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In Silico Examination of *Tinospora cordifolia* Phytochemical Constituents towards Sars Cov-2, Dengue and Hepatitis Viruses by Molecular Docking Approach

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ABSTRACT

The experiment was conducted during 2023 at Tamilnadu Agricultural University dept. of medicinal and aromatic crops. *Tinospora cordifolia* is considered valuable in terms of its immense medicinal properties. Medicinal plants containing phytochemical compounds are considered to be safer and non-toxic than synthetic medicines and *in silico* analysis of these phytochemical compounds is cost effective, rapid, helps to make decisions and simulate virtually besides useful in optimizing and refining long time experimental trials thereafter. Hence, the present study was mainly focused on *in silico* research of phytocompounds from *T. cordifolia* towards dengue, hepatitis A viruses and SARS-CoV-2. The compounds were docked employing AutoDock Vina in PyRx 0.8 a online screening system, onto the crystal patterns of SARS CoV-2 main protease (PDB ID- 2GZ9), dengue virus non-structural protein NS1 (PDB ID- 4OIG) and Hepatitis A virus 3C proteinase (1HAV). The ligands were shortlisted based on their hydrogen bond interactions and binding affinities. The top-ranking molecules showed the range's energy state of bonding of covid (-7.6 to -6.7 kcal mol^{-1}), dengue (-7.9 to -7.3 kcal mol^{-1}) and hepatitis (-8.0 to -6.9 kcal mol^{-1}). Based on good binding energy, drug-likeness and efficient pharmacokinetics properties, it was evident that the compounds 3, 3-Dimethyl-1, 5, 13 , 14-tetraoxa-10, 19-diazacyclotricosane-6, 9, 20, 23-tetrone, tdnosporinone, and cordifolioside were conceived as possible deterrents for SARS CoV-2 main protease (Mpro), dengue virus non-structural protein NS1 and hepatitis A virus 3C proteinase respectively.

KEYWORDS: *Tinospora cordifolia*, phytochemicals, in silico, binding energy, viruses

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1. INTRODUCTION

Medicinal plants are store house of valuable secondary metabolites that find usage in food, medicine, cosmetics, natural colours and beverage (Basak et al., 2020). India is embodiment of plant biodiversity with array of plant species that have been used by people for many centuries to treat day today health ailments like cough, cold, digestion, fever, bone fracture and many others (Dharumarajan et al., 2016). As per the World Health Organisation, it is calculated at nearly 80% of the global populace nonetheless is dependent upon the herbal drugs for their health care (Vidula et al., 2021). *Tinospora cordifolia* (Willd) Miers, is one of the clinically significant perennial, climbing shrub of family Menispermaceae (Geetha and Maiti, 2023). It is a deciduous, succulent shrub, large spreading, widely observed in the tropical regions from the Himalayas to the Northern and Southern parts of India (Akhilraj et al., 2023). This medicinal herb is also grown in countries like Indonesia, Malaysia, Vietnam, Thailand, Philippines and China as well as South, West and North Africa (Kumawat et al., 2019). The plant has numerous medicinal value in Ayurveda. It is used to prepare 'Rasayana' and mainly is suggested to promote longevity, increase overall body strength and as an adaptogen and anti-stress (Kumar et al., 2020). Each component of the plant have medicinal value, but stem and leaf are highly important contains phytochemicals including steroids, coumarin, proteins, carbohydrates, phytosterol, diterpenes, flavonoids, alkaloids and saponins. It is rich in various compounds like rhamnose, simple sugars, glucosinolates and isothiocyanates (Pandey et al., 2020). Also high amount of minerals and elemental substances were reported in this plant (Chatterjee and Ghosh, 2015). Pharmacological activities of *T. cordifolia* have been reported for antifungal, antibacterial, antipyretic, antiperiodic, antispasmodic, anti-inflammatory, immunomodulatory or immunostimulatory, cognition, antitumor, antihyperglycemia, antineoplastic, antioxidant, antihyperlipidemia, gastrointestinal, antituberculosis, antiangiogenic, anti-osteoporotic, antiallergic antimalarial and antipyretic properties (Reddy and Reddy, 2015).

