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A Review of the *Artemisia* Species with Antiviral and Immunomodulatory Potential

BORDEAN Maria-Evelina[1], Georgiana S. MARȚIS[1]*, Anamaria POP[1], Rodica UNGUR[2], Ileana M. BORDA[2], Carmen POP[1], Marcel M. DUDA[3],

[1]University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Faculty of Food Science and Technology, 3-5 Calea Mănăștur, 400372, Cluj-Napoca, Romania

[2]Department of Medical Rehabilitation, University of Medicine and Pharmacy "Iuliu Hatieganu" 400000 Cluj-Napoca, Romania

[3]University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Faculty of Agricultural, 3-5 Calea Mănăștur, 400372, Cluj-Napoca, Romania

*Correspondence: georgiana.petrut@usamvcluj.ro

Abstract: Herbal medicines are useful in the treatment of a wide range of illnesses. Considering their potential for strong therapeutic values and acceptability by patients with a variety of health issues, herbal medicines offer therapeutic benefits. Herbal medicine uses a plant's whole, a portion of it, or a specific isolated phytoconstituent. The modern era's quest for novel medications sparked a renewed interest in the discovery of herbal medications derived from various natural resources. The pharmaceutical business has been more interested in finding new natural medications in recent years. However, the identification of active ingredients, their characterisation, pharmacological activity, toxicity/adverse effects, medication interactions, and, most significantly, their regulatory requirements present a number of problems in the discovery of such new innovative phytomedicines. The historical use and current developments in phytochemistry of specific *Artemisia* species, along with their corresponding therapeutic, insecticidal, and nutritive qualities, thorough phytochemical and pharmacological research and their long-term preservation will produce trustworthy compounds with pharmacological significance for improved medical treatment.

Keywords: *Artemisia* species, herbal medicine, phytoconstituents, phytomedicines.

Introduction

Traditional herbal remedies have been used to treat illnesses as part of local or regional healing practices. The World Health Organization (WHO) describes them as naturally occurring, plant-derived compounds with little or no industrial processing. The yearly global market value of herbal medicines has surpassed US$ 60 billion in recent years (Barkat et al., 2020). At the moment, developed nations support and advertise the use of herbal remedies to treat a range of conditions. The usage of phytomedicine, often known as herbalism, has developed from the long-standing custom of treating a variety of illnesses with natural medications made from plants, herbs, or plant extracts. A number of variables include the aging population, rising consumer knowledge, minimal side effects, and the introduction of contemporary good manufacturing standards (CGMP).

With over 400 species, the genus *Artemisia* is the biggest and most widely dispersed member of the Asteraceae family of plants. The majority of Artemisia species are herbaceous decorative, medicinal, biennial, perennial, or shrubs with scented leaves. Because terpenoids and sesquiterpene lactones are present, they have a strong scent and a harsh flavor and can be silver, black, or blue-green in color. Due to their extensive phytochemical diversity, certain well-known species are said to provide multiple medical benefits. Eighty-nine chemical constituents in all, both volatile and non-volatile, phenylpropanoids, flavonoids, terpenes, lignans, phenolics, fatty acids, fatty esters, hydrocarbons, and other miscellaneous compounds are among them, have been linked (many of them) to a variety of biological activities, including analgesic, anti-inflammatory, hypolipidemic, antinociceptive, antimicrobial, antioxidant, hepatoprotective, antiulcerogenic, anti-malarial, anti-leishmanial, anti-cancer, anti-tumor, anti-diabetic, anticonvulsant, anti-promastigote, anti-convulsant, anxiolytic, and antidepressant (Koul et al., 2018).

Ethnopharmacology

The Nobel Committee awarded the 2015 Nobel Prize in Physiology or Medicine for its influence on public health as a result of the isolation and identification of powerful compounds from the

genus Artemisia, particularly artemisinin and its derivatives, employing cutting-edge drug discovery techniques (Tambo et al., 2015; Su and Miller, 2015). Many scientists became interested in researching the pharmacological and phytochemical characteristics of other Artemisia species as a result of this.

