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Andrographis paniculata Usage in the Treatment of Viral Diseases

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ABSTRACT

Andrographis paniculata (*A. paniculata*) is a herbaceous plant used as a remedy for many diseases in traditional medicine. Numerous beneficial effects of *A. paniculata* have been demonstrated in multiple *in vitro* and *in vivo* studies, this study systematically reviews the relevant literature and provide a summary on the antiviral properties of *A. paniculata* in relieving viral diseases. This systematic review used the databases, Science Direct and PubMed for studies published from 1st of January, 1990 to 1st of May, 2021. To obtain further data, a manual search was also carried out on the bibliography of the referred articles. The following number of articles were identified in the literature search, Science direct = 167 and PubMed = 33. A total of 20 articles are included in this review. *Andrographis paniculata* has beneficial health effects in viral diseases such as Dengue, Chikungunya, Upper Respiratory Tract Infections (URTI), Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV). The wide range of medicinal effects observed from this plant is putatively from the phytochemicals andrographolide, neoandrographolide and andrographiside. The available evidence suggested that *A. paniculata* is a potential candidate to ameliorate multiple viral diseases, however randomized controlled clinical trials are needed to validate this hypothesis.

KEYWORDS

Andrographis paniculata, viral diseases andrographolide, clinical trials, phytochemicals

INTRODUCTION

Andrographis paniculata, a relatively common herbaceous plant[1] is present in the ethnopharmacopeia of many tropical nations. It is used to treat a variety of disorders as traditional medicine. *Andrographis paniculata* contains several secondary metabolites showing robust bioactivity in multiple disease models[2]. The examined data from peer-reviewed studies focusing on the antiviral properties of andrographolide, a potent phytochemical of *A. paniculata* and its application in the treatment of viral diseases. Present data on its use in treating viral diseases and summarize the finding, focusing on the mechanisms of action. The data is reviewed to establish whether *A. paniculata* is done ameliorate multiple viral diseases and to establish a rationale for randomized controlled clinical trials towards establishing its efficacy.

Andrographis paniculata is an annual, 30-90 cm tall, erect herb, belonging to the Acanthaceae family, distributed throughout tropical Asian countries. It can be found in a variety of habitats such as plains, coastlines, hillsides and cultivated areas such as roadsides and farms[1]. It is traditionally used as a medicinal

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plant by different cultures around the world. The leaves are linear-lanceolate in shape with simple-opposite leaf arrangement while the stem is quadrilateral in shape (). All the parts of this plant such as leaves, seeds, fruits and flowers are used for medicinal purposes. The active phytochemicals in *A. paniculata* are andrographolide, neoandrographolide andrographiside, 14-deoxy-11,12-didehydroandrographolide, deoxyandrographolide and arabinoglycan proteins. Among them andrographolide, a diterpene lactone compound, is the principal active agent of this plant[2].

Many synonyms have been used in different languages to identify this plant including "*Kaalmegha*", "*Mahathikthaka*", "*Heen bin kohomba*", "*Shankhini*", "*Neelavembu*", "*Kirata*", "*King of bitters*", etc[3]. In traditional medicine *A. paniculata* is considered a remedy for many digestive problems and skin diseases. Its medical actions are digestive, purgative, antipyretic and anthelmintic. It aids in the treatment of fever, worm infestations, skin diseases, liver diseases and digestive disorders[4]. Numerous beneficial health effects of *A. paniculata* have been identified in the ethnopharmacopea from different parts of the world as an antipyretic[5,6], anti-microbial, anti-inflammatory, anti-diabetic and in reducing the risk of cancer. This study aims to systematically review the scientific literature and to summarise the potential medicinal benefits of *A. paniculata* focusing on the treatment of viral diseases.

Methodology for data collection: A systematic review was carried out by using the published studies reporting on the anti-viral properties of *A. paniculata*, in viral diseases. A comprehensive systematic review was conducted by using the databases, PubMed and Science Direct for studies published from 1st of January, 1990 to 1st of May, 2021. The keywords used in this subject were *Andrographis paniculata*, medicinal properties, antiviral and viral diseases. Results were obtained only from the studies published in English while excluding commentaries and duplicate articles. The appropriate articles were selected and initially searched by reading the title and their abstracts. In this step articles that did not fulfil the requirements of inclusion criteria, were excluded. Thereafter, the remaining articles were screened by reading the complete text and synthesizing the data. Those articles which did not satisfactorily meet the inclusion criteria were excluded again. Additionally, relevant texts and internet sources were used for gathering the necessary information on *A. paniculata*. This research process was conducted independently and the articles which were to be included in the review was determined by an iterative consensus process at the final stage.

