In silico Investigation of Tridax procumbens Phyto-Constituents Against SARS-CoV-2 Infection

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Abstract: Tridax procumbens is a popular medicinal plant traditionally used for wound healing and bronchial catarrh. In the current study, in silico computational analysis of 22 active phytoconstituents of T. procumbens was performed against SARS-CoV-2. Molecular Docking studies against six key targets of SARS-CoV-2 including PDB ID: 6LU7, a main protease 3CLpro/Mpro; PDB ID: 6NUR, SARS-Coronavirus NSP12 polymerase bound to NSP7 and NSP8 co-factors, PDB ID: 6m71, SARS-Cov-2 RNA-dependent RNA polymerase (RdRp), PDB ID: 6CS2, SARS Spike Glycoprotein - human ACE2 complex a Stabilized variant; PDB ID: 6VXX, spike glycoprotein of SARS-CoV-2 and its receptor Angiotensin-converting enzyme-2 (PDB ID: 1R42) were accomplished. Additionally, in silico prediction studies using pharmacokinetics (ADMET) properties and the protection profile to identify the paramount drug candidates were also done using online SwissADME and pkCSM web servers. Comprehensive docking analyses confirmed that out of 22 screened phytoconstituents, 6 compounds: Bergenin, beta-Sitosterol, Centaurein, Procumbentin, Luteolin, and Puerarin showed high binding affinity with studied SARS-CoV-2 target proteins. Pharmacokinetics prediction studies further verified that all selected phytoconstituents were safe with good quality ADMET properties and lacking carcinogenic and tumorigenic properties. Thus, these selected drugs can effectively control COVID-19 and improve immunity, which can be confirmed by further studies.

Keywords: SARS-CoV-2; Tridax procumbens; molecular docking; ADMET analysis.

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1. Introduction

At the end of December 2019, a novel strain of coronavirus was detected in Wuhan city of China. It caused a pneumonia-like epidemic and is titled Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [1]. World Health Organization (WHO) on 11th March, 2020, announced this coronavirus disease (Covid-19) as a global pandemic in three months of its first case appearance [2-3]. Afterward, Covid-19 disease has been outspread to 216 countries encompassing India and allied zones, causing over 14, 731, 563 established cases and over 611,284 deaths as of July 22, 2020 (https://www.who.int/emergencies/diseases/novel-coronavirus-2019). COVID-19 sufferers show common symptoms like cold, flu, fever, and similar associated signs like sore throat, coughing, etc. However, in severe infection, it leads to acute respiratory distress syndrome (ARDS) with rarely collapsing vital organ functions,, including kidney failure, thus ultimately leading to death [4].

Even though all-inclusive efforts are being taken to cure the pandemic, clinically-proven prophylaxis, and therapeutic strategy are still demanding [5]. For active management
of COVID-19, numerous drugs have been tried or repurposed and designed predominantly targeting the host cells or immune system and directly inhibiting SARS-CoV-2 [6]. Hitherto from clinical interventions tried worldwide, to date, no medicine is available that has the ability to cure the COVID-19 completely.

Hence, in the current pandemic condition, investigation of novel bioactive compounds having a strong potential of fighting against SARS-CoV-2 viral infection is crucially essential. These compounds should also offer immunity and reinforce us to overcome this infection. Indian medicinal plants are well known for developing drugs to cure various diseases and strengthen our immune system. Besides this, the hopeful part of plant-based drugs is that they reveal less or no side effects due to their structure, which strongly reacts with pathogens and/or their toxins in such a manner that can cause the least damage to host’s important bio-molecules or physiology. Throughout the COVID-19 pandemic, consumption of immuno-modulatory supplements is essential to sustain our immune system to combat the SARS-CoV-2 infection. This is also specified by India’s Ministry of AYUSH by the statement, “Ayurveda’s immunity-boosting measures for self-care during COVID-19 crisis” [7].

*Tridax procumbens* (Jayanti Veda) is a common, widespread weed commonly known as coat buttons plant found throughout India and a famous ethno-botanical, Ayurvedic, and Unani medicinal plant. *T. procumbens* extracts showed the existence of alkaloids, carotenoids, flavonoids (especially catechins and flavones), saponins, tannins, flavonoids (centaureidin and centaurein) and bergenin [8], lipid components like luteolin, glucoluteolin, quercetin, isoquercetin, and fumaric acid [9]. It is also an abundant source of minerals like iron, copper, manganese, sodium, and zinc [10] and other trace minerals such as magnesium, phosphorous, potassium, selenium, and calcium [11].

Its leaves are traditionally used for diabetic and non-diabetic wound healing [12-15] and procoagulant activity [16]. Its drink is also used to cure bronchial catarrh, diarrhea, dysentery [17]. Its extract possess antihyperuricemia, antioxidant, and antibacterial [18-19], antifungal [20], anti-leshmanial [21], antibiotic against challenging multidrug-resistant urinary tract bacterial isolates [22], anti-hyperglycemic [23], anti-diabetic [24], hepato-protective [25], hypotensive [26], vasorelaxant [27], immuno-modulatory [28], anti-arthritic [29], analgesic [30], anti-osteoporosis [31], anti-inflammatory [32] and anti-tubercular activity [33], and antitumor activities [34]. It is also used to cure asthma [35] and possesses antiviral activities [36-37].

So, the current study is aimed to reconnoiter the medicinal prospective of *Tridax procumbens* bioactive constituents against various proteins of SARS-CoV-2 by implementing computational methodologies. The data engendered is very promising and recommends that *Tridax procumbens* indeed has the competency to treat the SARS-CoV-2 infection effectively.

2. Materials and Methods

2.1. Protein retrieval and preparation.

Six fundamental targets: PDB ID: 6LU7 a main protease 3CLpro/Mpro; PDB ID: 6m71 SARS-CoV-2 RNA-dependent RNA polymerase (RdRp); PDB ID: 6NUR a recently identified SARS-Coronavirus NSP12 polymerase bound to NSP7 and NSP8 co-factors; PDB ID: 6CS2, SARS Spike Glycoprotein - human ACE2 complex a Stabilized variant; PDB ID: 6VXX, spike glycoprotein of SARS-CoV-2 and its receptor Angiotensin-converting enzyme-2 (PDB ID:
1R42) were selected for the current study. The structures were obtained from the https://www.rcsb.org/ website in PDB format. Further, the 3D PDB file of these proteins as processed using ‘A’ chain and eliminating allied ligands along with crystallographic water molecules, and adding polar hydrogen atoms.

2.1.1. Positive control.

Four known FDA drugs Chloroquine (CQ), Hydroxychloroquine (HCQ), Remdesivir (RDV), and Favipiravir, were selected as positive controls for the execution of blind docking. Their structures were also acquired in PDB format from the https://www.rcsb.org/ website.

2.1.2. Ligand structure preparation.

In total 22 active phyto-constituents of T. procumbens [38] were selected as dynamic inhibitory ligands for the existent study (details of compounds are illustrated in Supplementary Table S1. All selected ligand structures except Procumbentin were attained in SDF format from the https://pubchem.ncbi.nlm.nih.gov/ website and changed to PDB format using Online SMILES translator and structure file generator tool [39]. Procumbentin .MOL file was generated from ChemSpiderweb tool and converted to smiles.txt file and PDB file using website: https://cactus.nci.nih.gov/translate/. The 2D structures were retrieved from the ChemSpider: an online chemical information resource website. [40]. The particulars of PubChem CID, molecular formulae, and 2D structures are displayed in Supplementary Table S1.

2.2. Molecular docking.

First, PDB files of all selected molecules were changed in the .PDBQT format using PyRx software [41] and saved for further examination. The macromolecules, as well as ligands, were primed, and minimization of the energy was achieved. The grid box size was set at 40 X 40 X 40 the X, Y, and Z coordinates; the conf file was created using the details of PDBQT files name and grid box properties. Then by using the receptor.PDBQT file, ligand.PDBQT file and the X, Y, and Z coordinates; the binding affinity was calculated using AutoDock–Vina [42]. The best pose with the lowest binding affinity was mined for each selected ligand and positive controls. The visualization of the 3D structure of the receptor-ligand interactions together with the 2D structure of the molecular interactions was done using the Biovia Discovery Studio20.1.0 [43].

