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A phylogenetic perspective of antiviral species of the genus Artemisia (Asteraceae-Anthemideae): A proposal of anti SARS-CoV-2 (COVID-19) candidate taxa

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ABSTRACT

Introduction: Different classes of disease-causing viruses are widely distributed universally. Plant-based medicines are anticipated to be effective cures for viral diseases including the COVID-19, instigated by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2). This study displays the phylogenetic perspective of Artemisia and proposes some candidate taxa against different viral diseases, including SARS-CoV-2.

Methods: Data of Artemisia with antiviral activity were obtained from different published sources and electronic searches. A phylogenetic analysis of the nrDNA ITS sequences of reported antiviral Artemisia species, along with the reference species retrieved from the NCBI GenBank database, was performed using the maximum likelihood (ML) approach.

Results: In total, 23 Artemisia species have been documented so far with antiviral activity for 17 different types of viral diseases. 17 out of 23 antiviral Artemisia species were included in the ITS phylogeny, which presented the distribution of these antiviral Artemisia species in clades corresponding to different subgenera of the genus Artemisia. In the resultant ML tree, 10 antiviral Artemisia species appeared within the subgenus Artemisia clade, 2 species appeared within the subgenus Absinthium clade, 3 species appeared within the subgenus Dracunculus clade, and 2 species appeared within the subgenus Seriphidium clade.

Discussion: Artemisia species from different subgenera with antiviral activity are prevalent in the genus, with most antiviral species belonging to the subgenus Artemisia. A detailed analysis of taxa from all subgenera, particularly the subgenus Artemisia, is therefore proposed in order to discover compounds with potential anti-SARS-CoV-2 activity.

1. Introduction

Asteraceae is the largest eudicot angiosperm family and includes many species with medicinal and economic significance. Artemisia L. is the leading genus of this family, with ~500 species occurring commonly in the north hemisphere (Oberprieler et al., 2009; Bora and Sharma, 2011). However recently in the Plant List and World Flora Online, almost 2200–2300 species of the genus Artemisia have been stated. Abundant secondary metabolites retrieved from Artemisia extracts are used to treat certain health problems, such as stress, anxiety, depression, epilepsy, irritability, insomnia, and psychoneurosis (Walter et al., 2003). Many Artemisia species are reported with antimalarial, antibacterial, antirheumatic, antiseptic, antispasmodic, hepato-protective, antitumor (Terra et al., 2007; Koul and Taak, 2017; Hussain et al., 2017, 2022;... Abrreviations: BVD, Bovine viral diarrhea virus; DEN 2, Dengue virus type 2; FCV, Feline calici virus; FIV, Feline immunodeficieny virus; HBV, Hepatitis B virus; HeLa, Henrietta Lacks cells; HCV, Hepatitis C virus; HIV (HSV), Human alphaherpesvirus (Herpes simplex virus); HHV-4 (EBV), Human gammaherpesvirus type 4 (Epstein-Barr virus); HIV-, Human immunodeficiency virus; HBeAg, Hepatitis B e-antigen; HBsAg, Hepatitis B surface antigen; IV, Influenza virus; JUN V, Junin virus; MDBK, Madin-Darby bovine kidney cells; MDCK, Madin-Darby canine kidney cells; MTTA, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide assay; MNV, Murine norovirus; NDV, Newcastle disease virus; SARS CoV2, Severe acute respiratory syndrome corona virus 2; SV, Sindbis virus; PV, Polio virus; VERO, Verda reno cells; YFV, Yellow fever virus.

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availability of potential antiviral treatments to keep the population safe.

