Biological and Clinical Sciences Research Journal
eISSN: 2708-2261; pISSN: 2958-4728
www.bcsrj.com
DOI: https://doi.org/10.54112/bcsrj.v2023i1.285
*Biol. Clin. Sci. Res. J., Volume, **2023**: 285*
Original Research Article

IN SILICO SCREENING OF COMPOUNDS DERIVED FROM TECTONA GRANDIS LEAVES AGAINST COVID-19 NSP12 AND NSP15 THROUGH MOLECULAR DOCKING APPROACH

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(Received, 25th November 2022, Revised 20th March 2023, Published 26th May 2023)

Abstract: *The novel SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) has caused immense unrest in the world. The emerging pathogenic viral strains and increasing numbers of victims demand rapid and efficient therapeutic regimens to be introduced in clinics, which are safe and easily accessible. In this regard, plant-based chemical compounds can serve as a healthy alternative treatment approach. Thus, in the current study, 53 compounds present in the leaves of Tectona grandis plant were screened through in silico tools against proteins (NSP12 and NSP15) encoded by the SARS-CoV-2 genome. Among them, only 7 compounds, namely syringaresinol, rhinocerotinoic acid, 1,4,5,8-tetrahydroxy-2 isopentadienyl anthraquinone, 1-hydroxypinoresinol, solidagonal acid, 19-hydroxyferruginol and oleanolic acid demonstrated high affinity for the viral proteins, complemented with lowest binding energy scores and promising druglike properties. However, 1-hydroxypinoresinol and rhinocerotinoic acid were identified as potential multi-targeting compounds for the SARS-CoV-2 nonstructural proteins. Hence, these compounds can be proposed as favorable candidates for designing direct-acting anti-viral drugs against the SARS-CoV-2 virus.*

Keywords: *Tectona grandis*; SARS-CoV-2; *in silico;* NSP12; NSP15

Introduction

The novel coronavirus outbreak started in Wuhan city, China in 2019, has proved to be a major threat worldwide and affected almost 220 countries and terrestrial territories (Kramer et al., 2020). It has affected approximately 754 million people and caused 6.81 million deaths (https://covid19.who.int/). Currently, no specific treatments are available against COVID-19 (coronavirus infectious disease 2019), and therapeutic strategies rely upon precautionary drugs (Rasool et al., 2020). Among prevalent attempts to combat the novel SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2), combinations of existing drug candidates like anti-HIV drugs including remdesivir, arbidol, disoproxil, lopinavir/ritonavir, lamivudine, and tenofovir are popular in clinics (Lu, 2020). But the urgent need for direct-acting anti-SARS-CoV-2 drugs remains the need of the hour. In this regard, plant-based remedies can be an alternative approach (Narkhede et al., 2020). Several pharmacological approaches have been proposed against SARS-CoV-2, such as monoclonal bodies, interferon therapies, oligonucleotide therapy, vaccines, and molecular drugs but without much success (V'kovski et al., 2020). Thus, motivating us to explore more by using Phyto-constituents of medicinal plants. The use of natural compounds as therapeutic agents has revolutionized the medical field. Being cheap and easily available, many plants are used for their pharmacological and medicinal activities to produce drugs. Molecular docking is a renowned structure-based approach to investigate the amino acid interaction between the targeted protein and the ligand at low energy conformation (Shah et al., 2020). Thus, *in silico* screening of phytoconstituents may provide an encouraging platform for SARS-CoV-2 drug development.

Among medicinally important traditional plants, *Tectona grandis*, also known as the teak tree, has been reported as anti-HIV (Vyas et al., 2018), and is of primary importance. The plant is used for the treatment of different diseases. Almost every portion of the teak tree has potential medicinal and pharmacological activity (Nidavani and Mahalakshmi, 2014). The leaves of the plant have been shown to possess haemostatic potential and are also helpful in leprosy, inflammation, indolent ulcers, and stomatitis. The pharmacological activities of the teak tree have been scrutinized over the past few years, and different activities have been reported so far. Tectoquinone and Acteoside from the leaf extracts of *Tectona grandis* are identified as the main protease

[Citation Tariq, S., Malik, A., Landry, K.B., Malik, M., Anjum, H., Latief, N., Malik, K., Ijaz, B. (2023). *In silico* screening of compounds derived from Tectona grandis leaves against COVID-19 NSP12 and NSP15 through Molecular docking approach. *Biol. Clin. Sci. Res. J.*, **2023***: 285*. doi: https://doi.org/10.54112/bcsrj.v2023i1.285]

inhibitors of SARS-CoV-2 (Kallingal et al., 2020). Thus, constituents from *T. grandis* leaves were virtually analyzed against SARS-CoV-2.

