Full Length Article

EVALUATION OF PHYTO CONSTITUENTS OF *Caesalpinia sappan* AGAINST SARS CoV-2 USING MOLECULAR DOCKING

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ABSTRACT

SARS CoV-2 is a global pandemic threatening mankind and is causing great economic losses. Remedies are sought by eminent scientists throughout the world from various sources of available medicine. The search for the efficient drug candidate to combat the dreaded pandemic is still on. Caesalpinia sappan Linn. is a common medicinal herb having various medicinal properties like cytotoxic, antitumorigenic, anticoagulant, antioxidant, anti-inflammatory, antibacterial, antiviral, immunostimulant, and hepatoprotective properties. In this study, a few promising phyto constituents of C. sappan were chosen and their effects against the important disease-causing protein receptors of SARS CoV-2 were studied in silico. Phyto-constituents of Caesalpinia sappan (Caesalpin J, Deoxysappanone B, Methylepisappanol, Methylsappanol, Quercetin) expressed superior or equivalent binding affinity against the three chosen receptors of SARS CoV-2 namely spike glycoprotein, main protease, and RNA dependent RNA polymerase. Hence, necessary in vivo studies may be undertaken to evaluate the antiviral properties of C. sappan against SARS CoV-2.

Keywords: *Caesalpinia sappan*, coronavirus, SARS CoV-2, viral attachment and replication

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INTRODUCTION

SARS CoV- 2 (Severe Acute Respiratory Syndrome Corona virus -2) first reported in Wuhan, China was identified as a cause of severe progressive pneumonia in human beings and has been transmitted throughout the globe leading to a deadly pandemic. The etiological agent of this deadly pandemic belongs to the genus β-corona virus (Zheng, 2020), a non-segmented enveloped positive-sense single-stranded RNA virus with ~29.9 kb genome size (Wu *et al.*, 2020). A very high mortality rate has been recorded due to SARS CoV-2 in some pandemics. SARS CoV-2 was thought to be originated from the bat and was transmitted to humans by various

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sources. Human to human transmission was also confirmed (Chan *et al.*, 2020). Owing to its impact on the overall livelihood of human beings, it is the need of the hour to explore an effective preventive measure from different sources of available medicines.

Indian medicinal plants are widely used against various viral infections since ancient times. *Caesalpinia sappan Linn.* is one of the medicinal herbs commonly known as brazilwood/ sappan wood /Indian redwood and Pathimugam in Tamil. *C. sappan*, a member of the family Leguminosae is a large spreading tree of the 10-meter height of which its leaves, stem, bark, and heartwood of the plant are used as traditional medicine. Leaves are reported to have antibacterial and antifungal properties. The wood of *C. sappan* has a characteristic of orange-red color, hard consistency, very heavy, straight-grained with fine and even texture. The hardwood is reported to possess dyeing and other medicinal properties like cytotoxic (Park *et al*., 2002), antitumorigenic (Benabadji *et al.*, 2004), anticonvulsant (Baek *et al*., 2002), anticoagulant, anti-inflammatory, antibacterial (Xu and Lee, 2004), antimicrobial (Lim *et al*., 2007), antioxidant (Badami *et al*., 2003), anti-anaphylactic activity, anticomplementary (Oh *et al*., 1998), enzyme stimulation (glutamate pyruvate transaminase and tyrosinase), enzyme inhibition (phosphodiesterase) immunostimulant(Badami *et al.,* 2004) and hepatoprotective properties (Srilakshmi *et al*., 2010). In Kerala, it is a dwelling tradition to drink red water (water boiled with a small piece of *C. sappan*) for its anti-thirst, blood purifying, antidiabetic, complexion enhancing properties, etc. A total of 42 phytoconstituents have been reported to be identified in *C. sappan*. Hence in this paper, a few promising phytoconstituents were chosen and their effect against the target sites of SARS –CoV2 was studied *in-silico*.