2.1. Data collection of Artemisia plants with antiviral activity

Data of Artemisia species with reported antiviral activity was attained from published sources including scientific journals, reports, books, theses, conference papers, and an electronic search of Biological Abstracts, BIOSIS, BioOne Previews, CabDirect, Cochrane Library, PubMed/Medline, GeoRef, Google Scholar, JSTOR, Journal Citation Reports, Mendeley, Publons, Researchgate, Scopus, SciELO, Springer Link, Science Direct, Web of Science, Taylor and Francis. The keywords used to search in the aforementioned databases include “Artemisia plants, antiviral activity, Artemisinin, A. annua, Antiviral compounds in Artemisia”. For plant synonyms and accepted names, The Plant List (www.theplantlist.org) database was searched. About 125 articles were looked over and some were designated as providing wide-ranging data of antiviral activity of Artemisia species. The compiled data of antiviral activity of Artemisia species is provided in Table 1, including region, extraction solvent and plant part used, investigated cell lines, virus type or strain, viral assay used against specific virus and active compounds tested against viral strains.

2.2. Phylogenetic analysis of Artemisia with ITS sequences

For the phylogenetic analysis, ITS sequences of nuclear ribosomal DNA (nrDNA) for a total of 147 Artemisia species, including the antiviral Artemisia species compiled (Supplementary file 1) for this study, were retrieved from GenBank, signifying all subgenera of the genus Artemisia revealed in earlier studies on the phylogeny of Artemisia by Torrell et al. (1999), Valles et al. (2003), Tkach et al. (2008), Pellicer et al. (2010), Garcia et al. (2011), Pellicer et al. (2011), Riggins and Seigler (2012), Hobbs and Baldwin (2013), Malik et al. (2017), Pellicer et al. (2018) and Hussain et al. (2019). The raw data of sequences retrieved were assembled with MEGA-7 software (Kumar et al., 2016). A multiple sequence alignment (MSA) (n = 147) was generated from ITS sequences of Artemisia species. Chrysanthemum dichroum (C.Shih) H. Ohashi & Yonek., Chrysanthemum indicum L., and Ajania fastijata (C.Winkl.) Poljakov were used as outgroup species from the same tribe using their ITS sequences (Hussain et al., 2019). The ITS sequences were edited with the BioEdit v.7.0.9 software (Hall, 1999) and then CLUSTAL X (Thompson et al., 1997) program in MEGA-7 software (Kumar et al., 2016) was used to align the sequences with some manual modifications for gaps. Using MEGA-7 software (Kumar et al., 2016), the maximum likelihood (ML) analysis was generated for the MSA (n = 147) with 1000 bootstrap (BS) replicates. The resultant tree was visualized in the software FigTree 1.4.3. (2018).

3. Results

Results showed that a total of 23 species of Artemisia were reported so far for the treatment and management of viral diseases and have potential antiviral activity. The antiviral activity is due to the presence of biologically active compounds with known mechanisms of action (Table 1). Among the reported Artemisia species, methanol, ethanol and aqueous extracts of A. annua have proven to be extensively used against different viruses including SARS-CoV-2, HBV, BVDV, HHV (HSV-1), HIV-1 and Influenza virus type A (IV-A), due to artemisinin, an active antimalarial as well as an antiviral compound. Methanol and aqueous extracts and tea infusion of Artemisia afra Jacq. Ex Wild. leaves were used against HIV-1, HIV-2 and SARS-CoV-2. Methanol extracts of Artemisia abyssinica Schultz Bip ex Richard. were tested against HIV-1 and HIV-2 with better results. Methanol and aqueous extracts of Artemisia absinthium L. were used against HHV (HSV-1), Sindbis virus (SV), Polio virus (PV), HIV-1 and HBV. Aqueous extracts of Artemisia arborescens Vaill. L. leaves and aerial parts were reported with promising antiviral activity against HHV (HSV). Artemisia campestris L. and its sub species’ methanol, ethanol and aqueous extracts were described with anti-HHV (HSV-1) and anti-HIV-1 activities. The extracts from whole plant, buds and aerial parts of Artemisia capitata Thum., were recognized with potential anti-humanherpes virus type 4 (HHV-4), HIV and HBV activities.

