

Review Article on Phytochemical Constituents and Biological Activity of *Artemisia Annua* L.

Rodina M. Hussien¹, Dina T. Mokhtara¹, Ahmed M. AbdEl-sameaaa¹, Mohamed A. El stenya¹, Nehal G. Qwaidera¹, *

¹Pharmacognosy Department, Faculty of Pharmacy, Sinai University, Arish, Egypt

*Corresponding author

Correspondence:

Nehal G. Qwaidera
nehal.aly@su.edu.eg

Citation:

Hussien, R.M , Mokhtara, D.T. , AbdEl-sameaaa, A.M. , El stenya, M.A. , Qwaidera, N.G. "Review article on phytochemical constituents and biological activity of *Artemisia annua* L.", SINAI International Scientific Journal (SISJ), volume 1, Issue 2, pp. 64-80, 2024

Received: 25 April 2024

Accepted: 13 July 2024

Copyright © 2024 by the authors. This article is an open access article distributed under the terms and conditions Creative Commons Attribution-Share Alike 4.0 International Public License (CC BY-SA 4.0)

ABSTRACT

Artemisia annua is an aromatic plant belonging to the Asteraceae family, found around Africa, Asia, Europe, and North America. The World Health Organization has recommended *A. annua* as an antimalarial drug. Numerous phytochemical classes, such as phenolics, flavonoids, steroids, coumarins, triterpenoids, monoterpenoids, lipids, aliphatic compounds, lignans, as well as fatty acids, have been found through phytochemical investigation. The plant was chosen due to a well-researched biological study that revealed it to have antimalarial, antioxidant, antimicrobial, antiviral, anti-inflammatory, anticancer, and immunosuppressive activity. This review focuses on the phytochemical components of this significant and beneficial plant, as well as the various promising biological activities that make the plant a good candidate for developing pharmaceutical products. Definitively, the plant extract of *A. annua* is a good source of health-promoting aspects that can be employed for curative and nutritional purposes. However, more research on the active chemicals of this plant is needed to optimize their medicinal and nutritional potential.

KEYWORDS: *Artemisia annua*, Asteraceae, Phytochemicals, Biological.

1. INTRODUCTION

The Asteraceae family includes a huge number of genera, among which *Artemisia* is one of the largest and most widely distributed [1]. *Artemisia* L. is a widespread genus with around 500 species distributed throughout all continents except Antarctica. The genus adapts to many environments from sea level to high altitudes [2].

Artemisia annua, a plant belonging to the Asteraceae family, is a widely used medicinal plant [3-5], sometimes known as "annual absinthe". It is an annual herbaceous plant, thus its name "annua." The plant is grown in Asia, India, Central and Eastern Europe, in the temperate regions of America, Africa, and Australia, as well as in tropical regions [6, 7]. In the mild climates of Asia (specifically China and Korea), it is widely utilized as a medicinal plant, herbal tea, and spice in food [8]. Qing Hao is an ancient Chinese name for *A. annua*, which means "green herb. There are two main hypotheses on the origin of name. According to the first theory, *Artemisia* is named after the Greek goddess "Artemis", which means "she who heals sickness." According to a second theory, it was named after the queen of Turkey, Artemisia of Caria [9]. For many years, the traditional medical practices of Asia and Africa have utilized *A. annua*, either as squeezed juice or tea, to cure fever and malaria [10, 11]. The dried herb *A. annua* is officially listed as a treatment for fever and malaria in China's current pharmacopeia. The

recommended daily dosage is 4.5–9 g of dry herb made as an infusion [12]. Additionally, *A. annua* has anti-hyperlipidemic, anti-plasmodial, anti-convulsant, anti-inflammatory, anti-microbial, anti-cholesterolemic, and antiviral effects [13-15]. It also has essential pharmacological properties such as being anticancer, as well as anti-obesity [16-18].

Several bioactive metabolites have been found in *A. annua*. Artemisinin is the lactone sesquiterpene endoperoxide that has been investigated the most [19]. Because of its antimalarial properties, artemisinin is effective against chloroquine-resistant *Plasmodium falciparum* in the treatment of cerebral malaria [20, 21]. Several thousand malaria patients in China have benefited from the use of this substance, beside those who were infected with strains of *Plasmodium falciparum* that were resistant to chloroquine. Artemisinin presents a promising new class of antimalarial medication [22]. In addition to this active compound, *A. annua* has an interesting nutritional profile that includes amino acids, vitamins and minerals, as well as other important elements for health [23]. *A. annua* has been the subject of extensive research on its chemical composition since its discovery. Over 600 secondary metabolites have been discovered throughout the plant [24], including a number of steroids, flavonoids, coumarins, alkaloids, benzenoids, triterpenoids, and monoterpenoids [3, 25, 26].

The purpose of this review was to provide a comprehensive overview of *A. annua*'s traditional use and pharmacological studies, as well as innovative insights into its use in the treatment of numerous diseases.

2. MATERIAL AND METHODS

Using well-known scientific resources including Google Scholar, Scopus, Science Direct, Henriette's Herbal Homepage, PubMed, King's American Dispensatory, Ethnobotanical Databases, Dr. Duke's Phytochemical and SciFinder, this review carefully reviewed the material that was available. Books on taxonomies and ethnopharmacology that were available were consulted for specific details. The Plant List (<http://www.theplantlist.org>) was used to obtain this data. After collating the published papers, the findings were examined and organized through the theme of the portion or review. A total of eighty published papers were gathered, and the library of publications retrieved included materials that were either published before 1990 (ten), or not written in English (eight).

3. RESULTS AND DISCUSSION

3.1. Chemical Constituents Reported from *Artemisia annua*

Phytochemical investigation of *Artemisia annua* revealed the presence of many bioactive compounds, such as flavonoids, coumarins, phenolics, terpenoids, steroids, phenolic acid derivatives, alkyl alcohols, fatty acids, lipids, Lignans and essential oils (Table 1).