It is genetically diverse plant used to control various viruses. Viruses are nowadays main problem throughout the world (Jain et al., 2023). Most of the viruses envelop single stranded RNA as their genetic material that belongs to different families like *Corona viridae* (Corona virus) and *Flaviviridae* (Dengue and Hepatitis) (Enkhtaivan et al., 2015; Chen et al., 2018). It cause many diseases in plant and animal kingdom. In 2020, COVID 19 has emerged as a pandemic worldwide affecting mostly all countries globally (Sharma et al., 2023). Mainly these viruses are transmitted through birds and rodents and it cause severe damage to human being like fever, cough, cold, joint pains (arthritis), muscular pain, rashes, headache, fatigue, digestive complaints, respiratory illnesses, vomiting, diarrhea, haemorrhaging and conjunctivitis (Chatterjee and Ghosh, 2016; Geetha and Maiti, 2023). The pathogenesis of these viruses infection in human is still poorly understood. These viruses are prevalent specially in the tropical and subtropical regions and it is a top priority for World Health Organization (WHO) (Maiti et al., 2016). Till date, the abruptly extending universal footprint of these viruses is a public health dispute with financial hardship that is not fulfilled by drugs or vaccines and vector control schemes. In this regard, the quest for novel anti-viral compounds from traditional medicinal herbs has important one than in the past (Palai and Kesh, 2021). Therapeutical plants contain variety of compounds are used globally to heal a variety of vector borne illness (Poonia et al., 2023). The demand for medicinal plant drugs is presently increasing's as they are usually regarded to be non-toxic and healthier than synthetic medicines (Harinarayanan et al., 2022). Biologically disease controlling mechanism have been necessary for human health. Hence, in this study mainly focusing the *In silico* analysis of phytoconstituents of *Tinospora cordifolia* against viruses by molecular docking approach.

2. MATERIALS AND METHODS

The current research was executed at Department of Medicinal and Aromatic Crops and Department of Bioinformatics, TNAU, Coimbatore, Tamil Nadu, India during 2022.

2.1. ADME prediction

The compounds were present in *T. cordifolia* chosen to serve as ligands. For the purpose of evaluating the ADME (absorption, distribution, metabolism, and excretion) characteristics, the canonical SMILES version of the aforementioned chemicals was obtained from the Pubchem database. These chemicals were retrieved in SDF format for a simulated screening procedure from the Pubchem database (Ritche et al., 2011).

2.2. Protein preparation

The X-ray crystal structures of main protease of SARS Co V2 (PDB ID: 2gz9) (Nallusamy et al., 2021), dengue (PDB ID: 4OIG) (Poonsiri et al., 2018) and hepatitis (PDB ID: 1HAV) (Feng, 2020) were as from RCSB PDB downloaded (Protein Data Bank) database (Pierucci et al., 2019). For the preparation of the protein in docking, Kollman united atom charges, solubilization parameters, plus polar hydrogens also added to the receptors. Gasteiger energy was allocated and non-polar hydrogens were then combined because ligands are not peptides. The docking ligand must have pre-calculated grid maps one for each kind of atom present

in order to record the potential energy that arises. This grid must encircle the macromolecule's active site, or the area of interest (Morris et al., 1998).

2.3. Active site prediction

CASTp 3.0 was used to estimate the target proteins' active site residues: service for the generated atlas of protein surface topology (Binkowski et al., 2003).

