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Original Article

Some Selected Phytoconstituents from *Rhus succedanea* as SARS CoV-2 Main Protease and Spike protein (COVID-19) Inhibitors

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Abstract

Rhus succedanea (Anacardiaceae) was used to treat multiple human afflictions. Literary works demonstrate that it has many biological activities. Today's research aims to recognize Rhus succedanea Phyto-derived anti-viral compounds against the main protease and spike protein of the viral agent of COVID-19 (SARS-CoV-2) gain insight into the molecular interactions. In the current study, ten molecules taken from *R. succedanea* are analyzed through docking, derived from the PubChem database. Docking experiments with Autodock vina and PyRx tools were conducted. AdmetSAR and DruLito servers were eventually used for drug-like prediction. Our research shows that the phytoconstituents from *R. succedanea*, namely, Amentoflavone, Rhoifolin, and Agathisflavone acts against SARS CoV-2 main protease with the binding affinity of -9.3, -8.6 and -8.4 Kcal/mol; Hinokiflavone Robustaflavone and Amentoflavone acts against the SARS-CoV-2 receptor-binding domain of spike protein with a binding affinity of -10.5, -10.4 and -10.1 Kcal/mol respectively. These phyto-compounds can use contemporary strategies to develop effective medicines from natural origins. The substances identified potential anti-viral as likely. However, *In-vitro* studies are even more necessary to assess their effectiveness versus SARS CoV-2.

*Keywords***:** ADMET, In-silico, Lipinski's Rule, PyRx, Rhus succedanea.

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1. Introduction

WHO has currently stated a typical emergency and pandemic for the novel coronavirus (SARS CoV-2) that has proactively propagated worldwide. The virus SARS-CoV-2 can easily trigger signs and symptoms such as fever, coughing, pneumonia, nausea, as well as

exhaustion [1]. The infection's epidemiological history was believed to derive from a seafood market in Wuhan, China [2]. The exact origin of the preliminary transmission to human beings is still unidentified. Presently, more than 100 total genome patterns are recognized in the NCBI GenBank, coming from over ten nations. The variant in between these series is much less than 1%. The SARS-CoV-2 has led to significant respiratory system infections in humans by β-coronavirus using ACE2 receptor [3]. Chinese experts separated SARS-CoV-2 and sequenced the genome SARS-CoV-2 on January 7, 2020 [4]. The crystallized kind of SARS-CoV-2 main protease (M^{pro}) was displayed through a Chinese scientist, Liu et cetera (2020), that a possible medication aims at target protein for the inhibition of SARS-CoV-2 replication. M^{pro} is an essential protein needed to mature the virus [5]. Thus, targeting M^{pro} can effectively handle SARS-CoV-2 by inhibiting the viral polypeptide cleavage. SARS-CoV-2 spike (S) glycoprotein binds to the cell membrane protein receptor angiotensin-converting enzyme 2 (ACE2) to enter human cells. Interestingly, the SARS-CoV-2 virus does not use other coronavirus receptors such as aminopeptidase N and dipeptidyl peptidase 4 [6, 7]. While standard procedures of medicine finding might take years, the strategy taken right here to look for available medicines for the SARS-COV-2 resides *in silico* docking styles from proteins in the SARS-CoV-2, the spike glycoprotein, as well as the SARS-CoV-2 main protease. *In-silico* based testing has been confirmed as a handy tool to satisfy the obstacles of anti-viral medication invention. Variety of natural or synthetic substance collections through computational assessment strategies as docking conserves information in terms of money and time [8]. Natural substances have represented humans as easier, safer, and healthier substitutes for different diseases since the advent of therapeutic goods [9-11]. Thus, we have screened a small library of natural compounds against M^{pro} by *in silico* based screening. We have selected *Rhus succedanea* in the current research and authoritative anti-viral agent's authoritative source [12-14]. The traditional Indian medication used hundreds of years to treat different lung diseases, including pneumonia, is the *Rhus succedanea.* Several reports have also recently provided convincing and exposing scientific data of its anti-HIV, antimicrobial, hepatoprotective, cytotoxicity, antioxidant, anti-inflammatory [21] and antibacterial activity [15-22].