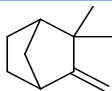
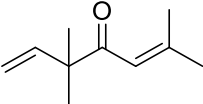
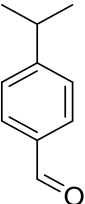
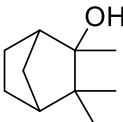
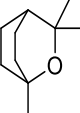
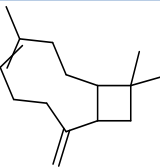
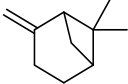
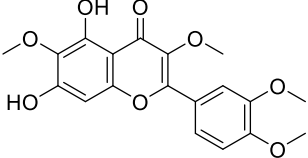
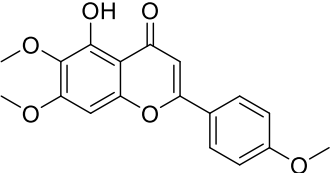
3.1.1. Essential Oil

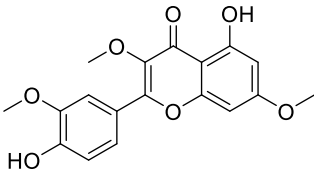
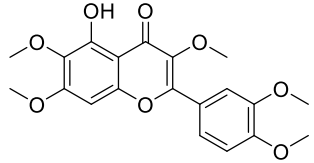
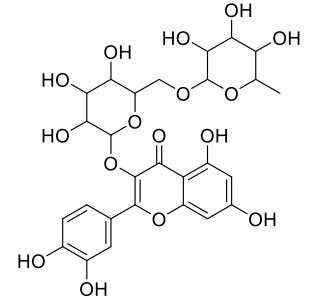
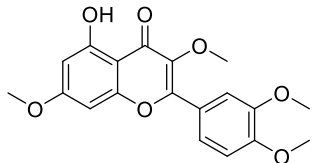
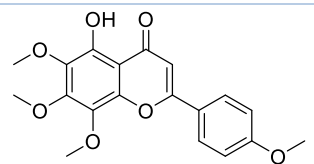
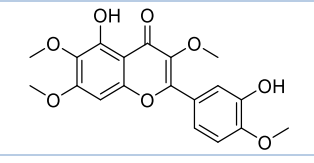
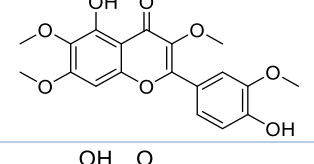
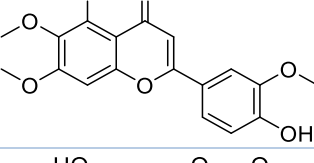
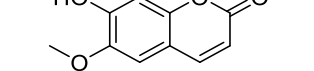
A. annua is known to consist of both volatile and non-volatile components. Among the volatile components are camphene, β -caryophyllene, β -pinene, artemisia ketone, 1, 8-cineole, camphene hydrate, and cuminal [27].

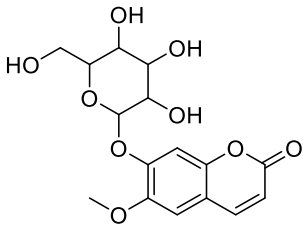
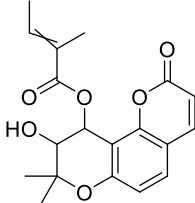
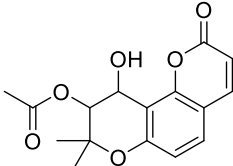
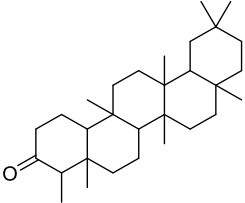
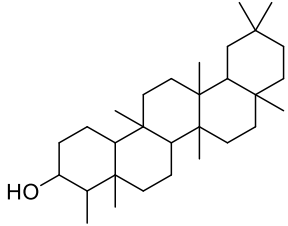
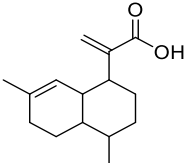
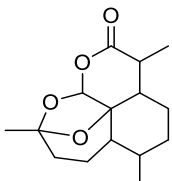
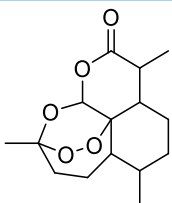
3.1.2. Flavonoids

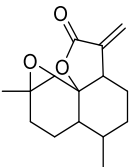
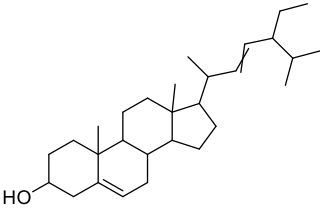
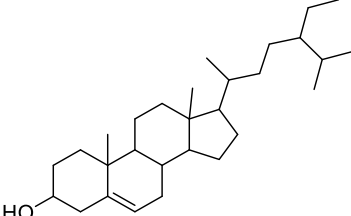
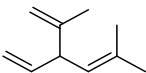

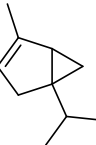
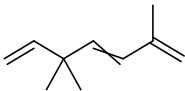
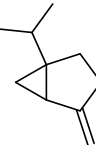
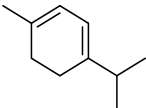
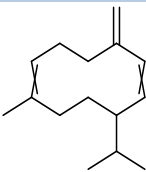
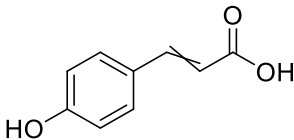
Flavonoid is one of the major phytoconstituents detected from *A. annua* including quercetagenin 3,6,3',4' tetramethyl ether, salvigenin, 5,4' dihydroxy 3,3',7 trimethoxy flavone (pachypodol), artemetin, rutin, chrysosplenetin, 5 hydroxy 3,7,3',4' tetramethoxy flavone, 5 hydroxy 6,7,8,4' tetramethoxy flavone [28], and casticin [29].

