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ORIGINAL ARTICLE

Computationally approached inhibition potential of *Tinospora cordifolia* towards COVID-19 targets

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Abstract The recent emergence of novel coronavirus (SARS-CoV-2) has been a major threat to human society, as the challenge of finding suitable drug or vaccine is not met till date. With increasing morbidity and mortality, the need for novel drug candidates is under great demand. The investigations are progressing towards COVID-19 therapeutics. Among the various strategies employed, the use of repurposed drugs is competing along with novel drug inventions. Based on the therapeutic significance, the chemical constituents from the extract of *Tinospora cordifolia* belonging to various classes like alkaloids, lignans, steroids and terpenoids are investigated as potential drug candidates for COVID-19. The inhibition potential of the proposed compounds against viral spike protein and human receptor ACE2 were evaluated by computational molecular modeling (Auto dock), along with their ADME/T properties. Prior to docking, the initial geometry of the compounds were optimized by Density functional theory (DFT) method employing B3LYP hybrid functional and 6–311 + + G (d,p) basis set. The results of molecular docking and ADME/T studies have revealed 6 constituents as potential drug candidates that can inhibit the binding of SARS-CoV-2 spike protein with the human receptor ACE2 protein. The narrowed down list of constituents from *Tinospora cordifolia* paved way for further tuning their ability to inhibit COVID-19 by modifying the chemical structures and by employing computational geometry optimization and docking methods.

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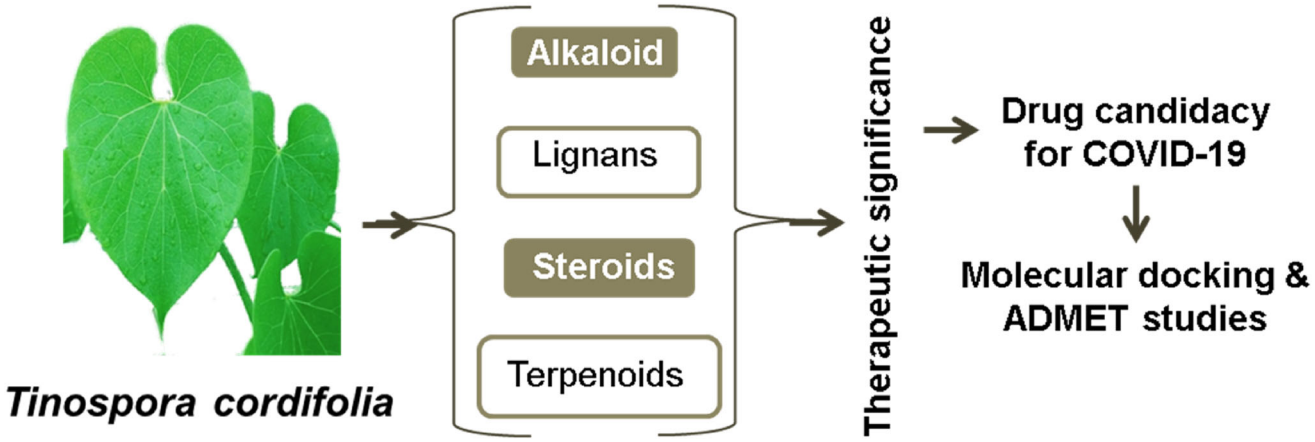
Graphic abstract



Keywords SARS-CoV-2; COVID-19 · Therapeutics · Inhibitors · *Tinospora cordifolia*

Introduction

The emergence of COVID-19 pandemic [1, 2] in December 2019, caused by the severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] [3, 4] has imposed severe social and economic burden in countries across the globe. Initially this viral infection was diagnosed to cause severe acute respiratory syndrome (SARS) in humans [5], and later reports revealed the susceptability of cats and ferrets also to have acquired COVID-19 infection. [6, 7]. It is believed that the viral spread is not air/water borne or through insects/animals. It has spread to many countries round the globe mainly through societal interactions including transmission from human-to-human through droplets, contaminated hand or surface contacts. Now there has been a daunting task for the scientists to not only control the morbidity but also the steeply raising mortality [8].

Though the mode of infection by SARS-CoV-2 is known to be very similar to SARS-CoV [9, 10], there exists the challenge of controlling the rate of infection and rapid treatment methods for the infected patients [11, 12]. Till date no antiviral drugs with proven efficacy nor are there vaccines for its prevention. Several clinically available antiviral drugs are reported in the literature and have been in use to suppress different viral particles [13, 14]. For the past 10–15 years, researchers are working on the development of antiviral drugs for SARS-CoV and MERS-CoV [15, 16] and till date no successful results appear. Now SARS-CoV-2 is added to the list.

Detailed investigations on various phytoconstituents of *Tinospora cordifolia* as potent drugs targeting the main protease (Mpro) of the virus was carried out recently [17]. The present focus of investigations resides on two other potential targets: 1. Virus (Receptor binding motifs—spike (S), envelope (E) and nucleocapsid (N) proteins, RNA dependent RNA polymerases and 2. Receptor motif on human ACE2 (angiotensin converting enzyme) and its associated functional proteins like TMPRSS2 and B^0AT1. It is difficult to have a complete evaluation of small molecular drug candidates for therapies directed towards the host with the inadequately available knowledge on the molecular details of the infection caused by SARS-CoV-2 [18, 19]. Recently, several research works have been published with novel and refurbished drug candidates to tackle the situation [14].

