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ARTICLE

Artemisia annua: Illuminating the Spectrum of Pharmacological Wonders

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ABSTRACT

Artemisia annua L., commonly called sweet wormwood, is famous for its therapeutic benefits gained from artemisinin and its rich phytochemicals. This review investigates flavonoids, such as quercetin, phenolic acids such as caffeic acid, monoterpenes like camphor, sesquiterpenes, coumarins, and essential oils, which support its roles as an antiparasitic, anticancer, antimicrobial, antiviral, anti-inflammatory, antioxidant, antihypertensive, antidiabetic, hepatoprotective and insect-repellent plant. Mechanisms include the generation of reactive oxygen species, disruption of microbial and parasitic functioning, modification of pathways (such as those controlled by NF-κB, COX/LOX, or JAK-STAT), and induction of cancer cell apoptosis through the transferrin receptor system. *Artemisia annua* is helpful in treating leishmaniasis, schistosomiasis and cancers by disrupting mitochondrial pathways and angiogenesis. Its oils are effective against *Staphylococcus aureus* and help keep pests away. Ionic liquids, nanoformulations and metabolic engineering, especially using the CRISPR/Cas9 system, greatly enhance the production and delivery of artemisinin. This review outlines the major phytochemicals, functions and usefulness of *Artemisia annua*, emphasizing that it is low in toxicity and can be used sustainably. Future investigations, including molecular docking, omics studies, and clinical trials, aim to overcome resistance and develop new treatments for infections, cancer, and inflammation.

Keywords: *Artemisia annua*; Artemisinin; Malaria; Pharmacology; Bioactive Compounds; Sweet Wormwood

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1. Introduction

Artemisia annua L., also known as sweet wormwood, is indeed a medicinal plant that has been celebrated for its potential therapeutic values, especially in inflammatory diseases, cancer, ulcers, liver, and cardiovascular diseases [1]. It has been used in traditional medicine for over 2,000 years, with its most notable use being for malaria treatment. It was believed that the flavouring substance in the leaves of artemisia could be extracted and used as an effective antimalarial drug in 1972. This act was taken, however, after 30 years of effectiveness of this monotherapy, and the World Health Organization recommended the inclusion of artemisinin in combination with other longer-acting antimalarials, such as lumefantrine, amodiaquine or mefloquine [2]. As much as artemisinin acts quickly, it is short-lived, thus requiring it to be combined with slower-acting agents to be effective in eliminating malaria. This is because its structure involves several rings, which is a challenge in preserving the compound or molecule. Modern pharmacological research evidence suggests the therapeutic potential of various bioactive elements present in different parts of the plant, including studies on their hepatoprotective, cardioprotective, and anti-inflammatory effects. This review aims to provide a detailed overview of these bioactive components, exploring their presence in the leaves, seeds, flowers, root bark, and gum of *A. annua* L., (**Figure 1**) along with their medicinal applications [1].

2. Phytochemical Profile and Pharmacological Significance of leaves

Artemisia annua has garnered substantial scientific interest due to its rich and diverse phytochemical profile, most notably for yielding artemisinin, a sesquiterpene lactone with exceptional antimalarial activity. Beyond artemisinin*, A. annua* harbors a complex matrix of bioactive constituents that contribute to its broad-spectrum pharmacological properties.

2.1. Phytochemical Constituents

Comprehensive phytochemical analyses have shown that *Artemisia annua* contains a diverse array of chemical constituents that contribute to its pharmacological potential. The plant is particularly rich in terpenoids, including monoterpenes such as camphor and 1,8-cineole, as well as sesquiterpenes like artemisia ketone and arteannuin B. It also possesses an abundance of flavonoids, notably luteolin, quercetin, apigenin, and their glycosidic derivatives, which are known for their antioxidant properties. Additionally, phenolic acids such as caffeic acid, ferulic acid, and chlorogenic acid are present, contributing to its anti-inflammatory and antimicrobial effects. The presence of coumarins, such as scopoletin and isoscopoletin, further enhances its bioactivity profile. Moreover, the plant contains steroids and phytosterols, including β-sitosterol and stigmaste rol, which are crucial for modulating lipid metabolism and immune function. Although alkaloids are found only in trace amounts, they may exert synergistic effects with other compounds. The essential oil fraction of *A. annua* includes both volatile and non-volatile aromatic compounds that contribute to its distinctive aroma and therapeutic properties. Enzymes such as β-glucosidase and β-galactosidase have also been identified, playing key roles in glycoside metabolism and potentially influencing the bioavailability of flavonoids and other glycosylated compounds [3].