MATERIALS AND METHODS

SARS - CoV-2 viral receptors

RNA-dependent RNA polymerase, a non-structural protein is an inevitable component of SARS virus replication and thereby serves as an important antiviral target. Surface glycoprotein helps the virion to attach to the host cell receptor and initiates viral infection. Surface glycoprotein is the key target for drug discovery against SARS COVID-2 (Sagar and Kumar, 2020). Another main protease of SARS CoV- 2 which is required for cleavage of structural protein for virus formation in host cells during replication was also chosen as a target (Ortega *et al*., 2020). The chosen structures of the SARS CoV-2 viral targets namely RNA dependent RNA polymerase (PDB Id: 6M71), surface glycoprotein (PDB Id: 6VSB), and main protease (PDB Id: 6Y84) were retrieved from protein databank as PDB files.

C. sappan phytoconstituents

The phyto constituents of *C. sappan* were obtained from a curated database of Indian Medicinal Plants, Phytochemistry, and Therapeutics (IMPPAT) (Mohanraj *et al*., 2018). The phytoconstituents of *C. sappan* are phytosterols, alpha-Amyrin, (+)-alpha-phellandrene, (E)-7-Hydroxy-3-(4-hydroxy benzylidene) chroman-4-one, 1-Octacosanol, 3-Deoxysappanone-B,3,4,5-

trihydroxypentanal,3,4,5-trihydroxypentanal, 3'-Deoxysappanone B, 3'-O-Methylbrazilin, 4-O-methylepisappanol, 4-O-methylsappanol, 8-methoxybonducellin, bis (Acetic acid), tannins, brazilin, caesalpin J, caesalpin P, chloroform, D-galactose, D-glucose, DL-alanine-15N, DL-aspartic acid, DL-valine, echinatin, ethanol, glycine, L-leucine, L-norvaline, L-proline, L-sorbose L-threonine, maltose, octadeca-9,12-dienoic acid, octadecanoate, oleic acid, palmitic acid, protosappanin A, protosappanin B, protosappanin C, quercetin, rhamnetin, sappanone-B, taraxerol. Using the web tool Swiss-ADME, five phytoconstituents of *C. Sappan* were selected for this study (Daina *et al*., 2017) based on the physicochemical properties (lipophilicity, size, polarity, solubility, flexibility, and saturation), drug-likeness (Lipinski rule-of-five, Ghose, Veber, Egan and Muegge filters), bioavailability scores and medicinal chemistry (structural alert, lead likeness, and synthetic accessibility) with predicted absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties. They are listed in Table 1 with their Pubchem identifier.

Table 1. Phyto-constituents of *C. sappan* with Pubchem identifier

S. No.	Compound	Pubchem Id
1	Caesalpin J	127260
2	3'-Deoxysappanone B	57391100
3	4-O-Methylepisappanol	13888974
4	4-O-Methylsappanol	13888973
5	Quercetin	5280343

The structures of the selected phytoconstituents (caesalpin J, Deoxysappanone B, methylepisappanol, methylsappanol, and quercetin) were retrieved from the PubChem database in SDF format.

Docking

The ligands were converted to PDB file formats using the Biovia discovery studio visualizer. The protein targets were prepared and converted to PDBQT formats and kept ready for docking using Autodock Vina (Trott and Olson, 2010). Similarly, the ligands were also prepared and saved in PDBQT formats for docking. Each ligand was docked individually with the protein targets and binding affinity (kcal/mol) was recorded. To evaluate the efficiency of the chosen ligands of *C. sappan*, positive and negative controls were used. Standard antiviral drugs like Remdesivir, STGYC, and Lopinavir were used as a positive control against RNA-dependent RNA polymerase (6M71), Surface glycoprotein (6VSB), and Main protease (6Y84) respectively. Allicin (sulfoxide and a botanical anti-fungal agent) was used as negative control (Kumar, 2020). The protein-ligand interaction was visualized using pyMol v software (Seeliger and DeGroot, 2010).