Until recently, there was a speculation that hydroxychloroquine could inhibit the viral infection [20]. But there was no solid proof on the method of inhibition. With the current status on the spread of infection, it is mandatory on emergency basis to develop strategies to control the morbidity and mortality. A systematic understanding on the host dependencies of the SARS-CoV-2 virus to identify other host proteins is the need of the hour. Many therapeutic strategies target the host-virus interface, but such drugs are prone to induced severe side effects [20]. It is very unfortunate that we have very minimal knowledge on the molecular details of SARS-CoV-2 infection to further proceed with a comprehensive evaluation of small molecular therapeutic candidates directed towards the host. Several mathematical models [21, 22] and computational strategies [23] are being currently under investigation to identify the interactions at the interface. Moreover, to devise therapeutic strategies, it is important to know how the virus invades the humans during infection and this knowledge can be applied to develop new drugs and to repurpose the existing ones [24]. There are also reports on

various constituents from plants [25] of medicinal values as potential inhibitors and anti-viral drugs [26–28].

Recently, Government of India has released an advisory from the ministry of Ayurveda, to meet the challenges caused by the rapid spread of COVID-19 in India [29]. The major focus of this system was to bring lifestyle modifications and prophylactics to improve the immunity in humans. In this context, it was reported that an ayurvedic medicine Samshamani Vati (aqueous extract of *Tinospora cordifolia*), when administered at 500 mg, twice a day for 15 days, could serve as prophylaxis [30]. The same is also reported to induce immunomodulatory effect [31–33] in human immuno-deficiency virus positive patients. [34] The various constituents of *Tinospora cordifolia* are known to exhibit a broad spectrum of therapeutic activities including anticancer, antimicrobial, antitoxic, antidiabetic, hypolipidermic, wound healing, immunomodulation, etc. and 31 different constituents (or chemical compounds) of *Tinospora cordifolia* were reported in literature [35]. It belongs to the family of Menispermaceae and is known for the pharmacological activities exhibited by the chemical constituents like glycosides, terpenoids, alkaloids, essential oils, fatty acids, etc., present in different parts of the plant like root and stem. The plant possesses various medicinal properties [36] like anti-diabetic, anti-allergic, anti-stress, anti-leprotic, anti-malarial, anti-neoplastic, hepatoprotective, immunomodulatory, etc.

With the available scientific approaches and computational facilities to model proteins and investigate protein–ligand interactions it becomes more supportive to predict the binding of small molecular drugs to protein targets [28, 37, 38]. Employing density functional theory [39] the geometry of all the molecules proposed as COVID-19 drug candidates, were optimized to understand structural features and hence their contribution to the inhibition or druggable potential. For the first time in literature, herein we are reporting the inhibitory effects of selected constituents of *Tinospora cordifolia* on human ACE2 protein and the main protease of SARS-CoV-2 using molecular docking and pharmacokinetic studies. In this manuscript, we have investigated the various constituents of *Tinospora cordifolia* for their potency to inhibit the host receptor for SARS-CoV-2 by molecular docking interactions.

Materials and methods

Docking calculations

The X-ray structure were obtained from Brookhaven Protein Data Bank for SARS coronavirus spike receptor-binding domain complexed with its receptor (PDB id: 2AJF) and the main protease of COVID-19 in complex with an inhibitor (PDB ID: 6LU7) and were considered for docking studies. The protein structure coordinates for docking were obtained from the above by removing the bound receptors, inhibitors, water molecules and other hetero atoms. Further, using AutoDockTools-1.5.6, the Kollman charges [40] were assigned to the proteins after adding the hydrogen atoms. Employing molecular mechanics, the 3D coordinates of the proposed inhibitors were constructed and optimized. Auto Tors was used to define the possible torsions associated with the inhibitors. All the inhibitors were treated as flexible throughout the docking procedures. The already reported binding pocket in the proteins was used to generate a grid box to encapsulate the active site. The auto grid program was used to pre-calculate the grid maps of interaction energies between protein and various atom types present in the inhibitors. The conformational states of the flexible inhibitors were explored using Lamarckian genetic algorithm coupled with energy assessments based on AMBER force field. Docking calculations were performed with default parameters. The binding energy was evaluated using the following scoring function.

$$\Delta G = \Delta G_{vdw} + \Delta G_{hbond} + \Delta G_{elec} + \Delta G_{tor} + \Delta G_{desolv}$$

The free energy upon binding of the flexible ligand to the rigid target could be calculated using the equation that includes parameters like ΔG_{vdw} (dispersion/repulsion), ΔG_{elec} (electrostatic interaction), ΔG_{hbond} (hydrogen bonding), ΔG_{tor} (torsional constraints) and ΔG_{sol} (desolvation effects). The 3-dimensional interactions were generated using the visualizer associated with AutoDockTools-1.5.6 while the 2-dimensional interactions were generated using BIOVIA Discovery Studio visualizer (Figs. 1, 2 and ESI Fig. 1).

ADMET predictions

The pharmaco-kinetic properties such as absorption, distribution, metabolism, excretion and toxicity (ADMET) were predicted using the pkCSM/ADMET [41, 42]. This method employs graph-based signatures to develop predictive models for generating central ADMET properties for drug development. In absorption process, the drug reaches the blood stream from the site of the drug administration. The absorption of drugs depends on factors including polar surface area (PSA), membrane permeability (LogP), cell-based methods such as Caco-2, intestinal absorption, skin permeability levels, P-glycoprotein substrate or inhibitor. This approach uses various parameters such as the blood–brain barrier (logBB), CNS permeability (logPB), and the volume of distribution (VDss) are evaluating the distribution of drugs. Using CYP models for substrate (CYP2D6, CYP1A2, CYP2C19, CYP2C9, and

