DOI:10.5138/09750185.2409

AR JOURNALS ADVANCED RESEARCH

International Journal of Phytomedicine
2020;12(2):035-041

RESEARCH ARTICLE

Ayurveda and Siddha systems polyherbal formulations to treat COVID-19 caused by SARS-CoV-2 and brief insight on application of Molecular Docking and SWISS Target prediction tools to study efficacy of active molecules

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Abstract

Ayurveda and Siddha systems are the two ancient medical systems originated in India more than 4000 years ago had given many formulary and treatment methods against influenza like infections. Kabasura churan from Siddha system and Maha sudharshan churan from the Ayurvedic system are the two major formulations along with many other individual herbs mentioned in the texts to treat Influenza like infections. Kabasura churan and Maha Sudarshan churan both have antipyretic, analgesic and anti-inflammatory effects. Both formulations were prepared according to Siddha and Ayurvedic texts. Herbs mentioned in both formulations like Turmeric, Tulsi (Basil), Kalmegh (Andrographis), Black Pepper, Liquorice (Mulethi), and Dronapushpi (Leucas) etc., had direct antiviral effect. Herbs like Aswagandha, Ginger, Guduchi (Tinospora), Kulanjan (Galangal) etc., had immunomodulatory and anti-inflammatory effect. Active compounds from different herbs were selected to study their antiviral activity through molecular docking algorithm. Application of modern of tools like Bioinformatics and Highthroughput screening methods can predict the efficacy of the ancient documented formulations and can be compared as per their literature. Compounds like curcumin, Glycyrrhizin, Ursolic acid, Quercetin, Andrographolide, Coumarins etc. were showed polyspecific activity like inhibition of Spike protein, Furin, Main Protease (Mpro) and Papain like Proteases (PLpro). Thus we propose use of Kabasura churan and Maha Sudharshan churan as alternative complementary medicine as a palliative treatment against COVID-19 caused by SARS-CoV-2 by conducting proper Randomized Clinical Trials.

Keywords: COVID-19; SARS-CoV-2; Kabasura churan; Maha Sudarshan churan; Siddha system; Ayurvedic system of medicine

Introduction

The Ancient traditional Indian System of Medicine, namely, Ayurveda and Siddha are two well know and documented texts. Even though modern medical system has deep roots with ancient system of medicine somehow these systems are still considered as alternative treatments and been unable to attain status

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Received: 30 Apr 2020, Accepted:22 May 2020

of mainstream medicine. Validated clinical trial protocols and standardisation of drug dosage not been well established with thee system of medicine which makes them to be considered as alternative complementary medicines. Toxicity and efficacy studies can bring together the modern medicine and ancient system of medicine.

Ayurveda and Siddha are the two traditional Indian system of medicine has been widely accepted since centuries. Both systems had mentioned number of herbs and formulations to treat different types of diseases. Bhootayurveda (Bhoota means micro) is one system of Ayurveda that explains about microorganisms and their diseases. Siddha system of medicine is the ancient system of medicine originated from South India and dated to the times of Indus Valley civilization. Siddha system practiced by traditional healers called Siddhars [1]during ancient period. This system of medicine mainly dictates Do's and Don'ts while concentrating on diet and life style to control Tridoshas [2]. Kabasura churan is one such formulation mentioned in Siddha system of medicine to treat many fevers and flu like respiratory complications [3, 4] . Maha Sudarshan churan is one of the Ayurvedic formulation traditionally used as antipyretic, anti-malarial, antiviral and anti-diabetic [5]. It's a polyherbal formulation with Trikatu and Triphala as major ingredient mixtures. Analytical profiling of both traditional polyherbal formulations like Kabasura churan and Maha Sudarshan churan contains Flavonoids, Polyphenols, Saponins, Glycosides and Alkaloids [6, 7]. Here we separately studied the individual selective active compounds for their efficacy to inhibit SARS-CoV-2 virus through molecular docking methods.

COVID-19 I caused by SARS-CoV-2 is the disease that declared pandemic and took lives of many people around the world. It causes severe respiratory failure along with Fever, Diarrhea and inflammation as disease symptoms as per clinical data available [8]. As this type of virus is novel to mankind and healthcare system treatment protocols became difficult to ensure the efficacy of drugs available and it takes time to develop new drugs or vaccine. We need a proper treatment protocol that keeps the infected persons immunity active and also regulates inflammatory factors like IL-6, IL-8, IL-2 and TNF-α [9]. Some available data also suggests that the novel virus has ability to enter kidney cells and can sustain for longer time. As per clinical manifestations of the COVID-19 indicates we need multi approach medical interventions to cure the disease. One such approach should include use of Traditional system of medicine like Ayurveda, Unani, Siddha, Homeopathy, Tibetian Sowa-Rigpa and Chinese system of medicine.