By using the above-mentioned criteria, the literature search identified these number of articles in the databases, respectively, Science Directs (n = 167), PubMed (n = 33). Two additional articles were selected manually by searching the bibliography of the selected articles for the inclusion criteria. After removing duplicate articles, the total number of articles included in the present review was 20 in Fig. 1.

Medicinal properties of *Andrographis paniculata* in viral diseases

Dengue fever: The previous study demonstrated that isolated andrographolide from A. *paniculata* possesses anti-dengue activity against the dengue-2 virus, by using *in vitro* and *in silico* methods. Their results suggested the inhibition of dengue viral replication resulting in a reduction in dengue viral infection[7]. The inhibition of Dengue Virus (DENV) infection of liver cells by andrographolide was tested using a proteomic based approach, with andrographolide demonstrated to possess antiviral activity[8]. Another study, tested the anti-dengue viral activity of bothethanolic and aqueous extract of *A. paniculata*, using the 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) method and SYBR green quantitative real-time Polymerase Chain Reaction (PCR) method and revealed that *A. paniculata* has anti-dengue viral effects and proposed the use of *A. paniculata* as a natural plant product to fight against Dengue fever[9].

The anti-viral potential of andrographolide, derived from *A. paniculata,* against the Dengue virus, was evaluated, showing it may be used in the post-infection stage of the disease[10]. Here, the antiviral activity of andrographolide against Dengue Virus (DENV) serotype 2 was evaluated in two cell lines (HepG2 and HeLa) while the activity against DENV 4 was evaluated in one cell line (HepG2).

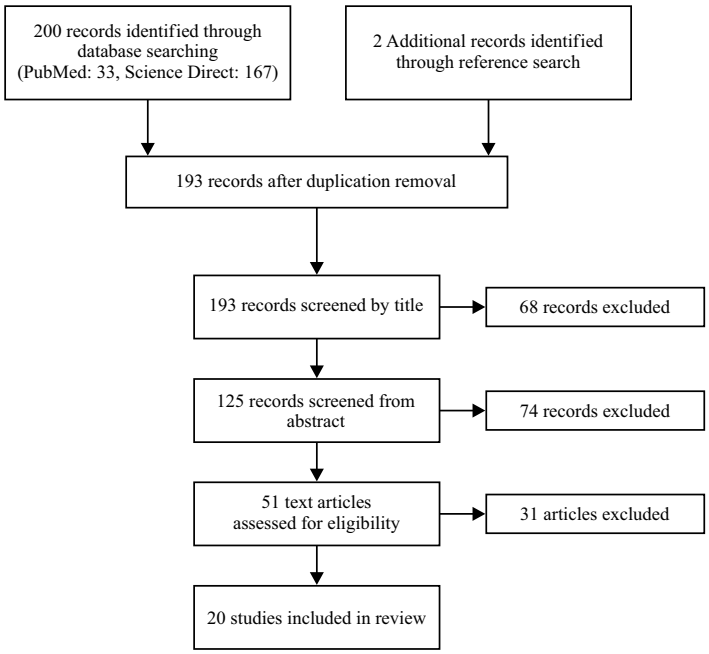

Fig. 1: Summarized search strategy of the review

The anti-dengue activity of andrographolide investigating the toxic effect of the compound andrographolide from *A. paniculata* leaf extract, against the dengue vector *Aedes aegypti*[11]. The ability to inhibit the activity of Dengue Virus Serotype 1 (DENV-1) in *in vitro* assays of the methanol extracts of *A. paniculata* was demonstrated and suggested that it may be used as an alternative treatment or dengue[12].

Common cold and influenza: The anti-influenza activity of andrographolide, a secondary metabolite of *A. paniculata* was shown as a therapy for influenza A virus infection, using mice[13]. Significant antiviral activity against the Highly Pathogenic Avian Influenza (H5N1) virus was shown by using both water and ethanol extracts of *A. paniculate*[14]. The study revealed that the anti-inflammatory activities of didehydroandrographolide (DAP) another secondary metabolite of *A. paniculata* can be used as a curative agent against influenza A viruses (IAV)[15,16].