2.3. Physiochemical, pharmacokinetic, and ADMET properties of Tridaxprocumbens phyto-constituents.

Drug-likeness properties were acquired using the SWISSADME prediction tool http://www.swissadme.ch/) [44]. Toxicity assessment of Phyto-constituents was achieved using the pkCSM online tool [45]. The prediction of probable side-effects or cross-reactivity of phytoconstituents was made using the Swiss target prediction web tool available with http://www.swisstargetprediction.ch_website [46].
3. Results and Discussion

The available literature was used to identify 22 active phytoconstituents of *T. procumbens*. These phytoconstituents were prepared for docking and then used for *in silico* screening against six proteins of SARS-CoV-2. Based on the Molecular docking score, the six best ligands were selected. The docking scores of all the phytoconstituents are given in Table 1.

Table 1. Docking results in the form of Binding Affinity of different phytoconstituents of *Tridax procumbens* used for *in silico* screening against various proteins of SARS-CoV-2 (AutoDock Vina scores are in kcal/mol).

| Sr. No | Name of Compound          | Docking score of *Tridax procumbens* phytoconstituents (kcal/mol) | RMSD Lower Bound | RMSD Upper Bound |
|--------|---------------------------|---------------------------------------------------------------|-----------------|------------------|
| 01     | 5(alpha)-cholestanate     | Distance from Best Mode: -5.9                                  | 6LU7            | 6M71             |
| 02     | alpha-Selinene            | -5.9                                                          | -5.7            | -6.5             | -6.8             | -6.8             | 8                |
| 03     | Bergenin                  | -6.4                                                          | -6.7            | -7.5             | -8.1             | -6.4             | -7               |
| 04     | beta-Amyrenone            | -6.5                                                          | -7.9            | -8.1             | -7.5             | -7.3             | -8.1             |
| 05     | beta-Sitosterol           | -6.4                                                          | -7.2            | -7.9             | -6.7             | -7.3             | -10.6            |
| 06     | Betulinic acid            | -5.7                                                          | -7.2            | -7.4             | -6.9             | -6.9             | -8.6             |
| 07     | Caryophyllene             | -6.2                                                          | -5.7            | -5.9             | -5.1             | -5.7             | -6.3             |
| 08     | Centaureidin              | -6.2                                                          | -7.5            | -7.4             | -6.8             | -7.5             | -6.9             |
| 09     | Centaurein                | -5.9                                                          | -9              | -8               | -6.4             | -7               | -8.3             |
| 10     | (3,5)-16,17-Didehydrofalcacarilol | -4.9                                                    | 6.6             | 12123            |
| 11     | Esculetin                 | -5.9                                                          | -6              | -6.4             | -6.6             | -6.3             | -6.6             |
| 12     | Falcarinol                | -4.6                                                          | -5.6            | -5.5             | -5               | -4.5             | -4.8             |
| 13     | Limonene                  | -4.9                                                          | -4.9            | -5.7             | -5.1             | -5.3             | -5.7             |
| 14     | Lupeol                    | -6                                                             | -7.6            | -7.6             | -7.4             | -6.9             | -8.3             |
| 15     | Luteolin                  | -7                                                             | -7.6            | -8.5             | -7.4             | -7.1             | -7.8             |
| 16     | Methyl 10-oxooctadecanolate | -4.4                                                    | -4.3            | -4.5             | -4.2             | -5.1             | -5.3             |
| 17     | Procumbentin              | -6.4                                                          | -8.5            | -8.7             | -7.6             | -6.7             | -8.7             |
| 18     | Puerarin                  | -6.7                                                          | -7.8            | -7.9             | -6.7             | -8.2             | -8               |
| 19     | Stigmatosterol            | -6.6                                                          | -7.4            | -8.3             | -7               | -7               | -8.3             |
| 20     | Taraxasterol acetate      | -6.3                                                          | -8              | -7.8             | -6.5             | -7.2             | -8.5             |
| 21     | Voacangine                | -5.8                                                          | -7.1            | -7.4             | -6.1             | -6.1             | -7.1             |
| 22     | Zerumbone                 | -6.4                                                          | -5.9            | -6.1             | -5.5             | -5.6             | -6.4             |

**Positive controls**

| | | | | | | | |
| 1 | Chloroquine | -5.3 | -5.4 | -6.2 | -5.8 | -5.6 | -6.8 |
| 2 | Favipiravir  | -5.7 | -5.3 | -5.7 | -5.7 | -5 | -5.5 |
| 3 | Hydroxychloroquine | -5.6 | -5.7 | -6 | -5.5 | -5.9 | -6.4 |
| 4 | Remdesivir   | -5.5 | -6.5 | -8.1 | -6 | -6 | -6.6 |

3.1. The binding affinity of selected compounds.

Among the 22 phytoconstituents screened (Table 1), the binding energies for about 9 compounds were lesser than the upper threshold (-6 kcal/mol), generally considered as a cut-off in ligand-binding studies, but we also observed that 5 of these compounds were very close to this threshold.

Table 1 shows the binding affinity of all 22 phytoconstituents toward six proteins of SARS-CoV-2 screened in this study. Table 1 also displays variation in binding energy amongst each ligand and various SARS-CoV-2 macromolecules tested. The frequency distribution
The range of obtained Docking scores (kcal/mol) of various phytoconstituents of *T. procumbens* against various proteins of SARS-CoV-2 is illustrated in Figure 1. Table 2 shows the six topmost ligands showing the highest docking score are listed based on binding energy.

**Table 2.** Six Topmost compounds with the highest binding energy selected using docking results arranged as per their binding affinity score.

| Sr. No | Name of Selected ligand  | Interaction with SARS-CoV-2 protein | Docking score (kcal/mol) | Interacting Residues |
|--------|--------------------------|------------------------------------|--------------------------|----------------------|
| 1.     | beta-Sitosterol (PubChem CID-222284) | 1R42 | -10.6 | PRO346<sup>a</sup>, PHE390<sup>b</sup>, ARG393<sup>d</sup>, PHE40<sup>d</sup>, ALA348<sup>d</sup>, HIS378<sup>a</sup> |
| 2.     | Centaurein (PubChem CID-5489090) | 6M71 | -9 | GLU811<sup>a</sup>, SER814<sup>a</sup>, LYS798<sup>a</sup>, LYS621<sup>c</sup>, PRO620<sup>c</sup>, TRP617<sup>c</sup>, TRP800<sup>c</sup>, ASP761<sup>c</sup>, PRO620<sup>c</sup>, LYS798<sup>d</sup> |
| 3.     | Procumbentin (PubChem CID-6NUR) | 6NUR | -8.7 | ARG249<sup>a</sup>, LEU251<sup>a</sup>, ARG349<sup>a</sup>, THR246<sup>b</sup>, THR319<sup>b</sup>, LEU245<sup>b</sup>, PRO323<sup>d</sup>, PRO677<sup>d</sup>, PHE396<sup>d</sup>, VAL675<sup>d</sup>, PRO461<sup>d</sup>, ARG249<sup>d</sup> |
| 4.     | Puerarin (PubChem CID-6VXX) | 6VXX | -8.2 | ASN317<sup>a</sup>, SER316<sup>a</sup>, TYR612<sup>c</sup>, VAL595<sup>c</sup>, PHE318<sup>c</sup>, LYS304<sup>c</sup>, THR302<sup>c</sup>, ALA292<sup>c</sup>, CYS291<sup>c</sup>, CYS301<sup>c</sup>, GLU298<sup>c</sup> |
| 5.     | Bergenin (PubChem CID-6CS2) | 6CS2 | -8.1 | LEU843<sup>a</sup>, ASP757<sup>c</sup>, LYS715<sup>c</sup>, ASP849<sup>b</sup>, PRO1039<sup>b</sup>, HIS1040<sup>b</sup>, PRO845<sup>d</sup> |
| 6.     | Luteolin (PubChem CID-6LU7) | 6LU7 | -7 | ARG105<sup>a</sup>, ILE152<sup>a</sup>, GLN110<sup>a</sup>, THR111<sup>a</sup>, GLN107<sup>a</sup>, ILE106<sup>b</sup>, PHE294<sup>d</sup>, VAL104<sup>d</sup>, ASP153<sup>d</sup>, PHE8<sup>c</sup>, ASN151<sup>c</sup>, THR292<sup>c</sup> |

a-Hydrogen bond; b-Carbon Hydrogen bond; c-van der Waals; d-Hydrophobic interactions