To understand the clinical efficacy of traditional formulations mentioned either we should consider the data given by traditional healers or the data mentioned in texts. Still because of some technical bias we need to establish the clinical efficacy of traditional formulations through proper randomized clinical trials. But at present situation it's a time consuming process, so we suggest use of modern bioinformatics and Highthroughput screening tools to understand mechanism of individual compound data available for the herbs mentioned in the formulations. One such method includes Molecular docking and SWISS ADMET and target prediction tools [10, 11].

Methods

Polyherbal formulation

Polyherbal formulations like Kabasura churan and Maha Sudarshan churan were studied and formulated as per tables 3 and 4. Polyherbal formulation mentioned in table 2 developed based on Kabasura churan and Maha Sudarshan churan. Preparation include collecting of herbs, cleaning, shade drying and blending using multimill using 60# which is a traditional method of churan preparation as per texts.

Ligand preparation

Gasteiger partial charges were added to the ligand atoms. Nonpolar hydrogen atoms were merged, and rotatable bonds were defined using Dockingserver. Ligand library prepared as mentioned in the Figure 1. Docking calculations were carried out on selected ligands for their binding and inhibition efficacy against protein targets.

Protein preparation

Protein crystal structure in PDB format obtained from RCSB database. SARS-CoV-2 proteins like Spike glycoprotein PDB ID: 6VSB, Main Protease (Mpro) PDB ID: 6LU7 and Papain like protease (PLpro) PDB ID: 6W9C crystal models were obtained from RCSB database [12, 13]. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of Autodock tools. Affinity (grid) maps of cx-27.36, cy11.91,cz24.86 grid points for 6W9C, cx-10.46, cy4.1, cz73.01 for 6LU7, cx173.27,cy243.26,cz217.59 for 6VSB and 0.375 Å. spacing were generated using the Autogrid program. Autodock parameter set- and distance-dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively [14–17].

Swiss target and ADME prediction

Swiss target and ADME prediction is a web based tool that predicts most probable proteins targets for the submitted molecule.

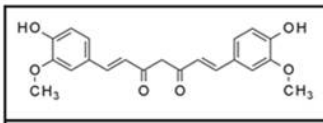
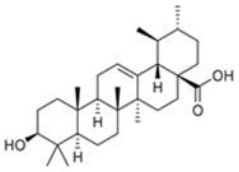
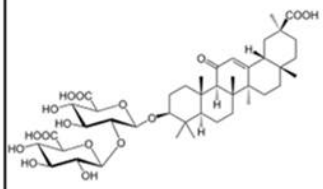
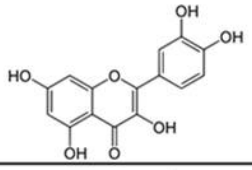
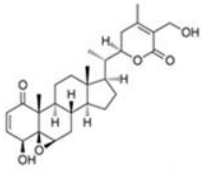
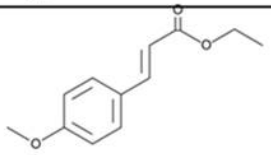
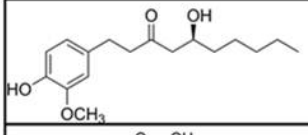
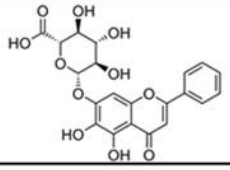
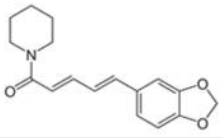
	Curcumin
	Ursolic acid
	Glycyrrhizin
	Quercetin
	Withanolide
	Galangal ester
	Gingerol
	Baicalin
	Piperine

