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Review Paper

# An Update on the Chemical Composition and Pharmacological Profiles of Artemisia species

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**Abstract**
Artemisia plants have traditional and ethnopharmacological uses in medicine, as well as in culinary items, seasonings, and drinks. Traditional medicine has used this genus as an anti-inflammatory, anti-cancer, anti-malarial, antioxidant, and anti-viral agent. All continents, except Antarctica, have seen its extensive spread. With this study, we want to compile all the available scientific information on the Artemisia genus, including its medicinal properties, chemical make-up, and distribution patterns. Using resources like Web of Science, Scopus, and PubMed/MEDLINE, we culled information from articles written on Artemisia plants. Information on phytochemicals and molecular pathways from preclinical pharmacological experiments was among the articles chosen for this revised review. Also, we looked at several old books and manuscripts. Artemisinin is a sesquiterpene lactone that can kill malaria parasites. Studies have also demonstrated the strong biological effects of other phytochemicals and essential oils from the Artemisia species. Artemisia absinthium L, one of the most well-known species of Artemisia, is the source of absinthe, a banned drink in most countries due to its neurotoxic effects. Research has shown that artemisia plants have several medicinal and traditional uses. Clinical and toxicological studies are the only ones that have provided any solid scientific evidence. As a result, these areas require further investigation in order to fully understand the molecular pharmacological process and therapeutic potential of this medicinal species.
**Keywords-** Artemisia, Clinical, Toxicological, Ethnopharmacological, Phytochemicals.

## Introduction

Throughout generations, one of the most vital fields of human study has been the investigation and creation of medicinal compounds derived from plant sources [1]. The 2015 Nobel Prize in Physiology or Medicine went to Chinese scientist You You Tu, who breathed fresh life into this field with her discovery of the unique antimalarial drug artemisinin. A plant with a long history of use in traditional Chinese medicine, Artemisia annua L., was the inspiration for this remedy [2]. There are several other famous members of the Artemisia L. genus besides this particular plant. One of the most globally widespread genera, Artemisia (Asteraceae), is home to around 400 species of grasses, shrubs, and, less often, trees [4]. The name comes from the Greek goddess Artemis, who was both a hunter and a fertility goddess. While some of these plants are in the Red Book, some are invasive in specific parts of the world, and many more are just weeds. Plants belonging to the Artemisia genus were widely used in traditional medicine because of their diverse component compositions, diverse pharmacological effects, and widespread distribution. This led to their investigation and eventual incorporation into official medicine [5–7]. For a long time, people have known about the aromatic and therapeutic uses of Artemisia. The plant produces volatile oil that finds application in cosmetics, medicine, and even food production [8]. While some Artemisia species are indeed edible, others, particularly those native to Korea, have a long history of use as a traditional remedy for ulcers and inflammations [9]. The traditional medicinal applications of A. annua and A. absinthium L. have made them the most well-known species globally [10, 11]. North America extensively uses Artemisia dracunculus L.'s antioxidant and antidiabetic properties to treat wounds [13, 14], while Artemisia afra Jacq. ex Willd. commonly treats inflammation, coughs, colds, malaria, fever, influenza, and diabetes [12]. The traditional medicinal herb Artemisia vulgaris L. also has a number of useful functions, including protecting the liver, preventing seizures, killing insects, and warding off malaria and other parasites [15–19]. Significant medicinal effects are possessed by several species of Artemisia, including Artemisia nilagirica (C.B. Clarke) Pamp., Artemisia dracunculus, Artemisia herba-alba Asso, Artemisia armeniaca Lam., and Artemisia scoparia Waldst. & Kitam. [20]. As a diuretic, choleretic, and hepatoprotective, A. scoparia has a lengthy history in medicine as well [21]. A. scoparia has a long history of medicinal usage, including the treatment of hepatitis, jaundice, ulcers, pruritus, asthma, gastritis, parasites, and spider bites. Traditional remedies for jaundice involve combining A. scoparia with Gardenia jasminoides J. Ellis and rhubarb (Rheum rhabarbarum L.) [21]. There are a number of biopharmaceutical products on the market now that use Artemisia extracts to treat a variety of illnesses [22]. The goal of this study is to provide a comprehensive overview of the most recent scientific findings about the chemical make-up, pharmacological action mechanisms, and toxicological profiles of plants belonging to the Artemisia genus.