India and the Indian subcontinent are home to about 45 different species of Artemisia, which is mostly employed as a medicinal plant (Koul et al., 2018; Joshi et al., 2016).

The term "prabhava" in the Ayurvedic medical system refers to a plant's "instinct intelligence" in producing a variety of therapeutic effects (Kumar et al., 2012; Katiyar, 2011). Because of their prabhava, Ayurveda regards *A. absinthium* with great respect and suggests them for skin and liver problems, infections, inflammation, respiratory issues, neurological disorders, and as an insecticidal ("krimighna") remedy (Bora et al., 2011; Koul et al., 2018).

Table 1 lists the pharmacological activities and characteristics of the several Artemisia species from different geographical areas.

Table 1

The characteristics and pharmacological effects of a subset of *Artemisia* species

Species	Uses	Phytochemicals Isolated
A. Absinthium	cardiac stimulant, anthelmintic, liver function, memory booster	Sesquiterpene lactones, polyphenolic compounds, flavonoids, tannins, lignins (Ivanescu et al., 2015; Batiha et al., 2020)
A. abrotanum	Insecticide, liver conditions	Flavonols, tannins, coumarins (Bora et al., 2011; Koul et al., 2018; Kumar and Kumari, 2018)
A. afra	coughs, colds, malaria, diabetes, bladder and kidney disorders	monoterpenoids, sesquiterpenes, glaucolides, guaianolides;

		flavonoids (Ivanescu et al., 2015; Liu, Van der Kooy and Verpoorte, 2009)
A. annua	Fever, malaria, fibrosis	Volatile oils, sesquiterpene lactones, phenolic compounds, flavones (Ivanescu et al., 2015; Batiha et al, 2020; Fu et al., 2020; Feng, 2020, Septembre-Malaterre, 2020)
A. asiatica	cancer, inflammation, infections and ulcers	Volatile oils, flavones, alkaloids (Bora et al., 2011; Ahuja, 2018)
A. arborescens	Anti-inflammatory, Antihistaminic, Blood decongestant	Terpenes, flavone, fatty acids (Bora et al., 2011; Costa, 2016)
A. douglasiana	premenstrual syndrome and dysmenorrhea	Monoterpenes, sesquiterpene lactones (Ivanescu et al., 2015; Adams, 2012)
A. dracunculus	antidiabetic and anticoagulant	Volatile oils,coumarins, polyphenolic compounds, glucoside (Allerton 2020;Majdan, 2020)
A. Judaica	Gastrointestinal disorders	Volatile components, phenolic compounds (Bora et al., 2011; Mokhtar, 2019)
A. maritima	anthelmintic, liver function, GI issues	Volatile oils, fatty acids, polyphenolic compounds, sesquiterpene lactones

		(Bora, et al., 2011; Costa, 2016)
A. scoparia	antibacterial, antiseptic, antipyretic	Volatile oils, fatty acids, coumarins, pyrogallol tannins, cholagogic components, flavonoids, flavones (Bora et al., 2011; Cho et al., 2019; Boudreau et al., 2019)
A. tripartite	cold, sore throats, tonsillitis, headaches and wounds	Guaianolides, polysaccharides (Bora et al., 2011; Xie et al., 2008)
A. verlotorum	hypertension	Volatile oils, fatty acids (Bora et al., 2011; Calderone et al., 1999)
A. vestita	inflammatory diseases	Volatile oils, flavonoids (Ding et al., 2019; Tian et al., 2019)
A. vulgaris	analgesic, anti-inflammatory, antispasmodic and liver disease	Terpenes, coumarins acids (Bora et al., 2011; Ragasa et al., 2018)

These different *Artemisia* species have a wide range of actions because they contain high concentrations of alkaloids, lactones, flavonoids, phenols, quinines, tannins, and terpenoids, all of which aid in plant growth or offer protection from pathogens and predators (Bora et al., 2011; Pandey and Singh, 2017; Willcox, 2009; Nigam et al., 2019)

Anti-Viral effect

We go over a few recent in vivo and in vitro investigations on different *Artemisia* extracts and formulations. Aqueous, methanolic,

chloroformic, or acetone extracts, essential oils, oil-based extracts, or dried powders of several *Artemisia* species were used in the research investigations. With very few human investigations, the research was done on animal models, cultured cells, and bacterial, viral, or fungal cultures.

