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Review Article

Artemisia annua L. and Its Derivatives: Their Antiviral Effects on COVID-19 and Possible Mechanisms

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Abstract

COVID-19 is a worldwide pandemic. Currently, there are a few approved effective antiviral drugs against COVID-19. Therefore, an effective way to treat an emerging disease is to use existing medicines, which usually have a safety profile. A large number of compounds are produced from traditional medicinal plants and some of them that have antiviral activity could be used as therapeutics, such as *Artemisia annua* L (*A. annua* L.). Here, we update the information on the therapeutic effects and possible antiviral mechanisms of *A. annua* L. and their derivatives against severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection will be updated. The *A. annua* L. derivatives might be effective alternatives for COVID-19 treatment. *A. annua* L. might act against the SARS-CoV-2 infection by inhibiting its invasion, angiotensin-converting enzyme2, cluster of differentiation 147, and transmembrane protease serine 2 expression, virus replication, reducing oxidative stress and inflammation by attenuating Nrf2 and NF-kB signaling, and mitigating lung damage in patients with COVID-19. However, clinical effectiveness needs to be demonstrated.

Introduction

In December 2019, a cluster of pneumonia cases emerged that was associated with a novel coronavirus (2019-nCoV) in Wuhan city, Hubei Province, China.[1] Based on a phylogenetic and genetic analysis of the viral taxonomy, the novel coronavirus 2019 was designated as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2 or Coronavirus-19), which caused coronavirus disease 2019 (COVID-19).[2] Until September, 2021, SARS-CoV-2 infection resulted in >224 million laboratory-confirmed cases with approximately 4 million deaths worldwide. Currently, limited antiviral drugs have been approved to treat SARS-coronavirus-2 infection although different types of vaccines are now available to prevent severe COVID-19 disease in humans.[3] Because COVID-19 has caused several waves of disease and severely affects social lives, an effective antiviral agent is needed to combat the current pandemic.

Clinically, there are a few antiviral drugs, anti-inflammatory medicines, and supportive therapies available to treat COVID-19 patients. For treatment and prophylaxis of the viral infection, the drug should be adequate, safe, and low cost.[4,5] Artemisinin is a safe drug in the clinic. Artemisia and their derivatives have an excellent safety profile, low toxicity and adverse effects, are relatively cheap, and are easily produced. In addition, these drugs have excellent pharmacokinetic and pharmacodynamic characteristics. Artemisinin can be used in combination with other drugs to increase therapeutic effectiveness and delay the development of drug resistance.[6,7] The discovery and marketing of new antiviral agents often take a long time (e.g., months to years). Therefore, an effective strategy to treat an emerging disease could be to repurpose clinically available medicines, which usually have a safety profile.

Artemisia annua L. is easily obtained and has a long history and safety record in the treatment of hyperlipidemia, malarial, plasmodial, and inflammatory diseases. Furthermore, *A. annua* L. has anticonvulsant, antiviral, antimicrobial, and anticholesterol activities.[4,8] Traditionally, artesunate (a derivative of artemisinin)

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Abbreviations: 3CL^{pro}, 3-chymotrypsin-like protease; ACE-2, angiotensin-converting enzyme-2; BSG, Basigin; CC, cytotoxic concentration; CD147, cluster of differentiation 147; COVID-19, coronavirus disease; EC, effective concentration; EMMPRIN, extracellular matrix metalloproteinase inducer; FDA, Food and Drug Administration; MAPK, mitogen-activated protein kinase; MMPs, matrix metalloproteinases; M^{pro}, main protease; PK, protein kinase; SARS, severe acute respiratory syndrome coronavirus; TMPRSS2, transmembrane protease serine 2.

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has been used for the treatment of malaria and viral diseases.[8,9] Recently, a clinical study indicated that treatment with artesunate could significantly shorten the duration of the hospital stay and reduce the symptoms in COVID-19 patients in China.[10]

Chemically, *A. annua* L. contains sterols, terpenes, flavonoids, phenolics, and polysaccharides.[8,11] Artemisinin is a bioactive component that is extracted from *A. annua* L., has high efficiency and low toxicity, and is approved by the Food and Drug Administration[9,12] and the World Health Organization (WHO) for the control of malaria.[13,14] Artemisinin and other compounds from *A. annua* L. have been used in the management of several types of diseases, including autoimmune diseases, diabetes, cancer, parasitosis, viral infections, and atherosclerosis.[4,8,9,12] The methanolic extracts from *A. annua* L. might be valuable for antiviral therapy, because they have higher activity against the Herpes Simplex virus type-1 than acyclovir.[12] The ethanolic extracts of *A. annua* L. have significant antiviral activity against SARS-coronavirus with a 50% cytotoxic concentration (CC_{50}) of 1,053 ± 92.8 µg/mL and 50% effective concentration (EC_{50}) of 34.5 ± 2.6 µg/mL. These observations suggest that *A. annua* L. might be valuable for the treatment of COVID-19.[15] In addition, *A. annua* L. might have potent inhibitory activities against the Epstein-Barr Virus, Cytomegalovirus, Herpes Simplex Virus 1, Human Herpes Virus 6A, and Human Papillomavirus.[8]