The binding affinity for COVID-19 6LU7, a main protease 3CLpro/Mpro was in the range -4.4 kcal/mol (for Methyl 10-oxooctadecanoate) to -7 kcal/mol (for Luteolin). Overall, the lowest binding scores for all ligands were observed against this macromolecule. The
binding affinity for COVID-19 6m71 RdRp was in the range -4.3 kcal/mol (for Methyl 10-oxooctadecanoate) to -9 kcal/mol (for Centaurein). The binding affinity for COVID-19 6NUR SARS-Coronavirus NSPI2 polymerase was in the range -4.5 kcal/mol (Methyl 10-oxooctadecanoate) to -8.7 kcal/mol (for Procumbentin). The binding affinity for COVID-19 6CS2, SARS Spike Glycoprotein - human ACE2 complex was in the range -4.2 kcal/mol (for Methyl 10-oxooctadecanoate) to -8.1 kcal/mol (for Bergenin). The lowest binding score was observed for this macromolecule compared to the other five with all ligand docking scores. The binding affinity range for COVID-19 6VXX, spike glycoprotein of SARS-CoV-2 was from -4.5 kcal/mol (for Methyl 10-oxooctadecanoate) to -8.2 kcal/mol (for Puerarin), and for spike glycoprotein receptor Angiotensin-converting enzyme-2, 1R42 ranged between -4.8 kcal/mol (for Methyl 10-oxooctadecanoate) and -10.6 kcal/mol for beta-Sitosterol which is the highest docking score obtained from all ligands.

Thus we can clearly say that the ligand Methyl 10-oxooctadecanoate showed the lowest binding affinity against all receptors tested, whereas Procumbentin showed the highest binding affinity for maximum receptors (four) amongst all ligands screened herewith.

Interestingly the known antiviral drugs tested show binding scores in the range of -5 to -8.1 kcal/mol, which is far less than the score obtained for the majority of *T. procumbens* phytocentrists. So we can confidently and intensely state that these phytocentrists have much superior COVID-19 receptor inhibition capacity tested herein than these well-known approved drugs used as a positive control.

For convenience, the best 6 phytocentrists of *T. procumbens* who showed noteworthy results against all six receptors checked were selected for further analysis and compared with Remdesivir. It showed an overall good docking score (Table 1).

The interaction between SARS-CoV-2 amino acid residues with these selected phytocentrists is displayed in Table 2. These phytocentrists have validated commendable free energy of binding interactions with SARS-CoV-2 proteins (Table 2). The possible binding orientation of these selected phytocentrists within SARS-CoV-2 proteins, along with conforming hydrogen bonds and hydrophobic interactions, are correspondingly exemplified in Table 2.

The binding orientation of these top 6 phytocentrists with each with receptor was studied using Discovery studio visualizer, and best poses in 2D and 3D were produced (Table 3). Furthermore, comprehensive docking analyses demonstrated that beta-Sitosterol, Centaurein, and Procumbentin show a high binding affinity with the studied target proteins SARS-CoV2 followed by others, and the highest binding affinity was displayed by beta-Sitosterol.

3.2. Prediction of pharmacokinetic and ADMET properties.

Lipinski’s rule of 5 by is treated as a great method for assessing drug likeliness, which helps discover whether a specific chemical compound has certain biological and physiochemical properties that would succeed as a feasible orally active drug in humans. Lipinski’s rule guesses five assorted properties imperative for drug designing. Lipinski’s rule of five states that (i) molecular mass less than 500 Daltons, (ii) no more than 5 H-bond donors, (iii) no more than 10 H-bond acceptors, (iv) O/W partition coefficient log P not greater than 5. Suppose the molecule violates more than 3 descriptor constraints. In that case, it will not fit into the drug likeliness standards, and it is not considered for drug discovery [47]. A standard TPSA clarifies that the ligand has copious transport properties.
Physiochemical and ADMET properties of *T. procumbens* phytoconstituents with drug likeliness and various rules like Lipinski rule of five are represented in Supplementary Table S2 & S3.

**Table 3.** Nonbonding interactions of best-selected phytochemicals of *Tridax procumbens* with various proteins of SARS-CoV-2 (pose predicted by AutoDockVina and visualized by Discovery studio visualizer).

| H bond Interaction | 3D Interaction | 2D Interaction |
|--------------------|----------------|----------------|
| Interactions of Luteolin with 6LU7 |
| Interactions of Centaurein with 6M71 |
| Interactions of Procumbentin with 6NUR |
| Interactions of Bergenin with 6CS2 |
From the data obtained, we can say that most of the compounds tried to follow the rules, and some of them not. Nearly all compounds showed good synthetic accessibility value suggesting all the phytoconstituents can be synthesized. Overall results strongly agree that active phyto-components of *T. procumbens* retain drug-likeness properties.

The pharmacokinetics properties and predicted ADMET properties of *T. procumbens* phytoconstituents were calculated using the pkCSM web tool. From the attained data, we can conclude that all studied compounds have the utmost gastro-intestinal absorption (> 85 %), human tissue distribution (VDss), and entire abundant clearance (Supplementary Table. S4). Betulinic acid and Taraxasterol acetate possess maximum bioavailability (> 98 %). In the Metabolism Properties, the Cytochrome P450 and P-glycoprotein simulation method for both substrate and inhibition was done for all *T. procumbens* phytoconstituents pkCSM web tool. The results indicate that most of them have lower CYP inducing and P-gp compatibility properties (Supplementary Table. S4). The toxicity assessment test revealed that only a few compounds have deviated from toxicity prediction. Overall, the study specifies that most *T. procumbens* phytoconstituents are devoid of carcinogenic, teratogenic, and tumorigenic properties (Supplementary Table. S4).

The details of Physiochemical and ADMET properties of 6 selected *T. procumbens* phytoconstituents are further presented in Table 4. The PSA is closely linked to the absorption properties of compounds. Except for Luteolin and Bergenin, the other five phytoconstituents’ PSA was greater than 140, signifying that these compounds had strong polarity and thus not
easily absorbed by the body. Luteolin and Bergenin showed good oral absorption or membrane permeability [48]. Except for beta-Sitosterol (LogP > 5) [49], all others were predicted as having the best lipophilicity (LogP ≤ 5).

The predicted Absorption properties include proCaco-2 permeability, intestinal absorption (human), skin permeability, and P-glycoprotein substrate or inhibitor. Only beta-Sitosterol showed the predicted value >0.90 showing high Caco-2 permeability and maximum absorption. Concerning intestinal absorption (human), the absorbance of less than 30% is measured to be poorly absorbed. All six selected compounds showed higher than this threshold, indicating good predicted absorption. For skin permeability, the log Kp>2.5 is reflected as low skin permeability. All six selected phytoconstituents showed high skin permeability. P-glycoprotein results recommended that all compounds are substrates of P-glycoprotein except for beta-Sitosterol and predicted to be actively released from cells by P-glycoprotein. beta-Sitosterol was predicted to be a P-glycoprotein inhibitor.

The distribution volume (VDss), Fraction unbound (human), CNS permeability, and blood-brain barrier membrane permeability (logBB) characterize the distribution of compounds. Procumbentin, Bergenin, and Luteolin high distribution volume (log VDss> 0.45). Except for beta-Sitosterol, all other selected phytoconstituents were non-permeable for blood-brain barrier membrane (logBB< -1). Only beta-Sitosterol and Luteolin were predicted to penetrate the CNS (logPS> -2). As Cytochrome P450s (CYP) is a vital enzyme system for drug metabolism in the liver, the results showed that excluding beta-Sitosterol, all other selected phytoconstituents were not substrates for CYP3A4. All selected compounds are CYP inhibitors proposing that they could be metabolized in the liver.