SARS-CoV2 is a positive sense, single-stranded RNA virus from the coronavirus family and is responsible for highly contagious respiratory illness in humans (Li et al., 2020). It is reported that 20kb out of ~32kb genome of the novel virus codes for 16 non-structural proteins (NSPs), which results when polyprotein 1ab is cleaved by main protease (3CLpro) (Romano et al., 2020). The main or chymotrypsin-like protease (Mpro and CLpro) is the key enzyme of SARS-CoV-2 that is involved in the entry and replication of the virus (Tiwari et al., 2020). Moreover, another essential enzyme for viral replication is NSP12 or RNA-dependent RNA polymerase (RdRp), which is responsible for gathering the entire replication machinery(Cheng et al., 2005). It has been investigated *in vitro* that NSP12 and its co-factors NSP7/NSP8 complex can boost the endoribonuclease NendoU activity of NSP15 (Zhang et al., 2018) reduces interferon production and signaling (Yuen et al., 2020), thus enabling the virus to escape host defense. Hence, inhibiting important SARS-CoV-2 enzymes (3CLpro, NSP12, and NSP15) is a frequent approach to discovering potent anti-viral.

Therefore, in this study, we docked 53 natural compounds present in *T. grandis* leaves against SARS-CoV-2 NSP12 and NSP15 proteins. Based on energy scores, 7 of the docked compounds are proposed here as potential inhibitors of SARS-CoV-2 infection. The successful compounds were mainly phenols, flavonoids, and lignin in nature. However, 1-hydroxypinoresinol and rhinocerotinoic acid were identified as potential multi-targeting compounds for the novel virus. Further evaluation and advancement of these chemical entities can lead to novel means of tackling the virus.

Material and methods

Protein preparation

3D structure of COVID-19 NSP12 (PDB ID: 6NUR) and NSP15 (PDB ID: 6XDH) were retrieved from PDB (protein data bank). The structures were processed via AutoDock tools (http://autodock.scripps.edu/) by eliminating water molecules, inserting Kollman charges and polar hydrogen atoms and converted to PDBQT format (Prasanth et al., 2020). This helps to optimize structures for molecular docking by minimizing their energies.

Ligand preparation

Fifty-three *Tectona grandis* compounds were selected for molecular docking against SARS-CoV -2 essential proteins. 2D and 3D structures of ligands were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/) in SDF formats. These files were first converted to PDB format through Pymol software (https://pymol.org/2/), later optimized for docking analysis and saved to PDBQT format via AutoDock tools (http://autodock.scripps.edu/).

Molecular Docking

The *in silico* approach to studying ligand-protein interaction for purposing the highest affinity drug-like molecules against targeted proteins is known as molecular docking. The current study used AutoDock tools and AutoDock Vina (http://autodock.scripps.edu/) for docking purposes. Herein, all fifty-three *Tectona grandis* compounds were docked against selected SARS-CoV-2 proteins. For this purpose, the ligand and protein structures were processed in AutoDock tools to eradicate constraints and gaps for energy minimization. Further, these files were renewed to PDBQT format, which is necessary to execute docking analysis using AutoDock Vina. The interaction energy between ligand and targeted proteins was allotted by "grid point" set on default parameters. Ten conformations were generated for each ligand, and only one with minimum binding energy was selected.

Drug likeness and ADME properties

Drug likeness of ligands was determined following Lipinski's rule of five (Chen et al., 2020). Whereas pharmacokinetic and pharmacodynamic properties were determined via SwissADME (http://www.swissadme.ch/) software. These properties include absorption, distribution, metabolism, and elimination of ligand compounds.