Table 1: Examples of some compounds isolated from *Senna*

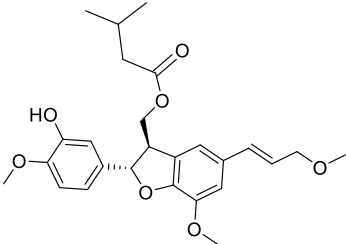
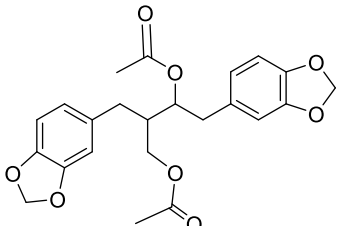
Compound	Structure	Biological Activity	References
Camphene		Anti-viral Anti-leishmanial	[27,48,49]
Artemisia ketone		Anti-bacterial	[27, 50]
Cuminal		Antioxidant	[27, 51]
Camphene hydrate		Anti-microbial	[27, 52]
1, 8-cineole		Cytotoxic activity	[27, 53]
β -caryophyllene		Anti-bacterial	[27, 54]
β -pinene		Anti-microbial	[27, 55]
Quercetagenin-3,6,3',4'-tetramethyl ether		Antioxidant	[28, 56]
Salvigenin		Anti-inflammatory Analgesic properties	[28, 57]

5,4'-dihydroxy-3,3',7-trimethoxy flavone		Antioxidant Androgenic potential	[28, 58]
Artemetin		Anti-edematogenic	[28, 59]
Rutin		Anti-amyloidogenic Antioxidant	[28, 60]
5-hydroxy-3,7,3',4'-tetramethoxy flavone		Anti-fungal	[28, 61]
5-hydroxy-6,7,8,4'-tetramethoxy flavone		Anti-bacterial Anti-fungal Insecticidal activities	[28, 62]
Casticin		Anti-osteoporosis Cytotoxic activity	[29, 63]
Chrysosplenetin		Anti-viral	[28, 64]
Cirsilineol		Anti-bacterial	[65, 66]
Scopoletin		Anti-fungal Anti-hypertensive	[30,67,68]

Scopolin		Anti-ulcerogenic	[30, 69]
Qinghaocoumarin A		Anti-fungal	[25]
Qinghaocoumarin B		Anti-fungal	[25]
Friedelin		Anti-hyperglycemic Anti-malarial	[32,70,71]
Friedelan -3-ol		Anti-ulcerogenic	[32, 72]
Artemisinin acid		Anti-inflammatory Anti-mycobacterial	[32,73,74]
Deoxyartemisinin		Anti-mycobacterial	[32, 74]
Artemisinin		Anti-viral	[31, 75]

Arteannuin B		Cytotoxic activities Anti-fungal	[31,76,77]
Stigmasterol		Anti-microbial Cytotoxic activities	[31,78,79]
β -sitosterol		Anti-bacterial anti-inflammatory	[31,80,81]
Santolina triene		Anti-inflammatory Antioxidant Anti-bacterial	[33, 82]
Tricyclene		Anti-platelet Anti-bacterial	[33, 83]
α -thujene		Antioxidant Cytotoxic activities	[33, 84]
Artemisia triene		Anti-microbial Antioxidant	[33, 85]
Sabinene		Anti-fungal Antioxidant Anti-inflammatory	[33, 86]
α -terpinene		Antioxidant	[33, 87]
Germacrene D		Anti-bacterial	[33, 88]
<i>p</i> -coumaric acid		Anti-angiogenic	[34, 89]

Chlorogenic acid		Anti-bacterial	[34, 90]
Caffeic acid		Diabetic Neuropathy Antioxidant Anti-inflammatory	[34, 91]
Cinnamic acid		Anti-microbial	[34, 92]
Sinapic acid		Antioxidant Anti-inflammatory Cytotoxic activities Anti-mutagenic Anti-glycemic	[34, 93]
Rosmarinic acid		Cytotoxic activities Epileptiform activity	[35,94,95]
3,4-Dicaffeoylquinic acid		Hepatoprotection Anti-hyperglycemic Antioxidant	[36].
3,5-Dicaffeoylquinic acid		Hepatoprotection Anti-hyperglycemic Antioxidant	[36].
3-Feruloylquinic acid		Hepatoprotection Anti-hyperglycemic Antioxidant	[36].
3,4-Dicaffeoylquinic acid methyl ester		Hepatoprotection, Anti-hyperglycemic Antioxidant	[36].
Docosan-9β-ol		Antiviral	[37, 96]
1-octacosanol		Insecticidal Juvenomimetic	[37, 97]
n-nonadecan-2β-ol		Anti-inflammatory	[37, 98]

QinghaolignanA		Anti-fungal	[25]
QinghaolignanB		Anti-fungal	[25]

3.1.3. Coumarins

Some coumarins were found in *A. annua* such as scopolin (coumarin glycoside), and scopoletin [30] in addition to two new coumarin (qinghaocoumarin A and (\pm)-qinghaocoumarin B) that were also isolated from *A. annua* [25].

3.1.4 Terpenoidal and Steroidal Compounds

From *A. annua*, Tang et al. isolated some cadinane compounds, artemisinin and arteannuin B, as well as β -sitosterol, and stigmasterol [31]. Zheng et al. detected artemisinic acid, deoxyartemisinin, friedelin, and friedelan 3β -ol [32]. Ruan et al. isolated monoterpenes including santolina triene, tricyclene, artemisia triene, α -thujene, α -terpinene, germacrene D, and sabinene [33].

3.1.5 Phenolic Acid Derivatives

In the study of *A. annua*, hydroxycinnamic acids were discovered consisting of *p*-coumaric acid, chlorogenic acid, caffeic acid, cinnamic acid, sinapic acid [34], as well as rosmarinic acid [35]. Quinic acid derivatives, including 3,4-dicaffoylquinic acid, 3,5-dicaffoylquinic acid, 3-feruloylquinic acid and 3,4-dicaffoylquinic acid methyl ester, were isolated from *A. Annua* [36].

3.1.6 Alkyl Alcohols, Fatty Acids, and Lipids

Phytochemical analysis of *A. annua* revealed the presence of alkyl alcohols, such as docosan-9 β -ol, 1-octacosanol, and *n*-nonadecan-2 β -ol [37]. In addition to the detected fatty acids from *A. annua*, including myristic acid, palmitic, palmitoleic, oleic acid, stearic acid, α -linolenic, and linoleic, other lipids have also been determined, like γ -tocopherol, and α -tocopherol [38].

3.1.7 Lignans

Two new lignans, qinghaolignan A and qinghaolignan B, were also isolated from *A. annua* [25].