Moreover, the methanol extracts of aerial parts of Artemisia chaemmetfolia Vill. were found to be active against HHV (HSV-1). Methanol extracts from whole plant and aerial parts of Artemisia carifulia Roxb. were active antiviral agents against HHV (HSV-1) and IV-A.
Table 1
Reported *Artemisia* species used against different viral diseases in different regions of the world.

| *Artemisia* taxa | Region | Extract used | Part used | Culture cells | Virus type/strain | Assay applied | Active compound | Effective concentration (IC<sub>50</sub>/ED<sub>50</sub>/EC<sub>50</sub>/CC<sub>50</sub>) | Reference |
|-----------------|--------|--------------|-----------|---------------|-----------------|---------------|----------------|-----------------------------------------------------|-----------|
| *A. annua* L.  | Korea  | Methanol     | ND        | T-lymphocytes | HIV-1           | Syncytium inhibition assay | ND            | 100 µg/mL                                             | Chang and Woo (2003) |
|                 | China  | Ethanol      | Whole plant | Vero E6 /HEPG2 | SARS-CoV/ BJOO1, BJOO6 | CPE/MTS assay | ND            | 1053.0 µg/mL                                         | Li et al. (2005) |
|                 | Spain  | ND           | ND        | EBTr          | BVDV            | Cytopathic assay | Arteiminin with mixture of interferon-α and ribavirin | 100 mmol/L                                           | Romero et al. (2006) |
|                 | ND     | ND           | Plant powder | Cardiac       | HBV, HCV and BVDV | ND            | Arteiminin     | ND                                                   | Efferth et al. (2008) |
|                 | Iran   | Methanol     | Aerial     | HeLa          | HHV (HSV-1)     | MTT assay      | ND            | 12.5 µg/mL                                            | Li et al. (2005) |
|                 | Africa | Tea infusion | Whole plant | Vero E6       | EBTr            | Toxicity test | DD            | 3.90 mg/mL                                             | Karamoddini et al. (2011) |
|                 | Germany| Aqueous      | Aerial     | Cardiac       | HBV, HCV and BVDV | ND            | Arteiminin     | ND                                                   | Lubbe et al. (2011) |
| *A. africana* Jacq. ex Willd. | Ethiopia | Methanol | Aerial | MT-4          | HIV-1 (IIIb), HIV-2 (ROD) | Anti-HIV cytotoxic assay | ND            | > 123.5 mg/mL                                         | Lubbe et al. (2011) |
|                 | Africa | Tea infusion | Whole plant | Vero E6 cells | SARS-CoV-2      | Plaque reduction and cell viable assay | DD            | 0.01–10 mg/mL                                         | Efferth et al. (2008) |
|                 | Germany| Aqueous     | Aerial     | Vero E6       | SARS-CoV-2      | Plaque reduction and cell viable assay | ND            | 0.01–10 mg/mL                                         | Li et al. (2005) |
| *A. afra* Jacq. ex Willd. | Ethiopia | Methanol | Aerial | MT-4          | HIV-1 (IIIb), HIV-2 (ROD) | Anti-HIV cytotoxic assay | ND            | > 103 mg/mL                                           | Asres et al. (2001) |
| *A. absinthium* L. | Morocco | Methanol | Aerial | Vero      | HBV (HSV-1), SV and PV | Antiviral photosensitizers activity | ND            | 100 µg/mL for SINV and HSV and 200 µg/mL for PV | Mouhajir et al. (2001) |
| *A. absinthium* L. | India   | Aqueous | Whole plant | HBsAg and HBeAg, Plasma | HBV | Loss of HBsAg and HBeAg, plasma HBV DNA level Tetrazolium-based colorimetric assay | ND            | 2.4 and 5.6 µg/mL for HSV-1 and 4.1 and 7.3 µg/mL for HSV-2 | Ansari et al. (2018) |
| *A. arborescens* (Vaill.) L. | Italy   | ND | Leaves | Vero | HHV (HSV-1) | Essential oil | DD            | 6. 25 µg/mL                                           | Sinico et al. (2005) |
| *A. arborescens* (Vaill.) L. | Italy   | Aqueous | Leaves | Vero | HHV (HSV-1) and HSV-2 | Plaque reduction assay, MTT assay | ND            | 6. 25 µg/mL                                           | Saddi et al. (2007) |
| *A. campestris* L. | Iran    | Methanol | Aerial | HeLa | HHV (HSV-1) | MTT assay | ND            | 14.62 µg/mL                                           | Lai et al. (2007) |
| *A. campestris* subsp. glutinosa (Besser) Batt. | Spain   | Ethanol and aqueous | Aerial | Lymphoblastoid | HIV-1 | Transcriptional activity test | DD            | 14.62 µg/mL                                           | Karamoddini et al. (2011) |
| *A. capillaris* Thumb. | Japan   | ND | Buds | Rat hepatocytes | Hepatitis (anti-hepatotoxicity activity) | Cytotoxicity assay | DD            | 14.62 µg/mL                                           | Tiicona et al. (2020) |
| *A. campestris* L. | Iran    | Methanol | Aerial | HeLa | HHV (HSV-1) | MTT assay | ND            | 100 µg/mL                                             | Kiso et al. (1984) |
| *A. campestris* L. | Korea   | Ethanol and aqueous | Whole plant mixture (KCT01) | HBV | Hydrodynamic injection model | DD            | 100 µg+/kg and 200 µg+ /kg | Kim et al. (2018) |