Table 4. Predicted ADMET properties of six selected phytoconstituents of T. procumbens.

| Properties                  | beta-Sitosterol | Centaurein | Procumbentin | Luteolin | Bergenin | Puerarin |
|-----------------------------|-----------------|------------|--------------|----------|----------|---------|
| Polar Surface Area (PSA)    | 187.039         | 208.748    | 206.858      | 117.313  | 129.813  | 169.199 |
| LogP                        | 8.0248          | 0.0757     | -0.5217      | 2.2824   | -1.2006  | 0.3861  |
| Synthetic accessibility     | 6.30            | 5.70       | 5.69         | 3.02     | 4.39     | 4.98    |
| Water solubility (log mol/L)| -6.773          | -2.995     | -2.918       | -3.094   | -1.853   | -2.72   |
| Caco2 per. (log Papp in 10^4| 1.201           | 0.294      | -1.418       | 0.096    | 0.289    | 0.223   |
| Intestinal ab (human) (%    | 94.464          | 35.872     | 31.97        | 81.13    | 63.774   | 67.446  |
| Skin Permeability (log Kp)  | -2.783          | -2.735     | -2.735       | -2.735   | -2.736   | -2.735  |
| P-gp substrate              | No              | Yes        | Yes          | Yes      | Yes      | Yes     |
| P-gp I inhibitor            | Yes             | No         | No           | No       | No       | No      |
| P-gp II inhibitor           | Yes             | No         | No           | No       | No       | No      |
| VDss (human) (log L/kg)     | 0.193           | 0.211      | 1.132        | 1.153    | 0.68     | 0.377   |
| Fraction unbound (human)    | 0               | 0.114      | 0.143        | 0.168    | 0.632    | 0.187   |
| BBB permeability (log BB)   | 0.781           | -1.976     | -2.407       | -0.907   | -1.091   | -1.204  |
| CNS permeability(log PS)    | -1.705          | -4.267     | -4.826       | -2.251   | -3.903   | -3.594  |
| (log ml/min/kg)             | No              | No         | No           | No       | No       | No      |
| CYP3A4 substrate            | Yes             | No         | No           | No       | No       | No      |
| CYP1A2 inhibitor            | No              | No         | Yes          | No       | No       | No      |
| CYP2C9 inhibitor            | No              | No         | No           | No       | No       | No      |
| CYP2C9 inhibitor            | No              | No         | No           | Yes      | No       | No      |
| CYP2D6 inhibitor            | No              | No         | No           | No       | No       | No      |
| CYP3A4 inhibitor            | No              | No         | No           | No       | No       | No      |
| Properties                        | beta-Sitosterol | Centaurein | Procumbentin | Luteolin | Bergenin | Puerarin |
|----------------------------------|-----------------|------------|--------------|----------|----------|----------|
| Total Clearance (log ml/min/kg)  | 0.628           | 0.536      | 0.429        | 0.495    | 0.427    | -0.007   |
| Renal OCT2 substrate             | No              | No         | No           | No       | No       | No       |
| AMES toxicity                    | No              | No         | No           | No       | No       | No       |
| MTD @ (log mg/kg/day)            | -0.621          | 0.56       | 0.531        | 0.499    | -0.013   | 0.642    |
| hERG I inhibitor                 | No              | No         | No           | No       | No       | No       |
| hERG II inhibitor                | Yes             | Yes        | Yes          | No       | No       | Yes      |
| ORT* (mol/kg)                    | 2.552           | 2.565      | 2.574        | 2.455    | 1.879    | 2.641    |
| ORCT# (log mg/kg_bw/day)         | 0.855           | 3.805      | 4.089        | 2.409    | 3.614    | 4.85     |
| MTD^                            | No              | No         | No           | No       | No       | No       |
| TPT+ (log ug/L)                  | 0.43            | 0.285      | 0.285        | 0.326    | 0.285    | 0.285    |
| Minnow toxicity (log mM)         | -1.802          | 6.387      | 7.199        | 3.169    | 5.688    | 4.188    |

Synthetic accessibility range (0-10) = very easy to very difficult to synthesize; *P-gp- : -glycoprotein; @MTD-Max. tolerated dose (human); *ORT-Oral Rat Acute Toxicity (LD50); #ORCT- Oral Rat Chronic Toxicity (LOAEL); HEP-Hepatotoxicity; *SS-Skin Sensitisation; +TPT-T.Pyriformis toxicity

**Color codes:** Dark Orange for highly positive (Yes); Orange for weak positive (Moderate); Light green for negative (No).

Figure 2. Top 25 of Target Predicted for six selected phytoco*nstituents of *T. procumbens* used for *in silico* screening against various proteins of SARS-CoV-2.
Excretion of Drug is dependent on its molecular weight and hydrophilicity. Excretion's prediction results demonstrated that all selected compounds’ total clearance is the higher; they are non-toxic in the AMES test; non-hepatotoxic, but may not inhibit the hERG channel not induce cardiotoxicity or skin sensitization.

Six best-selected compounds were further screened for target prediction analysis using the SwissTargetPrediction web tool [50]. The top 25 interpretations are shown in the pie chart format in Figure 2. The pie chart predicts % of various enzymes and receptors.

Thus, the predicted outcomes specify that the ADMET characteristics of most of the selected compounds are safe for humans.

3.3. Discussion.

In modern drug discovery, computer-aided drug design (CADD) has turned out to be a vibrant program as it not only considerably curtails the cost and labor involved in the drug discovery process but also speeds it up by allowing the scientists to limit their efforts during biological and synthetic testing [51]. Besides molecular docking, numerous ADMET tools are also available and are equally considered as an important constituent in the CADD due to their trustworthy predictions [52]. The compounds succeeding the Druglikeness tests without violating rules confirm their efficacy as a good drug in the biological systems and allow them for further biochemical analysis. In contrast, toxicity prediction approves its safety for human consumption [53].

The illustrious fact of modern drugs is to kill the virus without improving the host immunity customarily. In this concern, the phytoconstituents of *T. procumbens* were selected for the current study. As mentioned earlier, *T. procumbens* drink is traditionally used to treat bronchial catarrh [17] and asthma [35]. It also possesses antiviral [37], immunomodulatory [28], anti-inflammatory [32] and analgesic [30] properties.

The present study results highlighted that out of 22 selected phytoconstituents, 18 compounds showed good binding affinity. Compounds like beta-Amyrenone, Betulinic acid, Lupeol, Stigmasterol, Taraxasterol acetate, and Voacangine exhibited overall high binding affinity towards most targets selected. Likewise, they are also found to be vital drugs as they all have excellent synthetic accessibility.

Figure 2 represents the percentage of these six selected phytoconstituents to target various enzymes with different activities. Some of which have been mentioned in previously published studies.

In the current study, six compounds showed the highest antiviral activity against six proteins of SARS-CoV-2. These top six selected ligands, including beta-Sitosterol, is a proven potential antioxidant [54]; anti-inflammatory compound with the least toxicity and insignificant ulcerogenic activities [55]. The Interaction analysis was performed for each of the complex and was compared to other studies to infer the residue wise contribution in the activity. Angiotensin-Converting Enzyme-Related Carboxypeptidase has been proposed as a suitable target in different studies using in-vitro techniques [56]. Pro346, His 378 are conserved residues of the catalytic motif indicating interactions with these residues to be crucial for the Enzyme-Inhibitor complex's stability. Also, His378 is one of the residues that are conserved among sACE and tACE enzymes [57]. The carbonyl oxygen of Pro346 forms a hydrogen bond with the secondary amine of its known inhibitor MLN4760 [57].

6M71: The polymerase activity of RNA-dependent RNA polymerase is performed by forming a conserved arch which includes three subdomains Finger subdomain (Lys621), Palm
subdomain (His811, Ser814, Pro620, Trp617, Asp761, Lys 798, Trp800), and Thumb subdomain [58]. The interaction with these residues contributes to the polymerase activity of the enzyme. Centaurin strongly binds within the enzyme's active site (Table 2) by forming interactions with these residues. ASP761, LYS798, and Ser814 interact with the ligand while the other residues create an interface for the enzyme-ligand complex to interact. [59]. Lys 798 stabilizes the core domain of the enzyme while the interaction with Asp761 creates a catalytic domain, and Ser814 positions the nucleotides, which is in-line with the previously published research articles. [60-62]. The antiviral activity of Centurian has been previously studied [63].

6LU7: The main protease has been identified as a possible target. It plays a crucial role in the SARS virus's pathogenesis. Covalent interactions with Gln110 plays a vital role in the formation of the substrate-enzyme complex [64]. In previously published studies, a point mutation Thr292Ala shows an enzyme's enhanced activity [65]. Thr292 helps approach the domain III of the dimer more closely, due to which the hydrophobic backbone of the residues from a bed for the catalytic activity of the enzyme. Luteolin has been identified to inhibit the virus by anticomplementary activity [65-66]. Besides Mpro, Luteolin has shown inhibition against GST-S2, 3CLpro, Serine protease [66-68].