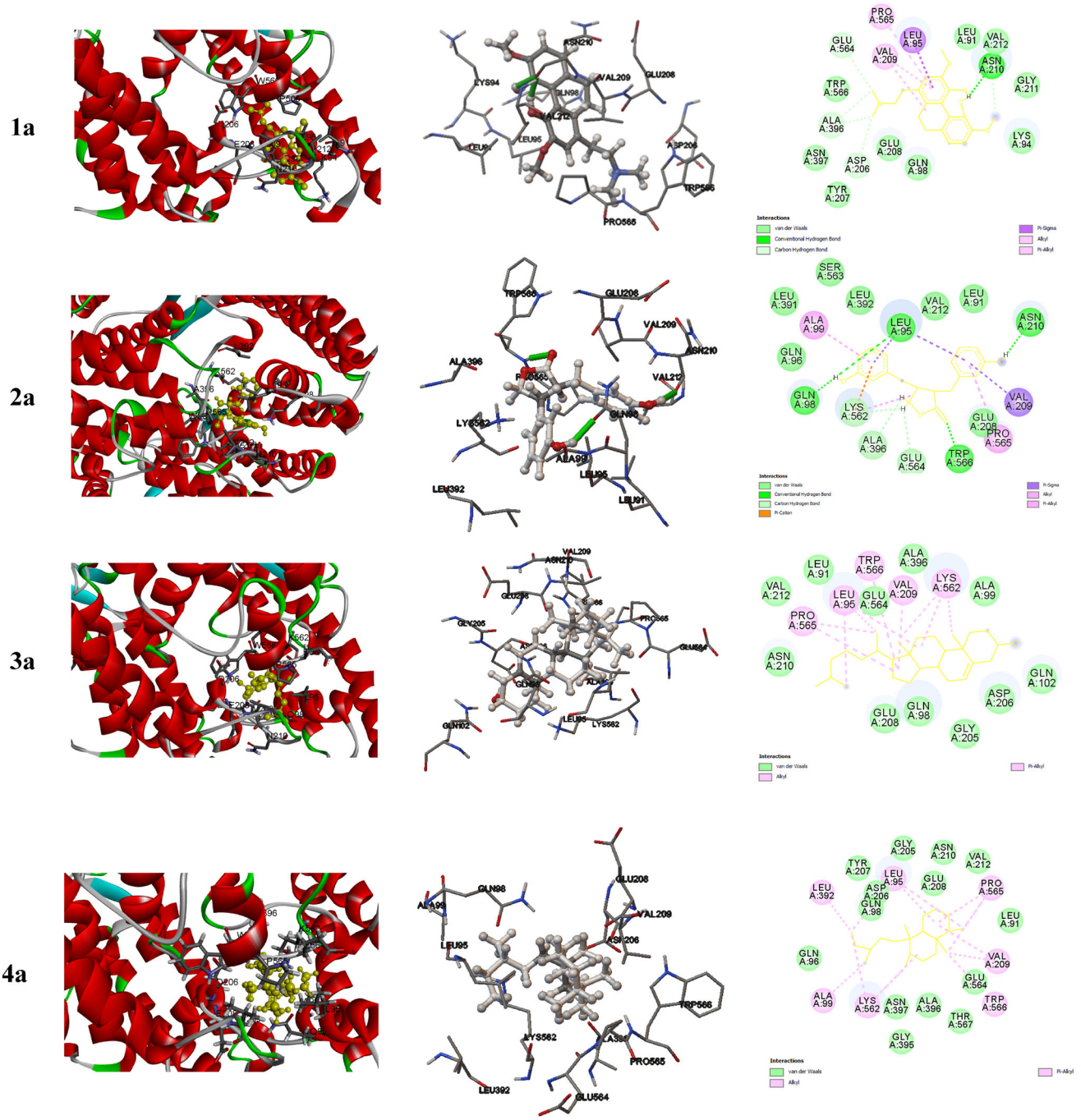


Fig.1 Representative docked conformation of various constituents of *Tinospora cordifolia* with 2AJF. The interaction of 3 dimensionally oriented molecules with the active site of 2ACE is shown (left); the interacting residues in the active site and the localization of the inhibitors is shown (middle); The 2 dimensional interactions with various residues in the active site and the nature of interactions are depicted (Right)

CYP3A4) the metabolisms of the drug molecules are evaluated. Excretion, a process where the body eliminates an unchanged drug or its metabolite, is predicted based on the total clearance model and renal OCT2 substrate. The toxicity of drugs is predicted based on AMES toxicity, hERG inhibition, hepatotoxicity, and skin sensitization [43, 44]. The PSA value relates the absorption properties of the inhibitor drugs. The PSA value of compounds greater than 140 indicates that the compounds have strong polarity and were poorly absorbed. The lipophilicity values are predicted by the LogP value. The LogP values less than 5 shows that the compound can easily permeable into cell