3.2. Biological Activities Reported from *Artemisia annua*

3.2.1. Antimalarial Effect

Artemisia annua aqueous and hydroalcoholic extracts were tested for antimalarial activity both in vitro and in vivo. These extracts were made by decoction and maceration using water and ethanol and were investigated for in vitro activity against *Plasmodium falciparum* strains. The extracts were further tested in vivo against *Plasmodium berghei* NK 173-infected mice using the 4-day suppression test. These extracts acted similarly in vitro to pure artemisinin at the same dose. However, in vivo investigations on mice reveal that we achieve the same efficacy with an aqueous extract of *A. annua* (artemisinin content of 20 mg/kg) than with pure artemisinin at a dosage of 140 mg/kg. The hydroalcoholic extract of *A. annua* (artemisinin concentration of 20 mg/kg) outperformed the two other conditions [39].

3.2.2 Anti-inflammatory effects

A. annua was first reported to have anti-inflammatory effects in 1993 in rat and mouse inflammatory models induced by dimethylbenzene (auricle smear method), egg white (injection under the aponeurosis), and yeast powder (injection under the aponeurosis). When taking *A. annua* water extraction (15, 30, and 60 g/kg) orally for four or six days in consecutive days, inflammatory responses dramatically decrease [40]. An in vitro study evaluated the anti-inflammatory activities of four artemisinin-containing extracts of *A. annua* (water, methanol, ethanol, and acetone). Acetone extract (100 µg/mL) with the highest artemisinin content inhibits Lipopolysaccharide (LPS)-activated nitric oxide (NO), prostaglandin E2 (PGE2), and pro-inflammatory cytokine interleukin (IL-1β, IL-6, and IL-10) production in RAW 264.7 macrophages [41].

In Chougou's investigation, similar results were obtained; the research extracts ethanol at the concentration of 6.25, 12.5, 25 and 50 µg/mL, and five isolated components (scopoletin, 3-O-β-D-glucopyranoside of sitosterol, chrysosplenin, artemisinin, and eupatin) at the concentration of 0.5, 2, 5 and 20 µg/mL all inhibited the production of NO in LPS-induced RAW 264.7 macrophages [42].

3.2.3. Anti-viral Activities

The volatile oil from *A. annua* was extracted and hydroxypropyl-β-cyclodextrin inclusion complex was produced. The volatile oil of *A. annua* was found to have anti-viral properties against RSV and Coxsackievirus 16 (CA16), with EC50 values of 3.12 and 9.14 µg/mL, respectively. The hydroxypropyl-β-cyclodextrin inclusion complex of the volatile oil had EC50 values of 0.28 and 0.59, respectively [43].

Artemisinin levels in various *A. annua* tea samples were analyzed, revealing that the most active sample had one of the lowest concentrations, while the highest content sample had the lowest activity. Pure artemisinin was inert at 25 µg/mL. The study found that artemisinin played a minor impact in *A. annua* is an anti-HIV activity. The methanol extract of *A. annua* had a mild inhibitory effect on virus-cell infusion (15.8%), potentially explaining its anti-viral activity [44].

3.2.4 Anti-cancer Activities

Artemisinin and its derivatives have been shown to have anti-cancer effects by arresting cancer cell proliferation, increasing apoptosis, and blocking tumor angiogenesis and invasion [45]. *A. annua* extract contains chrysosplenol D, arteannuin B, and casticin, which limit cell

proliferation, cause apoptosis, and reduce tumor growth. This indicates a possible anti-cancer efficacy. Meanwhile, the anti-cancer properties of dried leaf *A. annua* and artesunate against NSCLC cell line were evaluated at the same dose of comparable molar artemisinin [46]. Casticin and chrysosplenol D are two flavonoid compounds known to have anti-cancer properties. Casticin, a polymethoxy flavone present in many herbal plants, had a concentration of 1.07 ± 0.23 mg/g in *A. annua* [30].

3.2.5 Anti-asthmatic Activities

The chloroform extract of *A. annua* reduced high K^+ -induced contraction in mouse TRs in a dose-dependent manner ($IC_{50} = 0.316$ mg/mL). A chloroform extract of *A. annua* can also inhibit acetylcholine -induced contractions. Patch clamp technique and ion channel blockers were used to investigate the underlying mechanisms of *A. annua*'s anti-asthmatic activity. Results showed that blocking voltage-dependent Ca^{2+} channel-mediated Ca^{2+} influx was crucial, while enhancing Ca^{2+} -activated K^+ -mediated K^+ conductance was less important [47].

3.2.6 Immunoregulation Activities

Ethanol extract of *A. annua* at concentrations of 1–100 μ g/mL significantly reduced the splenocyte proliferations stimulated by concanavalin A (Con A) and LPS in a concentration-dependent manner. Moreover, in ovalbumin-immunized mice, intraperitoneally administration of *A. annua* ethanol extract at a single dose of 0.25, 0.5 and 1.0 mg significantly reduced the ovalbumin-specific serum IgG, IgG1 and IgG2b antibody levels and suppressed the splenocyte proliferation. Taken together, *A. annua* did showed immunoregulation activities, but it deserved more studies to be developed as immune modulator [47].

4. CONCLUSION

A comprehensive examination of the phytochemistry, pharmacological activities, and historical significance of *A. annua* is presented in this review. Phytoconstituents showing great therapeutic promise for the treatment of a range of infectious and degenerative disorders have been identified by the investigations. Numerous studies on the pharmacology of the *A. annua*. have supported the known traditional uses of the plant. As a result, it is critical to carefully examine isolation and clinical trials, as they may result in the discovery of novel bioresources and satisfy scientists' biotechnological needs for safe therapeutic drugs to treat today's health challenges.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

- [1.] Bora KS, Sharma A. The genus *Artemisia*: a comprehensive review. *Pharm. Biol.* 2011;49(1):101-9.
- [2.] Sanz M, Vilatersana R, Hidalgo O, Garcia-Jacas N, Susanna A, Schneeweiss GM, et al. Molecular phylogeny and evolution of floral characters of *Artemisia* and allies (Anthemideae, Asteraceae): evidence from nrDNA ETS and ITS sequences. *Taxon.* 2008;57(1):66-78.