6CS2: The spike protein residues Asp757 and Asp849 play a crucial role in the viral entry [69]. Proline residues restrain the bend conformation, which is favorable for the active site's interaction with the residue and constrains the flexible conformation as it has the highest turn induction propensity [70]. Leu843 contributes to a major antigenic determinant of SARS-COV Spike protein that helps neutralize antibodies. Also, the leucine zipper has been characterized as a conserved motif of many viral glycoprotein families and is seen to be conserved in the S-protein of the coronavirus as well [71]. Bergenin, which showed antiviral activity against the enzyme, shows antiviral activity against Influenza and HIV as well [72-73]. The anti-inflammatory activity of Bergenin is in standard with Ibuprofen, as mentioned in the previous study [74]. Also, the anti-inflammatory activity of the potential inhibitor has shown reasonable activity against IL-6 [75].

6VXX: The Phe318 has been identified as a conserved residue in the spike glycoproteins (closed state) of the virus [76]. It has been known that the coronavirus S glycoprotein is surface-exposed and mediates entry into host cells. Hence, it can be considered as the main focus of therapeutics and vaccine development. Puerarin has been known to have anti-inflammatory effects. It functions by affecting immunocytes, signaling pathways, and cytokines [77]. The pharmacodynamic properties of Puerarin are well studied [78]. It has been identified as an alternative to hydroxychloroquine with less or no side effects [79]. Puerarin has shown good activity against the spike protein and having a good ADME toxicity profile, as shown in the study also meets Lipinski’s rule to some extent [79].

6NUR: Coronavirus Nsp12 polymerase plays a crucial role in the RNA synthesis machinery of the virus [80]. The Arg249 is a subpart of the NIRAN domain, while the Leu251 is a part of the interface domain that acts as a junction and maintains interactions between the finger domain, NIRAN domain, and second subunit that together contribute to the enzyme activity [81]. Leu's presence, which is a mutation for Val, has been known to induce a better base pairing with nsp12 polymerase, excluding its analog in the active site. Arg249, Thr246, Leu245 are the residues that form the NIRAN subunit while Leu251, Thr319, Pro323, Arg349, Phe396 form the interface domain [82].

Centauraein possesses anti-inflammatory action by stimulating IFN-γ expression [83]. Luteolin possess anti-oxidant, anti-inflammatory, anti-allergic [84] and antitumor [85]
properties. Bergenin also displays anti-malarial [86], anti-hepatotoxic, anti-HIV, hepatoprotective, anti-inflammatory with immuno-modulatory properties [87], and also potential inhibitors against the main protease of SARS-CoV-2 [88]. Puerarin exhibited antioxidant and anti-inflammatory properties [89]. The most promising ligand found here is Procumbentin, which is known for its anti-nociceptive property [90]. In the current study, it showed a very good binding affinity against all studied macromolecules. So it would be very interesting to study it in detail in the future.

4. Conclusions

In the search for a new natural drug that can inhibit SARS-CoV-2 infection and provide immunity, by using molecular docking technique and ADMET analysis, total 22 phytoconstituents of *Tridax procumbens* were screened. Six molecules among these 22 were prequalified as they are fascinating both from a chemical and biological perspective. Hence it is recommended that these six molecules can be used as an inhibitor of various proteins of SARS-CoV-2 along with anti-inflammatory with immuno-modulatory potential. Additionally, they are also non-toxic and non-carcinogenic. Thus, this study proposes that these selected phytoconstituents of *T. procumbens* can effectively control COVID-19 and modify human immunity, validated by further studies.

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**Conflicts of Interest**

The authors declare no conflict of interest.

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## Supplementary Data

**Table S1.** Ingredients of *Tridax procumbens* used for *in silico* screening against various proteins of SARS-CoV-2.

| Sr.No | Name of Compound   | Molecular Formula | PubChem CID: | Structure |
|-------|--------------------|-------------------|--------------|-----------|
| 01    | 5(alpha)-cholestane| C_{27}H_{46}      | 10202        | ![Structure](image) |
| 02    | alpha-Selinene     | C_{15}H_{24}      | 10856614     | ![Structure](image) |
| 03    | Bergenin           | C_{14}H_{16}O_{9} | 66065        | ![Structure](image) |
| 04    | beta-Amyrenone     | C_{30}H_{50}O     | 12306160     | ![Structure](image) |
| 05    | beta-Sitosterol    | C_{29}H_{50}O     | 222284       | ![Structure](image) |
| 06    | Betulinic acid     | C_{30}H_{48}O_{3} | 64971        | ![Structure](image) |
| Sr.No | Name of Compound        | Molecular Formula | PubChem CID: | Structure |
|-------|-------------------------|-------------------|--------------|-----------|
| 07    | Caryophyllene           | C₁₅H₂₄            | 5281515      | ![Structure](image) |
| 08    | Centaureidin            | C₁₃H₁₆O₇          | 5315773      | ![Structure](image) |
| 09    | Centaurein              | C₂₃H₂₅O₁₃         | 5489090      | ![Structure](image) |
| 10    | (3,S)-16,17-Didehydrofalcarnol | C₁₇H₂₅O       | 6442009      | ![Structure](image) |
| 11    | Esculetin               | C₉H₆O₄            | 5281416      | ![Structure](image) |
| 12    | Falcarnol               | C₁₇H₂₅O           | 5281149      | ![Structure](image) |
| Sr.No | Name of Compound                        | Molecular Formula | PubChem CID: | Structure |
|-------|----------------------------------------|-------------------|--------------|-----------|
| 13    | Limonene                               | C\(_{10}\)H\(_{16}\) | 22311        | ![Limonene](https://doi.org/10.33263/BRIAC114.1212012148) |
| 14    | Lupeol                                 | C\(_{30}\)H\(_{50}\)O | 259846       | ![Lupeol](https://doi.org/10.33263/BRIAC114.1212012148) |
| 15    | Luteolin                               | C\(_{15}\)H\(_{10}\)O\(_6\) | 5280445      | ![Luteolin](https://doi.org/10.33263/BRIAC114.1212012148) |
| 16    | Methyl 10-oxooctadecanoate             | C\(_{19}\)H\(_{36}\)O\(_3\) | 543603       | ![Methyl 10-oxooctadecanoate](https://doi.org/10.33263/BRIAC114.1212012148) |
| 17    | Procumbentin                           | C\(_{23}\)H\(_{24}\)O\(_{14}\) | -            | ![Procumbentin](https://doi.org/10.33263/BRIAC114.1212012148) |
| 18    | Puerarin                               | C\(_{21}\)H\(_{20}\)O\(_9\) | 5281807      | ![Puerarin](https://doi.org/10.33263/BRIAC114.1212012148) |
| Sr.No | Name of Compound       | Molecular Formula | PubChem CID: | Structure |
|-------|------------------------|-------------------|--------------|-----------|
| 19    | Stigmasterol           | C_{29}H_{48}O_{5} | 5280794      | ![Structure](https://doi.org/10.33263/BRIAC114.1212012148) |
| 20    | Taraxasterol acetate   | C_{32}H_{52}O_{2} | 13889352     | ![Structure](https://doi.org/10.33263/BRIAC114.1212012148) |
| 21    | Voacangine             | C_{22}H_{28}N_{2}O_{3} | 73255       | ![Structure](https://doi.org/10.33263/BRIAC114.1212012148) |
| 22    | Zerumbone              | C_{15}H_{22}O_{5} | 5470187      | ![Structure](https://doi.org/10.33263/BRIAC114.1212012148) |
# Table S2. Physicochemical and ADMET properties of Ingredients of *Tridax procumbens* (using SwissADME).