A. annua, *A. absinthium*, *A. vulgaris*, *A. maritima*, and *A. indhana* are among the *Artemisia* species that are gaining more attention from researchers in light of the COVID-19 pandemic because of their strong potential for antiviral, anti-inflammatory, and anti-infectious properties (Bora et al., 2011; Obistioiu et al., 2014; Ekiert et al., 2020; Abad et al., 2012; Lee et al., 2013). These days, research is highlighting the fascinating functions of artemisinin and its derivatives (ARTs).

There is a notable antiviral activity in several phytochemicals that have been identified from different species of *Artemisia* (Efferth, 2018). With activity against influenza virus A, human herpes viruses HSV-1 and HSV-2, hepatitis B and C viruses, HIV-1, and low micromolar range, ARTs have emerged as the most promising antiviral medication candidates (Obeid et al., 2013; Romero et al., 2005; Uzun and Toptas, 2020; Efferth et al., 2008; D'Alessandro et al., 2020; Jang et al. 2015).

Promising anti-inflammatory, immunoregulatory, and antiviral qualities have led to the investigation of ARTs' efficacy against SARS-CoV-2 infection. To find out if artemisinin or its derivatives could physically bind any of the COVID-19 target proteins—such as the spike glycoprotein, spike ectodomain structural protein, the main protease of the virus (MPro), or the spike receptor-binding domain—and stop SARS-CoV-2 from attaching to the host receptor ACE2—researchers used in silico techniques (Rolta et al., 2021; Sharma and Deep, 2020; Cao et al., 2020; Sehailia and Chemat, 2020; Rai et al., 2020; Tomic et al., 2020; Alazmi and Motwalli, 2020). The results of the ADMET (absorption, distribution, metabolism, excretion, and toxicity) investigation of artemisinin indicated that it has a promising therapeutic potential, was non-cytotoxic, and had good water solubility and blood-brain barrier permeability. Additionally, artemisinin bound to all four proteins and in some cases showed superior binding modes than hydroxychloroquine, according to molecular docking studies (Cao et al., 2020; Sehailia and Chemat, 2020; Rai et al., 2020; Tomic et al., 2020; Alazmi and Motwalli, 2020). As a result, ARTs may be the

greatest starting point for future SARS-CoV-2 infection medication development.

In a controlled clinical experiment that was just reported, 41 patients with confirmed COVID-19 were split into two groups. The experimental group (n=23) received a combination of artemisinin and piperaquine (AP), while the control group consisted of 18 patients. AP was administered orally for six days at a low dose of one tablet per day (artemisinin 62.5 mg and piperaquine 375 mg) after a loading dose of two tablets (artemisinin 125 mg and piperaquine 750 mg) on the first day. The percentage of patients with undetectable SARS-CoV-2 on days 7, 10, 14, and 28 after therapy was the main result. The findings showed that: (1) the AP group required significantly less time on average to achieve undetectable SARS-CoV-2 RNA than the control group; (2) the AP group had a significantly higher elimination rate of SARS-CoV-2 RNA than the control group; and (3) the AP group's hospital stay was significantly shorter than the control group. Despite the study's inadequate sample size and trial design, AP is a great medication candidate to treat SARS-CoV-2 infection because of its safe toxicity profile and immunoregulatory properties (Li et al., 2020).

