PLANT SCIENCE TODAY
ISSN 2348-1900 (online)
Vol 12(1): 1-9
https://doi.org/10.14719/pst.3111

HORIZON
e-Publishing Group
HePG

REVIEW ARTICLE

Therapeutic potential of *Artemisia annua* and artemisinin in viral infections, cancer and global health advancements

Bakhtiyor K. Rakhmanov[1]*, Dilshod E. Usmonov[1], Azadakhan S. Imamkhodjaeva[1], Saidakhon I. Zakiryaeva[2], Khurshida A. Ubaydullaeva[1], Shukhrat E. Shermatov[1], Mirzakamol S. Ayubov[1], Zabardast T. Buriev[1] & Ibrokhim Y. Abdurakhmonov[1]

[1]Structural and functional genomics laboratory, Center of Genomics and Bioinformatics, Academy of Sciences of the Republic of Uzbekistan, Tashkent 111 215, Uzbekistan

[2]Soil microbiology and biotechnology laboratory, Institute of Microbiology, Academy of Sciences of the Republic of Uzbekistan, Tashkent 100128, Uzbekistan

*Email: bakhtiyor.rakhmanov@gmail.com

OPEN ACCESS

ARTICLE HISTORY

Received: 21 November 2023
Accepted: 17 November 2024

Available online
Version 1.0 : 11 February 2025
Version 2.0 : 22 February 2025

Check for updates

Additional information

Peer review: Publisher thanks Sectional Editor and the other anonymous reviewers for their contribution to the peer review of this work.

Reprints & permissions information is available at https://horizonepublishing.com/journals/index.php/PST/open_access_policy

Publisher's Note: Horizon e-Publishing Group remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Indexing: Plant Science Today, published by Horizon e-Publishing Group, is covered by Scopus, Web of Science, BIOSIS Previews, Clarivate Analytics, NAAS, UGC Care, etc
See https://horizonepublishing.com/journals/index.php/PST/indexing_abstracting

CITE THIS ARTICLE

Rakhmanov BK, Usmonov DE, Imamkhodjaeva AS, Zakiryaeva SI, Ubaydullaeva KA, Shermatov SE, Ayubov MS, Buriev ZT, Abdurakhmonov IY. Therapeutic potential of *Artemisia annua* and artemisinin in viral infections, cancer and global health advancements. Plant Science Today. 2025; 12(1): 1-9. https://doi.org/10.14719/pst.3111

Abstract

Artemisinin, originally derived from *Artemisia annua* as an antimalarial agent, has demonstrated broad therapeutic potential in recent years. This review aims to synthesize current research on artemisinin's efficacy beyond malaria, with a focus on its antiviral, anticancer and immunomodulatory applications. Methodologically, the review integrates findings from peer-reviewed studies, clinical trials and bioengineering innovations to offer a comprehensive perspective on artemisinin's mechanisms of action, therapeutic applications and advancements in production. Key findings highlight artemisinin's effectiveness in cancer and viral infections (including COVID-19), with recent bioengineering innovations enhancing its production through genetic modifications in *A. annua*, transgenic plants and yeast. These advancements improve accessibility and underscore the need for further clinical research to establish artemisinin's role as a broad-spectrum therapeutic.

Keywords

Artemisia annua; artemisinin; healthcare; medicinal compound

Introduction

Artemisia annua and the uniqueness of artemisinin

Artemisinin, a naturally occurring compound derived mainly from the leaves of the sweet wormwood plant *Artemisia annua* L. (Fig. 1), has attracted considerable attention in the field of medicine due to its remarkable anti-malarial properties. This sesquiterpene lactone with its distinctive peroxide bridge, has revolutionized the treatment of malaria, particularly in regions plagued by drug-resistant strains of the parasite. This structure was identified in 1975 (1, 2).

In 2022, an estimated 249 million malaria cases and 608000 malaria deaths were reported across 85 countries. The WHO African Region bore a significantly high proportion of the global malaria burden, with 94% (233 million) of cases and 95% (580000) of deaths occurring in this region. Children under 5 years old represented approximately 80% of all malaria-related deaths in the African Region (3). The emergence of resistance to conventional anti-malarial drugs has fueled the quest for novel and effective treatment strategies. The World Health Organization recommended artemisinin-based combination therapies (ACTs), which incorporate arte-

Fig. 1. *Artemisia annua* plant from our ongoing research in the Center of Genomics and Bioinformatics, Uzbekistan.

misinin or its derivatives, have proven to be a key tool in combating this deadly disease. These therapies have not only saved countless lives but also aided in reducing the transmission of malaria, bringing people closer to the ambitious goal of malaria eradication (1-4). The chemical structure of artemisinin features a unique endoperoxide bridge, which is believed to be essential for its antimalarial activity (1, 2, 4). This bridge undergoes a cascade of reactions in the presence of iron, generating reactive oxygen species that specifically target the malaria parasite, *Plasmodium* (4, 5). A comprehensive understanding of the chemical properties of artemisinin is essential to maximize its pharmacological activity and formulate novel drugs utilizing its structure (4). The effectiveness of artemisinin (Fig. 2) as an antimalarial drug relies on its precise activation and molecular targeting mechanisms (5).

The mechanism of artemisinin is initiated through the activation of its endoperoxide bridge, which occurs when it interacts with heme and iron, key components found in high concentrations within the *Plasmodium* parasite's digestive vacuole. This interaction results in the formation of reactive oxygen species and carbon radicals, which damage important cellular components, including proteins, lipids and nucleic acids. This damage triggers oxidative stress, ultimately leading to the death of the parasite. The effectiveness of artemisinin to selectively target *Plasmodium* derives from its reliance on the parasite's haemoglobin digestion process, which ensures that healthy red blood cells remain intact. By disrupting im-