2.2. Biological and Pharmacological Activities

The phytochemicals in *Artemisia annua* exhibit a broad spectrum of biological activities, supporting its medicinal value. Notably, its antimalarial effect is primarily attributed to artemisinin and its biosynthetic precursors, such as artemisinic acid, which act by inducing oxidative stress and alkylating essential parasitic proteins, thereby disrupting the life cycle of *Plasmodium* spp. The plant also demonstrates strong antioxidant potential, mainly due to its rich content of flavonoids and phenolic acids, which scavenge reactive oxygen species, reduce lipid peroxidation, and upregulate endogenous antioxidant enzymes, such as superoxide dismutase (SOD) and catalase (CAT) [4]. Its anti-inflammatory activity is mediated by sesquiterpenes and phytosterols, which downregulate pro-inflammatory cytokines such as TNF-α and IL-6, inhibit nuclear factor-kappa B (NF-κB) signaling pathways. Furthermore, *A. annua* shows antimicrobial efficacy, as its essential oils possess bactericidal and fungicidal properties, primarily

through disruption of microbial membranes and interference with key enzymatic systems. The plant also exhibits antitumor activity, where compounds such as artemisinin and flavonoids induce apoptosis via mitochondrial membrane depolarization, caspase activation, and inhibition of tumor angiogenesis. Additionally, antiviral properties have been observed; compounds such as 1,8-cineole and artemisinin derivatives have shown inhibitory effects against replication of RNA viruses, including SARS-CoV-2 and hepatitis viruses.

2.3. Essential Oil Composition and Functionality

The essential oil of *Artemisia annua*, primarily extracted from its leaves and flowering tops, comprises both volatile and nonvolatile components that, despite constituting only ~0.2–0.25% of the plant's dry weight, exhibit remarkable biological activities. Among the volatile constituents, monoterpenes such as camphor, β-pinene, 1,8-cineole, and camphene, along with sesquiterpenes like β-caryophyllene, isoartemisia ketone, and myrcene hydroperoxide, play significant roles in the plant's pharmacological profile. These compounds exert antimicrobial effects by disrupting microbial cell wall integrity, display insecticidal activity through interference with insect neurotransmission, and offer respiratory benefits, such as bronchodilation and mucolytic effects, highlighting their use in aromatherapy. The nonvolatile fraction includes sesquiterpenoids and flavonoids, which contribute to sustained antioxidant and anti-inflammatory responses. Additionally, steroidal phytochemicals such as β-sitosterol and stigmasterol exhibit lipid-lowering and immunomodulatory effects. The presence of enzymes involved in glycosidic bond hydrolysis further enhances the bioavailability of flavonoid glycosides and other complex phytoconstituents.

3. Artemisinin Discovery and the Multifaceted Therapeutic Potential of *Artemisia annua*

The discovery of artemisinin from *Artemisia annua* in 1972 by Tu Youyou marked a pivotal breakthrough in natural product chemistry and the development of antimalarial drugs. Artemisinin, a sesquiterpene lactone of the cadinane-type with an endoperoxide bridge, displays potent activity against *Plasmodium falciparum* by generating cytotoxic reactive oxygen species (ROS) within infected erythrocytes. Its isolation catalyzed the development of artemisinin-based combination therapies (ACTs), now considered the gold standard in the treatment of global malaria.

3.1. Artemisinin Yield and Variation in *A. annua*

Among over 400 species in the *Artemisia* genus, *A. annua* uniquely accumulates significant artemisinin levels, with leaf concentrations reaching up to 1.4% dry weight, although this is highly variable. Factors such as genetic diversity, developmental stage, climatic conditions, light intensity, soil nutrients, and harvest time have a significant influence on artemisinin biosynthesis. Moreover, the essential oil content of the plant ranges from 0.04% to 1.9%, comprising both monoterpenes and sesquiterpenes that contribute to its distinctive aroma and therapeutic properties [4].

3.2. Beyond Artemisinin: Other Bioactive Compounds

While artemisinin remains the hallmark compound of *Artemisia annua*, the plant's broad-spectrum phytochemical repertoire significantly contributes to its diverse medicinal applications [4]. Notably, coumarins such as scopoletin and scopolin exhibit strong antioxidant and neuroprotective effects by inhibiting nitric oxide synthase and mitigating the accumulation of reactive oxygen species (ROS) in neural tissues. In parallel, flavonoids like chrysosplenol-D and casticin display potent anti-tumor activities by suppressing cell proliferation and angiogenesis, primarily through the modulation of PI3K/AKT and MAPK signaling pathways [4]. Moreover, phenolic glycosides, including domesticoside, impart immunomodulatory, and hepatoprotective actions, whereas norannuic acid demonstrates anti-proliferative efficacy in various cancer cell lines via caspase activation and mitochondrial depolarization. These bioactive constituents work synergistically with artemisinin, broadening *A. annua*'s potential in integrative medicine, particularly in the management of oncology,

neurodegenerative diseases, and chronic inflammation.

3.3. Biosynthesis and Derivatives of Artemisinin

The biosynthesis of artemisinin in *Artemisia annua* initiates through the mevalonate (MVA) and methylerythritol phosphate (MEP) pathways, both of which contribute to the formation of farnesyl pyrophosphate (FPP)—a universal precursor for sesquiterpene biosynthesis. This sesquiterpenoid pathway proceeds through several key intermediates, including artemisinic acid, dihydroartemisinic acid, artemisinol, epoxyarteannuinic acid, and artemisilactone. These intermediates not only serve as metabolic precursors to artemisinin but also exhibit intrinsic bioactivities, including anti-inflammatory, antibacterial, and antiparasitic properties (**Table** 1) [5]. The structural versatility of these molecules enables chemical modification, making them attractive targets for semi-synthesis and the development of derivatives. Such strategies offer promising avenues in synthetic biology and metabolic engineering for optimizing artemisinin yields and generating novel analogues with improved pharmacokinetics and broader therapeutic potential.