The antiviral activity of *A. paniculata* ethanol extract was shown to reduce the viral load in A549 cells infected with Simian Retro Virus (SRV) using RT-PCR analysis[17]. The results revealed that *A. paniculata* ethanol extract reduced the SRV virus titer due to its anti-viral activity. The antiviral activity of *A. paniculata* was demonstrated with andrographolide inhibit neuraminidase activity of H1N1 (swine flu) positive patients[18].

A randomized, double-blind placebo-controlled clinical study was conducted to evaluate the efficacy of Kalm Cold, (an extract of *A. paniculata*), in patients with Upper Respiratory Tract Infection (URTI) and the study suggested that it was effective in reducing the symptoms of URTI[19]. Among plants tested for conditions associated with viral infection and inflammation, *A. paniculata* showed the highest inhibition of RANTES secretion by influenza A virus (H1N1) infected human bronchial epithelial cells (A5 49)[20].

Sharma *et al.*[21] conducted a randomized double-blind placebo study to evaluate the effectiveness of *A. paniculata* SHA-10 extract in reducing symptoms and signs of common cold, demonstrating high effectiveness in reducing symptoms of influenza infection with no adverse effects.

The results showed that, in 2010, a randomized, double-blind placebo-controlled clinical study was conducted by ChiehKo *et al.*[19], to evaluate the efficacy of an extract of *A. paniculata* and in the year 1999 also, a randomized double-blind placebo study has been conducted by Caceres *et al.*[21], to evaluate the effectiveness of *A. paniculata* SHA-10 extract in reducing symptoms and signs of the common cold.

Chikungunya virus infection: Silver nanoparticles (AgNPs) biologically synthesized from *A. paniculata*, *Phyllanthus niruri* and *Tinospora cordifolia* and evaluated their antiviral properties against Chikungunya virus. The effectiveness of AgNPs of plants as antiviral was demonstrated and proposed as an alternative treatment against viral diseases[22]. A study was carried out by Shi *et al.*[23], to determine the potential of andrographolide as a treatment for Chikungunya viral (CHIKV) infection and demonstrated that andrographolide inhibited CHIKV replication and could therefore be an effective therapeutic agent against CHIKV.

SARS-CoV infection: The suppression of the main protease (M^{pro}) activities of 2019-nCoV and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), by both andrographolide and its fluorescent derivative, the nitrobenzoxadiazole-conjugated andrographolide (Andro-NBD), was demonstrated. Their results suggested that further extensive investigation of andrographolide on the suppression of 2019-nCoV is warranted[24].

The immune-protection and anti-viral response of *A. paniculata* against COVID-19 infection were analyzed by using Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) metabolomics and combination synergy analysis based on network pharmacology. They concluded that, a synergy between andrographolide and other identified molecules, as safe and efficacious anti-inflammatory agents, of benefit to upper respiratory tract infections[22].

HIV infection: A study was conducted by testing a series of synthesized andrographolide derivatives, evaluating them for anti-HIV activity in a virus infectivity assay using TZM-bl cells. The results showed andrographolide derivatives are promising candidates for the prevention of HIV infection[25].

Zika virus infection: Andrographolide derivatives with quinoline moiety, against Zika virus infection studied, where the andrographolide derivatives were shown to be protective against Zika infection. The potential for developing andrographolide derivatives with quinoline and related moieties against Zika and other arboviruses was shown[26]. The results from the above studies are summarized in Table 1.

The available studies suggest that *A. paniculata* prevents cell infection and viral replications in the Zika virus HIV (Human Immunodeficiency Virus), Novel Coronavirus (2019-nCoV), Chikungunya virus, Influenza A virus (H1N1), Swine flu (H1N1) virus, Simian Retro Virus (SRV), A(H1N1) influenza virus, Avian influenza virus (H5N1), Influenza A Virus and Dengue virus in Fig. 2. The different parts of *A. paniculata* possess varying amounts of active secondary metabolites and this diversity of chemical constituents may underlie the wide range of medicinal effects as shown in traditional medicine, as rationalize for a spectrum of phytochemicals[27-29]. Further elucidation of the mechanisms underlying these medicinal effects awaits further investigation. "andrographolide", a bioactive phytochemical in *A. paniculata* has potent antiviral properties. However, the paucity of data from controlled clinical trials on the efficacy of *A. paniculata* as an effective treatment for human viral diseases, particularly as polyherbal preparations as used in traditional treatments, awaits further study.