## Methodology

For this review, we combed through two databases of biological literature: Utilising the following MeSH search phrases in PubMed/MEDLINE and Web of Science: "Artemisia/chemical research," phytochemicals, artemisinins, pharmacology, medicinal application, traditional medicine, phytotherapy, and related terms "Plant Extracts/pharmacology," "Plant Extracts/therapeutic use," "Plant Oils/pharmacology," "Plant Oils/therapeutic use," "Structure-activity relationship,"

"Animals" and "Humans." The following research was considered for inclusion: those pertaining to Artemisia spp., as well as their sources, acquisition methods, experimental pharmacology, toxicity, and safety data. We covered both in vivo and in vitro pharmacological investigations that support the molecular action mechanism. The following studies will not be considered for inclusion in this revised review: those of poor quality, duplicates, or data that is irrelevant to the review's purpose. World Flora Online has confirmed the accuracy of plant species taxonomy [23].

**Geographical Distribution of Artemisia spp.**

Every continent on Earth, with the exception of Antarctica, is home to plants of the genus Artemisia [24–26]. This diverse genus may be found anywhere from the ocean floor to elevations of around 4,000 metres [27]. Artemisia spp. is known to colonise the Northern Hemisphere to a lesser extent than the Southern Hemisphere, where it flourishes in abundance [27, 28]. Central Asia—roughly including Uzbekistan, Tadzhikistan, Turkmenistan, Kazakhstan, Kyrgyzstan, portions of Russia, China, and Mongolia—is home to the majority of Artemisia species. The western North American continent, the Iran-Turanian and Mediterranean areas, and other similar locations are also important diversity hotspots [29–33]. Artemisia has colonised and expanded over the majority of the Northern Hemisphere's temperate, subtropical, and arctic-alpine zones, much beyond its original range. From its northern Asian origins, this species mainly disperses over three primary routes: first, into Europe, Western Asia, the Mediterranean Basin, and Africa; second, into Siberia and western North America; and third, back into Asia proper [34, 35]. Although a minor diversity centre exists in South America and is present in Oceania as allochthonous taxa [32], there have only been a handful of species—not more than 25—reported from the Southern Hemisphere (Figure 1).


**Figure 1: Geographical distribution of Artemisia species.**

**Phytochemical Composition**

Aromatic extracts derived from plants are commonly known as essential oils. For millennia, the aromatic oils found in plants, known as essential oils (EOs), have been used as spices, medicines, and for their pleasant scent [36]. The invention of

distillation processes throughout the Middle Ages has made it feasible to use ancient applications in food, pharmaceuticals, and cosmetics [37]. As a result of its diverse therapeutic uses, the EO business has expanded into several industries in recent decades, introducing new dimensions and objectives. Various writers worldwide have documented the chemical makeup of essential oils from the Artemisia genus. The composition of essential oils (EOs) is influenced by several factors, such as the specific plant part used, the season in which the plant was grown, the age of the plant, the geographical region, the extraction techniques employed, the solvent used, and the timing of the extraction process [38].