Table 1. Major Classes of phytochemicals in *Artemisia annua* and their bioactivities.

Compound Class	Representative Compounds	Primary Biological Activities	Additional Information
Sesquiterpene Lactones	Artemisinin	Antimalarial, anticancer	Artemisinin is a sesquiterpene lactone with a peroxide bridge crucial for its antimalarial activity.
Sesquiterpene	Arteannuin B	Antimalarial, anticancer	Arteannuin B is a biosynthetic precursor to artemisinin and exhibits antimalarial properties
Flavonoids	Quercetin, Luteolin, Apigenin	Antioxidant, anti-inflammatory, neuroprotective	Quercetin and luteolin are flavonoids known for their antioxidant properties. They scavenge free radicals and modulate signaling pathways involved in inflammation and neuroprotection.
Monoterpenes (Volatile)	Camphor, 1,8-Cineole, β-Pinene	Antimicrobial, bronchodilatory, insecticidal	Camphor and 1,8-cineole are monoterpenes contributing to the aromatic profile of *A. annua*. They exhibit antimicrobial activity and are used in traditional medicine for respiratory ailments.
Phenolic Acids	Caffeic acid, Chlorogenic acid	Antioxidant, hepatoprotective	Caffeic acid and chlorogenic acid are phenolic compounds with strong antioxidant properties. They protect liver cells from oxidative damage and are involved in the plant's defense mechanisms.
Coumarins	Scopolin,Scopoletin	Antinociceptive, antiinflammatory, antioxidant, antipyretic	Scopolin,Scopoletin have anti-allergic and antioxidant properties.They cause sedation during pain and provide cooling effect to the body
Phenylpropanoids	Methyl cinnamate	Antimicrobial, anti-inflammatory, antioxidant, and antiadipogenic effects.	Methyl cinnamate inhibit the growth of microbes and improves the intestinal microbiota.
Terpenoids	Phytol	Antihyperalgesic, Anti-inflammatory, and Antiarthritic	Phytol reduces the pain and inflammation thereby reducing the damage in the joints
Phytosterol	β-Sitosterol, Stigmasterol	Anti-inflammatory and immunomodulatory	β-Sitosterol known for its modulating lipid metabolism, reducing cholesterol absorption, and supporting anti-inflammatory and immunomodulatory effects.
Phenolic Glycoside	Norannuic Acid, Domesticoside	Anticancerous	Norannuic Acid is a compound with anti-proliferative effects in cancer cell lines

3.4. Biotechnological and Pharmaceutical Implications

Given its complex biosynthetic architecture and therapeutic relevance, *A. annua* has emerged as a model species for plant metabolic engineering and biotechnological interventions. Genetic transformation techniques have been applied to overexpress key enzymes such as amorpha-4,11-diene synthase (ADS) and cytochrome P450 monooxygenases (CYP71AV1), significantly enhancing artemisinin production in planta. Furthermore, the heterologous expression of the artemisinin biosynthetic pathway in microbial hosts, such as *Saccharomyces cerevisiae* and *Escherichia coli,* has enabled the industrial-scale production of artemisinic acid, a precursor that is amenable to chemical conversion into artemisinin. More recently, CRISPR/Cas9 genome editing has been employed to knock out competing pathways, thereby redirecting metabolic flux toward the artemisinin pathway and improving yield efficiency. These integrated approaches offer sustainable alternatives to traditional extraction from plant biomass, effectively addressing the supply-chain limitations and cost constraints associated with artemisinin-based therapies. As such, the convergence of plant biotechnology, synthetic biology, and pharmaceutical innovation continues to expand the therapeutic applications and accessibility of artemisinin derivatives in combating malaria and other emerging diseases.

3.5. *Artemisia annua*

Figure 1. *Artemisia annua* plants.

4. Ethnopharmacological History

4.1. Traditional and Historical Uses

Artemisia annua, known as Qinghao in traditional Chinese medicine, has been esteemed for its medicinal properties for over two millennia. The earliest known reference appears in the *"Wushi'er Bingfang"* (*Fifty-two Prescriptions*, circa 168 BC), where it was recommended for treating hemorrhoids and described as resembling "cow lice," possibly indicating its use against parasitic infections. Although the original *Shennong Ben Cao Jing* is lost, historical accounts suggest it documented Qinghao's applications as a food preservative and a remedy for ailments such as summer heat and intermittent fevers. Further elaboration on its medicinal uses is found in the *Zhouhou Beiji Fang* (340 AD), which detailed water-soaked preparations of Qinghao for treating fevers and symptoms similar to malaria. Beyond its medicinal applications, *Artemisia annua* was traditionally used as a flavoring agent due to its distinctive fragrance, which later led to an interest in its essential oils in the perfume industry [7]. In traditional Chinese medicine, it has been used to treat conditions such as malaria, consumptive fever, jaundice, and wounds and to improve visual clarity[8]. In Iranian traditional medicine, it has been applied as an antispasmodic, carminative, and sedative/hypnotic remedy for infants. Decoctions of the plant have also been used to treat hemorrhage and diarrhea, indicating its hemostatic and astringent properties.