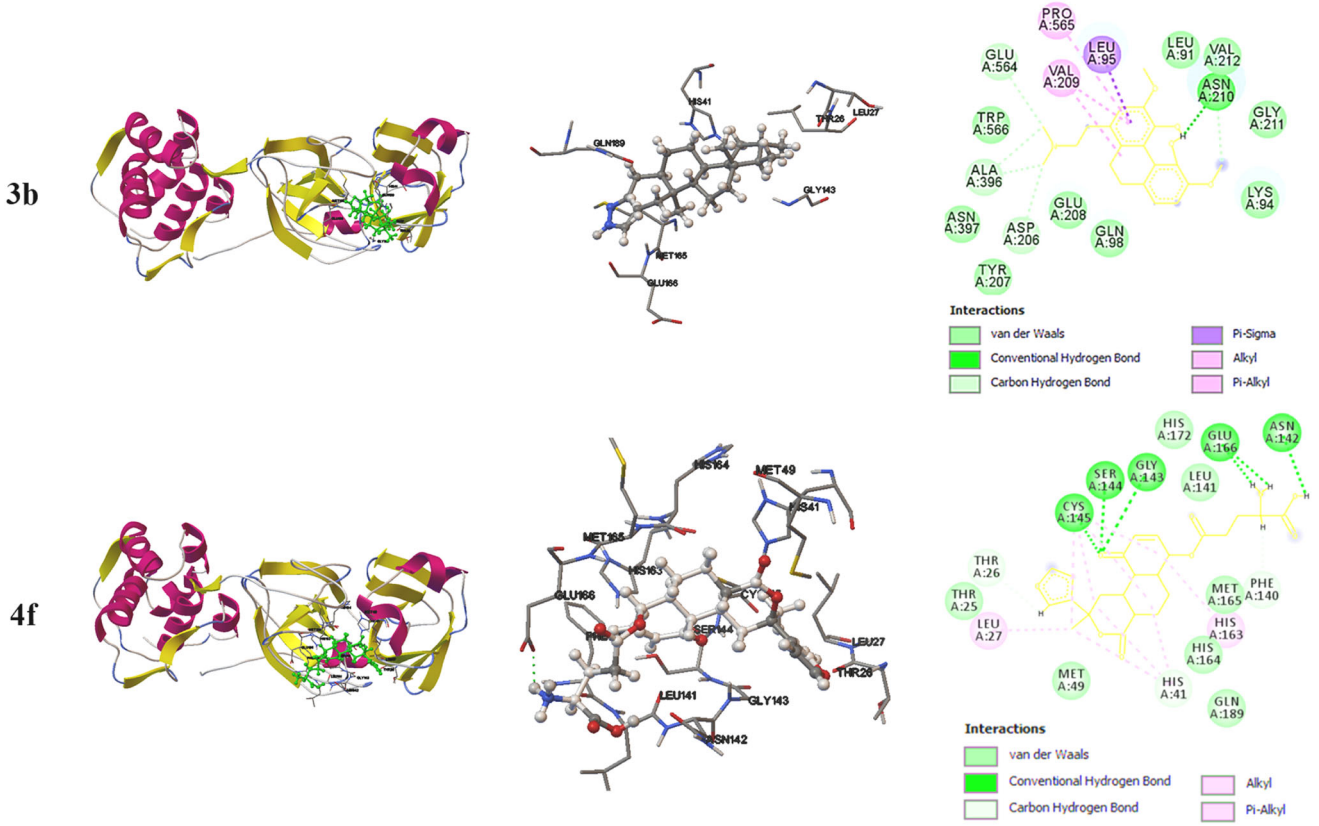
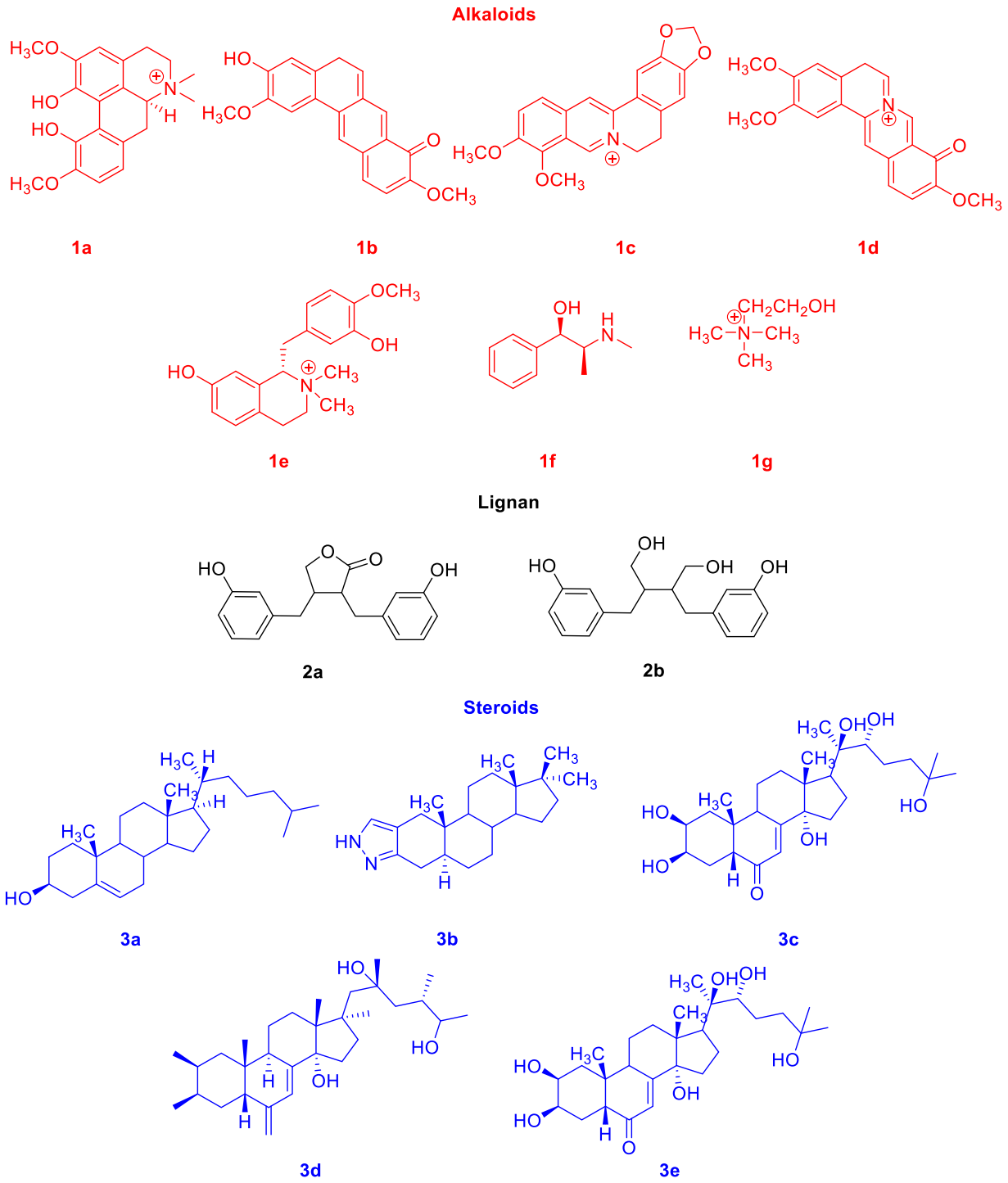