- [3.] Bhakuni R, Jain D, Sharma R, Kumar S. Secondary metabolites of *Artemisia annua* and their biological activity. *Curr. Sci.* 2001;35-48.
- [4.] Johnson TO, Adegboyega AE, Ojo OA, Yusuf AJ, Iwaloye O, Ugwah-Oguejiofor CJ, et al. A computational approach to elucidate the interactions of chemicals from *Artemisia annua* targeted toward SARS-CoV-2 main protease inhibition for COVID-19 treatment. *Fron. Med.* 2022; 9:907583.
- [5.] Soleimani T, Keyhanfar M, Piri K, Hasanloo T. Morphological evaluation of hairy roots induced in *Artemisia annua* L. and investigating elicitation effects on the hairy roots biomass production. *IJAT.* 2012; 2:1005-1013.
- [6.] Alesaeidi S, Miraj S. A systematic review of anti-malarial properties, immunosuppressive properties, anti-inflammatory properties, and anti-cancer properties of *Artemisia annua*. *Electron physician.* 2016;8(10):3150.
- [7.] Willcox M. *Artemisia* species: from traditional medicines to modern antimalarials—and back again. *J Altern and Complement Med.* 2009;15(2):101-9.
- [8.] Ko YS, Lee WS, Panchanathan R, Joo YN, Choi YH, Kim GS, et al. Polyphenols from *artemisia annua* L inhibit adhesion and EMT of highly metastatic breast cancer cells MDA-MB-231. *Phytother Res.* 2016;30(7):1180-8.
- [9.] Willcox M, Bodeker G, Bourdy G, Dhingra V, Falquet J, Ferreira JF, et al. *Artemisia annua* as a traditional herbal antimalarial. *Traditional medicinal plants and malaria.* 2004;4:43-59.
- [10.] Čavar S, Maksimović M, Vidic D, Parić A. Chemical composition and antioxidant and antimicrobial activity of essential oil of *Artemisia annua* L. from Bosnia. *Ind crops and prod.* 2012;37(1):479-85.
- [11.] Mueller MS, Karhagomba I, Hirt HM, Wemakor E. The potential of *Artemisia annua* L. as a locally produced remedy for malaria in the tropics: agricultural, chemical and clinical aspects. *J ethnopharmacol.* 2000;73(3):487-93.
- [12.] Gupta PC, Dutta B, Pant D, Joshi P, Lohar D. In vitro antibacterial activity of *Artemisia annua* Linn. growing in India. *IJGP.* 2009;3(3).
- [13.] Abad MJ, Bedoya LM, Apaza L, Bermejo P. The *Artemisia* L. genus: a review of bioactive essential oils. *Molecules.* 2012;17(3):2542-66.
- [14.] Wang D, Cui L, Chang X, Guan D. Biosynthesis and characterization of zinc oxide nanoparticles from *Artemisia annua* and investigate their effect on proliferation, osteogenic differentiation and mineralization in human osteoblast-like MG-63 Cells. *J. Photochem. Photobiol. B.* 2020;202:111652.
- [15.] Lubbe A, Seibert I, Klimkait T, Van der Kooy F. Ethnopharmacology in overdrive: the remarkable anti-HIV activity of *Artemisia annua*. *J Ethnopharmacol.* 2012;141(3):854-9.
- [16.] Ho WE, Peh HY, Chan TK, Wong WF. Artemisinin: pharmacological actions beyond anti-malarial. *Pharmacol. therapeut.* 2014;142(1):126-39.
- [17.] Kim MH, Seo JY, Liu KH, Kim J-S. Protective effect of *Artemisia annua* L. extract against galactose-induced oxidative stress in mice. *PloS one.* 2014;9(7):e101486.
- [18.] Wang Y, Chen J, Zhang D, Zhang Y, Wen Y, Li L, et al. Tumoricidal effects of a selenium (Se)-polysaccharide from Ziyang green tea on human osteosarcoma U-2 OS cells. *Carbohydr. polym.* 2013;98(1):1186-90.
- [19.] Castilho PC, Gouveia SC, Rodrigues AI. Quantification of artemisinin in *Artemisia annua* extracts by 1H-NMR. *Phytochem Anal.* 2008;19(4):329-34.
- [20.] Abdin MZ, Israr M, Rehman R, Jain S. Artemisinin, a novel antimalarial drug: biochemical and molecular approaches for enhanced production. *Planta Med.*