4.2. Pharmacological Activities

4.2.1. Antihypertensive Activity

Recent studies have highlighted the antihypertensive potential of *Artemisia annua*. Administration of aqueous extracts (100–200 mg/kg) significantly decreased phenylephrine-induced contractions and enhanced endothelium-dependent relaxation in rat aortic rings, suggesting vasodilatory activity. These effects are attributed to the extract's enhancement of nitric oxide-mediated vasodilation, which may be particularly beneficial in managing hypertension among patients with diabetes.

4.2.2. Antidiabetic and Hypolipidemic Effects

Artemisia annua also exhibits potential in managing diabetes and metabolic disorders. Oral administration of plant extracts (100–390 mg/kg) to diabetic rats and rabbits over 2–4 weeks led to significant reductions in fasting blood glucose and HbA1c levels, indicating improved gly-

cemic control. Additionally, lipid profiles enhanced due to reduced cholesterol and triglyceride levels, and the extract mitigated diabetes-induced body weight loss, suggesting systemic metabolic protection.

4.2.3. Anti-inflammatory and Immunomodulatory Effects

The anti-inflammatory effects of *A. annua* have been demonstrated in both acute and chronic models, where methanolic extracts have shown reductions in inflammation comparable to those of standard NSAIDs. Furthermore, ethanolic extracts inhibited the proliferation of splenocytes stimulated by concanavalin A and lipopolysaccharide, indicating immunosuppressive potential suitable for autoimmune and inflammatory diseases.

4.2.4. Antimicrobial and Antiviral Activities

The extracts and essential oils of *A. annua* exhibit strong antimicrobial activity. Essential oils have shown effectiveness against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* [9]. Recent studies also support its antiviral potential, suggesting inhibition of viral entry and replication processes, including effects against RNA viruses.

4.3. Hepatoprotective and Antioxidant Properties

Artemisia annua contributes to liver health and reduces oxidative stress. Liver Protection: Phenolic acids, such as caffeic and chlorogenic acid, in the plant exhibit hepatoprotective effects, safeguarding liver cells from oxidative damage. Antioxidant Activity: The plant's high content of flavonoids and other antioxidants helps neutralize free radicals, reducing oxidative stress and associated cellular damage.

4.4. Antifeedant Properties

Research into the antifeedant and insecticidal properties of *Artemisia annua* has expanded significantly over recent years. Scientific studies have demonstrated that its extracts possess robust feeding deterrent properties and exhibit regulatory effects on insect growth and ovicidal activities. This makes *A. annua* an attractive botanical agent for integrated pest management (IPM) strategies, particularly in organic farming. The bioactive compounds in *A. annua*, particularly artemisinin and its derivatives, are known to alter feeding behavior and disrupt various life cycle stages of pests.

4.4.1. Chemical Composition and Mechanism of Action

Artemisia annua extracts are rich in secondary metabolites, including sesquiterpene lactones, flavonoids, and essential oils, which have shown considerable effects in altering insect feeding patterns. Artemisinin, a potent sesquiterpene lactone, plays a central role in the insecticidal properties of *A. annua*. Recent studies have confirmed that artemisinin not only acts as an antimalarial compound but also exhibits dual functionality as an antihelminthic and insecticidal agent. For example, research with *Drosophila melanogaster* (fruit flies) has demonstrated that artemisinin strongly repels insect larvae and alters their feeding behavior. This finding aligns with earlier studies indicating the repellent effects of artemisinin, making it a promising candidate for pest control applications [10].

4.4.2. Mechanisms of Insecticidal Activity

Recent investigations have revealed that the insecticidal properties of *A. annua* are not solely due to feeding deterrence but also involve direct toxicity mechanisms at the cellular level. In laboratory studies, artemisinin has been shown to disrupt mitochondrial membrane potential in *Drosophila* cells, leading to impaired cellular function and, ultimately insect death. This mitochondrial dysfunction is believed to be a key factor in the insecticidal activity of artemisinin. The ability to target both behavioral repulsion and cellular toxicity suggests that artemisinin operates through dual pathways, thereby enhancing its efficiency as an insect defense compound [11].

Furthermore, studies have shown that *A. annua* extracts can impair insect development by interfering with molting processes and reproduction. The extracts act as ovicides, preventing the successful development of eggs and larvae into adults. This mechanism of action is funda-

mental in controlling insect populations by reducing their ability to reproduce [12].

4.4.3. Environmental and Ecological Impact

The use of *A. annua* in pest management is particularly significant in the context of sustainable agriculture. Unlike synthetic chemical pesticides, which often lead to the development of pest resistance, *A. annua* offers an environmentally friendly alternative with minimal negative impact on non-target organisms. The plant's natural defenses, including its chemical and physiological properties, provide a multi-layered approach to pest control. By combining deterrent feeding behavior with toxic effects on insect development and reproduction, *A. annua* provides a powerful tool for reducing the reliance on chemical pesticides, which can lead to long-term ecological damage and resistance development [13].

The potential for artemisinin derivatives to be incorporated into plant-based pesticides has sparked interest in their use for sustainable pest management in both organic farming and integrated pest management systems. Recent studies have highlighted the advantages of artemisinin derivatives, particularly in terms of their ability to protect crops from pest damage without contributing to the growing problem of pesticide resistance. The environmentally friendly profile of *A. annua* also suggests that it could play a crucial role in mitigating the negative effects of conventional pesticide use, especially in vulnerable ecosystems [14].