Fig.2 Docked conformation of various constituents of *Tinospora cordifolia* with 6LU7. The interaction of 3 dimensionally oriented molecules with the active site of 6LU7 is shown (left); the interacting residues in the active site and the localization of the inhibitors are shown (middle); The 2 dimensional interactions with various residues in the active site and the nature of interactions are depicted (Right)

membrane. Apart from these two parameters PSA and Log P, the following parameters such as Caco-2 permeability, intestinal absorption (human), skin permeability, and P-glycoprotein substrate or inhibitor were used to predict the absorption properties of the compounds. When the compounds exhibit the predicted value of > 0.90 indicated that the compound has high Caco-2 permeability and easily absorbed. The intestinal absorption (human), less than 30% is considered as poor absorption. The logKp value of greater than -2.5 is considered as poor skin permeability. The permeability glycoprotein (P-glycoprotein) also known as multidrug resistant protein or ATP binding Cassette (ABC) is an important protein in the cell membrane that eliminates the toxins and foreign substances from the cells. After the drug is absorbed from the membrane, the drug should be distributed to various tissues in the body to produce the pharmacological effects. The distribution volume (VDss) is a parameter which predicts the distribution of drugs in various tissues in the body. When the log VDss < -0.15 is considered as low distribution and higher than > 0.45 is considered as high distribution. After the drug absorbed in the body, the circulating drug exist in either bound or unbound state with the serum proteins in the blood. The efficacy of the drug may be affected by the fraction of drug binds with proteins within blood; the more bound state leads to poor efficacy. The blood brain barriers (BBB) protect the brain from exogenous compounds and selectively transport various nutrients, ions and other molecules that are crucial for neural functions. The BBB parameter is the important factor which is measured in vivo in animal models as logBB. The logBB value greater than 0.3 shows that the compounds can easily cross the BBB and logBB < -1 suggest that the compounds can't easily cross the BBB. Compounds with logPB > -2 are considered to penetrate the CNS, and logPB < -3 are considered unable to penetrate the CNS. The central nervous system (CNS) permeability is obtained by direct measurement of blood–brain permeability-surface area product. The CNS permeability between -3 to -2 is considered as penetrable to CNS. Cytochrome P450s plays important role in drug metabolism. Cytochrome P450s are classified into several groups depends on their biological functions. The major cytochromes subtypes involved in the drug metabolism are CYP2D6 and CYP3A4. The amount of the drug that is eliminated from the body is predicted by the total clearance.