Figure 1 Compound library

Table 1 Ayurvedic polyherbal formulation

Common name	Scientific name	Compound name
Sonth (dry ginger)	Zingiber officinale	Gingerol
Dhaniya seed	Coriandrum sativum	Flavonoids
Black pepper	Piper nigrum	Piperine
Adusa	Justicia adhatoda	Vasicine and similar derivatives
Jeera	Cuminum cyminum	Thymoquinone and volatile compounds
shankhapusphi	Convolvulus pluricaulis	Convolamine and sitosterols
kantakari	Solanum virginianum	Sitosterols, flavonoids and alkaloids
Bharangi	Clerodendrum Serratum	Sitosterols and flavones
Pippali	Piper longum	Piperine
Kulanjan	Alpinia Galanga	Galanga esters
Ajwain	Trachyspermum ammi	Phenols and thymols
Parppatakam	Hedyotis corymbosa	Flavonoids and anthraquinones
Mulethi	Glycyrrhiza glabra	Glycyrrhizin, Glycyrrhetic acid
Cane sugar	Saccharum officinarum	Sugars
Turmeric	Curcuma longa	Curcuminoids
Kutki	Picrorhiza kurrooa	Iridoid glycosides, apocynin
Kalmegh	Andrographis paniculata	Andrographilide
Dronapusphi	Leucas cephalotes	Baicalin and flavones
Tulsi	Ocimum sanctum	Ursolic acid and Tannins

Table 2 Kabasura churan Siddha formulation

Common name	Scientific name	Compound name
Sonth (dry ginger)	Zingiber officinale	Gingerol
lavang	Syzgium aromaticum	Aromatic
Black pepper	Piper nigrum	Piperine
Adusa	Justicia adhatoda	Vasicine and similar derivatives
Jeera	Cuminum cyminum	Thymoquinone and volatile compounds
shankhapusphi	Convolvulus pluricaulis	Convolamine and sitosterols
kantakari	Solanum virginianum	Sitosterols, flavonoids and alkaloids
Bharangi	Clerodendrum Serratum	Sitosterols and flavones
Pippali	Piper longum	Piperine
Kulanjan	Alpinia Galanga	Galanga esters
Ajwain	Trachyspermum ammi	Phenols and thymols
Parppatakam	Hedyotis corymbosa	Flavonoids and anthraquinones
Mulethi	Glycyrrhiza glabra	Glycyrrhizin, Glycyrrhetic acid
Cane sugar	Saccharum officinarum	Sugars
Turmeric	Curcuma longa	Curcuminoids
Kutki	Picrorhiza kurrooa	Iridoid glycosides, apocynin
Kalmegh	Andrographis paniculata	Andrographilide
Dronapusphi	Leucas cephalotes	Baicalin and flavones

These predictions are based on similarity principle and reverse screening from prepared chemical libraries. Data based on bioactivity model retrained and redefinition of threshold values assigned. Due to limited access to Natural compound physical samples computer models like SWISS ADME tools helps researchers to assess the absorption, distribution, metabolism and excretion (ADME) during drug discovery process and development [2, 10, 14, 18]. Swiss ADME tools predict physicochemical properties, pharmacokinetics, drug-likeness, medicinal chemistry likeliness and Bioavailability radar for the submitted molecules [11, 19, 20].

Molecular Docking

Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method. Initial position, orientation, and torsions of the ligand molecules were set randomly. All rotatable torsions were released during docking. Each docking experiment was derived from 100 different runs that were set to terminate after a maximum of 2500000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied [13, 21, 22].

Table 3 Maha Sudarshan churan Ayurvedic polyherbal formulation

Haridra	Curcuma longa (haldi)
Haritaki fruit	Terminalia chebula
Baheda rind o	Terminalia belarica
Amla fruit	Emblica officinalis
Daruharidra	Berberis aristata
Brihati	Solanum indicum
Kantakari	Solanum surattense
Shati	Hedychium spicatum
Pippali mool	Piper longum
Giloy	Tinospora cordifolia
Dhamasa	Fagonia cretica
Kutki	Picrorhiza kurroa
Pitta papra	Fumaria officinalis
Musta	Cyperus rotundus
Trayamana	Gentiana kurroo
Netrabala	Pavonia odorata
Nimba (Neem)	Azadirachta indica
Pushkarmool	Inula racemosa
Mulethi (licorice)	Glycyrrhiza glabra
Vatsak or bark	Holarrhena antidysenterica
Yavani (ajwain)	Trachyspermum ammi
Indra yava or seeds	Holarrhena antidysenterica
Bharangi	Clerodendrum serratum
Saurashtra (fuli fitkar)	aluminum sulfate
Vacha	Acorus calamus
Dalchini	Cinnamomum zeylanicum
Padamak kaath	Prunus puddum
Usheera	Vetiveria zizanioides
Chandana	Santalum album
Ativisha	Aconitum heterophyllum
Shalparni	Desmodium gangeticum
Prishniparni	Uraria picta
Vidanga	Embelia ribes
Tagar	Valeriana wallichii
Chitrak	Plumbago zeylanica
Devdaru	Cedrus deodara
Chavya	Piper retrofractum
Parval patra	Trichosanthes dioica
Jeevak	Malaxis acuminta
Rishabhaka	Microstylis muscifera
Lavang	Syzygium aromaticum
Vansh lochan	Bamboo manna
Kamal	Nelumbo nucifera
Kakoli	Roscoea procera
Tej patra	Cinnamomum tamala
Javitri	Myristica fragrans
Talis patra	Abies webbiana