(continued on next page)
| Artemisia taxa | Region | Extract used | Part used | Culture cells | Virus type/strain | Assay applied | Active compound | Effective concentration (IC<sub>50</sub>/ED<sub>50</sub>/EC<sub>50</sub>/CC<sub>50</sub>) | Reference |
|---------------|--------|--------------|-----------|---------------|------------------|---------------|----------------|---------------------------------|-----------|
| *A. carifulia* Roxb. | Bulgaria | Aqueous | Aerial | MDBK | HHV (HSV-2) strain BA | MTT assay | ND | 0.562 mg/mL | Karamoddini et al. (2011) |
| *A. douglasiana* Bens. | Nepal | Methanol | Whole plant | Vero cells/MDCCK | HHV (HSV-1), IV-A | Cytotoxicity Assay/dye uptake assay | ND | 92 mg/mL for HSV-1 and 22 mg/mL for IV-A | Angelova et al. (2019) |
| *A. fragrans* Wild. | China | Methanol | Aerial | HIV-1 protease | HIV-1 | HIV PR assay | Tri-<i>p</i>-coumaroylspermidine and dicafeoylquinic acids | 100 mg/mL | Ma et al. (2001) |
| *A. glabella* Kar. et Kir. | Argentina | Aqueous | Leaves | Vero | HHV (HSV-1), JUNV, DEN-2 | Plaque formation assay | α-thujone, β-thujone, borneol, p-cymene, 1.8-cineole, isocaryophyllene-epoxide | 65–125 ppm for HSV (HSV-1) and 60 and 150 ppm for DEN-2 | García et al. (2003) |
| *A. herba-alba* Ass. | Morocco | Methanol | Aerial | Vero | HHV (HSV-1), SV and PV | Antiviral photosensitizers activity | ND | 50 μg/mL for SINV and HSV and 100 μg/mL for PV | Mouhajir et al. (2001) |
| *A. incana* (L.) Druce | Iran | Methanol | Aerial | HeLa | HHV (HSV-1) | MTT assay | ND | Chrysantheneone | Asadli et al. (2020) |
| *A. kermanensis* Podl. | A. mendosauna D.C. (v. n. ajenjo) | Argentina | Aqueous | Leaves | Vero | HHV (HSV-1), DENV-2, JUNV | Virucidal test | ND | 298.61 ppm | Karamoddini et al. (2011) |
| *A. mendozana* D.C. | China | ND | ND | Hub-7 | HBV | Promoter activity analysis/Cell cytotoxicity assay | ND | 12.5 μg/mL | Dutschakský et al. (2005) |
| *A. persica* Boiss. | Morocco | Aqueous | Aerial | ND | SARS-CoV | ND | ND | 12.5 μg/mL | Karamoddini et al. (2011) |
| *A. princeps* var. orientalis | Korea | Aqueous | Aerial | RAW 264.7, CRFK, FCV-F9, MNV-1 | Plaque assays | α-thujone | ND | 0.01 and 0.1 μg/mL | Chung (2017) |
| *A. scoparia* Waldst. & K. | China | Ethanol | ND | MDCK | IV | Neuraminidase (NA) activity | ND | 0.2–0.6 μg/mL | Karamoddini et al. (2011) |
| *A. verlotiorum* Lamott. | Pisa Italy | Aqueous | Leaves | CRFK | FIV | Virus-induced syncytia, Viral reverse transcriptase activity, Viral capsid protein P24 expression | ND | 10<sup>-5</sup> mg/mL | Calderone et al. (1998) |
| *A. vulgaris* L. | Armenia | Aqueous | Whole plant | Vero | YFV (17D strain) | Plaque and cytotoxicity assay | α-thujone, β-thujone, 1,8-cineole, trans-carveol, sabineno | 100 μg/mL | Meneses et al. (2009) |
| *A. vulgaris* L. | Iran | Methanol | Aerial | HeLa | HHV (HSV-1) | MTT assay | ND | 25 μg/mL | Karamoddini et al. (2011) |