2.4. Molecular docking

Virtual Screening of the selected phytochemical compounds from *Tinospora* with the antiviral target proteins was performed using the Pyrx 0.8 programme. The AutoDock Vina program from PyRx 0.8 was used to carry out the docking study (Vali et al., 2022). The receptor's ligand-binding location was set on the grid map during docking. SARS-CoV-2 M_{pro} (2GZ9), dengue non structural protein NS1 (4OIG) and Hepatitis A virus 3C proteinase (1HAVcrystalline nature was employed as the receptor and a library of chemicals as the ligand. The estimation of binding affinity was accomplished utilizing PyRx AutoDock Vina (Trott and Olson, 2010). The active site of the crystal structure was first covered by a grid box with both the subsequent level in Å: For SARS Co V2 it was cantered as (*X*, *Y*, *Z*) = (25.44, -42.28, -5.43), dimensions (*X*, *Y*, *Z*) = (34.02, 32.18, 35.62), for dengue centered as (*X*, *Y*, *Z*) = (70.87, 91.01, 58.85), dimensions (*X*, *Y*, *Z*) = (107.40, -11.13, 29.46), for hepatitis centered as (*X*, *Y*, *Z*) = (8.09, 9.24, 8.53), dimensions (*X*, *Y*, *Z*) = (53.39, 48.76, 48.36) with an 8 completeness. Lastly, Discovery Studio Visualizer was used to analyse the results (Anonymous, 2020).

3. RESULTS AND DISCUSSION

3.1. ADME screening

The ADME attributes of the phytoconstituents, including their bioavailability, physicochemical characteristics, lipophilicity, liquidity, pharmacokinetics, and drug-likeness behaviour, were examined using the SWISS-ADME internet platform. The outcomes of this study are itemized in Table 1. Because of their unfavorable absorption, distribution, metabolism, and elimination (ADME) characteristics, numerous potential therapeutic

Table 1: ADME properties of phytochemical compounds

Name of the compound	Pub Chem Id.	MW (g mol^{-1})	NHD	NHA	Consensus logP	logS (ESOL)
Butane, 1, 1-diethoxy-	77225	146.23	0	2	2.10	-1.66
1-Butanol, 3-methyl-, acetate	31276	130.18	0	2	1.76	-1.80
dl-Glyceraldehyde dimer	533979	180.16	4	6	-1.96	1.29
3-Methyl-isoxazol-5(4H)-one	535031	99.09	0	3	-0.53	0.52
Pentane, 1, 1-diethoxy-	77223	160.25	0	2	2.48	-2.02
Decane	15600	142.28	0	0	4.16	-3.42
Propane, 1, 1, 3-triethoxy-	24624	176.25	0	3	1.83	-1.29
Thiomorpholine-3-carboxylic acid amide	568316	146.21	2	2	-0.33	-0.18
Dodecane	8182	170.33	0	0	4.94	-4.15
Cyclododecane	9268	168.32	0	0	4.16	-3.17
Tetradecane	12389	198.39	0	0	5.68	-4.88
Melezitose	92817	504.4	11	16	-5.00	1.25
Phenol, 2, 4-bis (1,1-dimethylethyl)	7311	206.32	1	1	3.99	-4.55
Desulphosinigrin	9601716	279.31	5	7	-0.92	-0.44
Heneicosane, 11-(1-ethylpropyl)-	292291	366.7	0	0	9.85	-9.37
1-Hexadecanol	2682	242.44	1	1	5.42	-4.90
Hexadecane	11006	226.44	0	0	6.42	-5.60
Benzophenone	3102	182.22	0	1	2.94	-3.48
1-Nonadecene	29075	266.5	0	0	7.56	-7.10
4-Octadecenal	5365018	266.5	0	1	5.89	-5.16
Heptadecane, 9-hexyl-	296566	324.6	0	0	8.97	-8.40

Table 1: Continue...