4.4.4. Future Directions and Challenges

Despite the promising insecticidal and antifeedant properties of *A. annua*, challenges remain in optimizing its use for large-scale agricultural applications. Further research is needed to explore the formulation and delivery methods of *A. annua* extracts to enhance their stability and effectiveness under field conditions. Additionally, understanding the genetic and biochemical pathways that govern the production of artemisinin and other bioactive compounds in *A. annua* could lead to more targeted and efficient pest control strategies. Advances in genetic engineering and synthetic biology also offer the potential for improving the yields of artemisinin and other bioactive compounds, making them more viable for commercial pest management applications. However, these methods must be developed carefully.

4.5. Antimicrobial Activity

Recent studies on the antimicrobial properties of *Artemisia annua* essential oils have revealed their significant efficacy against a broad spectrum of pathogens, except *Pseudomonas aeruginosa*, which remains resistant to the oil's action. Notably, the essential oil has demonstrated strong antifungal activity, with minimum inhibitory concentrations (MIC) of 2 mg/ml against *Saccharomyces cerevisiae* and *Candida albicans*. It also exhibits moderate antibacterial activity, with MIC values of 32 mg/ml against *Staphylococcus aureus* and 64 mg/ml against *Escherichia coli* [9]. While *Pseudomonas aeruginosa* shows resistance to *A. annua* essential oil, the plant's oil is effective against a variety of Gram-negative and Gram-positive bacteria, including *Enterococcus hirae* and *Bacillus subtilis*. The antimicrobial efficacy of *A. annua* has been attributed to its diverse chemical constituents. Key bioactive compounds such as scopoletin, sesquiterpene lactones, artemisinin, and its derivatives, including artemether, have been shown to exhibit significant antibacterial and antifungal properties. These compounds contribute to the inhibition of microbial growth through various mechanisms, including disruption of cell membrane integrity, interference with DNA replication, and inhibition of enzymatic functions [15].

4.5.1. Recent Advances in Mechanism of Action

Several studies have provided insights into the molecular mechanisms underlying the antimicrobial activity of *A. annua* extracts. For instance, *Artemisia* derivatives such as artemisinin and its precursor, artemisinic acid, have been shown to interact with microbial DNA, targeting DNA-gyrase in *Escherichia coli* and *Mycobacterium smegmatis* [16]. This interaction is thought to prevent DNA replication, thereby inhibiting microbial growth. Furthermore, artemether has been found to induce oxidative stress in bacterial cells, resulting in cell membrane damage and cell death. A more recent study by [17] demonstrated that artemisinin's derivatives exhibit synergistic effects when combined with conventional antibiotics, suggesting their

potential to overcome antimicrobial resistance (AMR). This discovery positions *A. annua* as a promising candidate in the development of next-generation antibiotics, especially as AMR continues to pose a significant global health threat.

4.5.2. Environmental and Therapeutic Implications

The antimicrobial properties of *A. annua* essential oils not only offer promising avenues for medical and therapeutic applications but also present opportunities for sustainable pest and disease control in agriculture. As *A. annua* is known to be relatively environmentally safe compared to synthetic chemical alternatives, it holds potential as a green solution for combating plant diseases and pests, especially in organic farming.

4.6. Anti-inflammatory Activity

Recent studies have expanded our understanding of the anti-inflammatory properties of *Artemisia annua* extracts, emphasizing their potential in treating both acute and chronic inflammatory conditions. The methanol and water extracts of *A. annua* have shown significant anti-inflammatory effects in experimental models, particularly in rat paw edema induced by carrageenan and egg albumin. A dose of 200 mg/kg resulted in a substantial reduction in inflammation, with inhibition rates of 55.44% and 53.16%, respectively.

4.6.1. Mechanisms of Action

The anti-inflammatory effects of *A. annua* are primarily attributed to its rich phytochemical profile, which includes triterpenoids, flavonoids, polyphenols, and coumarins. These compounds have been shown to modulate inflammatory pathways by inhibiting the production of pro-inflammatory mediators such as prostaglandins, cytokines, and histamines [18]. More recent studies have elucidated the mechanisms of action at the molecular level, demonstrating that *A. annua* extracts can inhibit the NF-κB signalling pathway, a critical regulator of inflammation [19].In addition to its effects on inflammatory mediators, *A. annua* has been found to modulate the activities of cyclooxygenase (COX) and lipoxygenase (LOX). These enzymes that play pivotal roles in the production of pro-inflammatory eicosanoids. Artemisinin, dihydroartemisinic, and artemether have been identified as key compounds responsible for these inhibitory effects. These molecules reduce the expression of COX-2 and inhibit LOX activity, thereby decreasing the synthesis of inflammatory mediators such as leukotrienes and prostaglandins [20].

4.6.2. Recent Insights into Cellular Pathways

Recent research by [21] has revealed that the anti-inflammatory effects of *A. annua* also involve the regulation of the NLRP3 inflammasome, a key component in the activation of the innate immune response. By inhibiting NLRP3 activation, *A. annua* reduces the production of interleukin-1β (IL-1β), a cytokine that plays a central role in the development of inflammation [22]. This novel pathway adds another layer of understanding to how *A. annua* can exert its anti-inflammatory effects, providing further support for its use in treating inflammatory diseases. In addition to these cellular and molecular pathways, *A. annua* has been shown to enhance antioxidant activity, which further contributes to its anti-inflammatory and tissue-protective properties. Studies have highlighted that the plant's flavonoids and polyphenolic compounds scavenge reactive oxygen species (ROS), which are often elevated during inflammatory responses. By reducing oxidative stress, *A. annua* extracts help to mitigate inflammation and prevent tissue damage in conditions such as rheumatoid arthritis and inflammatory bowel disease [23].