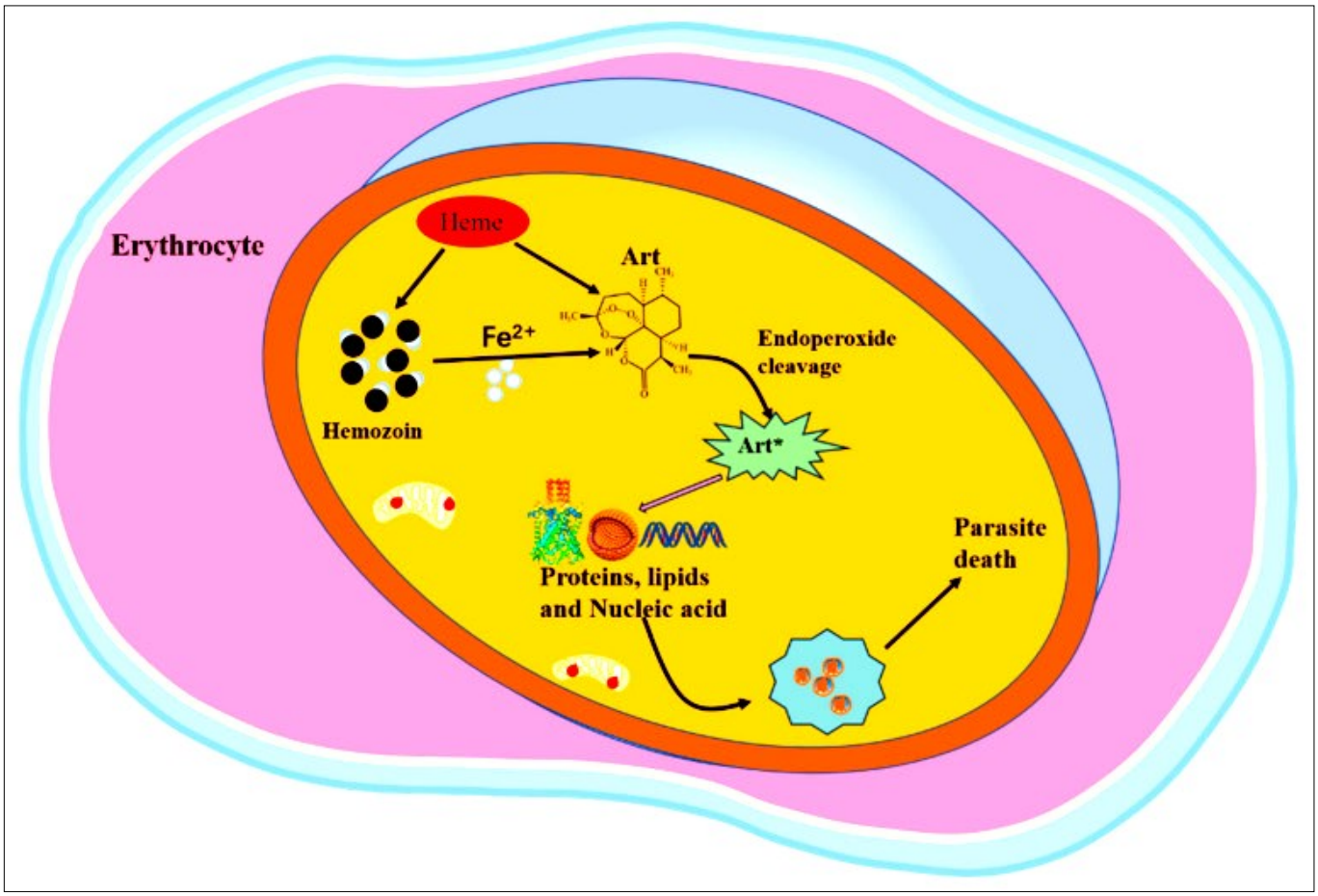

Fig. 2. Mechanism of action of artemisinin against malaria. Artemisinin is activated by heme and iron in malaria parasites, producing free radicals that damage key biomolecules and disrupt the parasite's functions, leading to its death. The asterisk denotes the activated form of artemisinin (ART). Abbreviation: Art - artemisinin.

portant metabolic and structural processes within the parasite, particularly at the red blood cell stage, artemisinin inhibits the parasite's ability to replicate, thereby preventing further malaria symptoms (1, 2, 4, 5).

An extremely important new class of antimalarial drugs, artemisinin and its derivatives are increasingly used worldwide. Artesunate, artemether, dihydroartemisinin and arteether are the most important artemisinin derivatives (4).

History and Discovery

Artemisinin, a remarkable compound with powerful antimalarial properties, has a long history deeply rooted in traditional Chinese medicine. The Artemisia genus including *Artemisia annua*, has been used in traditional Chinese medicine for centuries, a practice over 2000 years old (1, 4, 6). These ancient remedies often involved the use of Artemisia plants, which were known for their antipyretic properties. Artemisinin's breakthrough as a key antimalarial drug came amid the declining effectiveness of previous treatments such as chloroquine. The historical use of *Artemisia annua*, documented as early as 340 AD in the Zhou Hou Bei Ji Fang, set the stage for the discovery of artemisinin (1, 4, 6-8). In the 1970s, Chinese pharmacologist Tu Youyou faced the challenge of optimizing artemisinin extraction from *Annua* plant, including from fresh leaves. Traditional cooking, commonly used in herbal medicine extraction, was found to be detrimental to artemisinin activity. Tu's innovative approach involved testing various conditions and found that diethyl ether or alcohol as a solvent at temperatures below 60 °C effectively preserved the active components of artemisinin (1, 6). This method not only optimized the extraction but also demonstrated the remarkable stability of the extracted components, with anti-malarial activity largely retained even after 30 min of boiling (9). Youyou Tu's groundbreaking research heralded a pivotal moment in the history of artemisinin. Her systematic research into traditional Chinese herbal medicine led to the extraction of artemisinin from *Artemisia annua*. Rigorous testing confirmed its exceptional effectiveness against malaria parasites, particularly the deadliest strain, *Plasmodium falciparum*. Tu's discovery revolutionized malaria treatment and provided an effective weapon against drug-resistant parasites (1, 6). Tu Youyou's research not only revolutionized malaria treatment but also highlighted the importance of preserving and adapting traditional medical practices, setting a precedent for integrating herbal medicine into modern drug development. In 2015, Youyou Tu received the Nobel Prize in Physiology or Medicine for her groundbreaking work in discovering artemisinin, a key antimalarial drug, through an innovative approach rooted in traditional Chinese herbal medicine. This recognition underscores Professor Tu's significant contribution to revolutionizing malaria treatment and combating drug-resistant parasite strains (1, 4, 6-9).

Artemisia annua L. is native to Asia, particularly China, Japan and Korea. It has also been introduced and domesticated in various countries, including Poland, Brazil, Spain, France, Italy, Romania, the United States and Austria (10). Despite extensive geographic variation, these annual wormwood plants exhibit minimal morphological differences, but their chemical component and medicinal properties vary across geography (11). Artemisia plant is a fragrant annual plant of the daisy family with a smooth or finely hairy surface. Its erect, ribbed stem is green or violet-green, turning brown or violet-brown as it matures. Wild plants reach a height of 30–150 cm, while cultivated varieties can grow up to 300 cm. The green or yellow-green leaves have a honeycombed glandular pattern, are oval and 3 times pinnately divided into small, pointed leaflets. The stem leaves of the middle part are twice pinnate, while the upper leaves are smaller, simple and dark brown (12). The flowers of it are small, 1 to 2 mm in diameter, pale yellow and its leaves and flowers have a pleasant aromatic odor (7). *Artemisia annua* L. is an annual short-day plant (13). Its chromosome number in the diploid state is 2n=2x=18 with a nuclear genome sequence of 1.76 Gb (14). This plant has a long history of use in traditional Asian and African medicine as a tea or pressed juice to treat malaria and its associated symptoms (fever, chills) (15). Since its identification, more than 600 secondary metabolites have been identified in *Artemisia annua* through extensive phytochemical research (16).