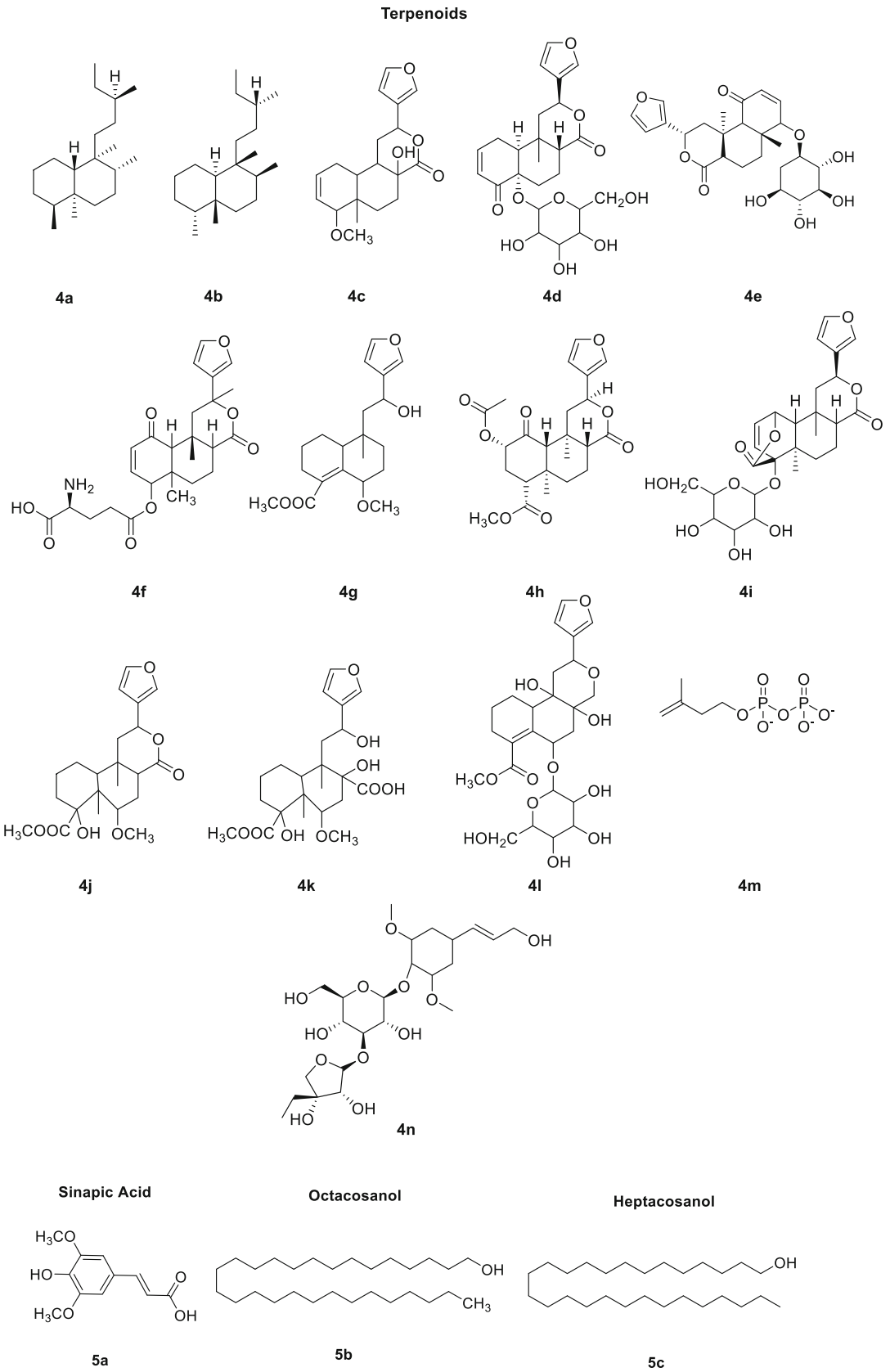


Scheme 1 Chemical constituents of *Tinospora cordifolia*

Results

Composition of *Tinospora cordifolia*

Tinospora cordifolia also known as Guduchi or Amrita is a medicinal plant possessing various therapeutic properties like jaundice, rheumatism, urinary tract infections, dermal diseases, anemia, inflammation, diabetes, etc. The constituents of this plant is known to support the immune system by increasing the body's resistance to infections and also to support the structure, function and levels of white blood cells. The observed pharmacological properties [32, 35, 45–47] of this plant is due to the presence of various constituents like alkaloids, steroids, terpenoids,



Scheme 1 continued

fatty acid mixtures, polysaccharides, etc. It is also reported that the extract of *Tinospora cordifolia* possesses broad-spectrum antiviral [17] and protease inhibitors [48]. Based on all the above pharmacological significance of these plant constituents, here in we have tried to investigate the interactions of various constituents with human host receptors for SARS-CoV-2, ACE2 [49–51] and main protease [52–54] by molecular docking [55].

The extract of *Tinospora cordifolia* consists of constituents that belong to different classes including alkaloids, steroids, terpenoids, lignans, glycosides, polysaccharides, aliphatic compounds, etc. [35]. The major and active chemical constituents along with their chemical structure are shown in Scheme 1. Structures **1a–g** belong to alkaloids, **2a–b** are lignans, **3a–e** are steroids, **4a–n** are terpenoids and **5a–c** belong to other categories. Most of these molecules are optically active and their stereochemistry plays a major role in their pharmacological properties. It is known that enantiomeric drugs possess different pharmacological properties.

Docking simulation

Recently, many natural products [28, 56] and refurbished drugs are reported in the literature as possible drug candidates for COVID-19. The broad spectrum therapeutic significance of *Tinospora cordifolia* has paved way for their investigation as potent inhibitors for SARS-CoV-2. To the best of our knowledge, till date there are no results related to SARS-CoV-2 inhibition through theoretical and experimental studies of compounds in *Tinospora cordifolia.* Herein we have chosen two targets to study the interaction of the constituents of *Tinospora cordifolia*: angiotensin converting enzyme (ACE2), an integral membrane glycoprotein, which serves as the human receptor for SARS-CoV-2 and the main protease (M^{pro}), which is involves in processing the polyprotein that is translated from viral RNA. With the above two targets we have carried out the molecular docking studies with 31 different constituents of *Tinospora cordifolia*. The results (ESI Table 1) indicate that **1a**, **2a, 3a–b** and **4a–e** exhibit strong interaction while **1b–f**, **2b, 3c–d**, and **4f–n** exhibit moderate interaction with 2AJF [57] (human ACE2 protein). In

Table 1 Energy parameters (kCal/mol) associated with docking interactions of various compounds in *Tinospora cordifolia* with human ACE2 (PDB id. 2AJF): A, Binding energy; B, van der Waals & hydrogen bond energy, C, Electrostatic energy, D, Torsional energy