- 2003;69(04):289-99.
- [21.] Tse EG, Korsik M, Todd MH. The past, present and future of anti-malarial medicines. *Malar. J.* 2019;18(1):93.
- [22.] Nosten F, White NJ, Progress D, BoMI, Medicine P, StVoAJ, Hygiene. Artemisinin-based combination treatment of falciparum malaria. *Am J Trop Med Hyg.* 2007;77(6):1-54.
- [23.] Brisibe EA, Umoren UE, Brisibe F, Magalhães PM, Ferreira JF, Luthria D, et al. Nutritional characterisation and antioxidant capacity of different tissues of *Artemisia annua* L. *Food Chem.* 2009;115(4):1240-6.
- [24.] 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(1):1-13.
- [25.] Li K-M, Dong X, Ma Y-N, Wu Z-H, Yan Y-M, Cheng Y-X. Antifungal coumarins and lignans from *Artemisia annua*. *Fitoterapia.* 2019;134:323-8.
- [26.] Zhao Y, Ni F, Song Y, Wang S, Huang W, Wang Z, et al. Chemical constituents from *Artemisia annua*. *Zhongguo Zhong yao za zhi= Zhongguo zhongyao zazhi. Chin. Med. J.* 2014;39(24):4816-21.
- [27.] Aftab T, Ferreira JF, Khan MMA, Naeem M. *Artemisia annua*-pharmacology and biotechnology: Springer;2014.
- [28.] Chu Y, Wang H, Chen J, Hou Y. New sesquiterpene and polymethoxy-flavonoids from *Artemisia annua* L. *Pharmacogn Mag.* 2014;10(39):213.
- [29.] Fu C, Zhang K, Wang M, Qiu F. Casticin and chrysosplenol D from *Artemisia annua* L. induce apoptosis by inhibiting topoisomerase II α in human non-small-cell lung cancer cells. *Phytomedicine.* 2022;100:154095.
- [30.] Fu C, Yu P, Wang M, Qiu F. Phytochemical analysis and geographic assessment of flavonoids, coumarins and sesquiterpenes in *Artemisia annua* L. based on HPLC-DAD quantification and LC-ESI-QTOF-MS/MS confirmation. *Food Chem.* 2020;312:126070.
- [31.] Tang HQ, Hu J, Yang L, Tan RX. Terpenoids and flavonoids from *Artemisia* species. *Planta medica.* 2000;66(04):391-3.
- [32.] Zheng G-Q. Cytotoxic terpenoids and flavonoids from *Artemisia annua*. *Planta medica.* 1994;60(01):54-7.
- [33.] Ruan J-X, Li J-X, Fang X, Wang L-J, Hu W-L, Chen X-Y, et al. Isolation and characterization of three new monoterpene synthases from *Artemisia annua*. *Front. Plant Sci.* 2016;7:638.
- [34.] Carvalho IS, Cavaco T, Brodelius M. Phenolic composition and antioxidant capacity of six *Artemisia* species. *Ind Crops Prod.* 2011;33(2):382-8.
- [35.] de Magalhães PM, Dupont I, Hendrickx A, Joly A, Raas T, Dessy S, et al. Anti-inflammatory effect and modulation of cytochrome P450 activities by *Artemisia annua* tea infusions in human intestinal Caco-2 cells. *Food Chem.* 2012;134(2):864-71.
- [36.] El-Askary H, Mohamed S, El-Gohari H, Ezzat SM, Meselhy M. Quinic acid derivatives from *Artemisia annua* L. leaves; biological activities and seasonal variation. *S AFR J BOT.* 2020;128(2020):200-8.
- [37.] Singh V, Ali M, Malik A, Sultana S. New aliphatic constituents from the aerial parts of *Artemisia annua* L. *Alger j nat prod.* 2017;5(2):515-23.
- [38.] Cherian G, Orr A, Burke I, Pan W. Feeding *Artemisia annua* alters digesta pH and muscle lipid oxidation products in broiler chickens. *Poult Sci.* 2013;92(4):1085-90.
- [39.] Zime-Diawara H, Ganfon H, Gbaguidi F, Yemoa A, Bero J, Jansen O, et al. The

- antimalarial action of aqueous and hydro alcoholic extracts of *Artemisia annua* L. cultivated in Benin: In vitro and in vivo studies. *J Chem Pharm Res.* 2015;7(8):817-23.
- [40.] Huang L, Liu J, Liu L, Li D, Zhang Y, Nui H, et al. Antipyretic and anti-inflammatory effects of *Artemisia annua* L. *Zhongguo Zhong Yao Za Zhi.* 1993;18(1):44-64.
- [41.] Kim W-S, Choi WJ, Lee S, Kim WJ, Lee DC, Sohn UD, et al. Anti-inflammatory, antioxidant and antimicrobial effects of artemisinin extracts from *Artemisia annua* L. *J Physiol Pharmacol.* 2015;19(1):21.
- [42.] Chougouo RD, Nguekeu YM, Dzoyem JP, Awouafack MD, Kouamou J, Tane P, et al. Anti-inflammatory and acetylcholinesterase activity of extract, fractions and five compounds isolated from the leaves and twigs of *Artemisia annua* growing in Cameroon. *Springerplus.* 2016;5:1-7.
- [43.] Feng X, Cao S, Qiu F, Zhang B. Traditional application and modern pharmacological research of *Artemisia annua* L. *J Pharmacol.* 2020;216:107650.
- [44.] Chang YS, Woo ER. Korean medicinal plants inhibiting to Human Immunodeficiency Virus type 1 (HIV-1) fusion. *Phytother Res.* 2003;17(4):426-9.
- [45.] Ho WE, Peh HY, Chan TK, Wong WF. Artemisinins: pharmacological actions beyond anti-malarial. *JPET.* 2014;142(1):126-39.
- [46.] Rassias DJ, Weathers PJ. Dried leaf *Artemisia annua* efficacy against non-small cell lung cancer. *Phytomedicine.* 2019;52(2019):247-53.
- [47.] Feng X, Cao S, Qiu F, Zhang B. Traditional application and modern pharmacological research of *Artemisia annua* L. *JPET.* 2020;216:107650.
- [48.] Orhan İE, Özçelik B, Kartal M, Kan Y. Antimicrobial and antiviral effects of essential oils from selected Umbelliferae and Labiatae plants and individual essential oil components. *TURK J BIOL.* 2012;36(3):239-46.
- [49.] Bharate SB, Singh IP. Quantitative structure–activity relationship study of phloroglucinol-terpene adducts as anti-leishmanial agents. *BMCL.* 2011;21(14):4310-5.
- [50.] Lafraxo S, El Barnossi A, El Moussaoui A, Bourhia M, Salamatullah AM, Alzahrani A, et al. Essential oils from leaves of *Juniperus thurifera* L., exhibiting antioxidant, antifungal and antibacterial activities against antibiotic-resistant microbes. *J Hortic.* 2022;8(4):321.
- [51.] Chen S, Rotaru A-E, Liu F, Philips J, Woodard TL, Nevin KP, et al. Carbon cloth stimulates direct interspecies electron transfer in syntrophic co-cultures. *Bioresour Technol.* 2014;173:82-6.
- [52.] Matasyoh JC, Kiplimo JJ, Karubiu NM, Hailstorks TP. Chemical composition and antimicrobial activity of essential oil of *Tarhachonanthus camphoratus*. *Food Chem.* 2007;101(3):1183-7.
- [53.] Moteki H, Hibasami H, Yamada Y, Katsuzaki H, Imai K, Komiya T. Specific induction of apoptosis by 1, 8-cineole in two human leukemia cell lines, but not a in human stomach cancer cell line. *Oncol Rep.* 2002;9(4):757-60.
- [54.] Moo C-L, Yang S-K, Osman M-A, Yuswan MH, Loh J-Y, Lim W-M, et al. Antibacterial Activity and Mode of Action of β -caryophyllene on. *Pol J Microbiol.* 2020;69(1):49-54.
- [55.] da Silva Rivas AC, Lopes PM, de Azevedo Barros MM, Costa Machado DC, Alviano CS, Alviano DS. Biological activities of α -pinene and β -pinene enantiomers. *Molecules.* 2012;17(6):6305-16.
- [56.] Ouarengi MV, González M, Tereschukl ML, Abdala LR. Comparative study of the antioxidant activity of leaves and flowers of *Tagetes campanulata* Griseb.
- [57.] Mansourabadi AH, Sadeghi HM, Razavi N, Rezvani E. Anti-inflammatory and analgesic properties of salvigenin, *Salvia officinalis* flavonoid extracted. *Adv. Herb. Med.*