4.7. Antiviral Activity

Broad-Spectrum Antiviral Effects: Artemisinin and its derivatives have demonstrated antiviral effects against various viruses, primarily by inhibiting the activation of cellular transcription factors, interfering with the viral replication cycle, inducing cell apoptosis, and preventing the virus from binding to host cells. Activity Against SARS-CoV-2: A hot water extract of *Artemisia annua* cultivars containing artemisinin in the range of 1.4–25.0 μM was effective against all five SARS-CoV-2 variants. The IC50 and IC90 values, based on dried leaf weight used to produce the tea infusions were within the ranges of 11.0–67.7

μg and 59.5–160.6 μg of dry weight, respectively. Mechanistic Insights via Network Pharmacology: Network pharmacology and molecular docking studies have explored Artemisia annua's antiviral effects, focusing on key active compounds and their interactions with viral protein targets, particularly within the JAK-STAT signaling pathway, a critical mediator of immune responses to viral infections [25].

4.8. Antioxidant Activity

Phenolic and Flavonoid Content: Ethanol extracts from Artemisia annua flowers and leaves are rich in phenolic compounds, including caffeoylquinic acids and flavonoids like rutin and 3-feruloylquinic acid. These compounds contribute to the plant's antioxidant capacity. *In Vitro* Antioxidant Assays: The extracts demonstrated moderate antioxidant activity in DPPH radical scavenging assays, with IC50 values ranging from 50 to 200 μg/mL. Additionally, they exhibited significant activity in FRAP and hydrogen peroxide scavenging assays, indicating a strong reducing power [26].

Reduction of Oxidative Stress Markers: *In vivo* studies using turpentine-oil-induced rat inflammation models demonstrated that Artemisia annua extracts significantly reduced markers of oxidative stress, including protein oxidation (AOPP), lipid peroxidation (MDA), and DNA oxidation (8-OHdG). These effects were comparable to standard anti-inflammatory and antioxidant drugs.

4.9. Immunosuppressive Activity

Scientific investigations have established the immunomodulatory potential of *Artemisia annua*, supporting its use in managing autoimmune conditions such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and inflammatory bowel diseases. Autoimmune diseases arise when an overactive immune system mistakenly attacks healthy tissues, often necessitating prolonged administration of corticosteroids and synthetic immunosuppressive agents. However, these treatments are frequently associated with adverse effects, thereby driving interest in plant-based immunotherapies with lower toxicity[27].

Ethanolic extracts of *A. annua* have demonstrated robust immunosuppressive activity in vitro, particularly through their inhibitory effect on splenocyte proliferation stimulated by concanavalin A (Con A) and lipopolysaccharide (LPS) mitogens. These mitogens mimic T-cell and B-cell activation, respectively, thus providing a model for cellular and humoral immune responses. *A. annua* extract inhibits both pathways with a dose-dependent suppression of immune activation [285]. Flavonoids such as quercetin, luteolin, and apigenin present in *A. annua* have been shown to play a central role in this immunomodulation. These polyphenolic compounds influence key immune cells, including macrophages, T-lymphocytes, and B-lymphocytes, by suppresing pro-inflammatory cytokines and inhibiting of the nuclear factor kappa B (NF-κB) signaling pathway, which is implicated in the pathogenesis of many autoimmune and inflammatory conditions [29].

Recent studies have demonstrated that artemisinin derivatives, particularly SM934 and artesunate, modulate immune responses more precisely. For instance, SM934 has been shown to suppress effector T cell responses while promoting the development of regulatory T cells in murine lupus models [16]. Oral administration of dihydroartemisinin significantly reduced serum anti-dsDNA antibody levels and pro-inflammatory cytokines, correlating with decreased renal inflammation and NF-κB activity [30]. Artesunate has also proven effective in experimental models of inflammatory bowel disease, significantly reducing colon damage and inflammatory cytokine expression [31]. These findings emphasize the therapeutic value of *A. annua* as an immunoregulatory agent that restores immune balance without inducing global immunosuppression. Importantly, the synergistic effects observed between *A. annua* extracts and conventional drugs suggest the potential for integrative treatment approaches with reduced adverse outcomes.

4.10. Antimalarial Activity

The antimalarial activity of *Artemisia annua* is primarily attributed to artemisinin, a sesquiterpene lactone endoperoxide, and its semi-synthetic derivatives, such as artesunate and artemether. Artemisinin acts by disrupting the hemoglobin degradation pathway in *Plasmodium* spp., particularly by alkylating heme and inhibiting hemozoin formation, which leads to the accumulation of toxic free heme and parasite death[32].