**Pharmacological Effects of Artemisia spp.**

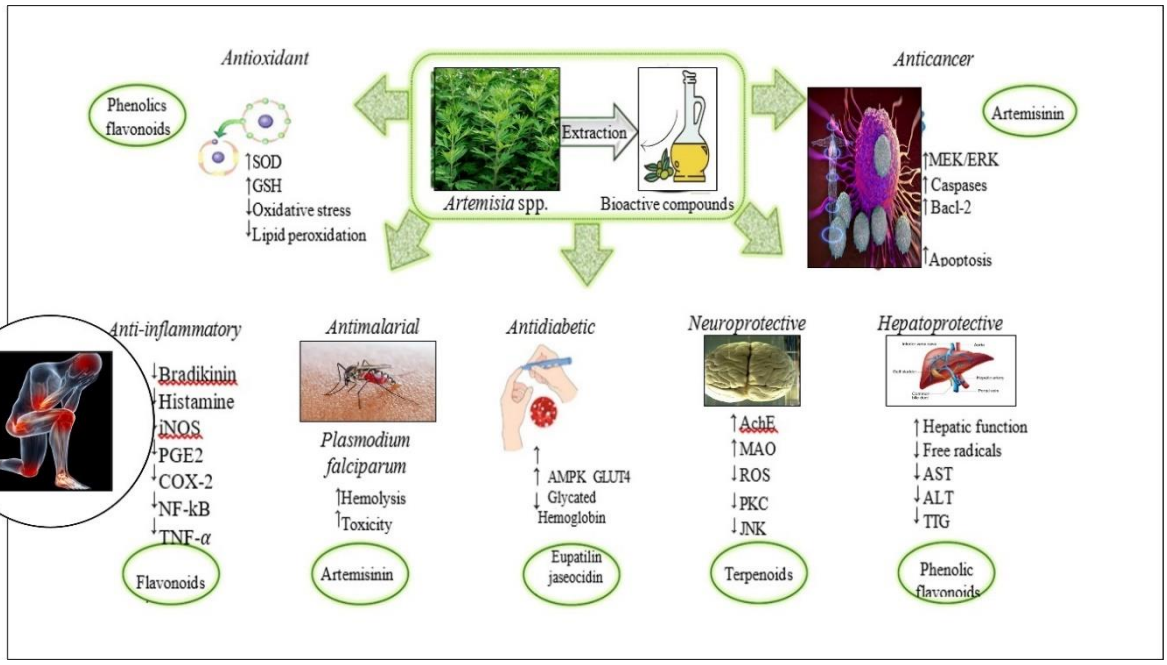


**Figure 2: A schematic representation of the most prominent pharmacological characteristics and potential mechanisms of action of the bioactive compounds found in Artemisia spp. increase; ↤: reduction; superoxide dismutase (SOD); glutathione (GSH); extracellular signal-regulated protein kinase/metagen-activated extracellular signal-regulated kinase; MEK/ERK. Inducible nitric oxide synthase; Bcl-2; iNOS; inducible nitric oxide synthase. Prostaglandin E2 (PGE2), cyclooxygenase-2 (COX-2), tumour necrosis factor α (TNF-α), NF-κB (Nuclear factor kappa B), AMPK (Adenosine monophosphate-activated protein kinase), and AST (Aspartate aminotransferase) are abbreviations for the following: GLUT4 stands for glucose transporter type 4, AchE for acetylcholinesterase, MAO for monoamine oxidase, ROS for reactive oxygen species, PKC for protein kinase C, JNK for Jun N-terminal kinase, and ALT for alanine transaminase.**

**Extracts and Its Bioactive:** At the fundamental level, molecular mechanisms Artemisia spp. has a wide array of pharmacological effects, including antiulcer, anticancer, hepatoprotective, antidiabetic, antioxidant, and antibacterial properties. The actions of these species in preclinical research are summarised in Table 1 and Figure 2. The leaves and flowers of A. annua produce artemisinin, a well-known medicine. Studies have shown that additional species, including A.

vulgaris, A. absinthium, A. dracunculus, and A. scoparia, possess anti-malarial properties despite lacking artemisinin. This activity is thought to be caused by the presence of essential oils (EOs) and other sesquiterpenes. In addition, additional research has indicated that A. annua extracts contain other antimalarial substances besides artemisinin [39–41].

**Antioxidant:** An antioxidant is a substance that inhibits the oxidation of other molecules, thereby preventing damage to cells and tissues. Antioxidants are a collection of substances that can aid in maintaining the stability of cells when exposed to free radicals, which are unstable molecules naturally produced by our body [93–95]. Therefore, natural antioxidants are crucial for the optimal functioning of the organism [96–98]. Various research has reported on the antioxidant activity of A. absinthium. The presence of phenolic substances such as gallic acid, coumaric acid, vanillic acid, syringic acid, and chlorogenic salicylic acid, as well as flavonoids like quercetin and rutin, in A. absinthium indicates that this plant has the ability to combat disorders associated with oxidative stress [42–44]. These chemicals decrease the process of lipid peroxidation, namely the formation of thiobarbituric acid-reactive substances (TBARS), and restore the levels of natural antioxidants such as superoxide dismutase (SOD) and glutathione (GSH).

**Anti-inflammatory:** Inflammation is an innate bodily reaction that serves to safeguard and facilitate recovery from an injury [45, 46]. Its primary role is to provide protection against hazardous chemicals and facilitate the regeneration of injured tissue [47, 48]. Extracts from A. absinthium have anti-inflammatory properties, which may be attributed to its secondary metabolites, including flavonoids and sesquiterpene-type compounds. These metabolites play a role in inhibiting inflammatory regulators such as bradykinins, histamine, prostaglandins, and serotonin. Additionally, they suppress the expression of proinflammatory mediators such as iNOS, PGE2, COX-2, NF-κB, and TNF-α [49].

**Anti-cancer:** Cancer is a pathological condition characterised by the uncontrolled proliferation of cells in the body, resulting in the formation of a tumour that has the potential to metastasize to several organs [49–54]. The anticancer effect of A. absinthium extract is attributed to the activation of the MEK/ERK signalling pathway, which subsequently triggers the mitochondrial pathway of caspase activation. This process regulates the activity of Bad and Bcl-2 family proteins, leading to apoptotic cell death in MCF-7 and MDAMB231 human cancer cells [55].