2AJF	A	B	C	D	Interacting residues
Alkaloids					
1a	− 5.5	− 6.63	− 0.95	2.09	***L91, K94, L95, Q98, D206, E208, V209, N210, V212, P565, W566***
1e	− 4.2	− 6.51	− 0.08	2.39	***L91, L95, A99, Q98, E208, V209, N210, L391, L392, A396, K562, E564, P565, W566***
Lignans					
2b	− 4.81	− 7.71	− 0.37	3.28	***L91, L95, Q98, A99, E208, V209, N210, V212, K562, P565, W566***
Steroids					
3a	− 5.83	− 7.63	0.01	1.79	***L95, Q98, Q102, G205, D206, E208, V209, N210, A396, K562, E564, P565, W566***
3c	− 4.84	− 7.53	− 0.29	2.98	***L91, K94, L95, Q98, D206, E208, V209, N210, A396, E564, P565, W566***
3d	− 4.62	− 6.8	− 0.21	2.39	***L85, K94, L95, Q98, N194, H195, Y196, V209, N210, V212, R219, P565***
3e	− 3.83	− 6.55	− 0.56	3.28	***L91, L95, Q98, Q102, D206, E208, N210, A396, K562***
Terpenoids					
4d	− 5.05	− 7.18	− 0.25	2.39	***L91, L95, Q98, G205, D206, E208, V209, N210, V212, A396, K562, P565, W566***
4e	− 4.88	− 7.09	0.12	2.09	*L91, L95, Q98, Q102, Y202, G205, D206, V209, A396, K562, E564, P565, W566*
4f	− 4.08	− 6.31	− 0.45	2.68	***L95, Q98, G205, D206, E208, V209, A396, K562, P565, W566***
4 g	− 4.03	− 6.09	− 0.03	2.09	***L91, K94, L95, Q98, E208, V209, N210, V212, E564, P565, W566***
4i	− 3.43	− 5.82	0.01	2.39	*Q86, E87, I88, L91, K94, L95, N210*
4 k	− 2.2	− 5.52	0.04	3.28	***L91, L95, Q98, G205, D206, E208, V209, A396, K562, E564, P565, W566***
4 l	− 2.06	− 5.37	− 0.27	3.58	***L95, Q98, A99, Q102, Y202, G205, G206, E208, A396, K562, E564, P565, W566***
4 m	− 1.84	− 4.17	− 0.36	2.68	***L95, D206, V209, N210, A396, K562, P565, W566***
4n	0.98	− 4.12	− 0.57	5.67	*Q102, Y196, Y202, G205, D206, N394, N397, G395, E398, K562*
Others					
5b	− 1.04	− 9.03	− 0.07	8.05	***L91, K94, L95, Q98, A99, D206, E208, V209, N210, A396, K562, E564, P565, W566***
5c	− 0.59	− 8.3	− 0.04	7.76	***L91, K94, L95, Q98, D206, E208, V209, N210, K562, E564, P565***

*Non-polar residues shown in bold

Table 2 Energy parameters (kCal/mol) associated with docking interactions of various compounds in *Tinospora cordifolia* with M^{pro} (PDB id. 6LU7): A, Bindind energy; B, van der Waals & hydrogen bond energy, C, Electrostatic energy, D, Torsional energy

6LU7	A	B	C	D	Interacting residues
3b	− 5.05	− 5	− 0.05	0	*T26, L27, H41, G143, M165, E166, Q189*
4f	− 5.09	− 6.22	− 1.55	2.68	*T26, L27, H41, M49, F140, L141, N142, G143, S144, C145, H163, H164, M165, E166*

*Non-polar residues shown in bold

order to narrow down, the molecules that contribute significantly towards destabilizing the binding interactions are only considered and are listed in Table 1. The inhibitory effect on 6LU7 [58] (main protease) as evaluated from various interaction energy parameters (ESI Table 3) indicate that **2a** and **4a** interact strongly while **3a–b** and **4b–e** show moderate inhibition. The strong binding of proposed candidates to the active site of the enzyme leads to activity inhibition. The corresponding interacting residues with 2AJF and 6LU7 are given in ESI Table 2 and ESI table 4 respectively.

The interacting resides from the binding pocket of 2AJF with various constituents are given in (ESI Table 2). The dominantly interacting compounds with 2AJF are depicted in Fig. 1.

The interaction parameters of selected compounds from the extract of *Tinospora cordifolia* with the main protease (6LU7) of SARS-CoV-2 are given Table 2 along with the interacting residues (ESI tables 3 & 4). Unlike the interactions with human ACE2, compounds **3b** and **4f** were found to exhibit strong interaction while moderate interactions were observed in the cases of **3a, 3d, 4a, 4b, 4e** and **4 h**. No significant interactions were observed with alkaloid class of compounds as such. The interacting residues are tabulated in (ESI table 4) and the significant inhibitory interactions from the selected compounds are depicted in Fig. 2.

Absorption, distribution, metabolism, excretion and toxicity studies [59–61]

Prediction of ADMET properties of alkaloids

The pharmacokinetic [30] parameters play important role in drug discovery process [62]. The predicted ADME/T properties are given in ESI table 5. It could be observed that compounds **1a, 1c** and **1d** are poorly absorbed due to their high polar nature, though they have high potential to penetrate the cell membrane. The absorption properties of the alkaloids are listed in ESI table 5. The listed alkaloids show high distribution, expect for **1 g**. All the listed alkaloids possess the ability to penetrate through the CNS except **1c**. All alkaloids can be easily cleared from the system except **1b**. The toxicology prediction shows that all alkaloids exhibit hepatotoxicity except **1a, 1e** and **1f** while **1e** exhibits cardiotoxicity.

Prediction of ADMET properties of lignans and steroids

The predicted ADME/T properties of lignans and steroids are given in ESI table 6. The results indicate that lignans possess better absorption ability than steroids. Among the lignans and steroids only **3b** shows high distribution potential. The compounds **3a** and **3d** can easily penetrate through the CNS. **2a, 2b** and **3d** show moderate levels for excretion. The compounds **2a, 2b, 3a, 3b** exhibit cardiotoxicity whereas hepatotoxicity is observed only for **3b** and **3d**.

