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Artemisia: Sweet worm wood used for folk remedies

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ABSTRACT

Artemisia genus comprises more than 2290 species that have been recorded. The genus Artemisia includes grassy and bushy plants with variable habitats. These small aromatic herbs were distributed almost in all continents except Antarctica. These plants are part of different ecosystems, but mostly of temperate zone. Species of Artemisia are distributed widely all over the world. Though, Artemisia vulgaris L. is native to Europe and Asia, however it has been located in Africa, North America, Himalayas and Australia. Some Artemisia species are become invasive due to easy adaptation to a new habitat and always remaining in RET category. The examples are Artemisia princeps Pamp., which is native to Japan, China and Korea but invasive in Belgium and Netherlands and Artemisia verlotiorum L. is also invasive in Croatia. The Artemisia species is used in traditional medicine and this genus has great ethno-pharmacological value. Artemisia annua L. is locally known as "Sweet worm wood" which has reported to be used for treating disease and symptoms like food borne fever, Jaundice, summer worts, tuberculosis, lice, scabies, dysentery and hemorrhoids. Artemisia nilagirica (C.B.Clarke) Pamp. locally known as "Indian worm wood" which has been used for treatment of inflammatory diseases, malaria/ hypoglycemia, stress related depression and other microbial pathogenic disorders.

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1. Introduction

India is one of the largest mega bio-diverse country in the world. Its civilization is very ancient and, the country as a whole has long been known for its rich resources of medicinal plants. Today, Ayurvedic, Homeo and Unani physicians utilize numerous species of medicinal plants that found their way a long time ago into the "Hindu Materia Medica". According to World Health Organization (WHO), more than 80% of the world's population relies on traditional medicine for their primary healthcare needs. Use of herbal medicines in Asia represents a long history of human interaction with the environment. Plant used for traditional medicine contain a wide range of secondary metabolites that can be used to treat chronic as well as systemic disease. A vast knowledge of how to use the plants against different illnesses may be expected to have accumulated in areas

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where the use of plants is still of great importance. One of such resources is folk medicine and systematic screening of the plants in the discovery of novel effective metabolites.

Artemisia absinthium L. is widely used to treat gastrointestinal disease, anti-parasitic, anti-hypertensive, anti-pyretic, and anti-inflammatory. Artemisia afra Jacq. is mostly used as herbal remedies to treat pain, cough, colds, inflammation, asthma, fever, influenza, diabetes, and malaria. Artemisia vulgaris L. "Mugwort or wild worm wood" used to treat gonorrheal sore, cold, headache, rheumatism, steam bath for pleurisy, pains of after birth. In Europe the Artemisia species are mainly used as food, spices and beverages. As per the traditional Mongolian and Chinese medicine records A. ordosica Krasch has many beneficial effects on the nasal bleeding, headache, sour throat and carbuncle. In Tuscany folk medicine A. verlotiorum L. is used for the reduction of hypertension.

Reports on drug preparation, uses and present scenario

Artemisia species in food industry;

Artemisia as a grassy and bushy herb of family Asteraceae is edible with multi-nutrients. This herb is used as spices, beverages and condiments in most Asian countries as well as North America. The following table is the enumeration of Artemisia as food, spice and flavoring agent.

Table-1

Distribution and uses of Artemisia species

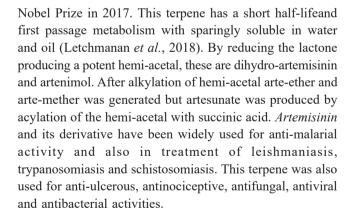
Many *Artemisia* species have been used as food. For example, the leaves of *A. vulgaris* L. are used for preparation of two different rice cakes, kusa-mochi andhishi-mocha. Shoot tips, leaves and stem of *A. dracunculus* L., *A. japonica* Thunb., *A. vulgaris* L. can be eaten directly as salad or used as any other food supplementation. The seeds of *A. dracunculoides* L. and *A. tridentata* Nutt. used in roasted form; powdered; to be used in raw or along with water. Several *Artemisia* species are used in preparation of different