**Neuroprotective.** Neurocerebral illnesses, particularly neurodegenerative ones, are a group of brain syndromes that gradually impact memory, cognitive function, behaviour, and emotions [56–59]. A. absinthium has demonstrated neuroprotective effects on brain damage caused by reperfusion through its activation of nicotinic and muscarinic receptors. The ethanolic extract of A. absinthium has a protective mechanism that is likely attributed to its anticholinesterase activity. Additionally, it has the ability to modify the behaviour of rats by restoring the activity of acetylcholinesterase (AChE) and monoamine oxidase (MAO) enzymes to levels close to normal. Caruifolin D, a sesquiterpenoid dimer discovered in A. absinthium, has potential therapeutic applications in treating neurodegenerative diseases like Alzheimer's or Parkinson's. This is because it inhibits the production of neuroinflammatory mediators and reactive oxygen species (ROS) in BV2 microglial cells. As a result, it has inhibitory effects on the activations of protein kinase C (PKC) and c-Jun N-terminal kinase (JNK) [60].

**Protective of the liver:** The hydroalcoholic extract of A. absinthium enhances liver function, reduces oxidative stress markers, and consistently promotes and maintains the structural integrity of the hepatocellular membrane, leading to decreased blood levels of aspartate (ASAT) and alanine aminotransferase (ALAT) activity. The suggested mechanisms for hepatoprotection are the inhibition of liver microsomal drug-metabolizing enzymes, the scavenging of free radicals, and the blocking of calcium channels [61].

**Antidiabetic:** Diabetes is a metabolic disorder characterised by elevated levels of blood glucose, sometimes known as hyperglycemia [62]. This illness is characterised by its incurability, meaning that there is no known cure. Once a person is diagnosed with this disease, they will need to undergo lifelong therapy in order to manage the condition [63]. Extracts of A. absinthium demonstrated insulin-sensitizing effects by stimulating adenosine monophosphate-activated protein kinase (AMPK) and promoting the translocation of glucose transporter type 4 (GLUT4) to the muscle cell surface [6]. 4 In rats with diabetes that were treated with A. absinthium, there was a change in the metabolic pathway, causing carbohydrates to be used as the main source of energy. This resulted in the preservation of proteins and lipids and an increase in their synthesis, thereby avoiding weight loss [65].

**Antimalarial medication:** Artemisinin, a sesquiterpene lactone found in A. annua, is utilised to treat Plasmodium parasites, which are known for their significant absorption and breakdown of haemoglobin. This process generates significant amounts of redoxactive heme and ferrous iron (Fe2+), which are believed to be responsible for artemisinin's specialised targeting of parasites. Infected red blood cells metabolise surplus heme into hematin, which is harmful to the parasite because it causes oxidative harm and ruptures the cell membrane. However, malaria parasites have developed a detoxification mechanism that employs a biocrystallization process to transform hematin into the less harmful and inactive crystallised hemozoin. Studies have demonstrated that activated artemisinin can hinder the formation of hemozoin by chemically modifying heme. Consequently, artemisinin's activator and target are both unbound heme molecules released from the breakdown of haemoglobin [67].

**Utilising Antiviral Activity as a Treatment Strategy for COVID-19 Infection:** Currently, the management of SARS-CoV-2 (COVID-19) infection involves the transposition of drugs already used in clinical practice [68, 69]. The World Health Organisation (WHO) has endorsed A. annua as a potentially effective treatment for COVID-19. However, the effectiveness and potential adverse effects of this medicine have not yet been determined [190]. (www.ClinicalTrials.gov, Identifier: NCT04530617). Furthermore, China recommends Jinhua Qinggan granule, which includes A. annua as a component, as part of its COVID-19 treatment plan [70]. Presently, a phase II clinical trial is being conducted to assess the effectiveness of A. annua in impeding the replication of the SARS-CoV-2 virus in patients who have high-risk factors such as diabetes and hypertension. You can find the study on www.ClinicalTrials.gov under the identifier NCT04530617. In addition, Saudi Arabian researchers have initiated a placebo-controlled experiment to assess the impact of artesunate on patients with mild symptoms of COVID-19. You can find the trial on www.ClinicalTrials.gov under the identifier NCT04387240. The scientific evidence supporting this technique may be attributed to the favourable anti-inflammatory, immunomodulatory, and antiviral activities of the bioactive chemicals found in several species of Artemisia, both in preclinical and clinical settings. We selected a