RESULTS AND DISCUSSION

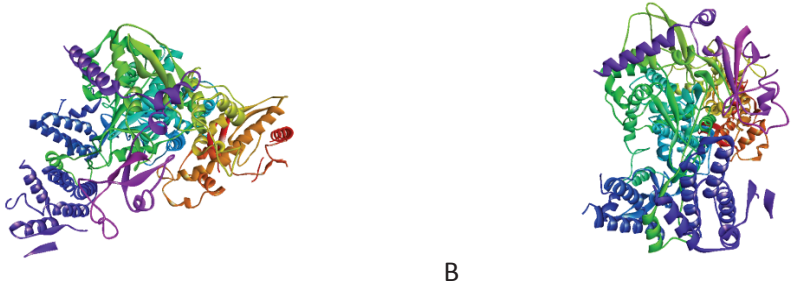
The phyto constituents of *C.sappan* **(**Caesalpin J, Deoxysappanone B, Methylepisappanol, Methylsappanol, Quercetin) exhibited superior binding affinity against both the surface glycoproteins and main protease (Table 2). The structural rendering of docking of phytoconstituents of *C. sappan* with the protein receptors of SARS CoV-2 is given in Fig. All the chosen phytoconstituents showed binding affinity equivalent to the positive control (Remdesivir) against the

receptor RNA-dependent RNA polymerase. Deoxysappanone B, Methylsappanol, and Methylepisappanol had the highest binding affinity against the main protease protein receptor. Binding affinity of the positive and negative controls against SARS CoV-2 targets was taken from the study named Molecular docking of natural compounds from tulsi (*Ocimum sanctum*) and neem (*Azadirachta indica*) against SARS-CoV -2 protein targets (Kumar, 2020).

Table 2. Binding affinity of phytoconstituents of *C.sappan* against SARS CoV – 2 target proteins

S. No.	Phyto constituents of C.sappan	Affinity (kcal/mol)		
		RNA dependent RNA polymerase (6M71)	Surface glycoprotein (6VSB)	Main protease (6Y84)
1	Caesalpin J	-6.30±0.23	-7.36±0.41	-7.67±0.29
2	3'-Deoxysappanone B	-6.46±0.38	-7.73±0.19	-8.53±0.44
3	4-O-Methylepisappanol	-6.27±0.34	-6.84±0.13	-8.00±0.21
4	4-O-Methylsappanol	-7.27±0.19	-7.02±0.18	-8.08±0.33
5	Quercetin	-7.23±0.34	-7.59±0.28	-8.09±0.45
6	Remdesivir (+ve control)	-7.69 ±0.29	-	-
7	STGYC (+ve control)	-	-5.51 ±0.27	-
8	Lopinavir (+ve control)	-	-	-6.97 ±0.45
9	Allicin (-ve control)	-2.81 ±0.17	-3.14 ±0.25	-3.58 ±0.14

Caesalpinia sappan had exhibited antiviral activity against Herpes simplex -1, Measles, poliovirus -1 *in vitro* and had also exhibited antiviral activity *in vivo* against Herpes simplex-1. *C. sappan* is also reported to exhibit anti-inflammatory, antibacterial, and immunostimulant activity (Badami *et al,* 2004).



A B

Fig. Structural rendering of the docked phyto constituents of *C. sappan* (caesalpin J, deoxysappanone B, methylepisappanol, methylsappanol, quercetin) surface glycoproteins complex (A) and main protease complex (B).

CONCLUSION

C. sappan exhibited superior binding efficacy than positive control against the spike glycoprotein which may prevent the viral attachment to host cells and the virus entry thereby preventing the disease. It has also exhibited superior and equivalent binding efficacy against viral proteins which are necessary for replication of the virus. Hence, from this study, it can be ascertained that compounds of *C. sappa*n can be used against SARS CoV-2 attributing to its antiviral properties along with its other pharmacological effects against the virus. The promising compounds of *Caesalpinia sappan* can be translated clinically as candidates of drug molecule against SARS CoV-2 which further necessitates studies.

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