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Review Article

Artemisinin-More than a Malarial Drug

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Abstract

In Asia, Artemisia annua L. tea and press juice are used to cure malaria and its associated symptoms. Artemisia annua comes under the Anthemideae tribe, which includes the roughly 500 species of Artemisia L., is primarily distributed in Asia, Europe, and North America. Due to the presence of numerous active components or secondary metabolites, artemisia typically exhibits a wide range of bioactivity. The drug's active component, Artemisinin (ARS), was created as an antimalarial and is used all over the world. It's interesting to note that the bioactivity is not just used to cure malaria. It is discovered that medications of the ARS type also exhibit anticancerous activity in vivo and in vitro. Artemisinin and its analogues have been demonstrated to reduce intracellular free iron levels in cancer cells, which are substantially higher than those in normal cells. Apoptosis, necrosis, necroptosis, tumour-related signal transduction pathways are responses to oxidative stress in cancer cells that are triggered by ARS and its derivatives. Artemisia annua L. extracts contain anti-inflammatory, antioxidant, and antifungal antimicrobial substances. The purpose of this review is to illustrate how artemisinin retrieves various illnesses and conditions. Another objective of ours is to compile an up-to-date report on the various activities of artemisinin

History

One of the biggest and most widely spread genera in the Asteraceae family is the genus *Artemisia*. It is a very scented herb and it is a heterogeneous genus with about 500 different species that are primarily found in temperate regions of North America, Europe, and Asia. These plants are tiny shrubs or perennial, biennial, and annual herbs [62,37]. It is also known as sweet wormwood. Before 168 BC, the usage of *A. annua* in Chinese traditional medicine was documented. *Artemisia annua* plant is native to Asia, and it most likely originated in China, namely in the regions of Suiyuan and Chahar. China has a long history of growing *A. annua* and is skilled at using a special process to extract artemisinin, thus it has become the first nation where artemisinin was isolated from plant extracts. Additionally, China has overtaken all other nations as the primary source of *A. annua's* raw materials on the international market, [10,16,24,54,66]. The Chinese naturalist Li Shi-Zhen wrote about using A. annua to treat malaria and other ailments in his 1596 book "Compendium of Materia Medica". A sesquiterpene with antimalarial activity called artemisinin was discovered in 1971 (K layman 1985). Several other ancient Chinese documented records also mention its numerous herbal uses. It is believed that it is not only indigenous to China but also found as native to Korea, Japan, Myanmar, Northern India, Vietnam, and Southern Siberia throughout Eastern Europe. Afterward, it spread to various other countries of North America and tropical areas (Willcox 2009; Liu et al. 2013). Numerous phytochemicals, including monoterpenoids, sesquiterpenoids, flavonoids, coumarins, and aliphatic hydrocarbons, have been found and isolated as a result of the search for additional relevant active substances.

A. annua not only has antimalarial properties [4], but exhibits anti-inflammatory, antipyretic, anticancer, antifungal, antiparasitic, antiulcerogenic, and cytotoxic [12] effects (Huang et al. 1993, Zheng 1994, Kim et al. 2002) This medicinal plant's essential oil composition has been intensively investigated, and hundreds of components have so far been found [6]. It is widely acknowledged that the chemical makeup of A. annua's essential oil varies depending on the plant's geographic origin and developmental stage. [4,6] (Holm et al., 1998; Verma et al., 2011; Lenardis et al., 2011; Bhakuni et al., 2002)

Characteristics on a Macroscale

A scented annual plant with deeply grooved branches is called A. annua. The aerial components and leaves typically exhibit variation. The base is asymmetrical yet the leaf edges are not complete. Light to dark green are the different shades of leaf colour placed in a pinna. Surfaces both inside and out are glabrous. Both surfaces have trichomes that are granular and nongranular. There are 4-6 layers of loosely organised cells in the spongey parenchyma [10]. An annua is a big shrub with alternating branches that is often single-stemmed and grows to a height of more than 2.0 m. The 2.5 to 5 cm long, deeply divided fragrant leaves are aromatic. Both 5-cell filamentous tri-

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chomes and 10-celled biseriate trichomes can be seen in leaves and flowers [43,51]. The stem has branches and is cylindric. Alternate, dark green or brownish green leaves are seen. While odour is distinctive and fragrant (Anna Rita Bilia et al 2014). The flavour is acrid. It has huge panicles of small, globules capitulum's (2–3 mm in diameter), whitish involucres, and pinnatisect leaves that vanish after the flowering time. It also has little, fragrant, pale-yellow flowers that are 1-2 mm in size.