Name of the compound	Pub Chem Id.	MW (g mol^{-1})	NHD	NHA	Consensus logP	logS (ESOL)
Ethanol, 2-(9-octadecenyloxy)-, (Z)-	5364713	312.5	1	2	5.93	-5.18
Lidocaine	3676	234.34	1	2	2.50	-2.58
Choline	305	104.17	1	1	-1.38	-0.10
9-Eicosene,(e),	5365037	280.5	0	0	7.70	-6.90
Hexadecanoic acid, ethyl ester	12366	284.5	0	2	5.90	-5.51
Cordifolioside	75111036	504.5	7	13	-1.27	-1.33
Phytol	5280435	296.5	1	1	6.22	-5.98
9, 12-Octadecadienoic acid (Z, Z)-	5280450	280.4	1	2	5.45	-5.05
Magnoflorine	73337	342.4	2	4	1.14	-3.91
9, 12-Octadecadienoic acid (Z, Z)-, octyl ester	5365200	392.7	0	2	8.23	-7.32
Tinosporinone	42607646	342.3	0	6	2.89	-4.09
Linoleic acid ethyl ester	5282184	308.5	0	2	6.09	-5.32
Ethyl Oleate	5363269	310.5	0	2	6.33	-5.70
Berberine	2353	336.4	0	4	2.53	-4.55
Heptacosane	11636	380.7	0	0	10.46	-9.59
17-Pentatriacontene	5365022	490.9	0	0	13.13	-12.33
Methyl 2, 2-dimethyl-3-hydroxypropionate	84152	132.16	1	3	0.64	-0.65
d-Glucosamine	439213	179.17	5	6	-2.37	1.32
Thymine	1135	126.11	2	2	0.15	-0.72
Clindamycin	446598	425.0	4	6	1.07	-3.31
4H-Pyran-4-one, 2, 3-dihydro-3, 5-dihydroxy-6-methyl-	119838	144.12	2	4	-0.22	-0.50
Heptanediamide, N, N'-di-benzoyloxy-	569848	398.4	2	6	3.05	-3.87
Benzofuran, 2,3-dihydro-	10329	120.15	0	1	2.00	-2.43
Alpha-l-sorbopyranose	441484	180.16	5	6	-2.15	0.90
3, 3-Dimethyl-1, 5, 13, 14-tetraoxa-10, 19-diazacyclotricosane-6, 9, 20, 23-tetrone	580963	416.5	2	8	0.76	-2.39
Cyclohexane, octyl-	15712	196.37	0	0	5.39	-5.19
Sumatriptan	5358	295.40	2	4	1.46	-2.31
Inositol, 1-deoxy-	101715	164.16	5	5	-2.03	0.86
Hexadecyl propyl ether	19018347	284.5	0	1	6.62	-5.98
Alpha-l-rhamnopyranose	439710	164.16	4	5	-1.46	0.46
2-Hexanone oxime	5357205	115.17	1	2	1.61	-1.35
Debrisoquine	2966	175.23	2	1	1.00	-1.67
1-Octadecene	8217	252.5	0	0	7.20	-6.73
Dibutyl phthalate	3026	278.34	0	4	3.69	-3.96
Gamolenic acid	5280933	278.4	1	2	5.24	-4.85
9,12,15-Octadecatrienoic acid, ethyl ester, (Z, Z, Z)-	5367460	306.5	0	2	5.82	-4.95
Octadecane, 3-ethyl-5-(2-ethylbutyl)-	292285	366.7	0	0	9.68	-9.25
Tetracosane, 11-decyl-	294707	478.9	0	0	12.89	-12.38