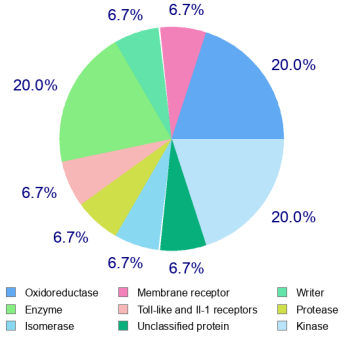


Figure 2 Comprehensive SWISS target prediction for selected herbal molecules

Results

Ligand library prepared based on traditional Ayurvedic and Siddha formulations as shown in figure 1. The prepared ligands were submitted to SWISS target and ADME prediction. Swiss target prediction summarized in figure 1. As per the results shown in figure 1 most of the molecules shown serine-kinase, metalloproteinase inhibition activity which are the main characterization of SARS-CoV-2 inhibitory molecules. Swiss ADME of ligand library predicted all the molecules had good GI absorption, no PAINS.

Ligands from the selected library were docked against viral proteins like Spike Glycoprotein, Main protease (Mpro) and Papain like protease (PLpro) and Human Furin protein. Furin is the one of the protease enzyme that cleaves envelope proteins of virus prior to viral assembly Furin also acts as precursor for metalloproteinase. Furins are utilized by virus to synthesize their precursor envelope proteins, so targeting Furins also an important site to inhibit viral maturation. SARS-CoV-2 proteins like Spike glycoprotein PDB ID: 6VSB, Main Protease (Mpro) PDB ID: 6LU7 and Papain like protease (PLpro) PDB ID: 6W9C and Furin PDB ID: 6HZD crystal models were obtained from RCSB database and preparation done using docking server. The results are shown in table 5. From the results we can convey that molecules present in polyherbal formulations mentioned in Ayurvedic and Siddha system of medicines can effectively inhibit the SARS-CoV-2 virus and its related disease complication like inflammatory factors. Thus we propose use of Kabasura churan and Maha Sudarshan churan as supportive medicine along with palliative antiviral treatment through conducting randomized clinical trials.

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Table 4 Docking study

Compound	Target protein PDB ID	Inhibition constant Ki	Free energy of Binding
Curcumin	Spike 6VSB, Mpro 6lu7, PLpro 6W9C	80μm, 150 μm, 35 μm	-6.58 kcal/mol, -5.54 kcal/mol, -6.98 Kcal/mol
Ursolic acid	Mpro 6LU7, Spike 6vsb	6.58μm,350 μm	-5.95 kcal/mol, -4.9 kcal/mol
Glycyrrhizin	Mpro 6lu7, Furin 6HZD	11.26μm, 52.76 μm	-6.04 kcal/mol, -5.02 kcal/mol
Quercetin	Mpro 6lu7, Spike 6vsb	125μm, 250 μm	-.3.98 kcal/mol, 4.56 kcal/mol
Withanolide	Furin 6HZD	1.25 μm	-5.96 kcal/mol
Ethylp-methoxycinnamate	Furin 6HZD, Spike 6VSB	35 μm, 90 μm	-6.69 kcal/mol, 6.78 kcal/mol
Gingerol	Furin 6HZD, Spike 6VSB	10μm, 2.95 μm	-7.05 kcal/mol, 6.69 kcal/mol
Baicalin	Mpro 6lu7, PLpro 6W9C Furin 6HZD	15 μm, 7.5 μm, 3.75 μm	-5.54 kcal/mol, -6.01kcal/mol, -6.75 kcal/mol
Piperine	Mpro 6lu7, PLpro 6W9C Spike 6VSB	25 μm, 2.5 μm, 1.25 μm	-5.1 kcal/mol, -6.65 kcal/mol, -7.01 kcal/mol

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