Table 1: Medicinal properties of *A. paniculata* in viral diseases

Disease	Used material/compound	Viral category	Identified mechanisms/role	References
Dengue	Andrographolide	Dengue virus	Isolated the andrographolide from the *A. paniculata* by supercritical fluid extraction technique and characterized the isolated compound along with with-it anti-dengue activity against DENV-2 *in vitro* and silico methods. Isolated compounds were capable of inhibiting dengue replication	Weerakoon *et al.*[5]
	Andrographolide	Dengue virus	A total of 17 (1D) and 18 (2D) proteins were identified as differentially regulated. The analyses identified proteins involved in chaperone activities, as well as energy production	Weerakoon *et al.*[6]
	Both ethanolic and aqueous extracts of *A. paniculata*	Dengue virus	*In vitro* antiviral activity was performed against the dengue virus by the 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method and SYBR green quantitative real-time polymerase chain reaction (PCR) method. Cytotoxicity was evaluated by MTT	Kaushik *et al.*[7]
	Andrographolide	Dengue virus	The antiviral activity of andrographolide against dengue virus (DENV) serotype 2 was evaluated in two cell lines (HepG2 and HeLa) while the activity against DENV 4 was evaluated in one cell line (HepG2)	Paemanee *et al.*[8]
	Leaf extract compound andrographolide	Dengue virus	The toxic effect of the leaf extract compound andrographolide from *A. paniculata* against the dengue vector	Ramalingam *et al.*[9]
	Standardized methanolic extracts of *A. paniculata*, *Citrus limon*, *Cymbopogon citratus*, *Momordica charantia*, *Ocimum sanctum* and *Pelargonium citrosum*	Dengue virus	The maximum non-toxic dose (MNTD) of the six medicinal plants was determined by testing the methanolic extracts against Vero E6 cells *in vitro*	Panraksa *et al.*[10]
Common cold and Influenza	Andrographolide	Influenza A virus	NF-κB and JAK-STAT signalling pathways were attenuated by andrographolide	Edwin *et al.*[11]
	Crude extracts of *A. paniculata*, *Curcuma longa*, *Gynostemmapentaphyllum*, *Kaempferia parviflora* and *Psidium guajava* were obtained by both water and ethanol extractions	Avian influenza virus (H5N1)	Both water and ethanol extracts of all the five plants showed significant antiviral activity against the H5N1 virus	Tang *et al.*[12]
	14-Deoxy-11,12-didehydroandrographolide (DAP), a major component of *A. paniculata*	A(H1N1) influenza virus	14-Deoxy-11,12-didehydroandrographolide (DAP), with the non-toxic concentration of 1000 mg/kg/day, effectively reduced the mortality and weight loss of mice lethally challenged with A/chicken/Hubei/327/2004 (H5N1) or A/PR/8/34 (H1N1) influenza A viruses (IAV) when initiated at 4 hrs before infection	Ding *et al.*[13]
	Ethanol extract of *A. paniculata*	Simian Retro Virus (SRV)	The antiviral activity of the extract was determined by observing its ability on inhibiting virus load in A549 cells transfected with Simian Retro Virus (SRV) by RT-PCR analysis	Sornpet *et al.*[14]