total of 85 individuals diagnosed with SARS to participate in a clinical investigation. Out of them, 62 patients were administered the experimental therapy together with traditional Chinese medicine (TCM), which includes the herb Artemisia as one of its components. The remaining 23 patients were assigned to the control group. The results showed a significant decrease in the overall symptom score among patients who received daily Traditional Chinese Medicine (TCM) treatment for 3 weeks. Additionally, improvements were observed in lung X-rays, hepatic function, quality of life, and the total score of mental sentiment elements [71]. According to recent reports, 1250 medical staff at Tongxu County Hospital consume one or more Traditional Chinese Medicine (TCM) decoctions daily. Additionally, they burn Artemisia argyi H.Lév. and Vaniot in the hospital corridor to prevent the spread of infections. A. argyi is known to have aromatherapy properties that can help prevent contagion. The number is 72. Artemisinin and its derivatives have demonstrated significant potential as antiviral medicines. For example, the effectiveness of artesunate (100 mg/day) was evaluated in treating a 12-year-old child with a human cytomegalovirus (HCMV) infection. This youngster had developed resistance to the antiviral medications foscarnet and ganciclovir after undergoing stem cell transplantation. The findings demonstrated a notable decrease in viral load on May 7th, with the virus's half-life ranging from 0.9 to 1.9 days. This indicates a successful interruption in viral reproduction [73].

**TABLE 1: Preclinical pharmacological studies of different *Artemisia* species [39-106]**

| Extract/compound | Doses | *In vitro*/*in vivo* | Route of administration/ assay | Model/cells | Activity | Potential effect |
|---|---|---|---|---|---|---|
| *A. nilagirica*/ethanolic extracts | 500 mg/kg | *In vivo* | Orally | Rats | Antiulcer | Gastroprotective, ↑proteins of mucus content |
| *A. nilagirica*/ methanolic extract | 150–250 mg/kg | *In vivo* | Orally | Swiss albino mice | | Gastroprotective compared to standard drug vincristine |
| *A. absinthium, A. vulgaris/flowers*/ methanolic extract | 62.5, 125, 250, 500 µg/mL | *In vitro* | MTT | MCF7 cells | | ↑cytotoxicity $IC_{50}$ = 221–500 µg/mL |
| *A. nilagirica*/ethyl acetate, hexane fractions | 100 µg/mL | *In vitro* | SRB | DLD-1 cells | | ↑cytotoxicity $IC_{50}$ = 15:42–23.4 µg/mL |
| *A. vulgaris/leaves*/ methanolic extract | 0.01–1.0 mg /mL | *In vitro* | MTT | Hepatocellular carcinoma cells | Anticancer | ↑apoptosis $IC_{50}$ = 0:1 mg/mL |
| *A. absinthium*/ methanolic extract | 20, 25 g/mL | *In vitro* | MTT | MCF-7 MDA-MB231 | | ↑cancer cells suppression |
| *A. armeniaca*/$CH_2Cl_2$ fraction | 6.25–200 µg/mL | *In vitro* | MTS | Apoptosis-proficient HL60 apoptosis-resistant K562 | | HL-60: $IC_{50}$ = 75 µg/mL, K562: $IC_{50}$ = 130 µg/mL |
| *A. dracunculus*/aerial parts, roots/ethanol, aqueous extracts | 250 mg/kg | *In vivo* | Orally | STZ-induced diabetic rats | | ↓TGL, ↓LDL, ↓HDL |
| *A. dracunculus* L. (PMI 5011)/ethanolic extract | PMI 5011 (1%) | *In vivo* | Diet | KK-Ä mice | Antidiabetic | ↑sensitivity of insulin, ↑insulin receptor signaling |
| *A. sieberi* (*A. herba-alba*)/aqueous extracts | 0.39 g/kg | *In vivo* | Orally | Alloxan-induced diabetic rats | | ↓blood glucose, ↑RBC, ↑WBC, ↑PCV, ↑ESR, ↑neutrophils, ↓heart rate |
| *A. persica*/aqueous, methanolic extracts | 300, 400, 500 mg/kg | *In vivo* | Orally | Sprague-Dawley rats | Antihypertensive | ↓systolic blood pressure in normotensive/hypertensive rats |
| *A. absinthium*/ aqueous extract | 50, 100, 200 mg/kg | *In vivo* | Orally | Kunming mice, NIH mice | Hepatoprotective | ↓inflammatory cells, ↓liver lipid peroxidation, ↑SOD, ↑GPx |
| *A. vulgaris*/aerial parts/crude extract | 150, 300, 600 mg/kg | *In vivo* | i.p. | Balb-C mice | | ↑liver structure, ↓parenchyma congestion, ↓cellular swelling, ↓apoptotic cells |
| *A. nilagirica*/leaf extracts | 32–512 µg/mL | *In vitro* | Agar disk diffusion method | 15 bacterial strains | Antibacterial | Methanol, hexane extracts, ↑inhibition against phytopathogens |
| *A. herba- alba, A. judaica, A. monosperma*/EO | 10.0, 5.0, 2.5, 1.0, 0.5 µL/ disc | *In vitro* | Agar disc diffusion method. | *Staphylococcus aureus* ATCC29213, *Escherichia coli* ATCC 25922 | | $IC_{50}$ = 0:5 – 2:5 µL *A. judaica*, A. *monosperma* plants had the highest MIC |