| Sr. No. | Name of Compound                      | Molecular weight (g/mol) | cLogP | cLogS | HBA | HBD | TSA (Å²) | GI absorption | BBB Permeability | Skin Permeation (cm/s) |
|---------|---------------------------------------|--------------------------|-------|-------|-----|-----|----------|----------------|-------------------|----------------------|
| 01      | 5(alpha)-cholestane                   | 372.67                   | 5.16  | -8.80 | 0   | 0   | 0.00     | Low            | No                | -0.71                |
| 02      | alpha-Selinene                        | 204.35                   | 3.31  | -4.95 | 0   | 0   | 0.00     | Low            | No                | -3.85                |
| 03      | Bergenin                              | 328.27                   | 1.55  | -1.61 | 9   | 5   | 145.91   | Low            | No                | -8.99                |
| 04      | beta-Amyrenone                        | 424.70                   | 4.53  | -9.08 | 1   | 0   | 17.07    | Low            | No                | -2.61                |
| 05      | beta-Sitosterol                       | 414.71                   | 4.79  | -9.67 | 1   | 1   | 20.23    | Low            | No                | -2.20                |
| 06      | Betulinic acid                        | 456.70                   | 3.68  | -9.28 | 3   | 2   | 57.53    | Low            | No                | -3.26                |
| 07      | Caryophyllene                         | 204.35                   | 3.29  | -3.87 | 0   | 0   | 0.00     | Low            | No                | -4.44                |
| 08      | Centaureidin                          | 360.31                   | 2.98  | -4.94 | 8   | 3   | 118.59   | High           | No                | -6.52                |
| 09      | Centaurein                            | 522.46                   | 2.53  | -4.73 | 13  | 6   | 197.74   | Low            | No                | -8.78                |
| 10      | (3,S)-16,17-Didehydrofalcarnol        | 242.36                   | 4.00  | -5.13 | 1   | 1   | 20.23    | High           | Yes               | -4.25                |
| 11      | Esculetin                             | 178.14                   | 1.25  | -2.30 | 4   | 2   | 70.67    | High           | No                | -6.52                |
| 12      | Falcarnol                             | 244.37                   | 3.86  | -4.29 | 1   | 1   | 20.23    | High           | Yes               | 3.89                 |
| 13      | Limonene                              | 136.23                   | 2.72  | -4.29 | 0   | 0   | 0.00     | Low            | Yes               | -3.89                |
| 14      | Lupeol                                | 426.72                   | 4.89  | -10.22| 1   | 1   | 20.23    | Low            | No                | -1.90                |
| 15      | Luteolin                              | 286.24                   | 1.86  | -4.51 | 6   | 4   | 111.13   | High           | No                | -6.25                |
| 16      | Methyl 10-oxooctadecanoate            | 312.49                   | 4.37  | -4.65 | 3   | 0   | 43.37    | High           | Yes               | -3.70                |
| 17      | Procumbentin                          | 524.43                   | 2.37  | -3.20 | 14  | 8   | 228.97   | Low            | No                | -9.29                |
| 18      | Puerarin                              | 416.38                   | 1.96  | -2.94 | 9   | 6   | 160.82   | Low            | No                | -8.83                |
| 19      | Stigmasterol                          | 412.69                   | 4.96  | -7.46 | 1   | 1   | 20.23    | Low            | No                | -2.74                |
| 20      | Taraxasterol acetate                  | 468.75                   | 5.18  | -10.17| 2   | 0   | 26.30    | Low            | No                | -2.27                |
| 21      | Voacangine                            | 368.47                   | 3.63  | -4.34 | 4   | 1   | 54.56    | High           | Yes               | -6.06                |
| 22      | Zerumbone                             | 218.33                   | 2.72  | -3.68 | 1   | 0   | 17.07    | High           | Yes               | -4.83                |

**cLogP**: Consensus Log Po/w (Average of all five predictions); **cLogS**: < -4 = Soluble; **HBA**: Hydrogen Bond Acceptor; **HBD**: Hydrogen Bond Donor; **TSA**: Topological Polar Surface Area;
Table S3. Physiochemical and ADMET properties of Ingredients of *Tridax procumbens* -Predicted lead likeness, Drug likeness, and synthetic accessibility score (using SwissADME).

| Sr. No. | Name of Compound                     | Lipinski rule of five* | Ghose filters* | Veber (GSK) filter* | Egan filters* | Muegge (Bayer) filter* | Lead likeness | Synthetic accessibility |
|---------|--------------------------------------|------------------------|----------------|---------------------|---------------|------------------------|---------------|------------------------|
| 01      | 5(alpha)-cholestane                   | Yes; 1 violation: MLOGP>4.15 | No; 2 violations: WLOGP>5.6, #atoms>70 | Yes             | No; 1 violation: WLOGP>5.88 | No; 2 violations: WLOGP>5.88 | 5.20          | 5.02                   |
| 02      | alph-Selinene                         | Yes; 1 violation: MLOGP>4.15 | Yes            | Yes                 | Yes           | No; 2 violations: WLOGP>5.88 | 4.22          | 4.21                   |
| 03      | Bergenin                              | Yes                     | No; 1 violation: WLOGP<0.4 | No; 1 violation: TPSA>140 | No; 1 violation: TPSA>131.6 | Yes            | 4.39          | 4.39                   |
| 04      | beta-Amyrenone                        | Yes; 1 violation: MLOGP>4.15 | No; 3 violations: WLOGP>5.6, MR>130, #atoms>70 | Yes             | No; 1 violation: WLOGP>5.88 | No; 2 violations: WLOGP>5.88 | 5.90          | 5.80                   |
| 05      | beta-Sitosterol                       | Yes; 1 violation: MLOGP>4.15 | No; 3 violations: WLOGP>5.6, MR>130, #atoms>70 | Yes             | No; 1 violation: WLOGP>5.88 | No; 2 violations: WLOGP>5.88 | 6.30          | 6.30                   |
| 06      | Betulinic acid                        | Yes; 1 violation: MLOGP>4.15 | No; 3 violations: WLOGP>5.6, MR>130, #atoms>70 | Yes             | No; 1 violation: WLOGP>5.88 | No; 1 violation: XLOGP>5.5 | 5.63          | 5.63                   |
| 07      | Caryophyllene                         | Yes; 1 violation: MLOGP>4.15 | Yes            | Yes                 | Yes           | No; 1 violation: WLOGP>5.88 | 4.51          | 4.51                   |
| 08      | Centaureidin                          | Yes                     | Yes            | Yes                 | Yes           | Yes            | 3.57          | 3.57                   |
| 09      | Centaurein                            | No; 3 violations: MW>500, NorO>10, NH>5 | No; 1 violation: TPSA>140 | No; 1 violation: TPSA>131.6 | No; 3 violations: TPSA>150, Hacc>10, H-don>5 | No; 1 violation: TPSA>150, Hacc>10, H-don>5 | 5.70          | 5.70                   |
| 10      | (3,8)-16,17-Didehydrofalcarinol       | No; 1 violation: Heteroatoms<2 | Yes             | Yes                 | Yes           | No; 1 violation: Heteroatoms<2 | 4.26          | 4.26                   |
| 11      | Esculetin                             | Yes                     | No; 1 violation: #atoms<20 | Yes                 | Yes           | No; 1 violation: MW<200 | 2.61          | 2.61                   |
| 12      | Falcarniolic                          | Yes; 1 violation: MLOGP>4.15 | Yes             | Yes                 | Yes           | No; 2 violations: MW<200, Heteroatoms<2 | 4.33          | 4.33                   |
| 13      | Limonene                              | Yes                     | No; 1 violation: MW<160 | Yes                 | Yes           | No; 2 violations: MW<200, Heteroatoms<2 | 3.46          | 3.46                   |
|   | Compound                  | Lipinski Violations | Ghose, Veber, Egan, and Muegge Violations | Synthetic Accessibility Range |   |
|---|---------------------------|---------------------|-------------------------------------------|-------------------------------|---|
| 14| Lupeol                    | Yes; 1 violation: MLOGP>4.15 | No; 3 violations: WLOGP>5.6, MR>130, #atoms>70 | Yes                           | No; 1 violation: WLOGP>5.88 | No; 2 violations: XLOGP3>5, Heteroatoms<2 | No; 2 violations: MW>350, XLOGP3>3.5 | 5.49 |
| 15| Luteolin                  | Yes                 | Yes                                       | Yes                           | Yes                          | Yes                           | Yes                           | 3.02 |
| 16| Methyl 10-oxo-octadecanoate | Yes                 | Yes                                       | No; 1 violation: Rotors>10 | No; 2 violations: XLOGP3>5, Rotors>15 | No; 2 violations: Rotors>7, XLOGP3>3.5 | 2.73 |
| 17| Procumbentin              | No; 3 violations: MW>500, NorO>10, NHorOH>5 | No; 2 violations: MW>480, WLOGP<0.4 | No; 1 violation: TPSA>140 | No; 1 violation: TPSA<140, H-don<5 | No; 1 violation: MW>350 | 5.69 |
| 18| Puerarin                  | Yes; 1 violation: NHorOH<5 | Yes                                       | No; 1 violation: TPSA>140 | No; 2 violations: TPSA<140, H-don<5 | No; 1 violation: MW>350 | 4.98 |
| 19| Stigmasterol              | Yes; 1 violation: MLOGP>4.15 | No; 3 violations: WLOGP>5.6, MR>130, #atoms>70 | Yes                           | No; 1 violation: WLOGP>5.88 | No; 2 violations: XLOGP3<5, Heteroatoms<2 | No; 2 violations: MW>350, XLOGP3>3.5 | 6.21 |
| 20| Taraxasterol acetate      | Yes; 1 violation: MLOGP>4.15 | No; 3 violations: WLOGP>5.6, MR>130, #atoms>70 | Yes                           | No; 1 violation: WLOGP>5.88 | No; 1 violation: XLOGP3>5 | No; 2 violations: MW>350, XLOGP3>3.5 | 5.61 |
| 21| Voacangine                | Yes                 | Yes                                       | Yes                           | Yes                          | Yes                           | No; 2 violations: MW>350, XLOGP3>3.5 | 4.88 |
| 22| Zerumbone                 | Yes                 | Yes                                       | Yes                           | Yes                          | No; 1 violation: Heteroatoms<2 | No; 2 violations: MW<250, XLOGP3<3.5 | 3.47 |