Table 1: Continue

Disease	Used material/compound	Viral category	Identified mechanisms/role	References
	Andrographolide	Swine flu (H1N1) virus	The potential of andrographolide to inhibit neuraminidase activity of H1N1	Cai *et al.*[15]
	An extract of *A. paniculata*	Common cold viruses	Quantification of symptom scores by Visual Analogue Scale. Nine self-evaluated symptoms of cough, expectoration, nasal discharge, headache, fever, sore throat, earache, malaise/fatigue and sleep disturbance were scored	Churiyah *et al.*[16]
	Nine ethanol extracts of medicinal plants were screened for their effect on RANTES secretion	Influenza A virus (H1N1) epithelial cells	Plants tested at the concentration of 200 µg mL^{-1} possessed more than 50% suppressing effect on RANTES secretion by H1N1-infected A549 bronchial	Seniya *et al.*[17]
	Dried extract of *A. paniculata*	Rhino virus	The effectiveness of *A. paniculata* SHA-10 extract in reducing the prevalence and intensity of symptoms and signs of the common cold as compared with a placebo	Saxena *et al.*[18]
Chikungunya	Biologically synthesized AgNPs from *A. paniculata, Phyllanthus niruri* and *Tinospora cordifolia*	Chikungunya virus	Biological synthesis of AgNPs from *A. paniculata*, *Phyllanthus niruri* and *Tinospora cordifolia* and evaluated their antiviral properties against chikungunya virus	Ko *et al.*[19]
	Andrographolide	Chikungunya virus	Andrographolide showed good inhibition of CHIKV infection and reduced virus production by approximately 3log10 with a 50% effective concentration (EC50) of 77 µM without cytotoxicity. Time-of-addition and RNA transfection studies showed that andrographolide affected CHIKV replication and it was shown to be cell-type independent	Cáceres *et al.*[20]
SARS-CoV infection	Andrographolide and its fluorescent derivative, the nitrobenzoxadiazole-conjugated andrographolide (Andro- NBD)	Novel coronavirus (2019-nCoV)	Both andrographolide and its fluorescent derivative, the nitrobenzoxadiazole-conjugated andrographolide (Andro- NBD), suppressed the main protease (M^{pro}) activities of 2019-nCoV and severe acute respiratory syndrome coronavirus	Sharma *et al.*[21]
	Andrographolide	Novel coronavirus (2019-nCoV)	The molecules from *kalmegh* provide immune-protection and anti-viral response via involving different pathways, like toll-like receptor pathway, PI3/AKT pathway and MAP kinase pathways against COVID-19 infection	Wintachai *et al.*[22]
HIV infection	A series of andrographolide derivatives	HIV (Human Immunodeficiency Virus)	Andrographolide and derivatives inhibited gp120-mediated cell fusion. The computer-aided modelling revealed binding of these molecules to important residues of the V3 loop region of GP120 protein	Shi *et al.*[23]
Zika virus infection	Twenty-four analogues of 14-aryloxy andrographolide	Zika virus	The rational and optimal combined modification/s at 3-, 14- or 19-positions can make derivatives less toxic and more potent against Zika infection and both of 3 and 17bare suitable as leads for designing the new generation of andrographolide derivatives with quinoline or its structure- and property-related moieties against Zika virus and other arboviruses	Banerjee *et al.*[24]

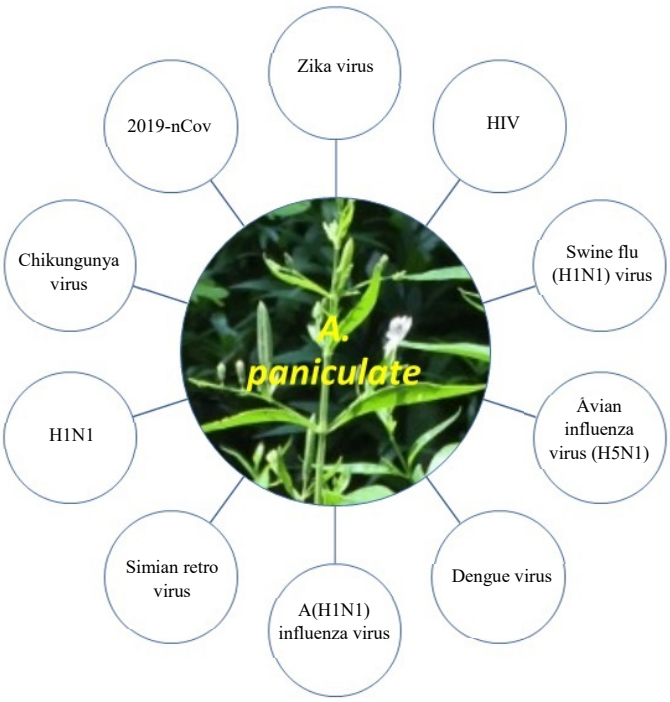

Fig. 2: *Andrographis paniculata* showed antiviral effects on multiple viruses

CONCLUSION

The data from available studies suggested that *A. paniculata* has beneficial medicinal properties in amelioration of currently prevalent viral diseases. Therefore, this medicinal plant which features in the ethnopharmacopeia of multiple cultures is a strong candidate for use in antiviral therapies, rationalizing further clinical trials towards establishing its clinical efficacy.

SIGNIFICANCE STATEMENT

This study reveals that *A. paniculate*, a plant used in traditional medicinal treatment, shows efficacy in the treatment of several viral diseases. Further validation of *A. paniculate*-based treatments in controlled clinical trials on viral diseases is rationalized by this review.

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