BVDV = Bovine viral diarrhea virus, COVID-19 = Coronavirus disease of 2019, DEN 2 = Dengue virus type 2, FCV = Feline calici virus, FIV = Feline immunodeficiency virus, HBV = Hepatitis B virus, HeLa = Henleitta Lacks cells, HCV = Hepatitis C virus, HHV (HSV-1) = Human alphaherpesvirus (Herpes simplex virus type 1), HHV (HSV-2) = Human alphaherpesvirus (Herpes simplex virus type 2), HHV-4 (EBV) = Human gamaherpesvirus type 4 (Epstein-Barr virus), HIV - 1 = Human immunodeficiency virus type 1, HIV-2 = Human immunodeficiency virus type 2, HBeAg = Hepatitis B e-antigen, HBsAg = Hepatitis B surface antigen, IV = Influenza virus, IV-A = Influenza virus type A, JUN V = Junin virus, MDCK = Madin-Darby bovine kidney cells MDCK = Madin-Darby canine kidney cells, MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide assay, MNV 1 = Murine norovirus type1, ND = Not defined, NDV = Newcastle disease virus, SARS-Cov 2 = Severe acute respiratory syndrome corona virus 2, SV = Sindbis virus, PV = Polio virus, Vero = Verda reno cells, YFV = Yellow fever virus
viruses. Aqueous leaves extracts of *Artemisia douglasiana* Bess. were reported to have active antiviral compounds against HHV (HSV-1), Junin virus (JUNV) and Dengue virus type 2 (DEN-2). Methanol extracts of aerial parts of *Artemisia fragrans* Willd. were shown to have antiviral activity against Human HHV (HSV-1), JUNV and DEN-2 viruses. Antiviral potentials of extracts from the aerial *Artemisia globella* Kar. et Kir. were demonstrated against Newcastle disease virus (NDV) LaSota strain (vaccine strain) and A/FPV/ Rostok 34 IV strain. Aqueous extracts from the aerial parts of *Artemisia herba-alba* Asso. were documented with antiviral activity against HHV (HSV-1), SV, PV and SARS-CoV-2. Methanol extracts of aerial parts of *Artemisia incana* L. Druce were found to be active against HHV (HSV-1). Aqueous extracts from aerial parts of *Artemisia kermanensis* Podl. were documented with potential anti-HHV (HSV-1) activity. *Artemisia morrisonensis* Hayata. extracts have proven antiviral activity against HBV. *Artemisia princeps* var. *orientalis* aqueous extracts from aerial parts were documented with antiviral activity against Murine norovirus-1 (MNV-1) and Feline calci virus (FCV). Methanol extracts of *Artemisia persica* Boiss. were reported as active antiviral candidates against HHV (HSV-1). Ethanol extracts of *Artemisia scoparia* Waldst. & K. Kit. were documented with potential anti-influenza virus (IV) activities. *Artemisia verlotiorum* Lamotte. aqueous leaves extracts were reported with anti-feline calci virus (FIV) activities. Methanol extracts from aerial parts of *A. vulgaris* were documented with antiviral activity against HHV (HSV-1) (Table 1). Based on the collected data of this study, *Artemisia* species were documented with antiviral activity for 17 different types of viral diseases where most species were described in more than one category of viral diseases (Table 2).