Artemisia annua in Central Asia and in Uzbekistan

According to scientific literature, there are about 180 species of *Annua* plant in Central Asia, including 47 in Uzbekistan; numerous scientific studies have been carried out on them (17-19).

Phytochemical research in *Artemisia* species

As a result of phytochemical studies, a unique substance, artemisinin, has been identified in several *Artemisia* species around the world using various extraction methods. Those *Artemisia* plants were also used for various medicinal purposes. These include the following types: *A. abrotanum, A. absinthium, A. anethifolia, A. anethoides, A. austriaca, A. aff. tangutica, A. annua, A. apiacea, A. bushriences, A. campestris, A. cina, A. ciniformis, A. deserti, A. diffusa, A. dracunculus, A. dubia, A. incana, A. indica, A. fragrans, A. frigida, A. gmelinii, A. japonica, A. khorassanica, A. kopetdaghensis, A. integrifolia, A. lancea, A. macrocephala, A. marschalliana, A. messerschmidtiana, A. moorcroftiana, A. myriantha, A. nilagarica, A. pallens, A. parviflora, A. pallens, A. roxburghiana, A. scoparia, A. sieberi, A. sieversiana, A. spicigeria, A. thuscula, A. tridentata, A. vachanica, A. vestita* and *A. vulgaris* (20-42) (Table 1).

Application of medicine in parasitic diseases

Schistosomiasis is a significant tropical disease affecting millions globally, requiring both humans as definitive hosts and snails as intermediate hosts for the *Schistosoma* parasites' lifecycle. Artemisinin and its derivatives, including artemether and artesunate, are promising against *Schistosoma* infections, particularly in the context of praziquantel resistance. Extracts from *Artemisia afra* provide dual effects on the parasite and its snail host. Artemisinin's mechanism, which generates reactive oxygen species, offers broad antiparasitic action, effectively reducing in-

Table 1. Geographical distribution and useful properties of some *Artemisia* species

***Artemisia* species**	**Geographical distribution**	**Growth habit**	**Medicinal uses**	**Reference**
A. abrotanum	Asia, Asia Minor, Central Asia, Europe and Arabian Peninsula	Shrub	Bronchopulmonary ailments, appetite, ulcers, skin diseases, few to name	(43)
A. absinthium	Asia, the Middle East, Europe, South America and North Africa	Perennial	Hepatitis, gastritis, jaundice, wound healing, splenomegaly, indigestion, stomach pain, anemia, anorexia, antifungals, antimicrobials, anti-	(25, 44)
A. anethifolia	Northern Asia	Perennial	Traditional medicine, antidiabetic agents, antibacterial and antifungal activity	(39, 45)
A. anethoides	East Asia, Siberia, Mongolia, Northern China	Annual or biennial	Traditional medicine, insecticidal and repellent activities	(39, 46)
A. austriaca	Mongolia, China, Europe, Iran; and Central Asian countries	Annual	Used in folk medicine, antiseptic, gastric disorders	(47)
A. aff. tangutica	Asia, Central Asia, and in other territories	Perennial	Folk medicine	(25)
A. annua	Native to China, Europe and Central Asia including Uzbekistan, also naturalized to many countries, worldwide except Antarcti-	Annual	Traditional medicine for centuries, against fever, antimalarial (source of artemisinin), antiviral, antibacterial, food, cosmetics	(48, 42)
A. apiacea	Asia, Eastern Asia including China, Korea and Japan, China	Perennial	Antimicrobial, against eczema oxidation, immune, inflammation, and liver diseases, useful	(49)
A. bushriences	Asia, Iran, Pakistan	Perennial	Local use in traditional medicine	(25, 50)
A. campestris	Asia, Europe, North America and North Africa	Perennial	Antimicrobial, digestive stimulant, anti-inflammatory	(51)
A. cina	Asia, Egypt, Central Asia (Kazakhstan, Kyrgyzstan, Uzbekistan)	Schrub	Antimalarial, antibacterial, antioxidant, anti-inflammatory, immunosuppressive, anti-	(24, 52, 53)
A. ciniformis	North America, Asia including Iran	Perennial	Traditional medicine, inhibit AGS cancer cell anticancer	(54, 55)
A. deserti	Asia, Central Asia, Europe, North America	Perennial	Traditional medicine, antihypertensive, antiallergy, antiviral, antitumor, antioxidant, and cytotoxicity activity against human cervical carcinoma	(49, 56, 57)
A. diffusa	Asia, Afghanistan, Iran, Kazakhstan and Uzbekistan.	Perennial	Antitumor, breast cancer	(58, 59)
A. dracunculus	America, Europe, Asia, Iran, Pakistan, Azerbaijan and India.	Perennial	Antioxidant, digestive aid, analgesic, hypnotic, antiepileptic, anti-inflammatory and antipyretic agent and as an effective remedy in the treatment of helminthiasis, used in culinary herbs (tarragon)	(60)
A. dubia	Europe, Asia	Perennial	In the traditional treatment of microbial infections, also parasitic diseases, cancer or skin	(48, 61-64)

fections from helminths such as *Toxocara*, *Trichinella* and *Echinococcus* as well as trematodes and monogeneans, which are significant in aquaculture and public health (65). Visceral leishmaniasis, caused by *Leishmania infantum*, has limited treatment options. Although artemisinin demonstrates antileishmanial potential, its low bioavailability restricts its use. To enhance its efficacy, artemisinin-loaded solid lipid nanoparticles have been developed, which improve bioavailability and targeted delivery. In studies with infected mice, these nanoparticles reduced parasite burdens in the liver and spleen by approximately 85%, alleviating hepatosplenomegaly and suggesting a more effective treatment for visceral leishmaniasis (66).

Additionally, artemisinin's broad efficacy against helminth infections makes it a valuable alternative, particularly as conventional treatments face resistance and side effects. Key applications include its effectiveness against *Toxocara* spp. and *Trichinella spiralis*, as well as *Echinococcus* species and *Echinostoma* spp., providing safer options for monogenean parasites in aquaculture (67).

