletin. The study concluded that the use of artemisinin derivatives malaria chemoprophylaxis should be discouraged due to their ineffectiveness and potential harm, and should be reserved only for malaria treatment.

In summary, the above reports on toxicological studies indicate that, overall, the use of *Artemisia* does not pose any serious health risks. This may explain its wide usage in traditional medicine.

CONCLUSION

This study provides a comprehensive overview of traditional uses, pharmacological activities, phytochemicals, and toxicity associated with *Artemisia* species. The findings reveal the presence of numerous intriguing chemical compounds with diverse biological activities. Many traditional uses have been validated by pharmacological investigations. However, there are still gaps in understanding of the traditional uses of all *Artemisia* species. Therefore, we strongly recommend further research to elucidate the scientific connections between traditional medicinal practices, pharmacological activities, mode of action of the isolated bioactive constituents, and toxicity profiles of other *Artemisia* species. This will help unravel their therapeutic potential and ensure safer clinical applications. While artemisinin has received significant research attention, other bioactive compounds also warrant exploration as they also possess properties that can be utilized for various pharmacological and ecological purposes. These molecules may hold potential for the development of drugs that target infectious diseases, including COVID-19 and cancer. The antioxidant properties of *Artemisia* extracts and biochemicals make them relevant in the treatment of neurological disorders associated with oxidative stress. Certain species such as *A. annua, A. absinthium, A. scoparia,* and *A. dracunculus* have demonstrated noteworthy anti-oxidant and anti-microbial activities. However, further in-depth studies are required on selected representative species of *Artemisia* before large-scale production of its active ingredients can be initiated. *Artemisia* species are primarily distributed in the temperate zones of Europe, Asia, and North America. They have exhibited adaptability over a wide range of climatic and soil conditions owing to the accumulation of various kinds of phytoconstituents. We have reported the widespread distribution of *Artemisia* species in the cold desert regions of Ladakh (Western Himalaya), India and have observed their remarkable adaptability to harsh climatic conditions which warrants in-depth investigation and could open new research and commercial avenues. *Artemisia* species also hold great potential in perfumery in-

dustry in the mountainous states of India that should be explored further. Additionally, investigating pre-cursor feeding, elicitation using various elicitors, mycorrhizal associations, heterologous expression of biosynthesis pathways, and suspension cultures and transgenic approaches may enhance the production of selected bioactive metabolites.

HIGHLIGHTS

(i). *Artemisia* is distributed all over the world and is used in the various traditional systems of medicine.

(ii). The wide usage of *Artemisia* species in preparation for traditional medicine is because of presence of many bioactive compounds like terpenoids, phenolics, alkaloids *etc.*

(iii). *Artemisia* essential oil and extract exhibited significant pharmacological activities.

(iv). *Artemisia* used in traditional medicines does not pose any report of serious health issue.

LIST OF ABBREVIATIONS

ABTS	=	2, 2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic Acid
ACT	=	Artemisinin-based Combination Therapy
API	=	Active Pharmaceutical Ingredients
ART	=	Artemisinin
BCE	=	Before Common Era
BHT	=	Butylated Hydroxytoluene
COVID-19	=	Coronavirus Disease-2019
CUPRAC	=	CUPric Reducing Antioxidant Capacity
DEET	=	N, N-diethyl-meta-toluamide
DPPH	=	2, 2 Diphenyl 1 Picrylhydrazyl
EMA	=	European Medicines Agency
ERK	=	Extracellular Signal-regulated Kinase
FISH	=	Fluorescence *In situ* Hybridization
FRAP	=	Ferric Reducing Antioxidant Power
GC-MS	=	Gas Chromatography-mass Spectrometry
IC_{50}	=	Inhibitory Concentration 50
LC_{50}	=	Lethal Concentration 50
LD_{50}	=	Lethal Dose 50
MAPK	=	Mitogen-activated Protein Kinases
MTT	=	3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl Tetrazolium Bromide
NSCLC	=	Non-small-cell Lung Cancer
Pf	=	*Plasmodium falciparum*
ROS	=	Reactive Oxygen Species
SARS-COV	=	Severe Acute Respiratory Syndrome Coronavirus
WHO	=	World Health Organization

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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