Microscopical Features

Average physiochemical analysis report 9.2 weight percent moisture, 8.3 weight percent total ash, 0.91% acid-insoluble ash, 6.2 weight percent alcohol, and 3.8 weight percent water in annua. In addition, the leaves and flowers have high protein, crude fat, and digestible fraction concentrations. Copper and manganese are abundant in plant tissue. This herb has a very rich amino acid and vitamin profile, which raises its nutritional value [10]. Histologically, the leaves are dorsiventral. The leaves have few stalks and anomocytic stomata with a large number of glandular and non-glandular trichomes on both sides. There are 4-6 layers of loosely organised cells in the spongey parenchyma. There are lignified reticulate xylems on the ventral surface of the leaf [19]. Stomatal number of the upper epidermis (32–47) and lower epidermis (62–66), stomatal index of the upper epidermis (0.05–0.08) and lower epidermis (4-9) palisade ratio (35.5–5.75), vein islet number (3-5), and vein termination number are among the characteristics of the Artemisia annua leaf [44].

Chemical Composition

In-depth phytochemical analysis of A. annua has increased since the discovery of the antimalarial medication artemisinin [61]. Steroids, coumarins, phenolics, flavonoids, purines, triterpenoids, lipids, and aliphatic chemicals have all been found through phytochemical study. Monoterpenoids, alkaloids, glycosides, and essential oils has been found [7,15,19]. Significant terpene derivatives have been found, including artemisia ketone [57], artemisinic alcohol, and myrcene hydroperoxide. Both volatile and non-volatile components can be found in essential oils. Camphene, 1-camphor, isoartemisia ketone, b-camphene, b-caryophyllene, b-pinene, artemisia ketone, 1, 8-cineole, camphene hydrate, and cumin are among the volatile components of essential oils [10,66,67]. Artemisia alcohol, 1.8-cineole camphor, germacrene D, camphene hydrate, alpha-pinene, beta caryophyllene, [16,31] flavonoids, coumarins, b-galactosidase, b-glucosidase, B-sitosterol, and stigmasterol are all found in the essential oil's non-volatile component [6]. The amounts of artemisinin and essential oils in the leaves of A. annua ranged from 0.01 to 1.4% and 0.04 to 1.9%, respectively, despite the fact that there are about 400 species of artemisia [9,17]. Artemisinin and other essential secondary metabolites are only found naturally in the leaves of A. annua and these compounds can be further processed to create derivatives of pharmacological significance [6,7,29,68].

Artemisinin

Artemisia annua, is the source of artemisinin. China is the place where more than 1500 years ago, when A. annua extracts were originally found, they were said to have antipyretic qualities. The Chinese government launched a remarkable, well-coordinated initiative in 1967 to find antimalarial properties in numerous medicinal herbs, including A. annua.A extremely effective substance named qinghaosu, which was obtained in 1971, is now known as artemisinin. Artemisinin was discovered to have antimalarial effects, and numerous more effective derivatives , including as artesunate, artemether, and dihydroartemisinin. When compared to other antimalarials, artemisinin derivatives have an outstanding safety record for treating malaria, a quick beginning of action, and are effective against the widest variety of Plasmodium spp. life cycle stages. Additionally, immature and growing gametocytes, sexual stages necessary for transmission are also killed by artemisinin which lowers gametocyte carriage and infectivity [1,40,65].

Artemisinin's Ability to Prevent Malaria

Haemoglobin serves as a source of amino acids for Plasmodium trophozoites and schizonts inside erythrocytes. Haemoglobin is harmful for plasmodia as heme-iron produces reactive oxygen species. Therefore, haemoglobin is changed by the malaria parasites into the non-toxic hemozoin. Free radical intermediates kill the Plasmodium modia during this reaction, in which the liberated heme-iron cleaves the Endoperoxide Bridge of the ARS by a Fe (II) Fenton-type reaction. There are several ways that antimalarial drugs work. ARS comprises

- The inhibition of redox cycling,
- The inhibition of a glutathione S-transferase termed Plasmodium falciparum exported protein 1 (EXP1),
- The inhibition of Plasmodium falciparum PfATP6, which represents a sarco- endoplasmic reticulum Ca2+ ATPase (SERCA),
- The inhibition of digestive vacuole cysteine protease, as well as