Antiviral potential of artemisinin

Antimalarial medications are emerging as promising therapeutic options for a variety of nonmalarial conditions, including viral infections such as human immunodeficiency virus, dengue virus, chikungunya fever and Ebola. The limited availability of effective antiviral agents for newly emerging viruses and drug-resistant strains, such as human cytomegalovirus, has sparked interest in repurposing antimalarials. The antiviral potential of four classes of antimalarial drugs, such as artemisinin derivatives, arylamino alcohols, aminoquinolines and antimicrobials was evaluated using *in vitro*, *in vivo* and clinical data. The aim was to explore how these antimalarial medications can be repurposed to address the critical need for effective antivi-

ral treatments in response to evolving viral threats (68). Artemisinin, its derivative artesunate and several other compounds were evaluated for their antiviral activity against the hepatitis B virus (HBV), leading to a classification of their efficacy. Compounds such as daidzein and quercetin showed no significant effect on HBV production, while others like berberine and tannic acid demonstrated a reduction in viral output but were limited by toxicity concerns. Curcumin and glycyrrhizic acid exhibited moderate antiviral activity without toxicity. Artemisinin and artesunate, however, stood out for their potent inhibitory effect on viral production with no adverse impact on host cells. Furthermore, a combination of artesunate and lamivudine demonstrated synergistic anti-HBV effects, underscoring their potential as promising antiviral agents against HBV (69).

COVID-19 and common viral infections

The COVID-19 pandemic has spurred interest in artemisinin and its derivatives from *Artemisia* species as potential antiviral agents. Studies have shown artemisinin compounds exhibit strong binding to SARS-CoV-2's main protease (Mpro), particularly at the Cys145 residue, indicating the potential for limiting viral activity through stable interactions and good bioavailability (70). Further, *Artemisia annua* extracts have demonstrated *in vitro* efficacy against SARS-CoV-2 variants, including Omicron, by inhibiting viral replication in Vero E6 and human lung cells, supporting their potential as a cost-effective treatment option for emerging COVID-19 variants (71). Specific compounds such as scopoletin and artemisinic acid have shown dose-dependent antiviral effects against the 3CLpro and Spike proteins of SARS-CoV-2, highlighting their utility against SARS-CoV-2 variants without compromising cell viability (72). In addition to these findings, WHO-supervised clinical trials are underway to assess artemisinin's therapeutic promise for COVID-19. The importance of enhancing artemisinin production via improved biosynthesis and biotechnological methods is underscored, as demand grows for its antiviral applications (73). Research also supports artemisinin's broad-spectrum activity, particularly against DNA viruses like cytomegalovirus and herpes viruses, while RNA viruses like HIV and hepatitis C respond minimally. Notably, artesunate acts synergistically with other antivirals and retains efficacy against ganciclovir-resistant HCMV, suggesting a promising future for expanded artemisinin-based antiviral treatments (74). These findings collectively underscore the need for a deeper understanding of artemisinin's mechanisms and further clinical trials to confirm its potential in viral therapeutics.

Cancer

Artemisinin and its derivatives show promising immunomodulatory and anticancer properties, effective across various cancers viz., colon, non-small cell lung cancer and melanoma. These compounds inhibit tumor-promoting pathways, such as PI3K/Akt and MAPK, while enhancing immune responses through mechanisms like T-cell differentiation and macrophage polarization (75). Dihydroartemisinin and artesunate, noted for better bioavailability, are effective in these roles but face pharmacokinetic limitations, spurring research into nanoparticle delivery systems for improved efficacy. Artemisinin derivatives also induce oxidative stress, apoptosis and ferroptosis, inhibiting angiogenesis and targeting pathways like Wnt/β-catenin and AMPK, although potential hepatotoxicity warrants careful clinical validation (15). Beyond artemisinin, *Artemisia annua* extracts contain active compounds such as chrysosplenol D and arteannuin B, demonstrating efficacy in triple-negative breast cancer models and offering affordable options in drug-resistant cancers (76). Given the low cost (USD 1 per dose), these treatments could be accessible alternatives for low- and middle-income countries, though comprehensive trials are still needed (77). Artemisinin's therapeutic scope also extends to kidney diseases, particularly in conditions related to inflammation and oxidative stress, like diabetic nephropathy (78). In colorectal cancer, artemisinin induces ferroptosis selectively in cancer cells, showing enhanced effects when combined with linoleic acid (79). Artesunate also exhibits *in vitro* anticancer efficacy, though its effects vary across patient-derived models, emphasizing the need for tailored clinical applications (80). Together, these findings highlight artemisinin's potential as a versatile therapeutic, though further trials are essential to confirm its broader applicability in cancer and kidney disease treatment.

Autoimmune diseases

Artemisinin and its derivatives have shown promising immunomodulatory effects relevant to autoimmune and inflammatory diseases. These effects are mediated through mechanisms targeting T and B cell activity, expanding regulatory T cells and inhibiting key inflammatory pathways such as NF-κB, MAPK and JAK-STAT. For example, artemether and the synthetic SM934 have been observed to suppress pro-inflammatory cytokines and limit pathogenic T-cell proliferation, showing efficacy in preclinical models of rheumatoid arthritis and systemic lupus erythematosus (81, 82). Artemisinin-based sesquiterpene lactones further support this anti-inflammatory potential by selectively promoting apoptosis in activated T cells while sparing resting cells, reducing the risk of broader immune suppression. Clinical studies on SM934, which is currently approved for clinical trials, underscore the potential of artemisinin derivatives as selective immunosuppressive agents with fewer side effects than traditional therapies. These findings highlight the versatility of artemisinin derivatives as promising candidates for treating autoimmune diseases, positioning them as a valuable addition to future clinical applications in selective immunotherapy (81, 82).

New strategies via bioengineering of plants and microorganisms for artemisinin production

Artemisinin, a valuable medicinal compound extracted from *Artemisia annua*, is constrained by low natural yields and high production costs. As the demand for artemisinin and its derivatives grows, especially for diverse medical applications, there has been a concerted effort to enhance its production through synthetic biology and genetic engi-

neering approaches. In *Artemisia annua*, the co-expression of key biosynthetic enzymes like *HMGR*, *FPS* and *DBR2* along with trichome-specific transcription factors such as *AaHD1* and *AaORA*, has led to a significant increase in artemisinin production, with levels rising by up to 2.2-fold, reaching 2.51% of the plant's biomass (83). Additionally, overexpression of *HMGR* and *ADS* has resulted in a remarkable 7.65-fold increase in artemisinin content (84). A further study found that the expression of *β-glucosidase* (*BGL1*) enhanced trichome density by 20% in leaves and 66% in flowers, leading to artemisinin concentrations of 1.4% in leaves and 2.56% in flowers, with a 5-fold increase in the latter (85). Beyond *A. annua*, significant strides have been made in engineering other plants and microorganisms to produce artemisinin or its precursors. For instance, transgenic *Nicotiana tabacum* plants were engineered to produce up to 120 mg of artemisinic acid per kilogram using a chloroplast-targeted genetic construct (86). Moreover, the introduction of 3 copies of the *HMGR* gene from *A. annua* into *Saccharomyces cerevisiae* resulted in enhanced artemisinic acid production compared to constructs with a single copy of the gene (87). These advancements highlight the potential of bioengineering in addressing the challenges of artemisinin production, contributing to a more sustainable and scalable supply for global medical needs.