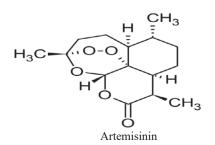
Species	Distribution	Edible part	Uses
A.abrotanum L.	South Europe	Young shoots	Flavoring cakes, salads, and herbal tea
A.absinthium L.	Europe, Asia	Whole plant	Flavoring beer, wine, vermouth, liquors
A.afra Jacq.	Africa	Whole plant	Flavoring, preparation of vermouth, as a tea
A.annua L.	South-East Europe to Asia	Leaves	Vermouth, as a vegetable
A.capillaries Thunb.	China, Japan, Korea	Leaves, stem, shoots	Soaked and boiled then eaten as food Supplement's in time of famines
A.indica Willd.	India, Japan and China	Leaves	Young leaves are cooked along with barley
A.japanica Thunb.	Korea, Japan, China	Young leaves	For cooking
A.maritima L.	Eastern-Asia, Europe	Leaves	Flavoring of Beer and liquor
<i>A.nilagirica</i> (C.B.Clarke) Pamp.	India	Stem and Leaves	Herbal tea
A.vulgaris L.	Europe and Asia	Leaves, flowering top	Flavoring in beer

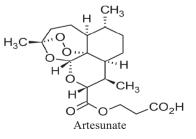
tonic, beverages, beer and vermouth. Thus *A. absinthium* L., *A. vulgaris* L. and *A. maritima* L. have been used as flavoring ingredient in beer production. A special kind of alcoholic drink, the absinthe and vermouth is prepared from *A. absinthium* L. Vermouth is a low alcoholic drink (Morata *et al.*, 2019). In Switzerland the spirit drink absin the was created by macerating leaves of *A. absinthium* L. with seeds of fennel and alcohol.

Artemisinin and its derivatives:

Potential terpene lactone which was discovered by Tu from *A.annua* L. *as* anti-malarial drug in 2015 brought him







Biological activities

Anti-parasitic activities: Mosquito-vectorial (i) diseases are one of the most uncontrollable deadly diseases, can be partly control by artemisinin combination therapy (ACT) as directed by the world health organization. Derivatives of artemisinin 1, 2, 4-trioxane moiety which is reported to be the main active component in artemisinin (Wang et al., 2019). A. annua L. decoction provides sufficient amount of anti-plasmodial activity. Besides the decoction the capsule or tablets that are produced from powdered leaves of A. annua L. have excellent antimalarial activity. The extracts from A. absinthium L. shows anti-protozoal activity against Trypanosoma brucci, T. cruzi, Plasmodium falciparum, Trichonema vaginalsis, Leishmania donovani and Entamoeba histolvtica. The ethanolic extract has the best inhibition effect of 96.2% against protozoa. The essential oil which was isolated from A. absinthium L. is used against Leishmania aethiopica and L. donovani. A. nilagirica (C.B. Clarke) Pamp. containsmany essential oils and other chemical compounds which are used to examine the larvicidal activity. It is concluded that artemisinin significantly act against Aedes albopictus the tiger mosquito of South-East Asia.

(ii) Antifungal activities: In recent times fungal infection has been reported in immune suppressed patients, suffering from endemic diseases like AIDS and cancer, organ or tissue transplantation and stem cell remedies. In *A.nilagirica* (C.B. Clarke) Pamp. essential oils can be used to control phytopathogenic fungi infecting agricultural crops and commodities. Extract from *A.annua* L. is used against fungi like *Candida malassezia* and pathogenic *Saccharomyces* species. *A. absinthium* has highly effective antifungal remedies. Several reports revealed the effectiveness of *A. annua* L. extracts against a plethora of microorganisms, this includes fungi such as *Aspergillus niger, Candida albicans*.

(iii) Antimicrobial activities: *A. annua* L. exhibits effective antimicrobial activities. The aerial parts and seeds of *Artemisia annua* L. unusually rich with essential oil like 1, 8-cineole, Camphor, Trans -3 (10)-caren-4-ol. which have significant anti-microbial activity. The extracts of *A. absinthium* L. are particularly effective against gram positive bacteria. As the protective phospho-lipid layer (Gram –ve) has greater resistance against antimicrobial agents. In 2011, international studies determined the antimicrobial potential of *A. absinthium* L. It has been marked for a metabolite i.e., caffeoylquinic acid, effective against gram +ve like *S. aureus, E. faecalis, E. coli and C. albicans* (fungi). Two active components of *A. absinthium* L., chlorogenic acid with low antimicrobial activity and the other is 4,5–di-O-caffeoylquinic acid which inhibits pump activity of Gram positives. The

essential oil of *A.absinthium* L. has been used against bacteria like *Anthrobacter* spp., *Bacillus mycoides*, *Micrococcus lylae*, *Pseudomonas aeruginosa*. The methanol extract of *A.nilagirica* (C.B. Clarke) Pamp. exhibits maximum activity against *Bacillus subtilis*, *Enterobacter aerogenes*, *E.coli*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Shigella flexneri* and *Yersinia enterocolitica*.