Results

Molecular docking

Fifty-three *Tectona grandis* leaves compounds were retrieved from the literature (Vyas et al., 2018) to investigate their theoretical probability for binding to essential COVID-19 proteins, i.e., NSP12 and NSP15. The compounds were specifically docked, via Autodock tools and Autodock Vina, against the catalytic residues of SARS-CoV-2 NSP12 protein, whereas NSP15 underwent blind docking. The best hits were picked based on their lowest binding energy and zero RMSD value, as illustrated in Table 1.

Potential inhibitors of NSP12

NSP12 (PDB ID: 6NUR) interacted with five natural compounds that can be potential inhibitors of this SARS-CoV-2 protein. A promising interaction between NSP12 and oleanolic acid was observed, where this natural compound exhibited -7.9 Kcal/mol affinity. Oleanolic acid effectively binds to catalytic (ASP760, ASP761) and other active site amino acids such as LYS551, ARG553, TRP617, ASP118, TYR619, CYS624 and GLU811. Rhinocerotinoic acid (-7.0 Kcal/mol binding affinity) is the second-best inhibitor that binds to the following residues: SER759, ASP760, THR556, ASP623, THR680, SER682, LEU758. Moreover, syringaresinol (-6.9 Kcal/mol), 1-hydroxypinoresinol (-6.9 Kcal/mol), and 1, 4, 5, 8-tetrahydroxy-2 isopentadienyl

anthraquinone (-6.4 Kcal/mol) also exhibited strong inhibiting potential against NSP12 protein. Syringaresinol strongly interact with ASP760, ASP761, ARG553, TRP617, LYS621, CYS622, ASP623, GLU811, SER814, while 1-hydroxypinoresinol (ASP760, TRP617, ASP618, and TYR619. LYS621, CYS622, ASP623, GLU811) and 1, 4, 5, 8-tetrahydroxy-2 isopentadienyl anthraquinone (SER759, ASP760, THR556, ASP623, ARG624, THR680, SER681, SER682).

Table 1. Phyto-compounds that showed the best interaction with the SARS-CoV-2 Proteins based on the lowest binding energy value. The interaction studies were carried out through Autodock

Protein	Compound name	PubChem ID	Binding Energy (Kcal/mol)	Active residues
SARS-CoV-2 NSP12 PDBID: 6NUR	Oleanolic acid	10494	-7.9	ASP760, ASP761, LYS551, ARG553, TRP617, ASP118, TYR619, CYS624, GLU811
	Rhinocerotinoic acid	11771531	-7.0	SER759, ASP760, THR556, ASP623, THR680, SER682, LEU758
	Syringaresinol	100067	-6.9	ASP760, ASP761, ARG553, TRP617, LYS621, CYS622, ASP623, GLU811, SER814
	1-hydroxypinoresinol	13824420	-6.9	ASP760, TRP617, ASP618, TYR619. LYS621, CYS622, ASP623, GLU811
	1,4,5,8-tetrahydroxy-2 isopentadienyl anthraquinone	137797416	-6.4	SER759, ASP760, THR556, ASP623, ARG624, THR680, SER681, SER682
NSP15 PDBID:6XDH	1-hydroxypinoresinol	13824420	-8.1	LYS71, LYS90, SER198, LEU252, ASP268, PRO271, MET272, AS273, SER274, THR275 LYS277, TYR279, ASP297
	Solidagonal acid	101285195	-7.7	LYS71, LYS90, SER198, ARG199, ASN200, LEU252, ASP268, PRO271, MET272, SER274, THR275, LYS277, TYR279, VAL295, ILE296, ASP297
	Rhinocerotinoic acid	11771531	-7.6	LYS90, ASN200, GLU201, SER198, LEU252, SER274, LYS277, ASP297.
	19-hydroxyferruginol	21632843	-7.1	LYS71, LYS90, SER198, L252, ASP273, SER274, LYS277