Conclusion

Artemisinin, originally a pioneering antimalarial derived from *Artemisia annua*, has emerged as a versatile therapeutic agent with broad potential across antiviral, anticancer and immunomodulatory applications. Research demonstrates its efficacy against viruses like SARS-CoV-2 and hepatitis B, along with its ability to inhibit tumor-promoting pathways and enhance immune responses in cancer treatments. In autoimmune diseases, artemisinin derivatives show promise by modulating immune cell functions and reducing inflammation. Advances in genetic engineering have further improved artemisinin production through modified *A. annua*, transgenic tobacco and yeast, facilitating greater accessibility and cost-effectiveness. This evolution in artemisinin's application underscores its relevance beyond malaria, particularly in addressing global health challenges involving treatment-resistant pathogens and complex diseases. As research advances, artemisinin is positioned to bridge traditional medicine and modern therapeutics, contributing significantly to integrative healthcare solutions worldwide.

Acknowledgements

The research was financed and supported by the project PZ-202102282, "Development of plant metabolomic engineering technology for the synthesis of biologically active substances", by the Ministry of Innovative Development of the Republic of Uzbekistan. We acknowledge each research group at the Center of Genomics and Bioinformatics for their support in preparing the manuscript.

Authors' contributions

BKR and ASI wrote the manuscript. DEU, SIZ, KhAU, ShESh, MSA critically read and analysed the manuscript. ZTB and IYA coordinated the project and approved the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest: Authors do not have any conflict of interests to declare.

Ethical issues: None

References

1. Tu Y. The discovery of artemisinin (qinghaosu) and gifts from Chinese medicine. Nat Med. 2011;17:1217–20. https://doi.org/10.1038/nm.2471
2. White NJ. Qinghaosu (artemisinin): the price of success. Science. 2008;320(5874):330–34. https://doi.org/10.1126/science.1155165
3. World Health Organization. World Malaria Report. 2023. ISBN: 978-92-4-008617-3. https://www.who.int/news-room/fact-sheets/detail/malaria
4. Meshnick SR. Artemisinin: mechanisms of action, resistance and toxicity. Int J Parasitol. 2002;32(13):1655–60. https://doi.org/10.1016/s0020.7519(02)00194-7
5. Zheng D, Liu T, Yu S, Liu Z, Wang J, Wang Y. Antimalarial mechanisms and resistance status of artemisinin and its derivatives. Trop Med Infect Dis. 2024 Sep 20;9(9):223. https://doi.org/10.3390/tropicalmed9090223
6. Chang, Z. The discovery of Qinghaosu (artemisinin) as an effective anti-malaria drug: A unique China story. Sci China Life Sci. 2016;9:81–88. https://doi.org/10.1007/s11427-015-4988-z
7. Klayman DL. Qinghaosu (artemisinin): an antimalarial drug from China. Science. 1985 May 31;228(4703):1049–55. https://doi.org/10.1126/science.3887571
8. Nobel Media AB. (2015). The Nobel Prize in Physiology or Medicine 2015. Nobel Prize. https://www.nobelprize.org/prizes/medicine/2015/tu/biographical/
9. Zheng WR, Li EC, Peng S, Wang XS. Tu Youyou winning the Nobel Prize: Ethical research on the value and safety of traditional Chinese medicine. Bioethics. 2020 Feb;34(2):166–71. https://doi.org/10.1111/bioe.12456
10. Klayman DL. *Artemisia annua*. In: Human medicinal agents from plants; ACS Symposium Series; ACS Publications: Washington, DC, USA; 1993. Volume 534: pp. 242–55. https://doi.org/10.1021/bk-1993-0534.ch017
11. Septembre-Malaterre A, Rakoto LM, Marodon C, Bedoui Y, Nakab J, Simon E, et al. *Artemisia annua*, a traditional plant brought to light. Int J Mol Sci. 2020 Jul 15;21(14):4986. https://doi.org/10.3390/ijms21144986
12. Li G, Li Y, Li Z, Zeng M. Artemisinin-based and other antimalarials: Detailed account of studies by Chinese scientists who discovered and developed them. Academic Press. 2018;Pages 69–128. ISBN 9780128131336, https://doi.org/10.1016/B978-0-12-813133-6
13. Wetzstein HY, Porter JA, Janick J, Ferreira JF. Flower morphology and floral sequence in *Artemisia annua* (Asteraceae). Am J