A phylogeny based on ITS sequences was used to determine the phylogenetic relationships and subgeneric placements of *Artemisia* species with reported anti-viral activity. Only 17 out of 23 reported *Artemisia* species with antiviral activity were included in the ITS phylogeny and 6 *Artemisia* species ( *A. aysinyscina*, *A. canepstriis* subsp. *glutinoso*, *A. carefulioca*, *A. kermanensis*, *A. morrisonensis*, *A. glabella*) with antiviral activity were not included, due to the unavailability of their ITS sequences from GenBank. The multiple sequence alignment (MSA) for ITS phylogeny comprised of 17 sequences of antiviral *Artemisia* species of this study, 127 reference sequences of other *Artemisia* species, and 3 outgroup species sequences from the GenBank (*n* = 147). The resulting consensus phylogram following 50 % majority rule MrB tree attained from the ITS dataset ( *MSA = 147*) is given in Fig. 1, where the monophyly of the genus is strongly supported (ML BS = 99 %). Overall, the subgeneric classification based on molecular data was resolved with the exception of some lineages. The ML tree based on ITS sequences attained largely corresponds to current understanding of the evolutionary relationships as given in the most recent phylogenetic studies, with some exceptions; for example, the placement of some *Artemisia* species are indicated in the ITS phylogeny of this study which were not previously addressed in the phylogenetic studies of the genus *Artemisia*. Outcomes of the ITS phylogeny displayed the dispersion of 17 antiviral *Artemisia* species in clades belonging to different subgenera of the genus *Artemisia*. In the resulting ML tree, 10 antiviral *Artemisia* species appeared within the clades corresponding to the subgenus *Artemisia*. Two species appeared within the subgenus *Absinthium* clade. Three species were appeared within the subgenus *Dracunculus* clade. Two species appeared within the subgenus *Seriphidium* clade.

### 4. Discussion

Details in Table 1 provide baseline data on *Artemisia* species used against viral diseases universally. This record could be a vital starting point for evaluating the effectiveness of these *Artemisia* species to treat viral diseases, specifically SARS-CoV-2, which causes Covid-19 disease, and the expansion of operative drugs to treat such pandemic diseases. In order to discover novel anti-SARS-CoV-2 therapeutic representatives, screening of these antiviral *Artemisia* species is imperative because of their widespread utilization around the world in treatment of fatal viral infections. On the basis of data collected in this study, *Artemisia* species were recognized with potential antiviral activity for 17 different types of viral diseases where most species were described against more than one virus, as shown in Table 2.