MW: Molecular weight; NHD: Number of hydrogen bond donors; NHA: Number of hydrogen bond acceptor

drugs lack efficacy in clinical trials. Beyond ADME, the probability of a drug's success significantly impacts scientific evaluations. The significance of pharmacokinetic parameters is paramount for orally administered medications. During this phase, absorption occurs as the compound is liberated from the intestines and subsequently transported to various locations throughout the body via the circulatory system or bloodstream. In order to facilitate the development of new therapeutic compounds, ADME prediction comes into play (Thakor et al., 2017). All the molecules exhibit molecular weights ranging from 99.09 to 504.5, hydrogen bond donor counts ranging from 0 to 11, and hydrogen bond acceptor counts ranging from 0 to 16. The consensus logP and logS values for the compounds 3, 3-Dimethyl-1, 5, 13, 14-tetraoxa-10, 19-diazacyclotricosane-6, 9, 20, 23-tetrone were 0.76 and -2.39, for berberine were 2.53 and -4.55, for magnoflorine were 1.14 and -3.91, and for tinosporinone were 2.89 and -4.09. The idea was to leverage multiple distinct logP prediction approaches on a diverse and extensive dataset. By tapping into the insights of each individual predictor, a potential avenue emerged for generating a novel training set. This potential was grounded in the fact that various prediction methods yield differing logP values for a given compound. Tetko and colleagues in 2005, pioneered the development of models trained on anticipated data. This approach facilitated knowledge transfer from organizations while safeguarding sensitive data. The consensus logP model, introduced by Mannhold et al. (2009) emerged as the most accurate predictor for proprietary data. This model constituted an average of the top-performing models. Consequently, the notion arose that crafting a training set using averaged projected values might similarly capture this level of performance. Just as combining multiple models into an ensemble enhances performance, there's a belief that the resultant model could yield more accurate forecasts. Essentially, our goal was to distill insights from several models into a singular, uncomplicated model, achieved through training with projected data (Hinton et al., 2015).

3.2. Virtual screening

Digital inspection was done for the compounds against the target proteins, was performed through AutoDock Vina in PyRx. In order to discover novel, potentially effective medications for curing SARS-CoV-2 M_{pro}, dengue non-structural protein NS1, hepatitis A virus 3C proteinase. Virtual screening of selected libraries of ligands and the target was carried out through AutoDock VINA and involved in the PyRx device where it for each ligand, several conformations that are categorised by ligand binding (kcal mol^{-1}) were created. The top-ranking compounds showing the range's free energy of bonding covid (-7.6 to -6.7 kcal mol^{-1}), dengue (-7.9 to -7.3 kcal mol^{-1}) and hepatitis (-8.0 to -6.9 kcal mol^{-1}) are shown in Table 2-4. To assess the selected compounds' interactions at the binding sites and the target proteins the exchanges were visualised BIOVIA Discovery Studio Visualiser and the Receptor- Ligand interactions were analysed. For SARS-CoV-2 M_{pro} as the best docked

Table 2: Best docked compounds of SARS-CoV-2 M_{pro}

Protein Name	Pub chem id	Ligand name	No. of H-bonds	Docking energy (Kcal mol^{-1})	Amino acids involved in H-bond interaction
2gz9	580963	3, 3-Dimethyl-1, 5, 13, 14-tetraoxa-10, 19-diazacyclotricosane-6, 9, 20, 23-tetrone	2	-7.6	THRA:26, HISA:41
	2353	Berberine	2	-7.2	THRA:25, GLUA:166
	73337	Magnoflorine	1	-7.0	GLUA:166
	42607646	Tinosporinone	3	-6.7	ASNA:142, THRA:190, GLNA:192

Table 3: Best docked compounds of Dengue Non-structural protein NS1

Protein name	Pub chem id	Ligand name	No. of H-bonds	Docking energy (Kcal mol^{-1})	Amino acids involved in H-bond interaction
4oig	42607646	Tinosporinone	1	-7.8	ARGE:314
	569848	Heptanediamide, N, N'-di-benzoyloxy-	2	-7.8	SERA:315, SERE315
	580963	3, 3-Dimethyl-1, 5, 13, 14-tetraoxa-10, 19-diazacyclotricosane-6, 9, 20, 23-tetrone	1	-7.6	SOA:4401
	73337	Magnoflorine	3	-7.3	ARGA:314, SOA:4405, LYSD:227