Molecular modeling was used to show that phytocompounds of artemisinin could bind to COVID-19.[16] Furthermore, *A. annua* L. has potent anti-inflammatory activity that might inhibit or reduce inflammation and lung injury in COVID-19 patients.[17] In the current article, the possible mechanisms underlying the actions of *A. annua* L. against SARS-CoV-2 will be highlighted.

Antiviral activities of *A. annua* L. derivatives against SARS-CoV-2

SARS-CoV-2 is a positive-sense single-stranded RNA virus; its structural proteins have a spike, envelope, membrane, and nucleocapsid; and SARS-CoV-2 contains the largest gene, the ORF1ab, coding the pp1ab protein and 15 nsps.[18] SARS-CoV-2 can interact with the cluster of differentiation 147 (CD147) and angiotensin-converting enzyme-2 (ACE-2) on host cells for invasion.[18,19] Drugs that interfere with ACE2, CD147 expression and spike proteins and their structures might inhibit viral entry, subsequent replication, and dissemination among other cells, mitigating COVID-19 disease.[19] It is well known that *A. annua* L. contains active compounds that have antiviral activities, such as artemisinin, arteannuin B, artemisinic acid, quinic acid, caffeic acid, quercetin, rutin, and crysosplenetin.[8] Artemisinin and artesunate can inhibit the replication of the Hepatitis C Virus, which, similar to the SARS-CoV-2 virus, is a positive-sense single-stranded RNA virus.[13] In addition, Artesunate can inhibit cytomegalovirus[20] and JC polyomavirus replication.[13]

A. annua L. can inhibit SARS-CoV-2 viral invasion and replication, and reduce oxidative stress, consequently reducing inflammation during COVID-19 (Fig. 1). The following route might provide a critical target for the development of effective antiviral agents. The pharmacological mechanisms of *A. annua* L. and their compounds might lead to the development of potential antiviral agents against COVID-19.

A. annua L. against SARS-CoV-2 invasion: ACE-2, TMPRSS2, CD147, and S

In host cells, ACE2, CD147, and extracellular matrix metalloproteinase inducer (EMMPRIN) are receptors for SARS-CoV-2.[18,19,21] The spike glycoprotein (S) of SARS-CoV-2 can bind to the ACE2 or CD147 on the host cell, and enter the cell, where the virus replicates and spreads to other cells.[19,22] The decrease in ACE2 and CD147 expression might be protective against COVID-19.[19,22]

During virus entry into cells, SARS-CoV-2 requires cellular proteases, such as trypsin-like protease cathepsins, and transmembrane protease serine 2 (TMPRSS2) that cleaves the S protein to promote fusion of the human and viral cellular membranes.[18,23,24] Therefore, a decrease in the activity of these enzymes might be important for the control of SARS-CoV-2 infection.

Of interest, a previous study reported that androgens can upregulate the expression of TMPRSS2 protein and ACE2.[25] Artemisinin can induce androgen receptor degradation via the 26S proteasome and disrupt the androgen response.[26] Therefore, Artemisinin might inhibit SARS-CoV-2 infection by limiting the expression of ACE-2 and TMPRSS2 in sensitive cells (Fig. 1).[18]

CD147 is a transmembrane glycoprotein encoded by the Basigin gene in humans. CD147 can increase the synthesis of matrix metalloproteinases (MMPs) and pro-inflammatory cytokines.[14] CD147 and MMPs expression can be enhanced by protein kinase (PK) and mitogen-activated protein kinase (MAPK) signaling.[14] Artemisinin at 20–80 µg/mL inhibited the expression of CD147 in human cells. In addition, artemisinin strongly blocked PMA-induced CD147 expression by attenuating PKCδ and MAPK phosphorylation in human monocytes.[14] Artesunate inhibited human cytomegalovirus replication by reducing PK activity.[27] Therefore, artemisinin might be effective in the control of SARS-CoV-2 infections.