Bot. 2014 May;101(5):875–85. https://doi.org/10.3732/ajb.1300329

14. Shen Q, et al., Brodelius PE, Rose JKC, Tang K. The genome of *Artemisia annua* provides insight into the evolution of Asteraceae family and artemisinin biosynthesis. Mol Plant. 2018 Jun 4;11(6):776–88. https://doi.org/10.1016/j.molp.2018.03.015
15. Efferth T. From ancient herb to modern drug: *Artemisia annua* and artemisinin for cancer therapy. Semin Cancer Biol. 2017 Oct;46:65–83. https://doi.org/10.1016/j.semcancer.2017.02.009
16. Van der Kooy F, Sullivan SE. The complexity of medicinal plants: The traditional *Artemisia annua* formulation, current status and future perspectives. J Ethnopharmacol. 2013;150. https://doi.org/10.1016/j.jep.2013.08.021
17. Kapustina LA, Torrell M, Valles J. Artemisia communities in arid zones of Uzbekistan (Central Asia). 2001. In: McArthur, E. Durant; Fairbanks, Daniel J., comps. Shrubland ecosystem genetics and biodiversity: proceedings; 2000 June 13-15. Provo, UT. Proc. RMRS-P-21. Ogden, UT: U.S. Department of Agriculture, Forest Service, Rocky Mountain Research Station. p. 104–12. https://www.fs.usda.gov/research/treesearch/44556
18. Vallès J, Torrell M, Garcia-Jacas N, Kapustina LA. New or rare chromosome counts in the genera *Artemisia* L. and *Mausolea* Bunge (Asteraceae, Anthemideae) from Uzbekistan. Bot J Linn Soc. 2001;135:391–400. http://dx.doi.org/10.1111/j.1095-8339.2001.tb00789.x
19. Nurlybekova A, Kudaibergen A, Kazymbetova A, Amangeldi M, Baiseitova A, Ospanov M, et al. Traditional use, phytochemical profiles and pharmacological properties of *Artemisia* genus from Central Asia. Molecules. 2022;27(16):5128. https://doi.org/10.3390/molecules27165128
20. Ekiert H, Klimek-Szczykutowicz M, Rzepiela A, Klin P, Szopa A. *Artemisia* species with high biological values as a potential source of medicinal and cosmetic raw materials. Molecules. 2022;29;27(19):6427. https://doi.org/10.3390/molecules27196427
21. Tan RX, Zheng WF, Tang HQ. Biologically active substances from the genus *Artemisia*. Planta Med. 1998;64(4):295–302. https://doi.org/10.1055/s-2006-957438
22. Bami SS, Khavari-Nejad RA, Ahadi AM, Rezayatmand Z. TiO_2 nanoparticles and salinity stress in relation to artemisinin production and ADS and DBR2 expression in *Artemisia absinthium* L. Braz J Biol. 2021;82:e237214. https://doi.org/10.1590/1519-6984.237214
23. Arab HA, Rahbari S, Rassouli A, Moslemi MH, Khosravirad FDA. Determination of artemisinin in *Artemisia sieberi* and anticoccidial effects of the plant extract in broiler chickens. Trop Anim Health Prod. 2006;38:497–503. https://doi.org/10.1007/s11250-006-4390-8
24. Aryanti BM, Ermayanti TM, Mariska I. Production of antileukemic agent in untransformed and transformed roots cultures of *Artemisia cina*. Annales Bogorienses. 2001;8:11–16
25. Mannan A, Ahmed I, Arshad W, Asim MF, Qureshi RA, Hussain I, Mirza B. Survey of artemisinin production by diverse *Artemisia* species in northern Pakistan. Malar J. 2010 Nov 4;9:310. https://doi.org/10.1186/1475-2875-9-310
26. Mannan A, Ahmed I, Arshad W, Hussain I, Mirza B. Effects of vegetative and flowering stages on the biosynthesis of artemisinin in *Artemisia* species. Arch Pharm Res. 2011;34:1657–61. https://doi.org/10.1007/s12272-011-1010-6
27. Kiani BH, Suberu J, Mirza B. Cellular engineering of *Artemisia annua* and *Artemisia dubia* with the rol ABC genes for enhanced production of potent anti-malarial drug artemisinin. Malar J. 2016;4;15(1):252. https://doi.org/10.1186/s12936-016-1312-8
28. Dogan K, Erol E, Orhan DM, Degirmenci Z, Kan T, Gungor A, et al. Instant determination of the artemisinin from various *Artemisia annua* L. extracts by LC-ESI-MS/MS and their *in-silico* modelling and *in vitro* antiviral activity studies against SARS-CoV-2. Phytochem Anal. 2022;33(2):303–19. https://doi.org/10.1002/pca.3088
29. Nganthoi M, Sanatombi K. Artemisinin content and DNA profiling of *Artemisias* species of Manipur. S Afr J Bot. 2019;125:9–15. https://doi.org/10.1016/j.sajb.2019.06.027
30. Hsu E. The history of qing hao in the Chinese materia medica. Trans R Soc Trop Med Hyg. 2006 Jun;100(6):505–08. https://doi.org/10.1016/j.trstmh.2005.09.020
31. Ranjbar M, Naghavi MR, Alizadeh H, Soltanloo H. Expression of artemisinin biosynthesis genes in eight *Artemisia* species at three developmental stages. Ind Crops Prod. 2015;76:836–43. https://doi.org/10.1016/j.indcrop.2015.07.077
32. Salehi M, Karimzadeh G, Naghavi MR, Badi HN, Monfared SR. Expression of artemisinin biosynthesis and trichome formation genes in five *Artemisia* species. Ind Crops Prod. 2018;112:130–40. https://doi.org/10.1016/j.indcrop.2017.11.002
33. Zia M, Abdul M, Chaudhary MF. Effect of growth regulators and amino acids on artemisinin production in the callus of *Artemisia absinthium*. Pak J Bot. 2007;39:799–805.
34. Van Geldre E, Vergauwe A, Van den Eeckhout E. State of the art of the production of the antimalarial compound artemisinin in plants. Plant Mol Biol. 1997;33(2):199–209. https://doi.org/10.1023/a:1005716600612
35. Shahrajabian MH, Sun W, Cheng Q. Exploring *Artemisia annua* L., artemisinin and its derivatives, from traditional Chinese wonder medicinal science. Notulae Botanicae Horti Agrobotanici Cluj-Napoca. 2020;48(4);1719–41. https://doi.org/10.15835/nbha48412002
36. Singh A, Vishwakarma RA, Husain A. Evaluation of *Artemisia annua* strains for higher artemisinin production. Planta Med. 1988;54:475–77. https://doi.org/10.1055/s-2006-962515
37. Ruan JX, Li JX, Fang X, Wang LJ, Hu WL, Chen XY, Yang CQ. Isolation and characterization of three new monoterpene synthases from *Artemisia annua*. Front Plant Sci. 2016;10(7):638. https://doi.org/10.3389/fpls.2016.00638
38. Hamidi F, Karimzadeh G, Monfared SR, Salehi M. Assessment of Iranian endemic *Artemisia khorassanica*: Karyological, genome size and gene expressions involved in artemisinin production. Turk J Boil. 2018;42:322–33. https://doi.org/10.3906/biy-1802-86
39. Pellicera J, Saslis-Lagoudakis CH, Carrió E, Ernst M, Garnatje T, Grace OM, et al. A phylogenetic road map to antimalarial *Artemisia* species. J. Ethnopharmacol. 2018;225:1–9. https://doi.org/10.1016/j.jep.2018.06.030
40. Honmore V, Kandhare A, Zanwar AA, Rojatkar S, Bodhankar S, Natu A. *Artemisia pallens* alleviates acetaminophen induced toxicity via modulation of endogenous biomarkers. Pharm Biol. 2015;53(4):571–81. https://doi.org/10.3109/13880209.2014.934382
41. Ding J, Wang L, He C, Zhao J, Si L, Huang H. *Artemisia scoparia*: Traditional uses, active constituents and pharmacological effects. J Ethnopharmacol. 2021;12;273:113960. https://doi.org/10.1016/j.jep.2021.113960
42. Numonov S, Sharopov F, Salimov A, Sukhrobov P, Atolikshoeva S, Safarzoda R, et al. Assessment of artemisinin contents in selected *Artemisia* species from Tajikistan (Central Asia). Medicines (Basel). 2019;31;6(1):23. https://doi.org/10.3390/medicines6010023
43. Ekiert H, Knut E, Świątkowska J, Klin P, Rzepiela A, Tomczyk M, Szopa A. *Artemisia abrotanum* L. (Southern wormwood)- History, current knowledge on the chemistry, biological activity, traditional use and possible new pharmaceutical and cosmetological applications. Molecules. 2021 Apr 25;26(9):2503. https://doi.org/10.3390/molecules26092503