Many inquiries have acknowledged the inhibitory actions of medicinal plants extracts worldwide on the replication of numerous viruses. Predominantly, HHV (HSV-2) (Debiaggi et al., 1998), HIV-I and HIV-II (Asres and Bucar, 2005), Hepatitis B virus (HBV) (Kwon et al., 2005; Huang et al., 2006), and developing viral contagions linked with Poxvirus (PV) and SARS virus (Kotwal et al., 2005), were powerfully impeded by many plant extracts. Numerous investigations have reported the inhibitory effects of extracts from *Artemisia* species on several types of viruses (Chang and Woo, 2003; Li et al., 2005; Romero et al., 2006; Effert et al., 2008; Karamoddini et al., 2011; Lubbe et al., 2012; Tao et al., 2020; Nie et al., 2021 and references therein). This effect could be due to the presence of terpenoids and flavonoids, which are group of active antiviral compounds present in the *Artemisia* species extracts. A promising terpenoid compound, artemisinin (Tu et al., 1981; Tu, 2016, 2017), is among those antiviral agents obtained from *Artemisia* species widely used for the treatment and management of malaria (Daddy et al., 2017; Pellicer et al., 2018; Zeb et al., 2018 and references therein) and some deadly viruses (Romero et al., 2005, 2006; Paeshuyse et al., 2006; Effert et al., 2008; Lubbe et al., 2012; Cao et al., 2020 and references therein). Artemisinin is a sesquiterpenoid lactone present in the extracts of different *Artemisia* species, including A. annua (Covello, 2008; Ikram and Simonsen, 2017; Pellicer et al., 2018; Nganthoi and Sanatombi, 2019) A. apiacea, A. macrocephala and A. thuscula (Pellicer et al., 2018), with 1, 2, 3-trioxane structure and an endo-peroxide bridge (Mannan et al., 2010). A number of *in vitro* studies exhibited that lower concentrations of artemisinin has antiviral properties on IV-A (Krishna et al., 2008), HBV and HCV (Romero et al., 2005; Paeshuyse et al., 2006), bovine viral diarrhea virus (Romero et al., 2006) different human herpes viruses, including Human gammaherpesvirus type 4 (Epstein-Barr virus) (HHV-4) and Human betaherpesvirus type 5 (human cytomegalovirus) (HHV-5) (Effert et al., 2008); Cao et al. (2020) emphasized the anti-SARS-CoV-2 potential of artemisinin and provided leading candidates for anti-SARS-CoV-2 drug research and development. Artesunate is another promising compound obtained from *Artemisia* species with demonstrating efficacy in decreasing HHV-5 (HCMV) in an immunosuppressed child with no toxic effects (Shaipira et al., 2008).

Together with terpenoids like artemisinin and artemesunate in natural plant materials, flavonoids are also of increasing interest because of