A. annua L is now widely known throughout the world and is now used in over 50 countries as a potent medicine replacement against malaria, particularly chloroquine-resistant malaria [21,33,67]. Numerous additional flavonoids with antiplasmodial activity have been identified through studies, including artemin, casticin, chrysoplenetin, chrysoplenol-D, cirsilineol, and eupatorine [13,34]. Although artemisinin causes antiplasmodial effects by alkylating proteins that are particular to malaria [4]. Early in China researchers choose sodium artesunate, artemether, and artemisinin for clinical testing in the 1970s. In certain investigations, almost 3000 malaria patients received artemisinin and its derivatives as a kind of therapeutic treatment. According to these findings, artemisinin compounds have a greater therapeutic potential, especially when used to treat drug-resistant P. falciparum [45,64]. Clinical comparison studies have been done to compare the effectiveness of A. annua whole herb with chloroquine. In comparison to chloroquine, organic extracts of A. annua have been proven to be more efficient, quicker, and less poisonous malaria prevention [24,56]. By enhancing macrophage phagocytic activity, it greatly lowers parasitaemia and enhances immunological response. Due to the presence of multiple phytoconstituents that have synergistic antimalarial potential, whole plant extract activity is more evident.

Beyond Malaria

Interestingly, during the past few years, there have been a lot of indications that ARS activity is not just limited to malaria and that it may potentially have therapeutic value for a number of other disorders. Tu Youyou was the first to report evidence that anti-ds-DNA antibodies, TNF secretion, and the NF-B signalling pathway can be inhibited by dihydroartemisinin, potentially making it useful for the treatment of lupus erythematosus-related nephritis (W.D. Li, Y.J.et al 2006) Dong. Additionally,

ARS-type medications showed bioactivity against cancer in vitro and in vivo, human cytomegalovirus (HCMV), trypanosomiasis, schistosomiasis, and even plant malignancies [12] (R. Liu, H. F et al, W.E. Ho, H.Y. Peh et al 2014, T. W. Jiang et al 2016, H.J. Woerdenbag et al 1993, H. Lai, N.P. Singh et al 1995). According to recent research, A. annua and ARS may help reduce glucose levels and combat diabetes mellitus in addition to being effective against infectious and cancerous disorders (J. Li, T. Casteels 2017).

Microbiological Activity

Research has been done to assess the essential oils derived from A. annua's antibacterial properties. Research showed that essential oil demonstrated antibacterial activity against a variety of Gram-positive, Gram-negative, and fungal microorganisms. Extracts of A. annua have exceptional antibiotic activity against fungus, particularly Candida albicans and Saccharomyces cerevisiae [10,26]. Additionally, these tests showed that essential oils had stronger impact against fungal strains than they did against Gram-positive bacterial strains [59]. Studies using plant extracts as a test subject showed that phytoconstituents are what give these substances their antimicrobial ability. Scopoletin and sesquiterpene lactone endoperoxide are the most important molecules that have been investigated for this bioactive potential [58]. A range of different derivative chemicals, including artemisinin. These compounds' molecular mechanisms of action in Escherichia coli, Mycobacterium smegmatis, and Mycobacterium tuberculosis have been investigated.

An Anti-Inflammatory Effect

A variety of inflammatory models have been used to assess the aqueous methanolic extract's anti-inflammatory efficacy for both acute and chronic inflammation. Aqueous extract has anti-inflammatory effects that are dose-dependent and have a noticeable anti-edema effect. Numerous significant chemical groups are present according to phytochemical research, including triterpenoids, flavonoids, polyphenols, and coumarin. Therefore, in both acute and chronic settings, these drugs exert an inhibitory effect upon the edema response and operate additively [10]. More anti-inflammatory substances are also reported by other research analyses, including scopoletin (a coumarin) [46], artemisinin, dihydro artemisinin, and arteether. These substances significantly suppress the humeral responses at higher concentrations, according to in vivo tests. But according to certain other trials, pure substances did not significantly reduce the persistent hypersensitive response [4]. Additional research on murine macrophages like RAW 264.7 cells demonstrated the impact of scopoletin in a way that is dose-dependent. Consequently, a number of studies have suggested scopoletin as a potential option for an anti-inflammatory drug [58].

Activity of Antioxidants

A. annua is a strong source of antioxidants and several nutritious components [10]. According to studies, raw organic extracts of aerial parts have a high antioxidant capacity, which is most likely a result of the large concentration and variety of flavonoids found in leaves, including the recently described C-glycosyl flavonoid as a potential antioxidant component. A. annua contains flavonoids and essential oils, both of which have antioxidant potential. Due to its great antioxidant activity, these investigations placed A. annua among the most effective therapeutic plants [16,26]. There are several major categories of hydroxylated and polymethoxylated flavonoids that have been found, such as casticin, artemetin, chrysosplenol-D, cirsilineol, eupatin, and chrysoplenetin [19]. Five bioactive flavonoids have been found in studies, and they were also submitted to structural analysis. These include quercetin, blumeatin, 5,40-dihydroxy-3,7,30-trimethoxyflavone, 5-hydroxy-3,7,40-trimethoxyflavone, and 5-hydroxy-6,7,30,40-tetramethoxyflavonol [69].