*Applied Lipinski rule of five- Ghose, Veber, Egan, and Muegge rules; Synthetic accessibility range (0-10) = very easy to very difficult to synthesize*
Table S4. Pharmacokinetic Properties- Predicted ADMET properties of Ingredients of *Tridax procumbens* (using pkCSM).

| Sr. No. | Name of Compound                  | Water solubility (log mol/L) | Caco2 permeability (log Papp in 10^-6 cm/s) | Intestinal absorption (human) (% Absorbed) | Skin Permeability (log Kp) | P-gp substrate | P-gp I inhibitor | P-gp II inhibitor |
|---------|-----------------------------------|-----------------------------|---------------------------------------------|-------------------------------------------|----------------------------|----------------|-----------------|------------------|
| 01      | 5(alpha)-cholestane               | -5.619                      | 1.263                                       | 97.135                                    | -2.724                    | No             | No              | Yes              |
| 02      | alpha-selinene                    | -6.074                      | 1.401                                       | 94.127                                    | -1.461                    | No             | No              | No               |
| 03      | Bergenin                          | -1.853                      | 0.289                                       | 63.774                                    | -2.736                    | Yes            | No              | No               |
| 04      | beta-Amyrenone                    | -6.741                      | 1.332                                       | 96.254                                    | -2.733                    | No             | Yes             | Yes              |
| 05      | beta-Sitosterol                   | -6.773                      | 1.201                                       | 94.464                                    | -2.783                    | No             | Yes             | Yes              |
| 06      | Betulinic acid                    | -3.122                      | 1.175                                       | 99.763                                    | -2.735                    | No             | No              | No               |
| 07      | Caryophyllene                     | -5.555                      | 1.423                                       | 94.845                                    | -1.58                     | No             | No              | No               |
| 08      | Centaureidin                      | -3.221                      | 0.161                                       | 77.207                                    | -2.735                    | Yes            | No              | Yes              |
| 09      | Centaurein                        | -2.995                      | 0.294                                       | 35.872                                    | -2.735                    | Yes            | No              | No               |
| 10      | (3,S)-16,17-Didehydrafalcarinol    | -5.712                      | 1.513                                       | 94.685                                    | -2.028                    | No             | No              | No               |
| 11      | Esculetin                         | -2.497                      | 0.301                                       | 86.291                                    | -2.796                    | Yes            | No              | No               |
| 12      | Falcarnol                         | -5.84                       | 1.513                                       | 94.209                                    | -2.028                    | No             | No              | No               |
| 13      | Limonene                          | -3.568                      | 1.401                                       | 95.898                                    | -1.721                    | Yes            | No              | No               |
| 14      | Lupeol                            | -5.861                      | 1.226                                       | 95.782                                    | -2.744                    | No             | Yes             | Yes              |
| 15      | Lateolin                          | -3.094                      | 0.096                                       | 81.13                                     | -2.735                    | Yes            | No              | No               |
| 16      | Methyl 10-oxooctadecanoate        | -5.946                      | 1.614                                       | 93.432                                    | -2.712                    | No             | Yes             | No               |
| 17      | Procumbentin                      | -2.918                      | -1.418                                      | 31.97                                     | -2.735                    | Yes            | No              | No               |
| 18      | Puerarin                          | -2.72                       | 0.223                                       | 67.446                                    | -2.735                    | Yes            | No              | No               |
| 19      | Stigmasterol                      | -6.682                      | 1.213                                       | 94.97                                     | -2.783                    | No             | Yes             | Yes              |
| 20      | Taraxasterol acetate              | -5.804                      | 1.218                                       | 98.464                                    | -2.737                    | No             | Yes             | Yes              |
| 21      | Voacangine                        | -3.427                      | 1.108                                       | 93.462                                    | -2.905                    | Yes            | Yes             | No               |
| 22      | Zerumbone                         | -4.027                      | 1.432                                       | 95.781                                    | -2.06                     | No             | No              | No               |