44. Batiha GE, Olatunde A, El-Mleeh A, Hetta HF, Al-Rejaie S, Alghamdi S, et al. Bioactive compounds, pharmacological actions and pharmacokinetics of wormwood (*Artemisia absinthium*). Antibiotics (Basel). 2020 Jun 23;9(6):353. https://doi.org/10.3390/antibiotics9060353

45. Dylenova EP, Tykheev ZA, Zhigzhitzhapova SV, et al. Composition of fatty acids from *Artemisia anethifolia*, *A. desertorum* and *A. pubescens*. Chem Nat Compd. 2023;59:128–30. https://doi.org/10.1007/s10600-023-03932-w

46. Liang JY, Wang WT, Zheng YF, Zhang D, Wang JL, Guo SS, et al. Bioactivities and chemical constituents of essential oil extracted from *Artemisia* anethoides against two stored product insects. J Oleo Sci. 2017 Jan 1;66(1):71–76. https://doi.org/10.5650/jos.ess16080

47. Xu JL, Turak A, Sagdullaev S, et al. New chemical constituents from *Artemisia austriaca*. Chem Nat Compd. 2024;60:65–67. https://doi.org/10.1007/s10600-024-04255-0

48. Sharifi-Rad J, Herrera-Bravo J, Semwal P, Painuli S, Badoni H, Ezzat SM, et al. *Artemisia* spp.: An update on its chemical composition, pharmacological and toxicological profiles. Oxid Med Cell Longev. 2022 Sep 5;2022:5628601. https://doi.org/10.1155/2022/5628601

49. Ding K, Wang J, Liu N, Zhang F. Effect of *Artemisia apiacea* Hance on growth performance, cecal opportunistic bacteria and microbicidal peptides in rabbits. R Bras Zootec. 2019;48:e20190118. https://doi.org/10.1590/rbz4820190118

50. Salehi M, Karimzadeh G, Naghavi MR, Badi NH, Monfared RS. Expression of key genes affecting artemisinin content in five *Artemisia* species. Sci Rep. 2018 Aug 23;8(1):12659. https://doi.org/10.1038/s41598-018-31079-0

51. Dib I, El Alaoui-Faris FE. *Artemisia campestris* L.: review on taxonomical aspects, cytogeography, biological activities and bioactive compounds. Biomed Pharmacother. 2019 Jan;109:1884–906. https://doi.org/10.1016/j.biopha.2018.10.149

52. Sakipova Z, Giorno TBS, Bekezhanova T, Siu Hai Wong N, Shukirbekova A, Fernandes PD, Boylan F. Pharmacological evaluation of *Artemisia cina* crude CO_2 subcritical extract after the removal of santonin by means of high speed countercurrent chromatography. Molecules. 2020 Jun 12;25(12):2728. https://doi.org/10.3390/molecules25122728

53. Hegazy A, Mostafa I, Elshaier YAMM, Mahmoud SH, Abo Shama NM, Shehata M, et al. Robust antiviral activity of santonica flower extract (*Artemisia cina*) against avian and human influenza A viruses: *In vitro* and chemoinformatic studies. ACS Omega. 2022 Nov 2;7(45):41212–23. https://doi.org/10.1021/acsomega.2c04867

54. Aslany S, Tafvizi F, Naseh V. Characterization and evaluation of cytotoxic and apoptotic effects of green synthesis of silver nanoparticles using *Artemisia ciniformis* on human gastric adenocarcinoma. Mater Today Commun. 2020;24:101011. https://doi.org/10.1016/j.mtcomm.2020.101011

55. Rahimivand M, Tafvizi F, Noorbazargan H. Synthesis and characterization of alginate nanocarrier encapsulating *Artemisia ciniformis* extract and evaluation of the cytotoxicity and apoptosis induction in AGS cell line. Int J Biol Macromol. 2020 May 5;158:338–57. https://doi.org/10.1016/j.ijbiomac.2020.05.006

56. Noori A, Amjad L, Yazdani F. The effects of *Artemisia deserti* ethanolic extract on pathology and function of rat kidney. Avicenna J Phytomed. 2014 Nov;4(6):371–76.

57. Mollaei S, Shamsuzan A, Ghanavi J. Cytotoxic and antioxidant properties of *Artemisia deserti* essential oil obtained by different extraction methods. Biomedical and Biotechnology Research Journal. 2024;8(1):p 37–44. https://doi.org/10.4103/bbrj.bbrj_31_24

58. Bazarov B, Rajamuradov Z, Safin M, Rajabov A, Khaitov D, et al. The productivity, chemical composition and nutritional value of pastures dominated by *Artemisia diffusa* and *Cousinia resinosa* in arid lands of southwestern Uzbekistan. Biodiversitas Journal of Biological Diversity. 2023;24(7):3916–23. https://doi.org/10.13057/biodiv/d240730

59. Ivanescu B, Miron A, Corciova A. Sesquiterpene lactones from *Artemisia* genus: Biological activities and methods of analysis. J Anal Methods Chem. 2015;2015:247685. https://doi.org/10.1155/2015/247685

60. Ekiert H, Świątkowska J, Knut E, Klin P, Rzepiela A, Tomczyk M, Szopa A. *Artemisia dracunculus* (Tarragon): A review of its traditional uses, phytochemistry and pharmacology. Front Pharmacol. 2021; Apr 13;12:653993. https://doi.org/10.3389/fphar.2021.653993

61. Kiani BH, Ullah N, Mirza B. Transgenic *Artemisia dubia* WALL showed altered phytochemistry and pharmacology. Arabian Journal of Chemistry. 2019;12(8):2644–54. https://doi.org/10.1016/j.arabjc.2015:04.020

62. Kiani BH, Safdar N, Mannan A, Mirza B. Comparative Artemisinin analysis in *Artemisia dubia* transformed with two different Agrobacteria harbouring rol *ABC* genes. Plant Omics J. 2012;5:386–91.