Immune Suppressing Behavior

The ability of A. annua to inhibit the immune system has been studied. Concanavalin A (Con A) and lipopolysaccharide (LPS)-stimulated splenocyte proliferation was considerably inhibited by ethanolic extract of A. annua, and this action increases as the dose is increased. Additionally, research has demonstrated that an ethanol extract of A. annua can reduce the cellular and humoral response [10]. There is evidence that the flavonoids found in leaves, which have the ability to influence immune response, have immunosuppressive potential [19].

Activity Against Arthritis

Experimental investigations have shown that the A. annua-derived artemisinin derivative SM905 inhibits the inflammatory and Th17 responses that result in the arthritis brought on by collagen is getting better. Through oral administration of the artemisinin derivative SM905, these research on Collagen-Induced Arthritis (CIA) using type II bovine collagen model (CII) in DBA/1 mice have been conducted. Disease prevalence and severity were routinely assessed. Additionally, the level of T helper (Th) 17/Th1/Th2 type cytokine production has been investigated. Results of this study showed that SM905 chemical played a crucial role in reducing the incidence of arthritis by delaying the beginning of the disease. Additionally, it lessens the overexpression of a range of cytokines and chemokines that are associated with inflammation [10].

Cancer Prevention

A.annua is well known for its pharmacological uses in common medicines, and research studies are currently being conducted on it in an effort to develop a cure for cancer [7]. The cytotoxic activity of organic extracts of A. annua was examined in HeLa cancer cells and Trypanosoma b. brucei (TC221 cells). According to these analyses, dichloromethane extracts are less cytotoxic than methanol extracts [12]. Studies on the cytotoxicity of artemisinin and quercetagetin-6, 7, 3, and 4-tetramethylether against a variety of tumour cells, such as P-388, A-549, Ht-29, KB, and MCF-7 cells, demonstrated their effectiveness [4,46].

Promising results from in vitro and in vivo anticancer testing for artemisinins are found, and subsequent research reveals its mode of action, giving an understanding of its constitutional property. It is included into its design. An endoperoxide group in artemisinin confers anticancer properties. Artemisinin reacts with ferrous iron to produce free radical species, much like other chemicals like hydrogen peroxide. These free radicals start the process of fighting cancer. Further in-depth research studies reveal that the inclusion of iron complexes in cell culture enhances these anticancer effects. The iron transport protein transferrin, which forms a covalent bond with artemisinin, is found in humans. Artemisinin and transferrin conjugate are actively transported inside cancer cells via the Transferrin Receptor (TfR)-mediated endocytosis pathway, and this result in pronounced anti-tumor effects. This also explains the significance of iron metabolism in enhancing artemisinin's anticancer properties. Additionally, by activating a cytochrome C-mediated mechanism that results in programmed cell death in cancer

cells, artemisinin and its derivatives into apoptosis [19]. As a result, artemisinin was found to be a powerful anticancer agent in various research studies [24,47] and was advised against using it as a medication therapy for cancer [16,19,70]. Its chemical and structural properties support its use as a lead compound, which can then serve as the foundation for the development of new drugs [4]. Studies have also discovered some additional essential substances with anticancer properties, like scopoletin [58],

Antiviral Function

The very first scientific evaluation of A. annua tea infusions' antiviral properties against HIV has taken place. There are two separate cellular systems utilised in toxicity research. At a very low concentration (2.0 lg/mL), the A. annua tea infusion has highly substantial action. However, at greater concentrations (25 lg/mL), artemisinin was discovered to be inert. In a similar vein, no cellular cytotoxic effects of tea infusion at higher concentrations were noted. As a result, this in vitro investigation demonstrated that artemisinin has a restricted effect and may work in concert with other substances to counteract anti-HIV action [34]. Other in vitro research have made claims concerning the hepatitis B virus's inhibitory effects [66]. The potential of artemisinin and its derivatives to combat a variety of ailments is now being researched in scientific investigations.

Regulation of Plant Growth Activity

Research indicates that A. annua contains a range of essential chemicals, some of which function naturally to control plant growth activities. These substances have also been suggested for use in agriculture as natural pesticides. These substances include abscisic acid, abscisic acid methyl ester, bis (1-hydroxy-2-methylpropyl) phthalate, artemisinin, and its derivatives [4].

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