Potential inhibitors of NSP15

Non-structural protein 15 (PDB ID: 6XDH) prominently interacted with four natural compounds that were 1-hydroxypinoresinol, solidagonal acid, rhinocerotinoic acid and 19-hydroxyferruginol. 1-hydroxypinoresinol produced the best results upon blind docking with NSP15. It bound to LYS71, LYS90, SER198, LEU252, ASP268, PRO271, MET272, AS273, SER274, THR275 LYS277, TYR279, and ASP297 residue at the lowest binding affinity (-8.1 Kcal/mol). Moreover, docking of solidagonal acid with NSP15 resulted in second best affinity score (-7.7 Kcal/mol) followed by rhinocerotinoic acid (-7.6 Kcal/mol) and 19-hydroxyferruginol (-7.1 Kcal/mol). These natural compounds posed well into the active pocket of NSP15 while prominently interacting with the following amino acid residues: solidagonal acid (LYS71, LYS90, SER198, ARG199, ASN200, LEU252, ASP268, PRO271, MET272, SER274, THR275, LYS277, TYR279, VAL295, ILE296, ASP297), rhinocerotinoic acid (LYS90, ASN200, GLU201, SER198, LEU252, SER274, LYS277, ASP297) and 19-hydroxyferruginol (LYS71, LYS90, SER198, L252, ASP273, SER274, LYS277). Conclusively, low binding affinities of these compounds against NSP15 suggest them as potential inhibitors for future drug discovery against COVID-

19. Convincingly, the molecular docking study implies two potential multitarget Phyto-compounds i.e., 1-hydroxypinoresinol and rhinocerotinoic acid, as COVID-19 proteins inhibitor as depicted in Fig.1 and Fig 2.