| Extract/compound | Doses | *In vitro*/*in vivo* | Route of administration/ assay | Model/cells | Activity | Potential effect |
|---|---|---|---|---|---|---|
| *A. judaica*/ethanol extract | 250, 500, 1000, 2000, 4000 µg/mL | *In vitro* | (mic90) growth inhibition | Protozoan parasite (blastocystis) | Antiprotozoal | $IC_5$ = 4000 µg/mL, ↓growth, ↑destruction of blastocystis |
| *A. nilagirica*/EO | 0.33 µL/mL | *In vitro* | Inverted petri plate technique | *A. flavus*, *A. niger*, *A. ochraceus* | Antifungal | $IC_{50}$ = 1:6 µL/mL, ↓fungal growth, ↓mycotoxin secretion, ↓aflatoxigenic, ↓ochratoxigenic strains |
| *A. annua*/leaves/EO ethanolic extract | EO = 470 mg/kg ethanol extract = 450 mg/kg | *In vivo* | i.p. | Wistar rats | Antidepressant | ↑immobility time in the FST, ↓other activities in the OFT depressors of SNC |
| *A. absinthium*/aerial parts/methanolic extract | 125, 250, 500, 1000 mg/kg | *In vivo* | i.p. | Swiss albino mice | | ↓immobility period in the fst and tst. dose-dependent antidepressant activity |
| *A. vulgaris*/leaves/ methanolic extract | 50, 100, 300 mg/kg | *In vivo* | i.p. | Swiss albino mice | Antiepileptic | Anticonvulsant activities were noticed using EPM and MBT |
| *A. capillaris*/herba/ ethanolic extract | 50, 100, 200, 400 mg/kg | *In vivo* | Orally | Mice | | Anticonvulsivant effect through the GABA-ergic neuron |
| *A. nilagirica*/leaves/ ethanolic, aqueous extracts | 100, 200 mg/kg | *In vivo* | i.p. | Swiss albino mice | Anti-Alzheimer | Confirmation of the anti-Alzheimer's activity of ethanol extract after object recognition and y-maze tests |
| *A. nilagirica*/leaves/ ethanolic, aqueous extracts | 100, 200 mg/kg | *In vivo* | i.p. | Swiss albino mice | Anti-Parkinson | ↓catalepsy score in animals treated with ethanolic extract, ↑locomotor activity, ↑rotarod readings |
| *A. annua*/aqueous, ethanolic extracts | 2 g/L | *In vitro* | ABTS, ORAC, FRAP | – | | ↑protection against the oxidative deterioration of oil-in-water emulsion |
| *A. dracunculus* L./ leaves/methanolic extract | 20 µL | *In vitro* | DPPH | – | | ↑antioxidant activity by phenolics |