A. annua L. against SARS-CoV-2 replication: $3CL^{pro}$

The conserved 3-chymotrypsin-like protease ($3CL^{pro}$) or main protease (M^{pro}), controls coronavirus transcription and virus replication. Their inhibition can reduce virus replication. A recent study showed that *A. annua* L. could inhibit the enzymatic activity of $3CL^{pro}$ that is produced by SARS-CoV-2 during COVID-19 infection, which inhibits COVID-19 replication.[17]

A. annua L. against SARS-CoV-2 infection: Nrf2 and NF-kB

Nrf2 is a transcription factor and can regulate the cellular antioxidant response. Nrf2 signaling can reduce oxidative stress, which contributes to disease progression.[28] In addition, Nrf2 can attenuate pulmonary fibrosis by upregulating antioxidant expression and defense enzymes.[29] Enhanced oxidative stress is associated with pulmonary fibrosis and acute respiratory distress syndrome. Of note, pulmonary fibrosis contributes to the progression of COVID-19, which leads to high mortality in COVID-19 patients.[30] Hence, modulation of Nrf2 activity might be valuable for the control of COVID-19 related pulmonary fibrosis.

A. annua L. can activate Nrf2 signaling that suppresses oxidative stress and inflammation.[28,31] *A. annua* L. has potent antioxidant activity and high phenolic content.[32] Artesunate, an *A. annua* L. derivative, is a promising agent that could improve lung fibrosis by inhibiting the activity of profibrotic molecules.[33] Artemisinin, which is a derivative of *A. annua* L., is an Nrf2 activator and has antioxidant and anti-inflammatory effects. Treatment with artemisinin inhibits bleomycin-induced lung damage in wild-type mice.[28] Mechanistically, artemisinin can activate and stabilize Nrf2 by reducing its ubiquitination and degradation. An *A. annua* L. medicinal approach that targets Nrf-2 might offer antioxidant activity for humans against