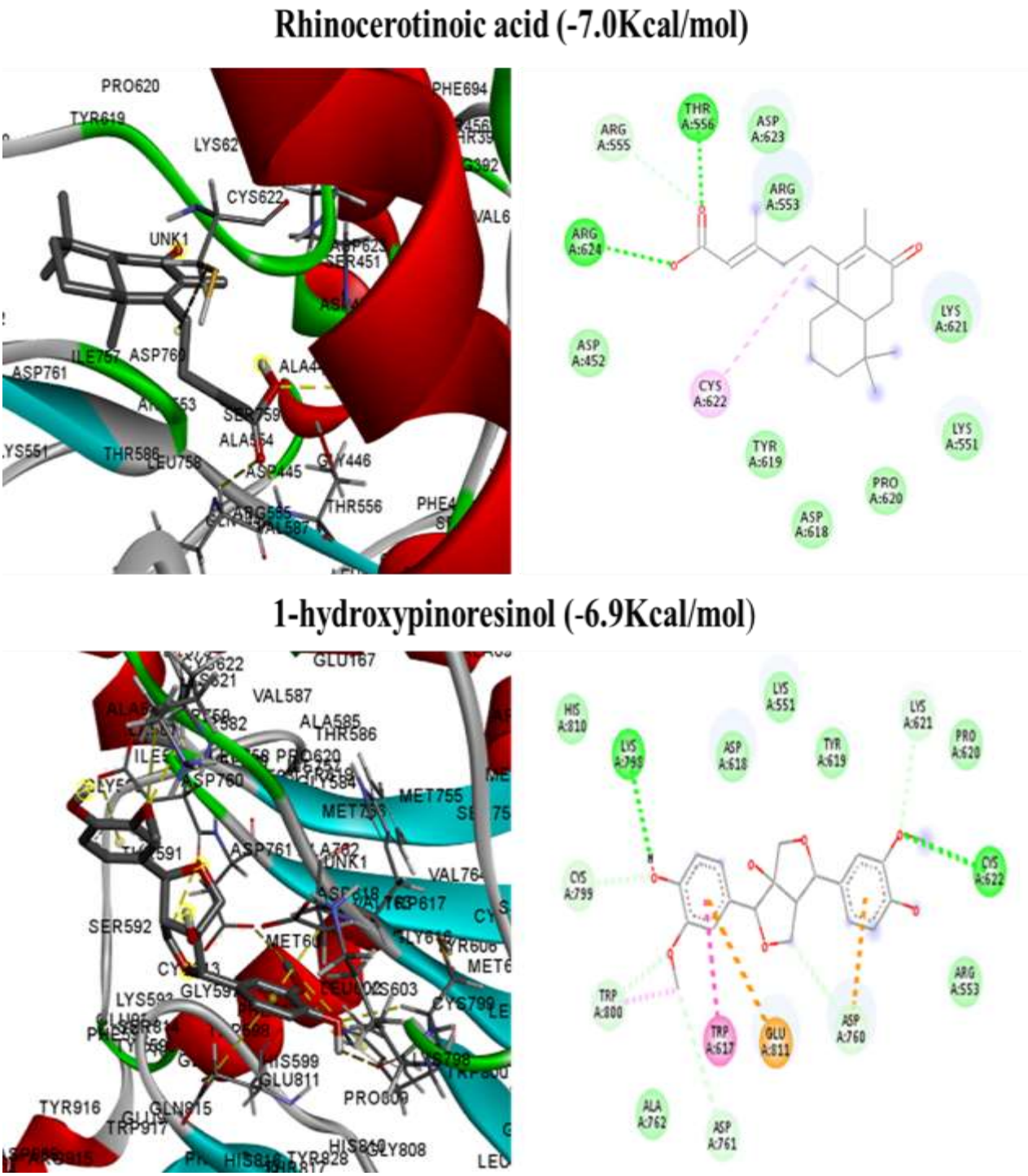

Fig.1: Two- and three-dimensional interaction diagram of multitargeted Phyto-compounds (1-hydroxypinoresinol and Rhinocerotinoic acid) with NSP12 protein. (left: 3D, Right:2D)