| Extract/compound | Doses | *In vitro*/*in vivo* | Route of administration/ assay | Model/cells | Activity | Potential effect | R |
|---|---|---|---|---|---|---|---|
| *A. aucheri*/methanolic extract | 25, 50, 100 mg/mL | *In vitro* | Scolicidal tests | *Echinococcus granulosus* | | ↓effect on the protoscolices of hydatid cysts | |
| *A. vulgaris*/ethanolic extract | 1, 5, 10, 50, 100, 500, 1000 ppm | *In vitro* | Method recommended by WHO | *Aedes aegypti* | | $LC_{50}$ = 65:8 ppm in 1 h and 18.6 ppm in 24 h, ↓ *A. aegypti* in various stages of its lifecycle | |
| *A. scoparia, A. spicigera*/n-hexane, DCM, MeOH extracts | 20, 40, 80 mg/mL | *In vitro* | Toxicity bioassay | *Tribolium castaneum* (red flour beetle) | | Insecticidal properties, ↑activity of DCM extract | |
| *A. scoparia*/butanol fraction | 20 mg/site | *In vivo* | Topically | BALB/C mice | Annatopic dermatitis | ↓clinical symptoms in a DNFB mouse model that induced lesions, ↓inflammatory cytokines | |
| *A. scoparia*/aerial parts/methanolic extract | 150, 300 mg/kg | *In vivo* | — | Sprague-Dawley rats | Nephroprotective | ↓DNA damages, dose = 300 mg/kg, ↓oxidative stress | |
| *A. capillaris* Thumb/ extract | 10 mg/mouse/day | *In vivo* | Topically | Dermatophagoides farinae-sensitized NC/ NGA mice | Anti-inflammatory, anti-atopic dermatitis | ↓dermatitis scores, ↓bleeding, ↓hyperkeratosis, ↓hypertrophy in the dorsal skin and ear of the epidermis, ↓histamine | |
| *A. pallens*/aerial parts/ methanolic extract | 200, 400 mg/kg | *In vivo* | Orally | Wistar rats | Anti-inflammatory, antioxidative | ↓level of hepatic enzymes, ↑renal antioxidant enzymes | |
| *A. vulgaris*/leaf/ ethanolic extract | 250, 500, 750, 1000 mg/kg | *In vivo* | Orally | ICR mice infected with *P. berghei* | | ↓*P. berghei*, nontoxic | |
| *A. scoparia, A. spicigera*/ dichloromethane extracts | 0–2 mg/mL 10% DMSO | *In vitro* | Heme biocrystallization and inhibition assay | | | $IC_{50}$ = 0:778 mg/mL, $IC_{50}$ = 0:998 mg/ mL | |
| *A. annua*/aqueous, hydro alcoholic extracts | — | *In vitro* | Parasite lactate dehydrogenase (pLDH) | *Plasmodium falciparum* | Antimalarial | $IC_{50}$ = 3:27 nM, $IC_{50}$ = 4:95 nM | |
| *A. annua*/aqueous hydro alcoholic extracts | Aqueous extract 1000 mg/ kg/day, hydro alcoholic extract 500 mg/kg/day | *In vivo* | - | *Plasmodium berghei* NK173-infected m ice | | ↑activity on malaria of artemisinin, both extracts of *A. annua* are effective on malaria | |

↑: increase; ↓: decrease; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide; DCM: dichloromethane; DNFB: 2,4-*dinitrofluorobenzene*; EPM: elevated plus maze ; ESR: erythrocyte sedimentation rate; EO: essential oil; FST: forced swimming test; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MBT: marble-burying test; MIC: minimum inhibitory concentration; OFT: open-field test; PCV: packed cell volume; RBC: red blood cell; SRB: sulforhodamine B; TC: total cholesterol; TGL: triglycerides; WBC: white blood cell; WHO: World Health Organization: i.p. Intraperitoneally; FRAP: ferric-reducing ability of plasma; ABTS: 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid; ORAC: oxygen radical absorbance capacity.

## Limitations, Therapeutic Perspectives, and Clinical Gaps

Despite the promising uses of Artemisia spp. and its components as functional foods, nutritional supplements, and safe medications, the scientific literature has reported several negative effects [74]. A. absinthium, often known as big wormwood, has traditionally been a significant ingredient in the intensely anise-flavoured alcoholic drink called "Absinthe." During the late 19th century, Absinthe was the most popular alcoholic beverage in Europe [75]. The negative effects known as absinthism led to the ban of Absinthe at the start of the 20th century [76]. The symptoms of absinthism encompassed hallucinations, blindness, cognitive decline, and convulsions.