*P-gp- P-glycoprotein*
| Sr. No. | Name of Compound               | VDss (human) (log L/kg) | Fraction unbound (human) (Fu) | BBB permeability (log BB) | CNS permeability (log PS) |
|--------|--------------------------------|------------------------|------------------------------|--------------------------|---------------------------|
| 01     | 5(alpha)-cholestane            | -0.148                 | 0.012                        | 1                        | -0.648                    |
| 02     | alpha-selinene                 | 0.686                  | 0.186                        | 0.776                    | -1.865                    |
| 03     | Bergenin                       | 0.68                   | 0.632                        | -1.091                   | -3.903                    |
| 04     | beta-Amyrenone                 | 0.246                  | 0                            | 0.694                    | -1.747                    |
| 05     | beta-Sitosterol                | 0.193                  | 0                            | 0.781                    | -1.705                    |
| 06     | Betulinic acid                 | -1.18                  | 0.018                        | -0.322                   | -1.343                    |
| 07     | Caryophyllene                  | 0.652                  | 0.263                        | 0.733                    | -2.172                    |
| 08     | Centaureidin                   | 0.098                  | 0.067                        | -1.466                   | -3.256                    |
| 09     | Centaurein                     | 0.211                  | 0.114                        | -1.976                   | -4.267                    |
| 10     | (3,S)-16,17-Didehydrofalcariol | 0.308                  | 0.137                        | 0.775                    | -1.467                    |
| 11     | Esculetin                      | 0.528                  | 0.484                        | 0.025                    | -2.296                    |
| 12     | Falcariol                      | 0.313                  | 0.127                        | 0.765                    | -1.467                    |
| 13     | Limonene                       | 0.396                  | 0.48                         | 0.732                    | -2.37                     |
| 14     | Lupeol                         | 0                      | 0                            | 0.726                    | -1.714                    |
| 15     | Luteolin                       | 1.153                  | 0.168                        | -0.907                   | -2.251                    |
| 16     | Methyl 10-oxooctadecanoate     | 0.041                  | 0.056                        | -0.226                   | -1.834                    |
| 17     | Procumbentin                   | 1.132                  | 0.143                        | -2.407                   | -4.826                    |
| 18     | Puerarin                       | 0.377                  | 0.187                        | -1.204                   | -3.594                    |
| 19     | Stigmasterol                   | 0.178                  | 0                            | 0.771                    | -1.652                    |
| 20     | Taraxasterol acetate           | -0.165                 | 0                            | 0.622                    | -1.708                    |
| 21     | Voacangine                     | 1.321                  | 0.296                        | -0.051                   | -2.193                    |
| 22     | Zerumbone                      | 0.279                  | 0.395                        | 0.522                    | -2.647                    |
| Sr. No. | Name of Compound                      | (log ml/min/kg) | CYP3A4 substrate | CYP1A2 inhibitor | CYP2C19 inhibitor | CYP2C9 inhibitor | CYP2D6 inhibitor | CYP3A4 inhibitor |
|---------|---------------------------------------|-----------------|------------------|------------------|------------------|------------------|------------------|------------------|
| 01      | 5(alpha)-cholestane                   | No              | Yes              | No               | No               | No               | No               | No               |
| 02      | alpha-selinene                        | No              | Yes              | No               | No               | No               | No               | No               |
| 03      | Bergenin                              | No              | No               | No               | No               | No               | No               | No               |
| 04      | beta-Amyrenone                        | No              | Yes              | No               | No               | No               | No               | No               |
| 05      | beta-Sitosterol                       | No              | Yes              | No               | No               | No               | No               | No               |
| 06      | Betulinic acid                        | No              | Yes              | No               | No               | No               | No               | No               |
| 07      | Caryophyllene                         | No              | No               | No               | No               | No               | No               | No               |
| 08      | Centauretidin                         | No              | No               | Yes              | No               | No               | No               | No               |
| 09      | Centaurein                            | No              | No               | No               | No               | No               | No               | No               |
| 10      | (3,S)-16,17-Didehydrofalcarnol         | No              | Yes              | Yes              | No               | No               | No               | No               |
| 11      | Esculetin                             | No              | No               | Yes              | No               | No               | No               | No               |
| 12      | Falcarnol                             | No              | Yes              | Yes              | No               | No               | No               | No               |
| 13      | Limonene                              | No              | No               | No               | No               | No               | No               | No               |
| 14      | Lupeol                                | No              | Yes              | No               | No               | No               | No               | No               |
| 15      | Luteolin                              | No              | No               | Yes              | No               | Yes              | Yes              | No               |
| 16      | Methyl 10-oxooctadecanoate            | No              | Yes              | Yes              | No               | No               | No               | No               |
| 17      | Procumbentin                          | No              | No               | No               | No               | No               | No               | No               |
| 18      | Puerarin                              | No              | No               | No               | No               | No               | No               | No               |
| 19      | Stigmasterol                          | No              | Yes              | No               | No               | No               | No               | No               |
| 20      | Taraxasterol acetate                  | No              | Yes              | No               | No               | No               | No               | No               |
| 21      | Voacangine                            | Yes             | Yes              | No               | No               | Yes              | No               | No               |
| 22      | Zerumbone                             | No              | No               | No               | No               | No               | No               | No               |
| Sr. No. | Name of Compound                  | Total Clearance (log ml/min/kg) | Renal OCT2 substrate |
|--------|-----------------------------------|---------------------------------|----------------------|
| 01     | 5(alpha)-cholestane                | 0.57                            | No                   |
| 02     | alpha-selinene                    | 1.172                           | No                   |
| 03     | Bergenin                          | 0.427                           | No                   |
| 04     | beta-Amyrenone                    | -0.096                          | No                   |
| 05     | beta-Sitosterol                   | 0.628                           | No                   |
| 06     | Betulinic acid                    | 0.116                           | No                   |
| 07     | Caryophyllene                     | 1.088                           | No                   |
| 08     | Centaureidin                      | 0.562                           | No                   |
| 09     | Centaurein                        | 0.536                           | No                   |
| 10     | (3,S)-16,17-Didehydrofalcarniol   | 2.038                           | No                   |
| 11     | Esculetin                         | 0.671                           | No                   |
| 12     | Falcarniol                        | 1.952                           | No                   |
| 13     | Limonene                          | 0.213                           | No                   |
| 14     | Lupeol                            | 0.153                           | No                   |
| 15     | Luteolin                          | 0.495                           | No                   |
| 16     | Methyl 10-oxooctadecanoate        | 1.971                           | No                   |
| 17     | Procumbentin                      | 0.429                           | No                   |
| 18     | Puerarin                          | -0.007                          | No                   |
| 19     | Stigmasterol                      | 0.618                           | No                   |
| 20     | Taraxasterol acetate              | 0.057                           | No                   |
| 21     | Voacangine                        | 1.064                           | Yes                  |
| 22     | Zerumbone                         | 1.314                           | No                   |
| Sr. No. | Name of Compound             | AMES toxicity | MTD * (log mg/kg/day) | hERG I inhibitor | hERG II inhibitor | ORT* (mol/kg) | ORCT# (log mg/kg bw/day) | HEP | SS^ | TPT+ (log ug/L) | Minnow toxicity (log mM) |
|---------|------------------------------|---------------|-----------------------|------------------|-------------------|---------------|---------------------------|-----|-----|----------------|--------------------------|
| 01      | 5(alpha)-cholestane          | No            | -0.358                | No               | Yes               | 2.542         | 1.26                      | No  | No  | 0.296         | -2.617                   |
| 02      | alpha-selinene               | No            | -0.018                | No               | No                | 1.543         | 1.351                     | No  | Yes | 1.623         | 0.353                    |
| 03      | Bergenin                     | No            | -0.013                | No               | No                | 1.879         | 3.614                     | No  | No  | 0.285         | 5.688                    |
| 04      | beta-Amyrenone               | No            | -0.316                | No               | Yes               | 2.18          | 0.852                     | No  | No  | 0.389         | -1.738                   |
| 05      | beta-Sitosterol              | No            | -0.621                | No               | Yes               | 2.552         | 0.855                     | No  | No  | 0.43          | -1.802                   |
| 06      | Betulonic acid               | No            | 0.144                 | No               | No                | 2.256         | 2.206                     | Yes | No  | 0.285         | -1.174                   |
| 07      | Caryophyllene                | No            | 0.351                 | No               | No                | 1.617         | 1.416                     | No  | Yes | 1.401         | 0.504                    |
| 08      | Centaureidin                 | No            | 0.594                 | No               | No                | 2.286         | 2.224                     | No  | No  | 0.319         | 1.86                     |
| 09      | Centaurein                   | No            | 0.56                  | No               | Yes               | 2.565         | 3.805                     | No  | No  | 0.285         | 6.387                    |
| 10      | (3,S)-16,17-Didehydrofalcarnol| No            | -0.284                | No               | No                | 1.287         | 1.098                     | No  | Yes | 2.286         | -0.102                   |
| 11      | Esculetin                    | No            | -0.262                | No               | No                | 2.337         | 1.504                     | No  | No  | 0.39          | 2.341                    |
| 12      | Falcarnol                    | No            | -0.279                | No               | No                | 1.326         | 1.116                     | No  | Yes | 2.291         | -0.181                   |
| 13      | Limonene                     | No            | 0.777                 | No               | No                | 1.88          | 2.336                     | No  | Yes | 0.579         | 1.203                    |
| 14      | Lupeol                       | No            | -0.502                | No               | Yes               | 2.563         | 0.89                      | No  | No  | 0.316         | -1.696                   |
| 15      | Luteolin                     | No            | 0.499                 | No               | No                | 2.455         | 2.409                     | No  | No  | 0.326         | 3.169                    |
| 16      | Methyl 10-oxooctadecanoate   | No            | 0.288                 | No               | No                | 1.547         | 2.757                     | No  | Yes | 1.638         | -1.195                   |
| 17      | Procumbentin                 | No            | 0.531                 | No               | Yes               | 2.574         | 4.089                     | No  | No  | 0.285         | 7.199                    |
| 18      | Puerarin                     | No            | 0.642                 | No               | Yes               | 2.641         | 4.85                      | No  | No  | 0.285         | 4.188                    |
| 19      | Stigmasterol                 | No            | -0.664                | No               | Yes               | 2.54          | 0.872                     | No  | No  | 0.433         | -1.675                   |
| 20      | Taraxasterol acetate         | No            | -0.465                | No               | Yes               | 2.568         | 2.112                     | No  | No  | 0.303         | -2.031                   |
| 21      | Voacangine                   | Yes           | -0.598                | No               | Yes               | 3.161         | 0.616                     | No  | No  | 0.414         | -0.413                   |
| 22      | Zerumbone                    | No            | 1.314                 | No               | No                | 0.534         | No                        | No  | Yes | 1.385         | 1.033                    |

*MTD-Max. tolerated dose (human); *ORT-Oral Rat Acute Toxicity (LD50); #ORCT- Oral Rat Chronic Toxicity (LOAEL); $HEP-Hepatotoxicity; ^SS-Skin Sensitisation; +TPT+T.Pyriformis toxicity