In vitro studies have demonstrated that artemisinin inhibits the digestive vacuole proteases of *Plasmodium*

falciparum, thereby impairing hemoglobin digestion and leading to parasitic death [33]. Additionally, *A. annua* contains methoxylated flavonoids such as casticin, chrysoplenetin, and eupatorin, which enhance artemisinin activity by facilitating its activation through interaction with heme iron. While these flavonoids do not exhibit direct antiplasmodial activity, they synergize with artemisinin to boost efficacy against *P. falciparum* and *P. yoelii* [34]. Recent advances in extraction methods have led to improved yields of artemisinin from *A. annua*. For instance, cholinium-based ionic liquids have been employed to extract artemisinin with greater efficiency and selectivity, resulting in extracts with higher bioactivity than synthetic artemisinin alone [35]. These whole-plant extracts exhibit enhanced antimalarial efficacy, likely due to the presence of additional phytochemicals that modulate immune responses and increase macrophage phagocytic activity [36]. Clinical studies have substantiated these findings. Over 3000 patients with malaria, including drug-resistant *P. falciparum* cases, have been successfully treated with artemisinin-based therapies. Comparative clinical trials have shown that organic *A. annua* extracts are faster-acting, more effective, and less toxic than chloroquine. Furthermore, the use of *A. annua* infusions has demonstrated efficacy across multiple parasite life stages, including blood, liver, and gametocyte forms, underscoring its potential in malaria eradication programs[37]. Taken together, these insights highlight the remarkable antimalarial potential of *Artemisia annua*, not only through direct parasiticidal effects but also via modulation of host immune responses. The integration of *A. annua* into combination therapies offers a promising strategy for overcoming artemisinin resistance and improving treatment outcomes in endemic regions.

4.11. Antiparasitic Activity

Research studies indicate that artemisinin drugs demonstrate promising antiparasitic potential against various parasites, including Leishmania, Trypanosoma, Babesia, Eimeria, coccidiosis, and trematode blood fluke species such as *Schistosoma spp*. Notably, the use of artemisinin in the livestock industry has been on the rise due to its efficacy against parasites affecting animals [38].

Neospora canum, is a protozoal parasite affecting mammals. Cultured Vero cells or mouse peritoneal macrophages infected with *N. canum* and treated with artemisinin for 14 days exhibited complete elimination of all microscopic foci of *N. canum* at concentrations of 20 or 10 µg/ml after 11 days. Similarly, complete elimination was observed at a concentration of 0.1 µg/ml after 14 days, indicating artemisinin's potential to reduce the intracellular multiplication of *N. canum* tachyzoites [1]. In another study, the effect of artemether was tested against larval stages of Schistosoma mansoni. Animals treated with artemether did not develop schistosomiasis, demonstrating the parasite's pronounced susceptibility compared to the untreated controls. Recent research also highlights the significant activity of n-hexane extracts of *A. annua* leaves and seeds against *Leishmania donovani.* This antileishmanial activity involves inducing morphological changes in promastigotes, as well as apoptosis and cell-cycle arrest at the cellular level. In a separate study against *Neospora canum*, cultured host cells infected with *N. caninum* tachyzoites and supplemented with artemisinin at concentrations of 20, 10, 1, 0.1, and 0.01 µg/ml resulted in the complete elimination of all microscopic foci of *N. canum* at 20 or 10 µg/ml after 11 days. Similarly, at 1 µg/ml for 14 days, the same results were achieved [2]. The research found that water, alcohol and chloroform extracts from *Artemisia annua* have potential uses in acanthamoebiasis treatment as decrying solutions or antimicrobial agents with antibiotics. The extracts from *Artemisia annua* demonstrated their activity through both *in vitro* and *in vivo* experiments. The pure artemisinin preparation exhibited anti-amoebic effects that were 100 to 300 times stronger than those observed with the studied extracts. The chloroform extract proved to be the strongest effective agent against acanthamoeba. Tests conducted on experimental animals infected with amoebae demonstrated that these extracts significantly extended the survival period of these animals [39].

4.12. Antiparasitic Activity

Artemisinin and its derivatives have demonstrated significant antiparasitic potential against a broad spectrum of parasites, including *Leishmania*, *Trypanosoma*, *Babesia*, *Eimeria*, and trematode blood flukes such as *Schistosoma* spp. The increasing application of artemisinin in the livestock sector further highlights its efficacy against parasites impacting animal health [40]. In vitro studies on *Neospora*

caninum, a protozoan parasite affecting mammals, revealed that cultured Vero cells and mouse peritoneal macrophages infected with *N. caninum* and treated with artemisinin showed complete elimination of microscopic foci. Treatment with concentrations of 20 or 10 µg/mL resulted in total clearance by day 11, while even lower concentrations (0.1 µg/mL) achieved similar outcomes by day 14. These findings highlight the potential of artemisinin in inhibiting the intracellular multiplication of *N. caninum* tachyzoites [41].

Similarly, artemether has shown high efficacy against larval stages of *Schistosoma mansoni*, preventing the development of schistosomiasis in treated animals and highlighting the parasite's pronounced susceptibility. Additionally, *Artemisia annua* extracts particularly the n-hexane fractions of leaves and seeds exhibited notable antileishmanial activity. These effects were attributed to morphological disruptions, induction of apoptosis, and cell cycle arrest in *Leishmania donovani* promastigotes [42]. Artemisinin also showed promise in treating acanthamoebiasis. Water, alcohol, and chloroform extracts from *A. annua* exhibited antimicrobial effects both in vitro and in animal models. Among these, the chloroform extract demonstrated the most vigorous amoebicidal activity. Notably, purified artemisinin displayed 100 to 300 times greater potency compared to crude extracts, significantly extending survival in experimental animals infected with *Acanthamoeba* spp [43].