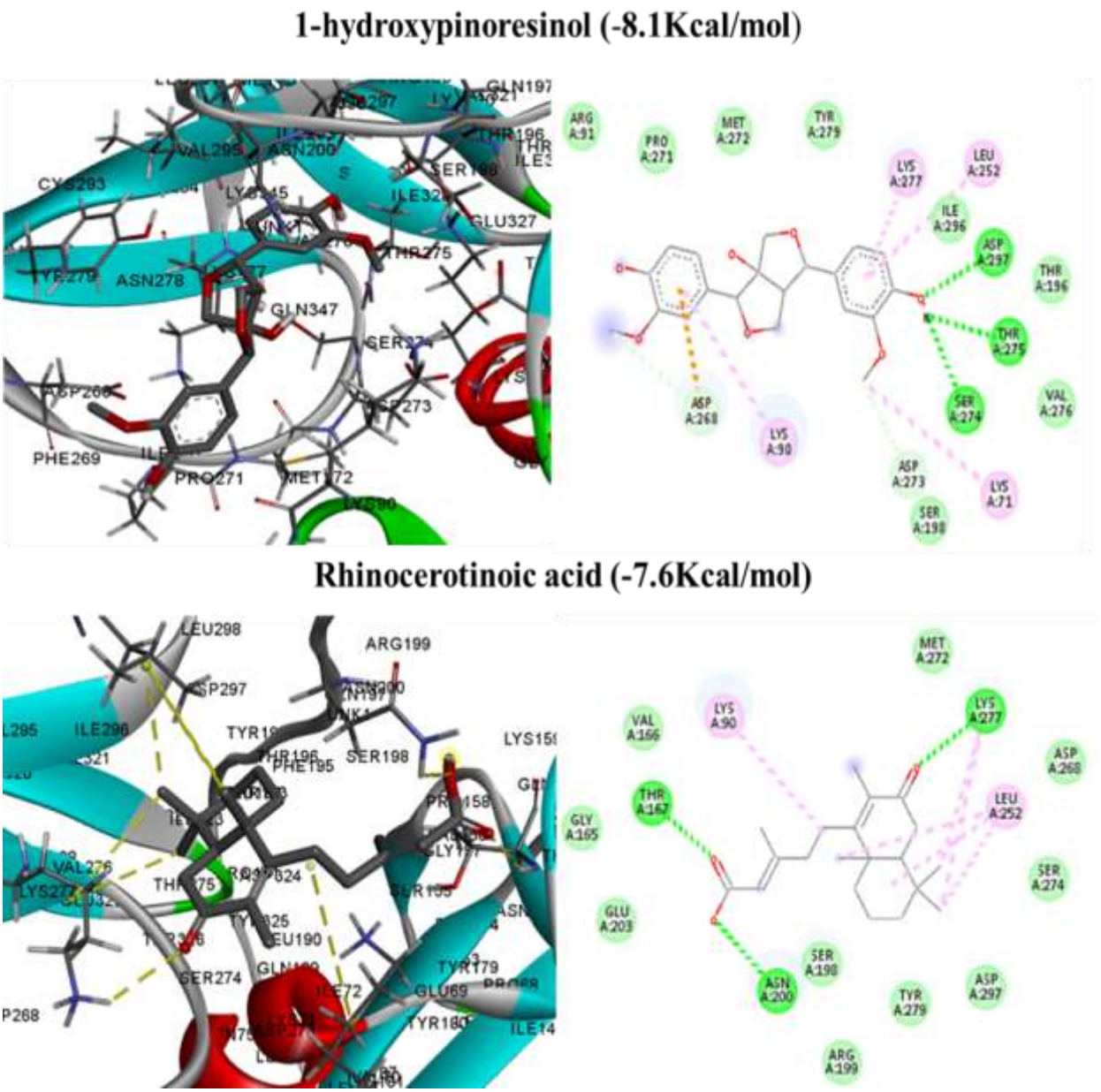

Fig.2: Molecular interaction of SARS-CoV-2 NSP12 protein with multitargeted Phyto-compounds (1-hydroxypinoresinol and Rhinocerotinoic acid). 3D structures are represented on left and 2D at right.

Drug likeness and ADME properties

Drug likeness of all the compounds was determined by Lipinski's rule of 5 which declares a compound as drug-like when it achieves the following criteria: Molecular weight (<500 DA), number of hydrogen bond acceptors (<10), number of hydrogen bond donors (<5), and LogP (<5). Six of 7 active *Tectona grandis* compounds were drugable with zero violations. However, oleanolic acid disobeyed this rule with only one violation, as mentioned in Table 2. Furthermore, ADME analysis of these compounds was carried out via the SwissADME server to detect their potential as a human drug for future clinical trials. Table 3 represents the molecular pharmacokinetic attributes such as blood-brain barrier penetration (BBB), gastrointestinal absorption, P-glycoprotein substrate, drug metabolism, distribution, and elimination. All the compounds are not permeable to cross the blood-brain barrier except rhinocerotic acid, solidagonal acid, and 19-hydroxyferruginol. Moreover, only oleanolic acid showed low gastrointestinal absorption among the active compounds. All the active compounds of *T. grandis* are non-substrate for P-glycoprotein inhibition except syringaresinol and 1-hydroxypinoresinol. Here, glycoprotein inhibition leads the drug to cells hence non-inhibitors compounds will not be easily engrossed by cells. In the case of metabolism, 1, 4, 5, 8-tetrahydroxy-2 isopentadienyl anthraquinone compound inhibits CYP1A2, CYP2C9, and CYP3A4

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enzyme. Furthermore, shinocerotinoic acid and solidagonal acid inhibit CYP2C9 and CYP2C19; syringaresinol, 1-hydroxypinoresinol and 19-hydroxyferruginol inhibit CYP2D6; solidagonal acid inhibits CYP3A4. Despite this, the distribution property of all seven compounds was assessed. Except for syringaresinol and 1-hydroxypinoresinol, all compounds inhibited P-glycoprotein, thus representing increased bioavailability.