(iv) Antiulcer activity: In the modern world peptic ulcer is a major concern of civilian society due to junk food and unhealthy easy going life style. A. nilagirica (C.B. Clarke) Pamp. is a rich source of essential oils which has potential antiulcer property. Limonene obtained from A. nilagirica (C.B. Clarke) Pamp. used as flavoring agent in beverages and food which reduces the toxicity of other additives. The essential oil of A. nilagirica (C.B. Clarke) Pamp. also have gastro-protective activity (Rozza et al., 2011). The extracts of A. nilagirica (C.B. Clarke) Pamp. used as a protectant against ulcer induced disease and increase the mucus content. Extracts of A. absinthium L. obtained by using various polar and non-polar solvents like ethanol, methanol, hexane, chloroform and carbon tetra-chloride were administered on rodents, both and after they had received acetylsalicylic acid. The extract couldn't affect the secretion of gastric juice but decreases the secretion of pepsin, gastric acid and a decrease in digestion rate by reducing the quantity of gastric juice. A. annua L. contains three sesquiterpene lactone like artemisinin, dihydro-epideoxyarteannuin-B and deoxyartemisinin which exhibited anti-ulcergenic activities by increasing prostaglandin level in gastric mucosa.

Anti-inflammatory activity: Artemisinin as an (v) anti-inflammatory agent have been investigated on autoimmune disease, septic and allergic hypersensitivity. Effective anti-inflammatory property of artemisinin evidenced mitogen activated protein kinase (MAPK), P13K/AKT signaling cascade, TLR9 and NF- KB activation (Wang et al., 2017). The aqueous extracts of A. annua L. have inhibited inflammatory activities. A. annua L.has major components like artemisinin, scopoletin, eupatin, casticin, chrysophanol, rosmarinic acid, 3-O-β-D- glucopyranoside of sitosterol that exhibit anti-inflammatory activity. The methanolic extract of A. absinthium L. exhibits significant anti-inflammatory effect. Similarly anti-inflammatory activity was also observed with different concentrations of aqueous extract and essential oil of A. absinthium L. Cardamonin is a chalcone analog isolated from A. absinthium L. has profound effect on two cell lines THP-1 and RAW-264.7 by inducing release of nitrites. Cardamonin was also experimentally analysed for its activation of the pathways of MAP kinase like ERK, JNK, P³⁸MAP kinases and NFKB pathway. A. absinthium L. has

reduced inflammation by inducing carrageenan and the venom of *Montivipera xanthina* in rats. *A. annua* L. extracts, 25 and 50 mg/kg has been quite effective for treatment of edema. However, 12.5, 25 and 50mg /kg was effective for carrageenan induced inflammation.

(vi) Anticancer activities: Artemisinin and its derivatives have anticancer properties via inducing tissue invasion of tumor, promoting apoptosis, arresting the cancerous cell cycle and a checkpoint for angiogenesis. A. annua L. exhibited anti-cancer activity by inducing reduced mitochondrial membrane potential, imbalancing cell glucose metabolism, reducing VCAM1-1 expression, arresting G1 and G2/M phase of cell cycle and inhibiting MMP-2, MMP-9 and EMT. Artemisinin is stimulatorily effective for cancerous cell lines. Besides Artemisinin other components from A. annua L.like flavonoid 6,7,3,4,- tetra methyl ether having toxicity against P-388, A-549, 4T-29, MCF-7 and KB cell line of tumors. The extracts of A. annua L. contains Chrysoplenol-D, Artemannuin-B and Castic in which vehemently opposed the cell growth and proliferation in tumor cells. This analysis helps in triggering apoptosis and inhibiting tumor growth (Lang et al., 2019). The dried leaf of A. annua L. possesses potential anti-cancer activity. It has also been reported that Artesunate has profound effect on lung cancer like artemisinin, (Raesias and Weather 2019). Two flavonoids, casticin and chrysoplenol-D possess anticancer property for other type of sarcoma, carcinoma or myeloma. The first one Casticin, a poly-methoxy flavone commonly obtained from other herbal drugs. However, the amount of casticin in A. annua L. is approximately, 1.07±0.23mg/g while Chryosplenol-D is approximately 0.64±0.14 mg/g (Fu et al., 2020).