63. Mannan A, Shaheen N, Arshad W, Qureshi RA, Zia M, Mirza B. Hairy roots induction and artemisinin analysis in *Artemisia dubia* and *Artemisia indica*. Afr J Biotechnol. 2008;7:3288–92. https://doi.org/10.5897/AJB08.516

64. Acharya M, Gautam R, Yang S, et al. Evaluation of *Artemisia dubia* folium extract-mediated immune efficacy through developing a murine model for acute and chronic stages of atopic dermatitis. Lab Anim Res. 2024;40:13. https://doi.org/10.1186/s42826-024-00201-x

65. Abad MJ, Bedoya LM, Apaza L, Bermejo P. The *Artemisia* L. genus: a review of bioactive essential oils. Molecules. 2012;17:2542–66. https://doi.org/10.3390/molecules17032542

66. Akbari M, Heli H, Oryan A, Hatam G. A novel outlook in the delivery of artemisinin: production and efficacy in experimental visceral leishmaniasis. Pathog Glob Health. 2024; Feb;118(1):40–46. https://doi.org/10.1080/20477724.2023.2212347

67. Lam NS, Long X, Su XZ, Lu F. Artemisinin and its derivatives in treating helminthic infections beyond schistosomiasis. Pharmacol Res. 2018;Jul;133:77–100. https://doi.org/10.1016/j.phrs.2018.04.025

68. D'Alessandro S, Scaccabarozzi D, Signorini L, Perego F, Ilboudo DP, Ferrante P, Delbue S. The use of antimalarial drugs against viral infection. Microorganisms. 2020;8;8(1):85. https://doi.org/10.3390/microorganisms8010085

69. Romero MR, Efferth T, Serrano MA, Castaño B, Macias RI, Briz O, Marin JJ. Effect of artemisinin/artesunate as inhibitors of hepatitis B virus production in an "*in vitro*" replicative system. Antiviral Res. 2005;68(2):75–83. https://doi.org/10.1016/j.antiviral.2005.07.005

70. Badraoui R, Saoudi M, Hamadou WS, Elkahoui S, Siddiqui AJ, Alam JM, et al. Antiviral effects of artemisinin and its derivatives against SARS-CoV-2 main protease: Computational evidences and interactions with ACE2 allelic variants. Pharmaceuticals (Basel). 2022;22;15(2):129. https://doi.org/10.3390/ph15020129

71. Nair MS, Huang Y, Wang M, Weathers PJ. SARS-CoV-2 omicron variants are susceptible *in vitro* to *Artemisia annua* hot water extracts. J Ethnopharmacol. 2023;23;308:116291. https://doi.org/10.1016/j.jep.2023.116291

72. Baggieri M, Gioacchini S, Borgonovo G, Catinella G, Marchi A, Picone P, et al. Antiviral, virucidal and antioxidant properties of *Artemisia annua* against SARS-CoV-2. Biomed Pharmacother. 2023;168:115682. https://doi.org/10.1016/j.biopha.2023.115682

73. Farmanpour-Kalalagh K, Beyraghdar Kashkooli A, Babaei A, Rezaei A, van der Krol AR. Artemisinins in combating viral infections like SARS-CoV-2, inflammation and cancers and options to meet increased global demand. Front Plant Sci. 2022;7;13:780257. https://doi.org/10.3389/fpls.2022.780257

74. Efferth T. Beyond malaria: The inhibition of viruses by artemisinin-type compounds. Biotechnol Adv. 2018;1;36(6):1730–37. https://doi.org/10.1016/j.biotechadv.2018.01.001

75. Wen L, Chan BC-L, Qiu M-H, Leung P-C, Wong C-K. Artemisinin and its derivatives as potential anticancer agents. Molecules. 2024;29(16):3886. https://doi.org/10.3390/molecules29163886

76. Lang SJ, Schmiech M, Hafner S, Paetz C, Steinborn C, Huber R, et al. Antitumor activity of an *Artemisia annua* herbal preparation and identification of active ingredients. Phytomedicine. 2019;62:152962. https://doi.org/10.1016/j.phymed.2019.152962

77. Augustin Y, Staines HM, Krishna S. Artemisinins as a novel anticancer therapy: Targeting a global cancer pandemic through drug repurposing. Pharmacol Ther. 2020;216:107706. https://doi.org/10.1016/j.pharmthera.2020.107706

78. Jin Q, Liu T, Chen D, Yang L, Mao H, Ma F, et al. Therapeutic potential of artemisinin and its derivatives in managing kidney diseases. Front Pharmacol. 2023;15(14):1097206. https://doi.org/10.3389/fphar.2023.1097206

79. Otto-Ślusarczyk D, Mielczarek-Puta M, Graboń W. The real cytotoxic effect of artemisinins on colon cancer cells in a physiological cell culture setting. How composition of the culture medium biases experimental findings. Pharmaceuticals. 2021;14(10):976. https://doi.org/10.3390/ph14100976

80. Niederreiter M, Klein J, Arndt K, Werner J, Mayer B. Anti-cancer effects of artesunate in human 3D tumor models of different complexity. Int J Mol Sci. 2023;25;24(9):7844. https://doi.org/10.3390/ijms24097844

81. Shi C, Li H, Yang Y, Hou L. Anti-inflammatory and immunoregulatory functions of artemisinin and its derivatives. Mediators Inflamm. 2015;2015:435713. https://doi.org/10.1155/2015/435713

82. Paço A, Brás T, Santos JO, Sampaio P, Gomes AC, Duarte MF. Anti-Inflammatory and immunoregulatory action of sesquiterpene lactones. Molecules. 2022; Feb 8;27(3):1142. https://doi.org/10.3390/molecules27031142

83. Hassani D, Taheri A, Fu X, Qin W, Hang L, Ma Y, Tang K. Elevation of artemisinin content by co-transformation of artemisinin biosynthetic pathway genes and trichome-specific transcription factors in *Artemisia annua*. Front Plant Sci. 2023; Feb 21;14:1118082. https://doi.org/10.3389/fpls.2023.1118082

84. Alam P, Abdin MZ. Over-expression of HMG-CoA reductase and amorpha-4,11-diene synthase genes in *Artemisia annua* L. and its influence on artemisinin content. Plant Cell Rep. 2011; Oct;30 (10):1919–28. https://doi.org/10.1007/s00299-011-1099-6

85. Singh ND, Kumar S, Daniell H. Expression of β-glucosidase increases trichome density and artemisinin content in transgenic *Artemisia annua* plants. Plant Biotechnol J. 2016 Mar;14(3):1034–45. https://doi.org/10.1111/pbi.12476

86. Fuentes P, Zhou F, Erban A, Karcher D, Kopka J, Bock R. A new synthetic biology approach allows transfer of an entire metabolic pathway from a medicinal plant to a biomass crop. Elife. 2016; Jun 14;5:e13664. https://doi.org/10.7554/eLife.13664

87. Paddon CJ, et al. High-level semi-synthetic production of the potent antimalarial artemisinin. Nature. 2013; Apr 25;496 (7446):528–32. https://doi.org/10.1038/nature12051