Table 2. Evaluation of effective compounds based on Lipinski rule of 5

	Syringaresinol	Oleanolic acid	Rhinocerotinoic acid	1,4,5,8-tetrahydroxy-2 isopentadienyl anthraquinone	1-hydroxypinoresinol	Solidagonal acid	19-hydroxyferruginol
Molecular weight (Da) (MW) <500	Compound Name	456.71	318.46	338.31	374.39	318.46	302.46
MLogP <5	2.62	6.72	4.52	4.27	1.64	4.87	5.24
H-Bond acceptor (<10)	8	3	3	6	7	3	2
H-Bond Donor (<5)	2	2	1	4	3	1	2
Number of violations	0	1	0	0	0	0	0

Table 3. Evaluation of effective compounds based on ADME properties

Compounds	Syringaresinol	Oleanolic acid	Rhinocerotinoic acid	1,4,5,8-tetrahydroxy-2 isopentadienyl anthraquinone	1-hydroxypinoresinol	Solidagonal acid	19-hydroxyferruginol
a. Absorption							
Blood-Brain Barrier	No	No	Yes	No	No	Yes	Yes
Gastro-Intestinal Absorption	High	Low	High	High	High	High	High
b. Distribution							
P-glycoprotein substrate	Yes	No	No	No	Yes	No	No
P-glycoprotein (Pgp) inhibition	No	Inhibitor	Inhibitor	Inhibitor	No	Inhibitor	Inhibitor
c. Metabolism							
CYP1A2 Inhibitor	No	No	No	Yes	No	No	No
CYP2C9 Inhibitor	No	No	Yes	Yes	No	Yes	No
CYP2D6 Inhibitor	Yes	No	No	No	Yes	No	Yes
CYP2C19 Inhibitor	No	No	Yes	No	No	Yes	No
CYP3A4 Inhibitor	No	No	No	Yes	No	Yes	No
d. Elimination							
MDCK cell permeability (nm/sec)	0.201466	0.0438929	117.784	5.43144	4.3395	109.576	106.313

CYP1A2: Cytochrome P1A2, MDCK: Madin Darby Canine Kidney

MDCK cell permeability (nm/s): low permeability (<25); middle permeability (range from 25 to 500); high permeability (>500).

Discussion

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The novel SARS-CoV-2, which triggered the COVID-19 pandemic, has gained a barbarous reputation worldwide. The increasing numbers of victims demand rapid and efficient therapeutic regimens to be introduced in clinics, which are safe and easily accessible. In this regard, plant-based chemical compounds can serve as a healthy alternative treatment approach. Thus, in this study, we screened 53 compoundsin the leaves of *Tectona grandis* plant through *in silico* tools against two important proteins (NSP12 and NSP15) encoded by the SARS-CoV-2 genome. Among them, 7 compounds, namely syringaresinol, rhinocerotinoic acid, 1,4,5,8-tetrahydroxy-2 isopentadienyl anthraquinone, 1-hydroxypinoresinol, solidagonal acid, 19-hydroxyferruginol and oleanolic acid demonstrated high affinity for the viral proteins, complemented with lowest binding energy scores and promising druglike properties. Hence, these compounds can be proposed as favorable candidates for designing direct-acting anti-viral drugs against the SARS-CoV-2 virus.

Precisely, compounds from *T. grandis* leaves were docked against two non-structural proteins of the virus. SARS-CoV-2 replication is essentially dependent upon NSPs which are encoded by open reading frame 1a (ORF1a) and ORF1ab of the viral genome (Peng et al., 2020). Such proteins undergo proteolysis for maturation after initially being translated into polyproteins (V'kovski et al., 2020). Further, for viral replication and translation of its genome, NSPs assemble into a polymerase complex, of which NSP12 is the catalytic subunit having RNA-dependent RNA polymerase (RdRp) activity (Ahn et al., 2012). Additionally, NSP12 is highly conserved compared to the virus's surface proteins (Shi et al., 2013). Thus, NSP12 carries huge promise as a compelling antiviral drug target. Here, targeting SARS-CoV-2 NSP12 bound to NSP7 and NSP8 co-factors (PDBID:6NUR), oleanolic acid, rhinocerotinoic acid, syringaresinol, 1-hydroxypinoresinol, and 1,4,5,8-tetrahydroxy-2 isopentadienyl, anthraquinone phytoconstituents were found to interact with NSP12 with lowest energy scores. These proposed NSP12 inhibitors were analyzed for their drug-likliness and showed zero violation except for oleanolic acid which had one violation for Lipinski's rule of 5. Published docking studies are available for oleanolic acid and rhinocerotinoic acid as NSP12 inhibitors (Dwarka et al., 2020; Singh et al., 2020) but syringaresinol, 1-hydroxypinoresinol, and 1,4,5,8-tetrahydroxy-2 isopentadienyl anthraquinone are identified for their NSP12 antagonistic potential for the first time.