4.13. Anticancer Activity

Extensive research has explored the anticancer properties of *A. annua* extracts, particularly those targeting HeLa cervical cancer cells and the protozoan parasite *Trypanosoma brucei brucei*. Methanolic extracts showed superior cytotoxic activity compared to dichloromethane extracts, suggesting that polar compounds are primarily responsible for the observed effects. Key bioactive constituents, including artemisinin and quercetagetin-6,7,3',4'-tetramethylether, have shown promising antitumor activities. The anticancer efficacy of artemisinin is largely attributed to its unique endoperoxide bridge. This structural feature reacts with intracellular ferrous iron (Fe^{2+}) prevalent in cancer cells to generate reactive oxygen species (ROS). These ROS cause oxidative damage to DNA, proteins, and lipids, ultimately inducing apoptosis. Artemisinin also interacts with transferrin, a natural iron transporter. Cancer cells overexpress transferrin receptors (TfR) to support their rapid growth, which facilitates the selective uptake of artemisinin-transferrin complexes through receptor-mediated endocytosis. Once internalized, artemisinin induces programmed cell death via mitochondrial pathways. The release of cytochrome c activates caspases, initiating the apoptotic cascade. This mechanism confers artemisinin with the ability to selectively target cancer cells while sparing normal tissues, making it a promising candidate for cancer therapy with fewer side effects than conventional chemotherapeutics [44,45,46].

5. Future Prospects

Despite extensive research into the pharmacological activities of *Artemisia annua*, several avenues remain underexplored, offering promising prospects for future investigation. One of the foremost opportunities lies in the mechanistic elucidation through molecular docking, omics-based studies (including transcriptomics, proteomics, and metabolomics), and CRISPR-Cas9 gene-editing tools to unravel the specific targets of artemisinin and its analogs across various diseases. Additionally, the synergistic effects between artemisinin and other phytoconstituents, such as flavonoids and terpenoids, warrant further study, particularly in enhancing bioavailability and overcoming drug resistance. In the realm of drug development, nanoformulations of *A. annua* extracts such as artemisinin-loaded nanoparticles, liposomes, or solid lipid nanoparticles could significantly enhance therapeutic delivery, target specificity, and controlled drug release. Clinical trials remain crucial to validate the efficacy and safety of these compounds in treating cancers, parasitic infections, viral illnesses, and autoimmune conditions. Moreover, structure-activity relationship (SAR) studies may yield novel artemisinin derivatives with superior potency, lower toxicity, and improved pharmacokinetic properties [47].

From an agricultural and industrial perspective, biotechnological interventions such as metabolic engineering and synthetic biology can be utilized to enhance artemisinin yields in *A. annua* or in heterologous hosts, including *Saccharomyces cerevisiae* and *Nicotiana benthamiana*. Likewise, *in vitro* propagation, elicitor treatments, and ge-

nome editing could support commercial-scale production for pharmaceutical applications. Given the rising threat of antimicrobial and antiparasitic resistance, repositioning artemisinin-based compounds as adjuncts or alternatives in existing drug regimens could be pivotal. Furthermore, exploring *A. annua* in combination therapy alongside conventional drugs or immune modulators may yield additive or synergistic effects for chronic diseases, especially in cancer and infectious diseases [48,49,50].

6. Conclusions

Artemisia annua represents a pharmacological treasure trove, with its therapeutic versatility rooted in a complex matrix of bioactive compounds, most notably artemisinin. The plant has demonstrated significant promise in the treatment of a diverse range of ailments including malaria, parasitic infections, microbial diseases, cancer, inflammation, and viral infections, owing to its unique mechanisms of action, which include oxidative stress induction, DNA damage, immune modulation, and enzymatic inhibition. Its low toxicity profile, cost-effectiveness, and abundance in nature further enhance its appeal as a candidate for both modern drug development and integrative medicine. As drug resistance and chronic disease burdens continue to escalate globally, *A. annua* stands poised to serve as both a frontline and adjuvant therapeutic agent. Harnessing the full therapeutic potential of *Artemisia annua* requires multidisciplinary efforts involving pharmacologists, molecular biologists, chemists, agronomists, and clinicians. Future research should prioritize mechanistic clarity, clinical validation, and formulation innovations to translate this ancient herbal remedy into next-generation pharmaceuticals. The continued study and strategic utilization of *A. annua* will not only honor its ethnomedicinal roots but also pave the way for its integration into global health frameworks and pharmaceutical pipelines.

Author Contributions

Conceptualization, V.S.S. and Y.S.P.; methodology, V.S.S.; software, V.S.S.; validation, V.S.S. and Y.S.P.; formal analysis, V.S.S.; investigation, V.S.S.; resources, Y.S.P.; data curation, V.S.S.; writing—original draft preparation, V.S.S.; writing—review and editing, Y.S.P.; visualization, V.S.S.; supervision, Y.S.P.; project administration, Y.S.P.; funding acquisition, Y.S.P. All authors have read and agreed to the published version of the manuscript.

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