TGF-β, also known as transforming growth factor-beta, is involved in immune system modulation and exhibits varying behaviours on immune cell types. At its final stage, SARS-CoV-2 infection is followed by a cytokine storm, lung fibrosis, and edema. Moreover, SARS-CoV-2 increases TGF-β expression. This could provide some insight into the cytokine storm and lung fibrosis (Chen, 2020; Evans and Lippman, 2020; Uckun et al., 2020). An attempt is in progress to find new and targeted small compounds with the ability to effectively suppress TGF-β expression with very no negative effects. Relative to artemisinin, there has been evidence to be TGF-β suppressors in a number of inflammatory illness models (Wang et al., 2020; Yao et al., 2018; Wu et al., 2010; Cao et al., 2019). Adult COVID-19 patients with symptomatic mild-to-moderate COVID-19 are being studied in a randomized, open-label Phase IV trial to assess the safety and effectiveness of a proprietary ART formulation. The medication is anticipated to lessen the TGF-β induced inflammatory damage linked to the cytokine storm and viral sepsis in these patients in addition to its strong antiviral action. According to preliminary findings, individuals with mild-to-moderate COVID-19 infection recovered faster with the ARTs-based medication, which also has an

extremely positive safety profile (Trieu et al., 2020). Therefore, ARTs are excellent pharmacological candidates against SARS-CoV-2 infection because they reduce TGF-β signalling, which may be an appealing therapeutic strategy.

Anti-Inflamatory effect

Due to their ability to inhibit inflammation, a number of sesquiterpenes obtained from Artemisia and its derivatives, such as artemisinin, artesunate, dihydroteannuin, artemisolide, eupatilin, scoparone, capillarisin, and scopoletin, have drawn particular attention. ARTs have been shown to be successful in treating inflammatory diseases such as rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, and allergy disorders in animal models (Shi et al., 2015).

A few of the mechanisms that reduce inflammation are as follows: (1) blocking the iNOS and COX-2 pathways; (2) suppressing ERK and NF-κB signaling; (3) blocking the activation of pathogenic T cells; (4) suppressing the activation of B cells and the production of antibodies; and (5) blocking Akt phosphorylation and IκB degradation through the PI3K/Akt signalling pathway that occurs downstream of TNF-α (Qin et al., 2020; Zamani et al., 2019; Boudreau et al., 2020; Cheng et al., 2011).

Therefore, more research into the potential applications of these phytochemicals produced from *Artemisia* as therapeutic candidates for inflammatory and autoimmune illnesses is warranted given the variety of pathways by which they demonstrate their anti-inflammatory properties.

Anti-Bacterial and Anti-Parasitic effect

It has been demonstrated that plant extracts and chemicals derived from *Artemisia* species to be potent anti-parasitic and anti-bacterial agents (Pandey and Singh, 2017). Some of these phytochemicals have been shown through mechanistic investigations to have bactericidal effects against Gram-negative or Gram-positive bacteria that cause the bacterial membrane to rupture (Pandey and Singh, 2017, Feng, 2020; Yang et al., 2020; Huang et al., 2018). ARTs are a noteworthy phytochemical that belong to a novel class of

antibacterials (Pandey and Singh P., 2017; Willcox, 2009; Antoine et al., 2014; Shah et al., 2013).

Upcoming paths

Many lead compounds and phytochemical derivatives derived from medicinal plants have been produced for a range of important therapeutic applications (Vellingiri et al., 2020; Akram et al., 2018; Chen, 2020; Haq et al., 2020). Researchers often look into medicinal plants in search of the one powerful ingredient that is causing the desired therapeutic outcome (Williamson, 2001). Research contrasting the effects of entire plants extracts to the activity of the refined preparation demonstrates that, frequently, the potency of at every stage of fractionation, the refined preparation gets less and less (Rasoanaivo, 2011). As the healing effect could be the outcome of the medication's mixture of various chemicals. In comparison to individual chemicals, a complex mixture of compounds has a higher influence on plants (Raskin and Ripoll, 2004). One of the benefits of using a combinatorial approach could be the synergy between the different components, improved bioavailability, compounding effects, and having an overall network impact of concurrent routes (Wagner and Ulrich-Merzenich, 2009).

Therefore, it is evident that the significance of *Artemisia* in traditional medicine and drug development systems presents a significant deal of opportunity for additional research into the plant's biological activity, particularly in relation to viral infection and inflammation. To promote the genus *Artemisia* as a safer medication, further thought, standardization, and clinical trials of its pharmacological potential are needed.

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