Table 4: Best docked compounds of Hepatitis A virus 3C proteinase

Protein name	Pub chem id	Ligand name	No. of H-bonds	Docking energy (Kcal mol^{-1})	Amino acids involved in H-bond interaction
1hav	75111036	Cordifolioside	3	-8.0	VALA:28, GLUA:49, HISA:145
	73337	Magnoflorine	2	-7.1	GLUB:139, GLNB:159
	580963	3, 3-Dimethyl-1, 5, 13, 14-tetraoxa-10, 19-diazacyclotricosane-6, 9, 20, 23-tetrone	1	-7.0	GLNB:206
	2353	Berberine	1	-6.9	HISA:145

compound was fixed through customary hydrogen bond to the ligand binding of SARS-CoV-2 Mpro with THRA:26, HISA:4 with binding energy of -7.6 Kcal mol^{-1} (Figure 1), for dengue nonstructural protein NS1 the best docked compound was fixed in the binding pocket via conventional hydrogen bond with ARG E:314 with bonding strength of -7.9 Kcal mol^{-1} (Figure 2) and for hepatitis A virus 3C proteinase the best docked compound was fixed in the bonding pocket via standard hydrogen bond with VALA:28, GLUA:49, HISA:145 with binding energy of -8.0 Kcal mol^{-1} (Figure 3).

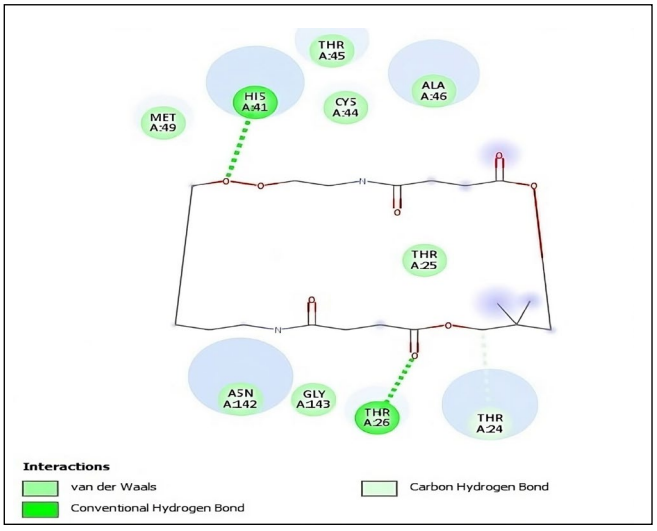

Figure 1: SARS-CoV-2 Mpro with 3, 3-Dimethyl-1, 5, 13, 14-tetraoxa-10, 19 diazacyclotricosane-6, 9, 20, 23-tetrone

In a similar manner, Chowdhury (2021); Krupanidhi et al. (2021); Thakkar et al. (2021) study employed network pharmacology, molecular docking, and molecular dynamics tools for an in silico investigation. This study revealed that within the array of phytochemicals from *T. cordifolia* under examination, berberine displayed the capability to modulate the 3CLpro protein's function through a straightforward inhibitory mechanism, consequently regulating viral replication. The selection of *T. cordifolia* for this study was