A. nilagirica (C.B. Clarke) Pamp. is dramatically active against cancer induced mice. Especially the ethanol and

methanolicextract of *A. nilagirica* (C.B. Clarke) Pamp. was active against cancerous albino mice.

(vii) Anti-oxidant activities: The antioxidant activity of A. absinthium L.with rich flavonoids and phenolics was estimated by DPPH radical scavenging assay. Methanol (70%), petroleum ether, chloroform, ethyl acetate and nbutanol were used as solvents for extraction. However ethylacetate, methanol, n-butanol, chloroform and ether as solvent were more potent for antioxidant activity. Quercetin 12.4 mg/g equivalent and Gallic acid 194.9 mg/g equivalent were obtained from methanolic extract of A. absinthium L.. It has shown an educational potential to be conjugated with iron (iii), ions for chelation of iron. The test proved that the flavonoid and phenol found in A. absinthium L. has effective antioxidant activity. The extract of A. absinthium L. from Spanish crops has a stronger antioxidant effect than the individual flavonoids by DPPH radical test. The individual test for flavonoids like artemisin, casticin and hydroxylpelenolide, evidenced that hydroxyl pelenolide has been shown to have a stronger antioxidant effect than others. As a result it was observed and reported that antioxidant activity of A. absinthium L. is a synergistical reaction of the phenolic profile present in the plant extract. In the various region of Tunisia, the methanolic extract of A. absinthium L. herb was tested by using the DPPH method which showed antioxidant activity. The results indicated that location of habitat from which the plant was harvested related to effectiveness of the antioxidant activity. Plants collected from northern part of the Tunisia have strongest antioxidant potential (IC50=9.38mg/ml) (Msaada et al., 2015). The essential oils of A. absinthium has significant antioxidant properties evidenced by DPPH and ABTS 2, 22 -Azinobis-(3-Ethylbenzothiazoline-6-Sulfonic Acid) methods. The essential oils of A. nilagirica (C.B. Clarke) Pamp. also reported with maximum DPPH radical scavenging property which helps to

Compounds	Cancers	Subjects	Effects
Polysaccharides	Hepatoma	Tumor xeno graft Mice induced by mouse Hepatoma H22cells	HQG inhibited tumor growth in a dosedependent manner. Increase the cell Apoptosis rate.
<i>A. annua</i> L. methanolic extract	Acute lymphoblastic leukemia	Acute lymphoblastic leukemia cell lines Nalm-6 and Reh	AAME exerted time and dose dependent cytotoxic effect increased them RNA expression Levels of caspase-3 and Bax
Polyphenol	Breast cancer	Human breast cancer cell line MDA-MB-231	PKAL inhibited MDA-MBA-231 cells in a dose dependent manner, inhibition of EM
Powdered dried Leaf of <i>A.annua</i> L.	Non-small cell lung cancer	NSCLC Cell lines A549, H12990 and PC9	DNA damage G2/M cell cycle arrest.

Table 2 Anti-cancer activities of Artemisia annua

scavenge radical related to cancerous cell growth (Tripathy *et al.*, 2015).

(viii) Anti-asthmatic activities: The respiratory tract diseases like asthma is mainly caused by common allergens present in the environment (Cazzoletti et al., 2010). Microbial load in the respiratory tract or any other allergen causes asthma in children. Most of the times bronchial asthma was prevalent due to generation of free radicals. However free oxygen radicals penetrate the membrane metabolites like lipid, protein or their glycans. The pathogen of asthma reacts with reactive oxygen species that induce bronchial hyper reactivity, promoting release of histamines from mast cells and mucous secretion from airway epithelial cells. The aqueous extracts of A. nilagirica (C.B. Clarke) Pamp. at a concentration of 200 mg/kg shows significant activity, Chloroform extract of A. annua L. has been inhibited high K⁺ induced contraction on dose dependent manner (IC50=0.316mg/ml), anti-asthmatic activities. In vitro investigation on anti-asthmatic activities of A. annua L. was reported by using tracheal rings and acute isolated airway smooth muscle cells of mice (Aparna et al., 2009).