Researchers likely linked the prohibition of Absinthe to the prevalence of chronic alcoholism [77]. It is advisable to consult a specialist before using Artemisinin, as it may potentially interact with several medicines and alter their effects. At the moment, both food and alcoholic beverages contain A. absinthium. According to the European Food Safety Authority (EFSA), the consumption of thujone from Artemisia should not go beyond 10 mg/kg. The European Medicines Agency (EMA) recommends a limit of 3 mg/day per person. Pregnant women should avoid certain species of Artemisia due to their impact on fertility and potential harm to the developing embryo, especially at larger dosages. For instance, administering A. herba-alba to pregnant mice significantly reduced the fertility ratio of their offspring [79]. Moreover, the use of A. kopetdaghensis "Krasch., Popov & Lincz. ex Poljakov" hydroalcoholic extract during pregnancy heightens the likelihood of miscarriage [80]. Exposure to several species of Artemisia has been linked to the development of skin contact dermatitis [81, 82]. A. vulgaris elicited good responses in the majority of individuals with allergic rhinitis and asthma, as demonstrated by skin prick testing. Therefore, we regularly advise those sensitive to Compositae to avoid contact with Artemisia species [84]. Sesquiterpene lactones in Artemisia cause dermatitis [85]. Pollen from Artemisia species can induce severe allergic rhinitis [86]. Artemisia pollen, leaves, and stems have been shown to be strong allergens that can cause allergic rhinitis and/or asthma in tests that include nasal challenge and bronchial provocation [87, 88]. For instance, mugwort pollen, specifically A. vulgaris, contains allergenic substances like profilin and other cross-reactive allergens that react with immunoglobulin E (IgE), causing severe type I allergic reactions [90]. Type I hypersensitivity is characterized by the process of mast cell degranulation, which leads to the release of inflammatory mediators, including histamine. This release of histamine can result in allergic responses, including anaphylactic shock [91]. Furthermore, A. vulgaris pollens had the highest amounts of endotoxin compared to other plants gathered from 100 different sites in Europe [92]. There was a lot of similarity and cross-reactivity between the pollen extracts of six different Artemisia species [93]. These species are A. annua, A. scoparia, A. vulgaris, A. princeps, Artemisia campestris L., and Artemisia tridentata Nutt. Additionally, this investigation demonstrated that both Korean and Norwegian patients had identical reactivity patterns towards A. vulgaris and A. princeps [94UsiUsing the sesquiterpene lactone artemisinin and its different forms, like arteether, arte-sunate, and artemether, in appropriate therapeutic amounts for short periods of time did not have any major negative effects on patients [95, 96]. Many biologically inactive metabolites of artemisinin are made in the liver. These include deoxyartemisinin, deoxyhydroartemisinin, crystaA CYP2B6 enzyme facilitates the reaction, while a CYP3A4 enzyme acts as a secondary catalyst. The smooth endoplasmic reticulum houses these enzymes as members of the cytochrome P450 group. Artemisinin derivatives undergo distinct metabolic processes. Initially, the compounds transform into dihydroartemisinin (DHA). DHA is a potent antimalarial compound that remains active in the circulation for a duration of two to three hours [97]. Artesunate's only mechanism of antimalarial action is dihydroartemisinin (DHA) [98]. One minute after absorption, artesunate converts to dihydroartemisinin (DHA). Blood plasma typically attaches approximately 90% of DHA. The cytochrome P450 enzyme system, which consists of CYP2A6, CYP3A4, and CYP3A5, metabolises DHA in the liver, converting it into inactive substances [99]. Glucuronidation is a process that all metabolites undergo, resulting in their elimination through urine or faeces. UDP-glucuronosyltransferases, namely UGT1A9

and UGT2B7, are accountable for the process [100]. The bile also eliminates DHA in the form of minor glucuronides like tetrahydrofuran acetate. Artemisinin is considered a safe bioactive molecule due to its fast metabolism [101]. We need to conduct further clinical investigations to fully understand the potential interaction mechanisms of artemisinin with other medications. Additional constraints arise from the quantities of bioactive compounds present in plants, which vary according to the growing region and climate conditions [102–104]. In order to enhance the effectiveness of therapeutic treatments, it is necessary to design pharmaceutical nano formulations that can improve the bioavailability and absorption of bioactive substances. This will result in a more rapid and varied absorption of these compounds, leading to greater therapeutic efficacy. [105, 106]

**Conclusion**

Artemisia spp. has long been employed for medicinal applications and as a consumable plant used in cuisine, seasonings, and drinks. The two most well-known Artemisia species are A. annua and A. absinthium. All over the world, this genus contains a wide range of chemical components, primarily essential oils (EOs) and polyphenols. Sesquiterpene lactones in these species primarily contribute to the medicinal potential of the Artemisia genus. Extensive research has supported the genus's antioxidant, anti-inflammatory, anticancer, antidiabetic, antimalarial, neuroprotective, and hepatoprotective properties with both experimental and clinical data. Artemisia spp. and its components have significant potential as dietary supplements, functional foods, and safe medications because of their ability to act as antimalarial, antioxidant, anticancer, antinociceptive, anti-inflammatory, and antiviral agents. The potential antiviral efficacy in the treatment of COVID-19 infection provides optimism for the ongoing epidemic. Nevertheless, it is crucial and imperative to conduct further research studies in order to uncover more secure pharmaceuticals generated from the Artemisia plant that may effectively treat various ailments

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