

A Review On Identification of Antiviral Potential Medicinal Plant Compounds Against with COVID-19

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Abstract: Coronavirus is not new for the china and worldwide. Coronavirus has been identifies from last decade. The coronaviruses causative disease is acute respiratory syndrome and also called as coronavirus (SARC-CoV) in the year of 2002 and 2003. But now it is called as COVID-19 named by World Health Organization (WHO) on January-2020. The genus coronavirus with its high mutation rate in the infected patients. The major drawback of this coronavirus is can be transmitted through an air. The objective of review article is medicinal plants have been widely used to treat a variety of infectious and non-infectious viral disease. According to standards of herbal medicine 25% of medicinal plants commonly used medicines contains compounds of isolated from plants. The scenario of new drugs development, several plants could offer a rich reserve for drug discovery of infectious diseases. The varieties of medicinal plants have been shown promises to treat different types of viral infections. This article discussed about potential of medicinal plants against towards group of viruses and coronaviruses, and also suggests the screening of plants processing towards antiviral effects against emerging viral infections.

Keywords: Coronavirus, COVID-19, Antiviral plant.

1. Introduction

The world history of medicinal plants has been research to the origin of human civilization on earth. Several of these medicinal plants may have been used to treat viral infections in the past, therefore, first recognized interest in them has been development as antiviral agent is the efforts of the Boots drug company (England) to screen 288 plants for anti-influenza activity [1].

Than several studies have reported the inhibitory effects of medicinal plants extracts on the replication of several viruses. Specially herpes simplex virus type 2 (HSV-2) [2], Human immune virus (HIV) [3, 4], hepatitis B virus (HBV) [5, 6] and emerging viral infections associated with poxvirus and severe acute respiratory syndrome (SARS) virus [7] were strongly inhibited using by various plants extracts. Most of these plant extracts studies have utilized either alcoholic extracts or water extract of medicinal plants, and limited efforts have been directed toward the identification of active natural ingredient

exhibiting antiviral effects. Moreover, recent studies showing antiviral potential of plant extracts against viral strains resistant to conventional antiviral agents (8,9) have challenged the modern drug discovery practices, and deem a very careful look toward exploring natural antiviral components of medicinal plants.

Coronaviruses are enveloped positive sense RNA viruses ranging from 60 nm to 140 nm in diameter with spike like projections on its surface giving it a crown like appearance under the electron microscope; hence the name coronavirus. Four corona viruses namely HKU1, NL63, 229E and OC43 have been in circulation in humans, and generally cause mild respiratory disease. There have been two events in the past two decades wherein crossover of animal beta corona viruses to humans has resulted in severe disease. The first such instance was in 2002–2003 when a new coronavirus of the β genera and with origin in bats crossed over to humans via the intermediary host of palm civet cats in the Guangdong province of China. This virus, designated as severe acute respiratory syndrome coronavirus affected 8422 people mostly in China and Hong Kong and caused 916 deaths (mortality rate 11%) before being contained. Almost a decade later in 2012, the Middle East respiratory syndrome coronavirus (MERS-CoV), also of bat origin, emerged in Saudi Arabia with dromedary camels as the intermediate host and affected 2494 people and caused 858 deaths (fatality rate 34%).

2. Literature review

Severe Acute Respiratory Syndrome (SARS) is a respiratory illness caused by the Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) [10]-[13]. This febrile respiratory illness was initially described in early 2003 [14]-[18] and is life threatening and highly contagious. Currently, worldwide there are no approved or universally recommended therapies for SARS. Treatment for the disease is mainly supportive. Scientists worldwide have been vigorously trying to develop efficacious antiviral agents for the treatment of SARS in the event that SARS comes back in the future. From the several

research, groups have suggested that some reagents, such as interferon and glycyrrhizin, pose anti-SARS-CoV activity [19]-[21].

In China, traditional herbal medicine has been frequently used in conjunction with conventional medicine to treat SARS. There is evidence showing that the herbal medicine is effective [22]-[25]. However, the mechanisms of this treatment have not been clearly understood. From this paper has been shown that natural plants contain antiviral activities to other coronaviruses [26], and the mechanism of action of these herbal products is mainly through inhibition of viral replication [27]. In this study, selected over, 200 in-house-made extracts of medicinal herbs that have been historically used for the treatment of virus-induced infectious diseases in China and tested their antiviral activities against SARS-CoV using a high throughput screening approach. The screening was based on a MTS assay [28]. The active samples from screening were then subjected to structure activity relationship (SAR) study to identify a single active chemical substance. The results of these studies and the potential usage of identified lead compounds in the treatment of SARS-CoV-induced infectious diseases are presented here. In searching for new reagents for anti-SARS-CoV, collected herbs were extracted by refluxing with 95% ethanol or chloroform for 3 h. The extracted solvents were filtered and lyophilized and then re-dissolved in dimethyl sulphoxide (DMSO) and stored in 96-well sample plates at -80 °C for assays and screening. Two strains of SARS-CoV (BJ001, BJ006) used for antiviral compound screening were obtained from the Laboratory of Virology at the Academy of Military Medical Sciences in

Beijing, China.