Further, to target the SARS-CoV-2 defense mechanism, NSP15 has opted for docking analysis. SARS-CoV-2 pathogenesis is partially characterized by early suppression of the host immune system posed by the virus (Yuen et al., 2020). To evade the host immune system, SARS-CoV-2, NSP15 protein, helps escape RNA sensors, halts apoptosis in macrophages, and reduces interferon production and signaling (Deng et al., 2017; Yuen et al., 2020). Thus, NSP15 was taken as a target for docking purposes. Four compounds, 1-hydroxypinoresinol, solidagonal acid, rhinocerotinoic acid and 19-hydroxyferruginol demonstrated preferable binding scores against NSP15 for the first time. They followed Lipinski's rule of 5 without any violation. ADME (Absorption, distribution, metabolism, and elimination) analysis of all the best-docked ligands was also conducted. This *in silico* analysis helps to eliminate potential drug candidates exhibiting undesirable detrimental effects. Molecules with inappropriate ADME properties are not encouraged for clinical trials (Abdelli et al., 2021). Overall results indicate that all effective compounds exhibited suitable ADME characteristics.

In silico observation in this study suggested 1-hydroxypinoresinol and rhinocerotinoic acid as potential multi-targeting entities that may curb SARS-CoV-2 replication, assembly and tendency to escape interferon response, since they showed an impressive affinity with NSP12 and NSP15 proteins. This proposed multi-target strategy using a single compound (1-hydroxypinoresinol or rhinocerotinoic acid) can be inexpensive to enhance efficacy and avoid viral resistance. Among the multi-target compounds identified, 1-hydroxypinoresinol is a furofuran lignan derivative with a chemical structure consisting of two phenylpropanoid units forming either a tetrahydrofuran ring, a furan ring, or a furofuan ring system (Cho et al., 2014). Various studies have reported the antifungal, antimicrobial, antioxidant, and anticancer activity of hydroxypinoresinol (Ekalu et al., 2019; Piao et al., 2009). Rhinocerotinoic acid is a labdane diterpene associated with plants having anti-inflammatory properties (Gray et al., 2003). Further investigation and manipulation of these multi-targeting phyto-compounds are required to unfold their potential as direct-acting anti-SARS-CoV-2 drugs.

Conclusion

The medicinally important leaves of *Tectona grandis*, previously discovered for anti-HIV potential, possess several important compounds that can target SARS-CoV-2. Among 53 compounds syringaresinol, rhinocerotinoic acid, 1,4,5,8-tetrahydroxy-2 isopentadienyl anthraquinone, 1-hydroxypinoresinol, solidagonal acid, 19-hydroxyferruginol and oleanolic acid demonstrated high affinity for the viral proteins, with lowest binding energy scores and encouraging druglike properties. The study reveals 1-hydroxypinoresinol and rhinocerotinoic acid as potential multi-targeting compounds for the virus.

Acknowledgments

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We are highly thankful for the PHEC/ARA/PIRCA/20409/18 grant to meet the publication charges of the journal.

Competing Interests

The authors declare no competing interests.

Authors' Contributions

Somayya Tariq, Ayesha Malik, and Koloko B Landry conducted the in silico molecular docking analysis and wrote the paper. Marrieum Malik and Hamza Anjum performed the drug-likeness and ADME analysis. Noreen Latief and Kausar Malik write and edit the article. Bushra Ijaz designed and supervised the study and critically reviewed and edited the paper.

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[Citation Tariq, S., Malik, A., Landry, K.B., Malik, M., Anjum, H., Latief, N., Malik, K., Ijaz, B. (2023). *In silico* screening of compounds derived from Tectona grandis leaves against COVID-19 NSP12 and NSP15 through Molecular docking approach. *Biol. Clin. Sci. Res. J.*, **2023***: 285*. doi: https://doi.org/10.54112/bcsrj.v2023i1.285]