- 2016;2(1):31-41.
- [58.] Ijaz MU, Rauf A, Mustafa S, Ahmed H, Ashraf A, Al-Ghanim K, et al. Pachypodol attenuates Perfluorooctane sulphonate-induced testicular damage by reducing oxidative stress. *Saudi J Biol Sci.* 2022;29(3):1380-5.
- [59.] Bayeux M, Fernandes A, Foglio M, Carvalho J. Evaluation of the antiedematogenic activity of artemetin isolated from *Cordia curassavica* DC. *Braz J Med Biol Res.* 2002;35(10):1229-32.
- [60.] Jiménez-Aliaga K, Bermejo-Bescós P, Benedí J, Martín-Aragón SJs. Quercetin and rutin exhibit antiamyloidogenic and fibril-disaggregating effects in vitro and potent antioxidant activity in APPswe cells. *Life Sci.* 2011;89(25-26):939-45.
- [61.] Çitoğlu GS, Sever B, Antus S, Baitz-Gács E, Altanlar N. Antifungal diterpenoids and flavonoids from *Ballota inaequidens*. *Pharm Biol.* 2005;42(8):659-63.
- [62.] Rehman A, Rehman A, Ahmad I. Antibacterial, antifungal, and insecticidal potentials of *Oxalis corniculata* and its isolated compounds. *Int J Anal Chem.* 2015;2015(1):842468.
- [63.] Zhang D, Li J, Li X, Liu W, Yu Y, Sun H, et al. Anti-osteoporosis activity of casticin in ovariectomized rats. *Toxicol Res.* 2024;13(2):tfae064.
- [64.] Zhu Q-C, Wang Y, Liu Y-P, Zhang R-Q, Li X, Su W-H, et al. Inhibition of enterovirus 71 replication by chrysosplenetin and penduletin. *Eur J Pharm Sci.* 2011;44(3):392-8.
- [65.] Yang S-L, Roberts MF, O'Neill MJ, Bucar F, Phillipson JD. Flavonoids and chromenes from *Artemisia annua*. *Phytochemistry.* 1995;38(1):255-7.
- [66.] Bazyłko A, Sliwiska A, Strzelecka H. Izolacja kirsilineolu i 8-metoksykirsilineolu z *Thymi extractum fluidum*. *Herba Pol.* 2002;48(3):130-5.
- [67.] Njankouo Ndam Y, Nyegue MA, Mounjouenpou P, Kansci G, Kenfack MJ, Eugène EE, et al. LC-MS quantification of scopoletin in cassava (*Manihot Esculenta* Crantz) varieties, local derived foods, and activity on some food spoilage fungi. *J Food Process.* 2020;44(4):e14387.
- [68.] Wigati D, Anwar K, Sudarsono, Nugroho AEAM. Hypotensive activity of ethanolic extracts of *Morinda citrifolia* L. leaves and fruit in dexamethasone-induced hypertensive rat. *J Evid Based Complement Altern Med.* 2017;22(1):107-13.
- [69.] Awaad AS, Al-Rifai AA, El-Meligy RM, Alafeefy AM, Zain ME. New activities for isolated compounds from *convolvulus austro-egyptiacus* as anti-ulcerogenic, anti-helicobacter pylori and their mimic synthesis using bio-guided fractionation. *Phyther Res.* 2015;29(9):1311-6.
- [70.] Sunil C, Irudayaraj SS, Duraipandiyan V, Alrashood ST, Alharbi SA, Ignacimuthu S. Friedelin exhibits antidiabetic effect in diabetic rats via modulation of glucose metabolism in liver and muscle. *J Ethnopharmacol.* 2021;268:113659.
- [71.] Azebaze A, Dongmo A, Meyer M, Ouahouo B, Valentin A, Laure Nguemfo E, et al. Antimalarial and vasorelaxant constituents of the leaves of *Allanblackia monticola* (Guttiferae). *Ann trop med parasitol.* 2007;101(1):23-30.
- [72.] Queiroga CL, Silva GF, Dias PC, Possenti A, De Carvalho JE. Evaluation of the antiulcerogenic activity of friedelan-3 β -ol and friedelin isolated from *Maytenus ilicifolia* (Celastraceae). *J Ethnopharmacol.* 2000;72(3):465-8.
- [73.] Zhu XX, Yang L, Li YJ, Zhang D, Chen Y, Kostecká P, et al. Effects of sesquiterpene, flavonoid and coumarin types of compounds from *Artemisia annua* L. on production of mediators of angiogenesis. *Pharmacol Rep.* 2013;65(2):410-20.
- [74.] Bhowmick S, Baptista R, Fazakerley D, Whatley KE, Hoffmann KF, Shen J, et al. The anti-mycobacterial activity of *Artemisia annua* L is based on deoxyartemisinin and