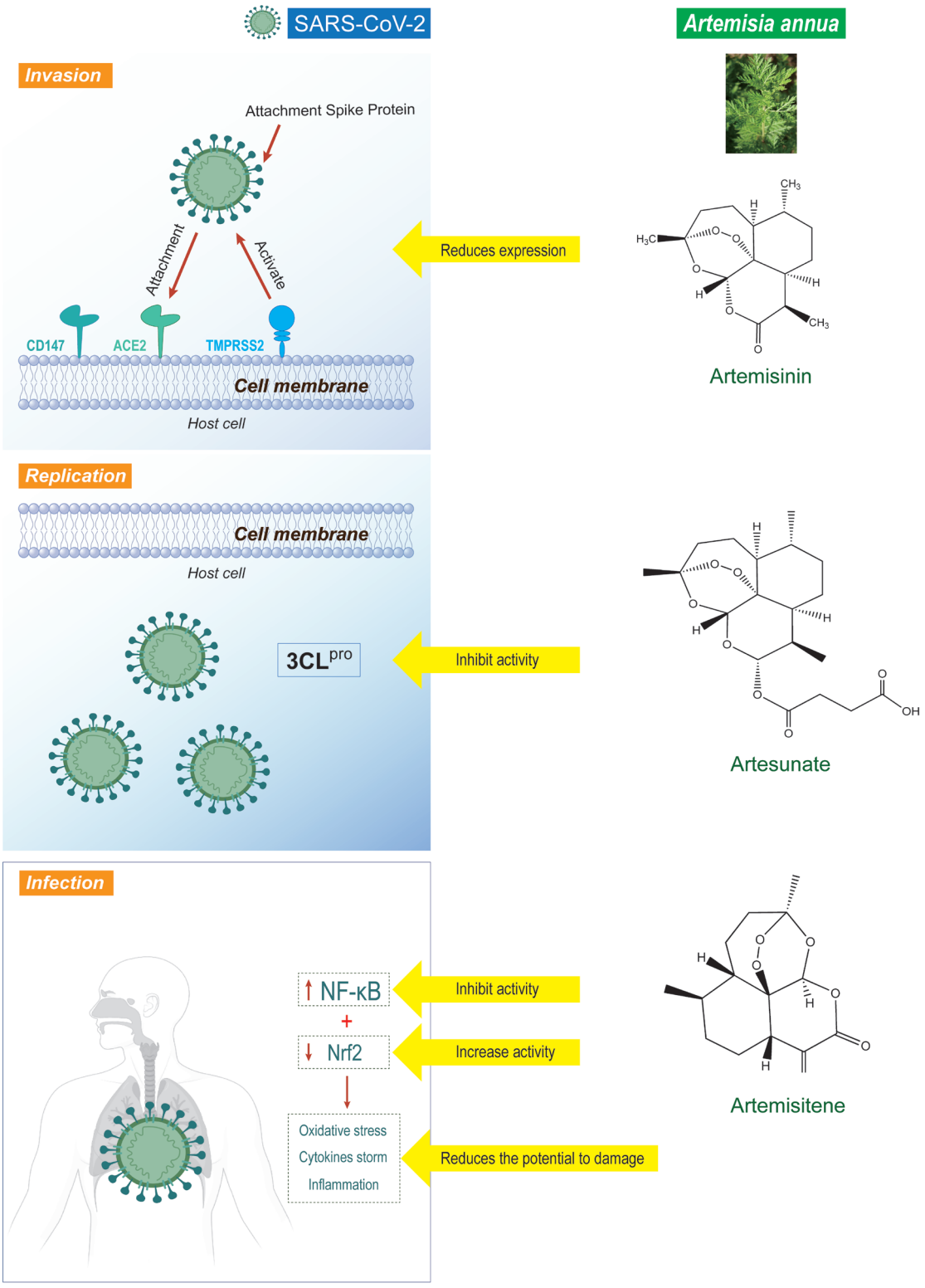

Fig. 1. *Artemisia annua* L. and their derivatives against SARS-CoV-2 infection. *A. annua* L. derivatives could fight against SARS-CoV-2 by inhibiting entry, ACE2, CD147, TMPRSS2, and S expression into host cells; reducing virus replication by inhibiting $3CL^{pro}$. *A. annua* L. derivatives can reduce oxidative stress by increasing Nrf2 expression, and inhibit the NF-κB signaling, limiting pro-inflammatory cytokine production, cytokine storm, inflammation, lung damage, and fatal inflammation that are caused by SARS-CoV-2. $3CL^{pro}$, 3-chymotrypsin-like protease; ACE2, angiotensin-converting enzyme2; CD147, cluster of differentiation 147; TMPRSS2, transmembrane protease serine 2.

tissue damage and antifibrotic activity against SARS-CoV-2 infection and confer protection against tissue damage in other organs.

NF-κB is a protein complex that regulates gene transcription, cell survival, and stimulates pro-inflammatory cytokine productions.[34] NF-κB signaling contributes to the pathogenesis of lung disease, including Acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome, and respiratory viral infections.[13,34] The increase in cytokine production results in a cytokine storm and leads to the accumulation of fluid in the air sacs of alveoli, which causes suffocation.[22] During COVID-19, severe disease can induce a cytokine storm, and cause fatal inflammation, leading to multiple organ dysfunction syndromes.[13,22] Therefore, the inhibition of NF-κB signaling might be valuable in the control of COVID-19.[13,22]

Artesunate is an *A. annua* L. derivate and can inhibit NF-κB signaling, limiting virus replication. Artesunate has been demonstrated to inhibit chloroquine-like endocytosis, which might be effective for the treatment of SARS-CoV-2 infection.[13] Therefore, artesunate might inhibit NF-κB signaling during SARS-CoV-2 infection to attenuate the cytokine storm. Artesunate might have the anti-inflammatory activity to reduce the inflammatory response, pro-inflammatory cytokine production, and lung inflammation that is caused by SARS-CoV-2 infection.

Future directions

The methanolic extracts of *A. annua* L. might be an appropriate candidate for antiviral therapy, because they have the highest antiviral potential against other viral replication. Furthermore, *A. annua* L. has shown preclinically that it has potent activities against SARS-CoV-2 infection and might be important for the control of COVID-19. However, the therapeutic efficacy and safety of these potential medicines for the treatment of COVID-19 need to be tested in clinical trials.

Conclusions

Repurposing drugs is an effective strategy to discover a therapeutic agent for the treatment of COVID-19. The *A. annua* L. derivatives might be potential candidates in COVID-19 treatment. *A. annua* L. can fight against SARS-CoV-2 infection by inhibiting its entry, ACE2, CD147, TMPRSS2, and S expression in host cells and reducing its replication by inhibiting $3CL^{pro}$. Furthermore, *A. annua* L. derivatives can reduce oxidative stress by increasing Nrf2 activity, inhibiting NF-κB signaling, reducing pro-inflammatory cytokine production, cytokine storm, inflammation, lung damage, and fatal inflammation that is caused by SARS-CoV-2. Their therapeutic efficacy and safety in the treatment of COVID-19 patients in clinical trials are urgently required.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

IA and FUH contributed to the study concept and design, ML and CHS performed data analysis, IA and RA drafted the manuscript, ML and FUH critically revised the manuscript.

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