Prediction of ADMET properties of terpenoids

The predicted ADME/T properties of terpenoids are given in ESI table 7. The results indicate that all terpenoids except **4a**, **4b** and **4n** are highly polar and show poor absorption. The compounds **4a and 4b** possess the ability to cross blood brain barrier while all terpenoids exhibit similar tendency to permeate CNS. Except **3f** all the terpenoids can be easily excreted from the body. **4 g**, **4j** and **4 k** show hepatotoxicity.

Prediction of ADMET properties of others

The predicted ADME/T properties of other constituents are given in ESI table 8. Compound **5a** exhibits very good absorption and membrane permeation. **5b** and **5c** possess the ability to cross the BBB easily while compound **5a** can penetrate the CNS. **5a** induces hepatotoxicity while compounds **5b** and **5c** are cardiotoxic. The predicted ADME/T properties of selected compounds are listed in Table 3.

Discussions

The results of molecular docking and pharmacokinetic analyses for the interactions with human receptor protein ACE2 have revealed that among the selected candidates

Table 3 Predicted ADME/T properties

Compounds	Polar surface area	LogP	BBB permeability	CNS permeability	Total clearance	Hepatotoxicity
1e	139.63	3.0607	− 0.221	− 2.403	0.743	No
3a	174.309	7.3887	0.777	− 1.746	0.589	No
4b	127.66	6.6914	0.853	− 1.399	0.986	No
4n	206.31	− 0.559	− 1.742	− 4.092	1.576	No
5b	185.387	10.1412	1.029	− 1.066	2.152	No
5c	179.022	9.7511	1.004	− 1.054	2.13	No

listed in Table 1, the major destabilizing contribution is from the torsional energy arising from the presence of freely rotating single bonds. This could be the reason for **1 g** to have very poor interaction among the alkaloids. The same can be extended for the case of lignans and steroids (**2a** and **3a-b** respectively) to have comparatively stronger affinity for the considered active site than **2b** and **3c-d** respectively. In case of terpenoids, **4a-d** binds strongly to the active site than the moderately binding **4e-g**. It could be observed from Table 1 and ESI Table 2 that the major interacting residues are non-polar in nature. In the case of **4d**, the stabilization caused by non-polar interactions is nullified by the high torsional energy of the molecule. Though there is a negligible difference in the intermolecular energy for all the above preferred molecules, the moderately binding ones have high torsional energy, which reduces their target interaction, while the imparted stability has its major contribution from hydrogen bond interactions and van der Waals interactions. **5b-c**, bind weakly to the target 2AJF, as the intermolecular stabilizing energy is neutralized by the high torsional energies.

In the case of interactions with viral main protease (M^{pro}), the results of molecular docking and pharmacokinetic analyses have revealed that the stabilizing interactions have its contribution from polar and acidic amino acids along with non-polar interactions. In compound **4f**, though the torsional energy is very high, the stabilizing effect is observed from the low internal energy of the molecule as shown in Table 2 and ESI table 4.

The docking results have revealed that compounds **1a**, **1e**, **2b**, **3a**, **3c–e**, **4d–g**, **4i**, **4k–n**, **5b** and **5c** possess the ability to bind to the proposed targets 2AJF and 6LU7. Some of the above candidates have poor binding affinities, by the fact that these molecules exhibit very high torsional energies that could potentially destabilize the interactions with target residues. But still their candidacy is considered, as these molecules could serve as lead compounds to engineering molecules with reduced torsions.

The pharmacokinetic analyses revealed that among the alkaloids (ESI table 5), the polar surface area of **1b**, **1e**, **1f** and **1g** were less than 140 and have high potential to get absorbed, while in the case of lignans (ESI table 6), both **2a** and **2b** were found to be more potent. Among terpenoids (ESI table 7), **4a** and **4b** and with other miscellaneous compounds listed in ESI table 8, 5a was highly polar. Based on the estimated lipophilicity, all alkaloids (**1a–g**) and lignans (**2a–b**) can easily penetrate the cell membrane. While among the steroids, (**3a** and **3d**) and terpenoids (**4a** and **4b**) and **5b** and **5c** does not possess the ability to penetrate cell membrane. All alkaloids except **1g**, **3b**, **4a** and **4b** possess very high drug distribution, while others exhibit moderate or poor distribution. Most of the alkaloids (**1a**, **1c–d**, **1f**) and steroids (**3b** and **3d**) were hepatotoxic, while terpenoids and other compounds were non-toxic. The potentiality of various chemical constituents from *Tinospora cordifolia* to inhibit SARS-CoV-2 was evaluated through computational methods. These compounds have been reported to possess numerous pharmacological activities. The docking results indicate that among all the constituent compounds **1a 1e**, **2a–c** and **3a–d** possess the ability to interact strongly with human ACE2 protein and **3b** and **4f** with the main protease of SARS-CoV-2. The above conclusion is based on the extent of interaction or their potential as lead compounds for further investigations to reduce their torsional energies. It is believed that strong interactions with human receptor for SARS-CoV-2 could prevent the entry of the virus and thus could act as a prophylactic for COVID-19. Further the evaluated pharmacokinetic properties narrowed down the above candidates based on their druggability. From the overall ADMET properties, it could be concluded that compounds **1a, 1e, 2a, 2b, 4a, 4g** and **5a** as potential drug candidates for COVID-19. Overall observation from combined results of docking analysis and ADMET properties revealed compounds **1e, 3a, 4b, 4n, 5b** and **5c** could be potential drug candidates out of 31 constituents of the extract from *Tinospora cordifolia*. The druggable potential of the above six constituents can be tuned by engineering the molecules with less torsional energies and by lowering their cardiotoxicity.

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Compliance with ethical standards

Conflict of interest The authors declare no competing financial interest**.**

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