The viruses were propagated in Vero E6 cells at 37 °C in a humidified atmosphere of 5% CO₂. Vero E6 and HepG2 cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) (Invitrogen) containing 5% heat-inactivated fetal bovine serum (FBS) (Hyclone) and sodium bicarbonate, 3.7 g/l; glucose, 4.5 g/l; and 15mM HEPES buffer. The virus-induced cytopathic effect (CPE) was determined by MTS method and by visualization of cellular morphology change. The number of viable cells is correlated with absorbance at 490 nm in MTS assay. Approximately, 4×10³ Vero E6 cells/well were seeded onto Corning 96-well tissue culture plates (Corning Incorporated) with final volume of 100_1 and cultured for 24 h. Ten micro liters of compounds or plant extracts at a concentration of 100 _g/ml were added into each well in duplicates before inoculating with virus stock. Interferon alpha (Hualida Biotech Company), developed proven to show antiviral activities against SARS-CoV [29], was used as the positive control. The viral titers were assessed by cytopathic effect (CPE) determined visually under the light-phase microscope 2–4 days post-infection (PI). The concentration to achieve 90% of cell lysis was used in antiviral compound screening.

The infected cells with or without compound were incubated at 37 °C in a 5% CO₂ atmosphere for 72 h. Then, 20_1 of MTS/phenazine methosulfate (PMS) (Promega) was added in each well. The cells were incubated for another 2 h in 37 °C. In the end, 50_1 10% SDS was added to stop color reaction. The plates were measured at 490 nm using a VERSAMax

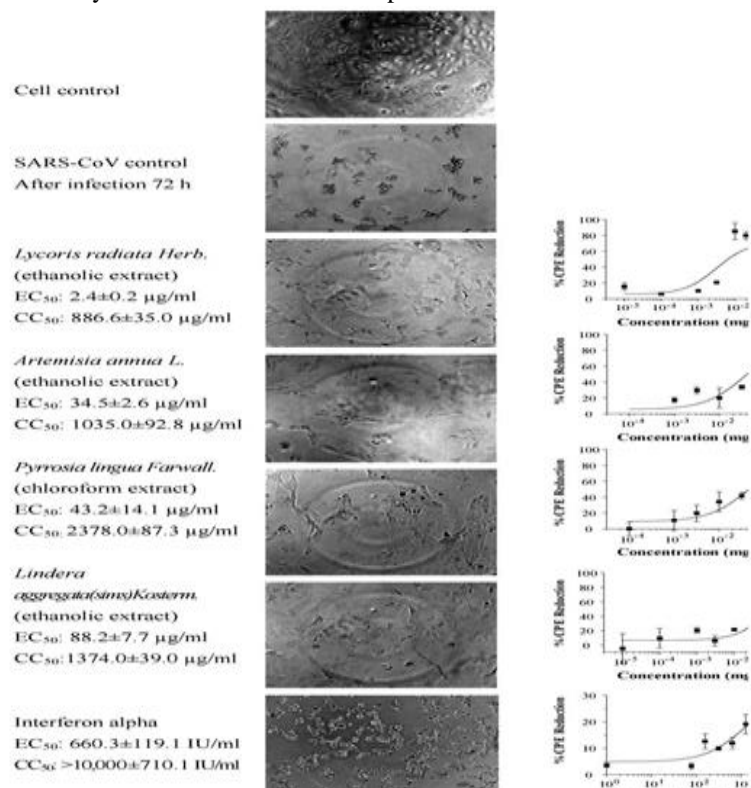


Fig. 1. Effects of herb compound extracts on replication of SARS-CoV

microplate reader (Molecular Devices). After primary screening, active compounds were cherry picked and a second round of test was performed for their antiviral effects. The pictures were taken to record cell morphology change caused by CPE and the inhibition effects of the compounds before MTS assay.