- artemisinic acid. bioRxiv. 2020:2020.10. 23.352500.
- [75.] Efferth T, Romero MR, Wolf DG, Stamminger T, Marin JJ, Marschall M. The antiviral activities of artemisinin and artesunate. *CID*. 2008;47(6):804-11.
- [76.] Klochkov S, Neganova M, Pukhov S, Afanas'eva S, Aleksandrova YR, Yandulova EY. New Arteannuin B derivatives and their cytotoxic activity. *Chem Nat Compd*. 2020;56:445-51.
- [77.] Mailafiya MM, Yusuf AJ, Abdullahi MI, Aleku GA, Ibrahim IA, Yahaya M, et al. Antimicrobial activity of stigmasterol from the stem bark of *Neocarya macrophylla*. *JOMPED*. 2018;2(1):1-5.
- [78.] Abinaya R. Isolation, characterization and biological activities of stigmasterol from leaf part of *crescentia alata kunth* (bignoniaceae). *European j med plants*. 2021;32(3):9-21.
- [79.] Luhata LP, Usuki T. Antibacterial activity of β -sitosterol isolated from the leaves of *Odontonema strictum* (Acanthaceae). *Bioorg. Med. Chem. Lett*. 2021;48:128248.
- [80.] Loizou S, Lekakis I, Chrousos GP, Moutsatsou P, research f. β -Sitosterol exhibits anti-inflammatory activity in human aortic endothelial cells. *Mol Nutr Food Res*. 2010;54(4):551-8.
- [81.] Foddai M, Marchetti M, Ruggero A, Juliano C, Usai M. Evaluation of chemical composition and anti-inflammatory, antioxidant, antibacterial activity of essential oil of Sardinian *Santolina corsica* Jord. & Fourr. *Saudi J Biol Sci*. 2019;26(5):930-7.
- [82.] Guzman L, Nerio LS, Venturini W, Macias JP, Donoso W, Forero-Doria O. Antiplatelet and antibacterial activities of Essential Oils obtained from rhizomes and leaves of *Hedychium coronarium* J. Koenig. *An Acad Bras Cienc*. 2020;92:e20190615.
- [83.] Silva AFC, Haris PI, Serralheiro ML, Pacheco R. Mechanism of action and the biological activities of *Nigella sativa* oil components. *Food Biosci*. 2020;38:100783.
- [84.] Lopes-Lutz D, Alviano DS, Alviano CS, Kolodziejczyk PP. Screening of chemical composition, antimicrobial and antioxidant activities of *Artemisia* essential oils. *Phytochem*. 2008;69(8):1732-8.
- [85.] Valente J, Zuzarte M, Gonçalves M, Lopes M, Cavaleiro C, Salgueiro L, et al. Antifungal, antioxidant and anti-inflammatory activities of *Oenanthe crocata* L. essential oil. *FCT*. 2013;62:349-54.
- [86.] Wang Y, Yang J, Zhu X, Ren Q, Zhang H. Effect of α -terpinene and 1-isopropyl-4-methylbenzene on oxidative damage induced by volatile oil from *Chenopodium ambrosioides* L. *J Agric Sci*. 2016;29(6):1302-6.
- [87.] Montanari RM, Barbosa LC, Demuner AJ, Silva CJ, Carvalho LS, Andrade NJ. Chemical composition and antibacterial activity of essential oils from verbenaceae species: alternative sources of (E)-caryophyllene and germacrene-D. *Quim Nova*. 2011;34:1550-5.
- [88.] Kong CS, Jeong CH, Choi JS, Kim KJ, Jeong JW. Antiangiogenic effects of p-coumaric acid in human endothelial cells. *Phytother Res*. 2013;27(3):317-23.
- [89.] Lou Z, Wang H, Zhu S, Ma C, Wang Z. Antibacterial activity and mechanism of action of chlorogenic acid. *J Food Sci*. 2011;76(6):M398-M403.
- [90.] Hou L, Ma J, Feng X, Chen J, Dong B-h, Xiao L, et al. Caffeic Acid and Diabetic Neuropathy: Investigating Protective Effects and Insulin-like growth factor 1 (IGF-1)-related Antioxidative and Anti-inflammatory Mechanisms in Mice. *Heliyon*. 2024.
- [91.] Guzman JD. Natural cinnamic acids, synthetic derivatives and hybrids with antimicrobial activity. *Molecules*. 2014;19(12):19292-349.
- [92.] Chen C. Sinapic acid and its derivatives as medicine in oxidative stress-induced diseases

- and aging. *Oxid Med Cell Longev*. 2016;2016(1):3571614.
- [93.] Konstantinou EK, Panagiotopoulos AA, Argyri K, Panoutsopoulos GI, Dimitriou M, Gioxari A. Molecular Pathways of Rosmarinic Acid Anticancer Activity in Triple-Negative Breast Cancer Cells: A Literature Review. *Nutrients*. 2023;16(1):2.
- [94.] Neuberger B, Mello FK, Mallmann MP, da Costa Sobral KG, Figuera MR, Royes LFF, et al. Beneficial Effects of Rosmarinic Acid In Vitro and In Vivo Models of Epileptiform Activity Induced by Pilocarpine. *Brain Sci*. 2023;13(2):289.
- [95.] Orabi A, Hussein A, Saleh AA, Megahed AM, Metwally M, Moeini H, et al. Therapeutic efficacy of n-Docosanol against velogenic Newcastle disease virus infection in domestic chickens. *Front microbiol*. 2022;13:1049037.
- [96.] Zavala-Sánchez MÁ, Rodríguez-Chávez JL, Figueroa-Brito R, Quintana-López CM, Bah MM, Campos-Guillén J, et al. Bioactivity of 1-octacosanol from *Senna crotalarioides* (Fabaceae: Caesalpinioideae) to control *Spodoptera frugiperda* (Lepidoptera: Noctuidae). *Fla entomol*. 2020;102(4):731-7.
- [97.] Abirami D, Gomathi R. Target and candidate agents for diabetes treatment in the framework of the food nexus. *Energy Nexus*. 2022;5:100041.

APPENDIX A: LIST OF ABBREVIATIONS

EC50	Half maximal effective concentration
g	Gram
HIV	Human immunodeficiency virus
IC50	Half maximal inhibitory concentration
IgG	Immunoglobulin G
IL-10	Interleukin 10
IL-1 β	Interleukin-1 beta
IL-6	Interleukin 6
Kg	Kilogram
LPS	Lipopolysaccharide
mg	Milligram
mL	Millimeter
NK	Natural killer
NO	Nitric oxide
NSCLC	Non-small cell lung cancer
PGE2	Prostaglandin E2
RSV	Anti-respiratory syncytial virus
TC221 cells	Trypanosoma brucei cell line
TRs	Tracheal rings
Mg	Microgram