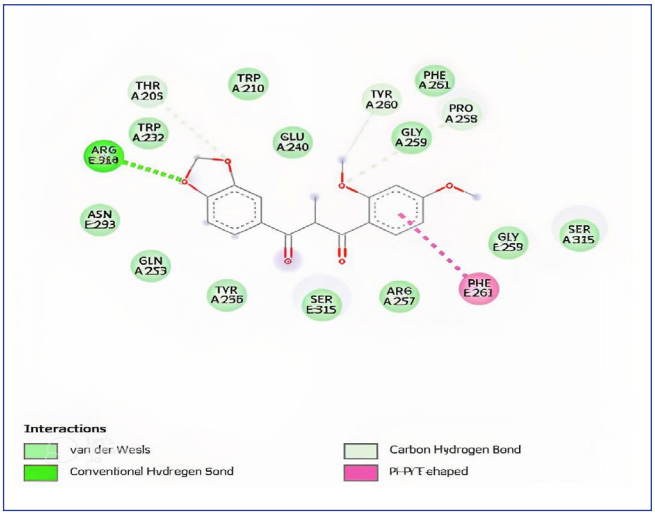

Figure 2: Dengue non-structural protein NS1 with Tinosporinone

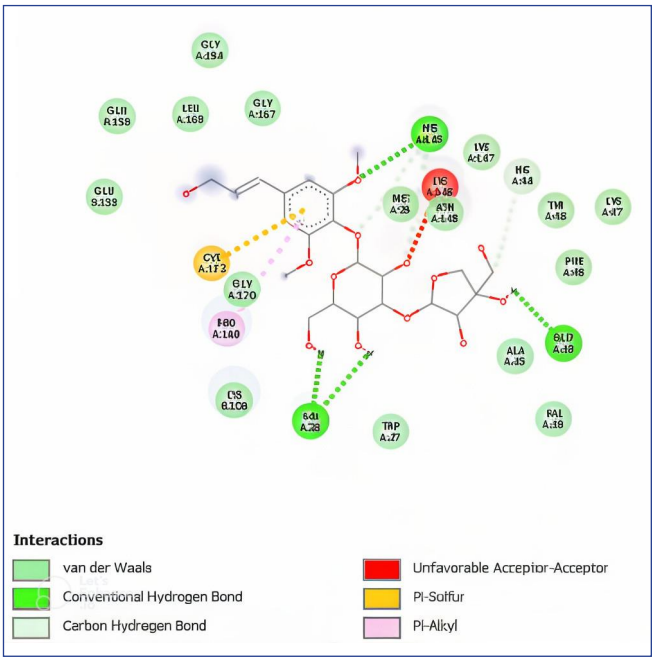

Figure 3: Hepatitis A virus 3C proteinase with Cordifolioside

influenced by its prominent constituents, acknowledged for their multifaceted antiviral properties and established usage in addressing conditions such as diabetes, rheumatoid arthritis, and jaundice. Kaushik et al. (2021) observed that both in silico and in vitro infection models indicated the potential therapeutic efficacy against DENV-2 of *T. cordifolia*'s crude extracts, bioactive fractions, and the bioactive synthetic compound magnoflorine (-9.22 kcal mol^{-1}). In 2023, Moharana and colleagues underscored the in-silico potential of phytocompounds derived from *T. cordifolia* against hepatitis viruses (HAV). By utilizing molecular docking, the researchers scrutinized the binding interactions between the phytocompounds and HAV. Among the studied chemicals, including chasmanthin, malabarolide, menispermacide, tinosporaside, and tinosporinone, molecular docking investigations revealed a superior affinity of these compounds towards HAV compared to other substances (Moharana et al., 2023). Based on good binding energy, drug-likeness and efficient pharmacokinetics properties it was evident that the compounds 3, 3-Dimethy l-1, 5, 13, 14-tetraoxa-10, 19-diazacyclotricosane - 6, 9, 20, 23-tetrone, tinosporinone, and cordifolioside were conceived as possible blockers for SARS-CoV-2 main protease (M_{pro}), Dengue virus non-structural Protein NS1 and Hepatitis A virus 3C proteinase, respectively.

4. CONCLUSION

The phytopharmaceutical compounds, namely 3, 3-Dimethyl-1, 5, 13, 14-tetraoxa-10, 19-diazacyclotricosane-6, 9, 20, 23-tetrone, tinosporinone, and cordifolioside were conceived as significant barriers to SARS-CoV-2, Dengue and Hepatitis A viruses. The present *in silico* study proved that *Tinospora cordifolia* plant as a potent, selective and nontoxic inhibitor of viruses like SARS-CoV-2, Dengue and Hepatitis A.

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