As shown in Fig. 1, four of the extracts, *Lycoris radiata*, *Artemisia annua*, *Pyrrhosia lingua*, and *Lindera aggregata* exhibited significant inhibition effects on virus-induced CPE when SARS-CoV strain BJ001 was used in screening. A dose dependency of antiviral activities was determined by serial dilutions of compounds. The percentage of CPE reduction was calculated by subtracting the mean value of virus-infected cell control (0%) from the measured absorbance, and resulting number was divided by the measured absorbance of uninfected cell control (100%). The mean values and the standard deviation (S.D.) were taken for result analysis. The inhibition effects of all four natural product samples showed dose-dependent patterns (Fig. 1).

The Vero E6 cell seeding, virus infection, compound addition, cell incubation, and measurement were described in the method. The percentage of CPE reduction was calculated by subtracting the mean of virus-infected cell control (0%) from the measured absorbance. The resulting number was divided by the uninfected cell control (100%). The mean values and the standard deviation (S.D.) are shown in the figures. Data presented are the average of duplicate values from three independent experiments. Magnification for visual observation: 200× (Cinatl, J et al., 2003).

microscope (photos not shown). The addition of active compounds significantly blocked viral infection or replication and kept cells in an able state. Interferon alpha also showed limited inhibition effects on virus-induced CPE, either judged by visual observation or MTS assay.

The inhibition for all four compounds to virus infection/replication was apparently more potent than that of interferon alpha judged by visual observation and color absorbance in MTS assay (Fig. 1). The cytotoxicity test for active compounds was based on the cell viability after cells were treated with various concentrations of compounds, and was determined by MTS method. Vero E6 and HepG2 cells in 96-well microplates incubated with serial 10-fold dilutions of testing compounds in DMEM containing 5% FBS. Cells were allowed to grow for an additional 72 h before the measurement. The CC50 values were determined as the concentration of the compounds that reducing the cell viability to 50% of control (cells without addition of compound). For the four active compounds, *L. radiata*, *A.annua*, *P. lingua*, and *L. aggregata*, the CC50 values range from 886.6±35.0 up to 2378.0±87.3 μ g/ml in assays using Vero cells (Table 1). The selective index (SI), which was determined as the ratio of CC50 versus EC50 for one of the potent active compound extracts, *L. radiata*, is more than 300. Three others also showed good SI values, with the exception of *L. aggregata*. In order to examine compound toxicity to different cell types, we tested all four extracts on both Vero E6 and human HepG2 cell lines. The CC50 values of *L. radiata*, *A. annua*, *P. lingua*, and *L. aggregata* were 690.5±21.0, 1022.9±55.1, 2127.3±178.9, and 1159.0±93.3 μ g/ml, respectively. The data obtained from these two cell lines were very similar (Table 1). The results suggested that there is no significant difference in compound toxicity against these two types of cell lines.

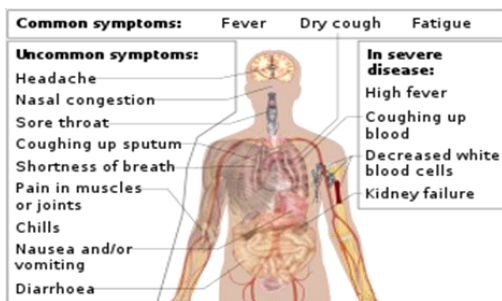


Fig. 2. Common symptoms and uncommon Coronavirus symptoms

EC50 values were determined as the concentration of the compounds needed to achieve the inhibition of SARS-CoV-induced CPE to 50% of control value (cells without viral infection) and data analysis for the assays was performed using Prism™ version 3 software (Graphpad Software, Inc.). The EC50 values of inhibition are 2.4±0.2, 34.5±2.6, 43.2±14.1, and 88.2±7.7 μ g/ml, respectively, much lower than previously identified compounds (29). To check whether there is any significant strain variation, we used SARS-CoV strain BJ-006 and tested the inhibition activity of active compounds. The results were quite similar for two viral strains (Table 1).

Viability of Vero cells measured by MTS assay was consistent with what we observed visually under the

Table 1
Effects of components isolated from *L. radiata* on SARS-CoV (BJ-001)

Sample	EC50 ^a	CC50 ^b	I ^c
Total alkaloid from <i>Lycoris radiata</i>	1.0 (±0.1)	93.9 (±7.4)	94
Commercial lycorine	48.8 (±3.6)	43210.0 (±2101.0)	885
Isolated lycorine from <i>Lycoris radiata</i>	15.7 (±1.2)	14980.0 (±912.0)	954

a) Determined as the concentration of the compounds needed to inhibit CPE to 50% of control value (cells without viral infection). Each value represents the mean±S.D. from three independent experiments. The unit for EC50 values shown in the table is μ g/ml for total alkaloid from *L. radiata*, and is nM for both forms of lycorine.

b) Determined as the concentration of the compounds that reducing the cell viability to 50% of controls (cells without addition of compound). Each value represents the mean±S.D. from three independent experiments. The unit for CC50 values shown in the table is μ g/ml for total alkaloid from *L. radiata*, and is nM for both forms of lycorine.

c) Selectivity index (CC50/EC50).