(ix) Cytotoxic effect: The methanolic extract of A. absinthium L. was effective against breast cancer cell lines, MDA -MB 231 line (non-oestrogen responsive) and MCF-7 breast adeno carcinoma cells oestrogen responsive. The treatment evidenced 50% inhibition of MDA-MB231 cells proliferation at 20g/ml and 50% inhibition of MCF-7 cells at 25g/ml. The above results indicate that A. absinthium L. has significant contribution which inhibits development of breast cancer and breast adeno carcinoma. In vitro assessment of anti-cancerous activities with essential oils of A. absinthium L. was analyzed for six cell lines-A548 (lung adeno carcinoma), NCI-H292 (Non-small cell lung cancer), HCT116 (Colon cancer), MCF-7 (Breast adeno carcinoma), SK-MEL-5 (Melanoma) and HS5 (Bone marrow stromal cell). An observable anti-cancerous activity was noticed against SK-MEL-5 and HCT116 cell lines with least against the MCF- 7 lines. The noticeable cytotoxic effect was due to the presence of caryophyllene and germacrene D with higher amount in the composition of essential oil (Martinez *et al.*, 2015).

Application in cosmetology: Along with biological activity, A. absinthium L. has been an additive for the preparation of cosmetics used for scalp, face and hair care. According to Cosmetic Ingredient database (Cosing) a European database gathering data on cosmetics ingredients that allows the use of A. absinthium L. in five forms. These are skin care products with antibacterial activity and fragrance (Cosing-accessed). The raw materials obtained from plants are used as concentric products such as shampoos, masks, essence, tonics, under eye patches and moisturizing creams with SPF filters. These forms of components used in cosmetics to protect, moisturize and cleanse the skin. These components are produced mainly with extract of the plant or distilled oil. After fermentation of leaves by Lacto bacillus species, filtrate was used for the production of different cosmetology components. The products containing absinthium found in foreign companies worldwide, amongst which South Korea, Russia and America cosmetic producers are leaders.

Artemisinin and its derivatives have been used for anti-inflammatory properties and to increase skin immunity. The extract of *A. annua* L. has been used in cosmetics to significantly repair the damage of skin barrier function, reduce the degree of skin redness and improve the condition of sensitive skin.

Application in Therapeutic uses: For treatment of various diseases *Artemisia* species were always used traditionally and research on their pharmacological effects, supports the therapeutic applications. *Artemisia* possesses a lot of properties like anti-malaria, anti-oxidant, cytotoxic, neuro-protective, anti-inflammatory, anthelmintic and antimicrobial. The supplementation of food material to pets with *A. annua* L. preparation helps in treatment of tumors

Table 3

Plant	Function	Plant Part
A.absinthium L. whole plant extract	Skin conditioning	Extract from whole worm wood herb
A.absinthium L. whole plant extract	Perfuming	Extract from blooming herb of worm wood
A.absinthium L. oil	Antimicrobial	Volatile oil obtained from whole plant
A.absinthium L. leaf extract	Skin conditioning	Obtained by fermentation of leaves by bacteria of the genus <i>Lactobacillus</i>
A.absinthium L. herb oil	Perfuming	Senti Essential oil obtained from whole worm wood plant