| S/No | Viral disease category | No of *Artemisia* species |
|------|------------------------|--------------------------|
| 1    | Bovine viral diarrhea virus (BVDV) | 01 |
| 2    | Dengue virus type 2 (DEN2) | 02 |
| 3    | Feline calci virus (FCV) | 01 |
| 4    | Feline immunodeficiency virus (FIV) | 01 |
| 5    | Hepatitis B virus (HBV) | 03 |
| 6    | Hepatitis C virus (HCV) | 01 |
| 7    | Human immune virus (HIV) | 07 |
| 8    | Human alphaherpesvirus (Herpes simplex virus) or HBV (HSV) | 16 |
| 9    | Human gammaherpesvirus type 4 (Epstein-Barr virus) or HHV-4 (EBV) | 01 |
| 10   | Influenza virus (IV) | 04 |
| 11   | Junin virus (JUNV) | 02 |
| 12   | Murine noro virus-1 (MNV 1) | 01 |
| 13   | Newcastle disease virus (NDV) | 01 |
| 14   | Severe acute respiratory syndrome corona virus 2 (SARS-CoV 2) | 03 |
| 15   | Sindbis virus (SV) | 02 |
| 16   | Polio virus (PV) | 02 |
| 17   | Yellow fever virus (YFV) | 01 |
their extended biological benefits. Flavonoids are classified into various types according to their structure and possess different activities depending on this. Flavonoids are natural compounds linked by three carbon chains, usually C6-C3-C6, and consist of an oxygenated heterocyclic ring (Xiao, 2017). Among the different plant sources containing flavonoids, the genus *Artemisia* is very diverse and widely distributed (Hussain et al., 2022). In a study, the total number of phenols and flavonoids identified was 32 in *A. annua*, 37 in *Artemisia iwayomogi* Kitam., and 14 in *Artemisia argyi* H.Lév. & Vaniot., out of which flavonoids accounted for 16 in *A. annua*, 27 in *A. iwayomogi* and 7 in *A. argyi* (Kim et al., 2020). Similarly in this study, polymethoxyflavonols were found to be prevalent in *Artemisia* species, as shown in Table 1. It has been shown that more than 10 types of flavonoids, like apigenin, catechin, genkwanin, quercetin, kaempferol, malvidin, rhamnetin, diosmetin, luteolin and dimethoxyflavone, from *Artemisia* species possess potential antiviral activity (Kim et al., 2020). These findings clearly indicate that terpenoids and flavonoids are a group of compounds found in different *Artemisia* species with potential antiviral activity. This study further validated the subgeneric grouping of *Artemisia* and its species with antiviral activity in the mL ITS phylogeny of the genus (Fig. 1). Current research possibilities anticipate that plant species selection for analysis could be ensured through phylogenetic analysis particularly, by plotting bioactivity and photochemistry data (Larsen et al., 2010; Zhu et al., 2011) with ethnobotanical uses (Forest et al., 2007; Saslis-Lagoudakis, 2008).
et al., 2012; Grace et al., 2015; Ernst et al., 2016 and references therein) on the phylogenetic trees. According to Saslis-Lagoudakis et al. (2012), phylogenies could be very useful in tracking medicinal folk data for the documentation of lineages with favorable medicinal attributes. Additionally, lineages with greater traditional uses are equivalent with the ones overrepresented in species with pharmacological action. The monophyly of the genus Artemisia in the present ITS phylogeny is strongly supported (mL BS = 99 %). The subgeneric classification based on ITS phylogeny was resolved. Some exceptions in lineages were observed, which were already reported in earlier studies (Torrell et al., 1999; Vallies et al., 2003; Sanz et al., 2008; Garcia et al., 2011; Pellicer et al., 2010; Riggins and Seigler, 2012; Hobbs and Baldwin, 2013; Malik et al., 2017; Pellicer et al., 2018 and references therein). Similarly, the position of some Artemisia species like Artemisia leucodes Schrenk., Artemisia alantica Coss. & Durieu., Artemisia batakensis Hayata., Artemisia lavandulifolia DC., Artemisia constricta Son.Garcia, Garnatje, McArthur, Pellicer, S.C.S., Artemisia spinescens D.C. Eaton., A. iwayomogi, Artemisia fahalautii Emb. & Maire., and Artemisia eremophila Kusch. & Butkov ex Poljakov. M., was not clearly addressed in previous studies concerning evolutionary relationships of the genus Artemisia, resulting from the analysis of DNA sequences. This study found that A. leucodes, A. atlantica, A. batakensis, A. lavandulifolia and A. constricta appeared within the clades corresponding to the species of the subgenus Artemisia. Similarly, A. spinescens appeared within the clades corresponding to the species of the subgenus Tridensatae. Two species, A. iwayomogi and A. fahalautii appeared within the subgenus Dracunculus clade. Moreover, A. eremophila was appeared within the subgenus Seriphidium clade. Furthermore, broad morphological, anatomical, karyological and phytochemical investigations coupled with molecular data on these species are required to confirm their phylogenetic relationships and to systematically identify candidate taxa from the genus for additional probing particularly for Artemisia due to complicated evolutionary relationships among its species (Pellicer et al., 2018).

Despite having possible antiviral applications and the presence of artemisinin, no drug from Artemisia species is currently in clinical trials against SARS-CoV-2 (COVID-19) disease. The antiviral information on Artemisia taxa presented herein is therefore essential for advancing the drug development of novel treatments against SARS-CoV-2 disease.

5. Conclusions

This study delivers baseline information on Artemisia against viral diseases and proposes some candidate taxa for the possible treatment of SARS-CoV-2. A leading conclusion of this inquiry is that Artemisia species from different subgenera with antiviral activities are extensively distributed in the genus. Specifically, the subgenus Artemisia had the greatest number of species with antiviral activities. Numerous vital flavonoids, such as polymethoxylflavonoids and terpenes, like artemisinin and artemesin, have been detected in different Artemisia with potential antiviral activity. A detailed analysis of these antiviral taxa with a focus on taxa from all subgenera, particularly the subgenus Artemisia, is therefore proposed to discover more antiviral species and compounds with potential anti SARS-CoV-2 activity.

CRediT authorship contribution statement

A.H. conceived of the presented idea, designed and performed the data compilation, derived the analysis and analysed the data and wrote the manuscript.

Declaration of Competing Interest

The author declare that there is no conflict of interest.

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Appendix A. Supporting information

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