Table 2
Medicinal plants used in different anti-viral effects [30]

Virus	Medicinal plants	Antiviral effect
Herpes simplex virus (HSV)	<i>Carissa edulis</i> Vahl.	A medicinal plant exhibiting strong anti-HSV 1, and 2 activities both <i>in vitro</i> and <i>in vivo</i>
	<i>Phyllanthus urinaria</i> L.	1346TOGDG and geraniin isolated from <i>Phyllanthus urinaria</i> inhibited HSV-1 and HSV-2, respectively
Influenza virus	<i>Geranium sanguineum</i> L.	A medicinal plant reducing the infectivity of various influenza virus strains <i>in vitro</i> and <i>in vivo</i>
	Elderberry extract	A randomized, double-blinded placebo-controlled study revealed that elderberry extract seems to offer an efficient, safe and cost-effective treatment for influenza
Hepatitis B virus	<i>Boehmeria nivea</i> L.	A root extract of <i>Boehmeria nivea</i> reduced HBV production in an <i>in vitro</i> and <i>in vivo</i> model
	<i>Polygonum cuspidatum</i> Sieb. & Zucc.	Inhibits hepatitis B virus in a stable HBV-producing cell line
Hepatitis C virus (HCV)	<i>Saxifraga melanocentra</i> Engl. & Irmsch.	A compound namely 1,2,3,4,6-penta-O-galloyl-beta-d-glucoside isolated from <i>Saxifraga melanocentra</i>
Poliovirus	<i>Guazuma ulmifolia</i> Lam	Both plants extract inhibited poliovirus replication, as well as, blocked the synthesis of viral antigens in infected cell cultures
Viral haemorrhagic septicaemia virus (VHSV)	<i>Olea europaea</i> L.	Leaf extract inhibited viral replication
Severe acute respiratory syndrome-associated coronavirus (SARS-CoV)	<i>Lycoris radiata</i>	Lycorine, isolated from <i>Lycoris radiata</i> possesses anti-SARS-CoV
Human immunodeficiency virus	<i>Phyllanthus amarus</i> Schum. & Thonn. Olive leaf extract (OLE)	Inhibits HIV replication both <i>in vitro</i> and <i>in vivo</i>
Human adenovirus type 1	Black soybean extract	Inhibition of human adenovirus type 1 and coxsackievirus B1 in a dose-dependent manner
Dengue virus type-2 (DEN-2)	<i>Azadirachta indica</i> Juss. (Neem)	The aqueous extract of neem leaves inhibited DEN-2 both <i>in vitro</i> and <i>in vivo</i>

3. Special care for this coronavirus

Care is most impotent for this coronavirus infection; the high risk of coronavirus infection is now worldwide. But that may change in the next few weeks. Hence, is recommended as healthcare providers should take travel history of all patients with respiratory symptoms, and any international travel in the past 2 wks as well as contact with sick people who have travelled internationally. They should set up a system of triage of patients with respiratory illness in the outpatient department and give them a simple surgical mask to wear. They should use surgical masks themselves while examining such patients and practice hand hygiene frequently. Suspected cases should be referred to government designated centres for isolation and testing (in Mumbai, at this time, it is Kasturba hospital). Commercial kits for testing are not yet available in India. Patients admitted with severe pneumonia and acute respiratory distress syndrome should be evaluated for travel history and placed under contact and droplet isolation. Regular decontamination of surfaces should be done. They should be tested for etiology using multiplex PCR panels if logistics permit and if no pathogen is identified, refer the samples for testing for SARS-CoV-2. All clinicians should keep themselves updated about recent developments including global spread of the disease. Non-essential international travel should be avoided at this time. People should stop spreading myths and false information about the disease and try to allay panic and anxiety of the public.

4. Conclusion

In this paper conclusion, the medicinal plants are key role to identified new molecules. Most of the olants are having anti-

viral activity. Here, some of the plant compounds extracted from *A. annua*, *L. radiata*, *P. lingua*, and *L. aggregata* have been identified to show antiviral activity against SARS-CoV in Vero cell-based CPE/MTS screening. The results from our study provide strong support for the usage of these herbs to treat SARS-CoV infectious diseases. From this article results also demonstrated that lycorine is a good candidate for the development of new antiviral medicine.

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