related to veterinary science (Saeed et al., 2020). In traditional Chinese medicine A. annua L.was used for curing fever, malaria, inflammation. However, it was also used in the repairment of arthritis of hip and knee joint pain management, heterophyid infection and curing of mosquito vector diseases. A. dracunculus L. remarkably used for insulin sensitive glycemic control, secretion of insulin, while A. princeps Pamp. used to control mild type- 2 diabetes and A. absinthium L. used to control insulin dependent diabetes. A. absinthium L. is particularly suppresses the activity of TNF- α and other Leukotriens used for arthritis of knee joints (Basiri et al., 2017). Cardamonin is one type of component that is present in plants responsible for antiinflammatory activity. A. vulgaris L. is used to treat itching in icteric and dialyzed patients with antihistamine and antiallergenic effects and also used as lotion to partially cure hypertrophic scars generated by burning. Sometimes Artemisia annua L. and A. vulgaris L. produced the highestlevel of allergens in their pollen which is a cause of allergic rhinitis. The extract of A. ordosica Krasch. used to control the allergic inflammatory response in rhinitis while A. abrotanum L. contains essential oil and flavonoids used as nasal spray preparation. A. afra Jacq. and A. annua L. contain artemisinin derivatives, artesunate and amodiaquine respectively used to treat malaria by infusion process. A. annua L. extract was used to repair sensitive skin, inhibit inflammation, repair damaged skin, and also reduces redness and other sensitive skin allergies. Beside this, A. annua L fresh leaves are used as salads in some Asian and United states and its ground leaf extract used as direct supplements (Askarya et al., 2020).

Adverse effects of Artemisia species: Pollinosis is a serious allergic disorder and most frequent in many parts of the world due to pollen variations in Artemisia. In recent research the observation of pollen allergen by nasal passage occurs not only by pollen but also by leaves and stems. Artemisia pollen can accelerate allergic rhinitis, along with asthma, or both (Gao et al., 2019). A. vulgaris L. pollen contains allergic substances with IgE reactivity, which induce hypersensitive type I allergic reaction like anaphylactic shock. In Europe it was detected that the pollen was collected from A. vulgaris L. contains highest levels of endotoxin (Oeteros et al., 2019). The spread of pollen of these species A. campestris L., A. annua L. and A. verlotiorum L. could affect human health, mostly the allergenic pollen dehisces and spread in autumn. The pollen when comes in contact with the skin reacts to generate hypersensitivity. About 43 % patient with allergic rhinitis and asthma attack has positive reactions to Mugwort on skin prick testing. In the year 1910-1920 many countries have prohibited consumption of absinthe because their consumption associated with reactive symptoms like absinthism, blindness, hallucination, convulsions and mental retardation. European parliament and council constituted a regulation for use of *A. absinthium* L.in foods and alcoholic beverages (European parliament and council 12th Oct 2020). While European Food Safety Authority (EFSA) regulates that preparation of absinthe should not exceed the addition of thujone amount 10 mg/ kg (Community Herbal Monograph). Some *Artemisia* species such as A. *annua* L., *A. vulgaris* L., *A. herba- alba* L., *A. arborescens* L. *and A. douglasiana* Bess. used for regulation of fertility but not at the time of pregnancy (De Boer *et al.,* 2014). The hydroalcoholic extract of *A. kopetdaghensis* Krasch. was used to treat pregnant rat from 2nd to 8th day of pregnancy. Abortion occurred due to high content of camphor which crosses the placenta.

Hotpoint research of *Artemisia* species used for treatment of COVID -19 infections: WHO (World Health Organization) declared a global health emergency for COVID-19 that belongs to the SARS family to threaten life on earth. The first case of COVID-19 infection was reported on January 27, 2020 in Kerala, India. It causes multisystem disease leading to death. To treat infection, WHO had proposed *Artemisia annua* L.which is a traditional Chinese patent herb having 13 therapeutic names (Lis *et al.* 2005). The extraction of *A.annua* L.inhibited cytopathy of SARS-CoV and showed activity against SARS CoV -2.

The review presents an overview of Artemisia species that are traditionally used as medicine, food, herb, tea, beverage, spices, and condiments. The plant is mainly used in flavoring food, tea, salads, while leaves and aerial parts are also used as edible materials. Some studies published the adverse effect of Artemisia, that cause pollen allergy, dermatitis and allergic rhinitis. Mostly sesquiterpene lactones artemisinin and its derivatives showed adverse effects. Well known drink absinthe causes adverse side effects and contains a high amount of thujone. Artemisia afra Jacq. causes reduction in fertility. The plant Artemisia has paramount pharmacological importance. It has been used to cure malarial, fungal, bacterial infections as well as in controlling allergic activities. WHO declared artemisinin and its derivative from A. annua L. to be used for treatment of the pandemic COVID- 19 after purification of the herb.

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