2. Materials and Methods

2.1. Data Source

A list of active phytochemicals was acquired from Indian Medicinal Plants, Phytochemistry, and Therapeutic Data Base [23, 24].

2.2. Drug-likeliness

The phytochemical components were downloaded from PubChem, and the structures were translated into SDF files and performed the drug-likeliness of the compounds by using DruLiTo software. Lipinski's parameters, including topological polar surface area (TPSA), relative molecular weight (MW), number of hydrogen bond donors (nOHNH), number of hydrogen bond acceptors (nON), and the partition coefficient log P, were assessed. [25, 26].

2.3. Docking Studies

2.3.1. Preparation of Protein

The protein's atomic coordinates, Viral agent of COVID-19 main protease (PDB ID: 6LU7), and receptor-binding domain of spike protein (PDB ID: 6LZG) were retrieved from the RCSB PDB site. The charge assignment, solvation parameters, and fragmental volumes to the protein were performed using Autodock Tool 4.2.6 (ADT) before study or docking. The protein molecule was further designed for molecular docking by using Biovia Discovery Studio 2020 version [26-28] (Figure 1

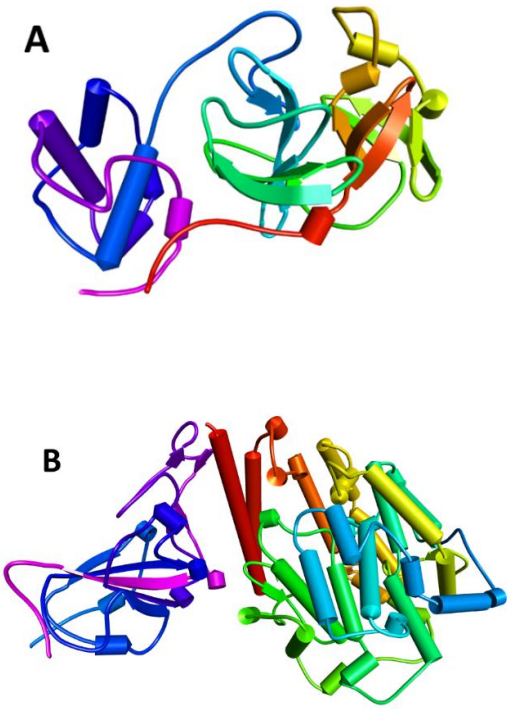

Figure 1. 3D Structures of Proteins (A) Main Protease (PDB ID: 6LU7) and (B) Spike Protein (PDB ID: 6LZG).

2.3.2. Ligands Preparation and Prediction of Drug-Likeliness

The crystal 3D structure of 10 active compounds from *Rhus succedanea* Hinokiflavone, Robustaflavone, Amentoflavone, Agathisflavone, Fisetin_7-glucoside, Rhusflavone, Rhoifolin, Rhusflavanone, Succedaneaflavanone and 2,6,3',4'-Tetrahydroxy-2-benzylcoumaranone were retrieved from the PubChem database. [29]. The drug likeliness properties of ligands were analyzed using DataWarrior tools for the selected active compounds[30-32] (Figure 2).

2.4. Active Site Prediction

An important step is a precise prediction of active sites throughout bioinformatics. Throughout this analysis, the Active Site of Main Protease and receptor-binding domain of spike protein was projected (Figure 3) by the Biovia Drug Discovery Studio Visualizer 2020 (PDB ID: 6LU7,6LZG).

2.5. Compound Screening Using Pyrx Program

The auto-dock wizard was used as a docking engine to molecular check all compound libraries with PyRx software [33]. The ligands were found versatile during the docking process, and the protein should be rigid. The grid parameter configuration file was created with PyRx with dimensions of (X = -10.711837, Y = 12.411388, Z = 68.831286 for 6LU7; X = -32.468000 Y = 24.127000, Z= -17.076000 for 6LZG). In this test, the amino acids in the active protein site reacting with the ligands have were known/predicted. The root-mean-square deviation (RMSD) tests of less than 1.0Å were deemed optimal and grouped to determine the desirable relation. The lowest (most negative) binding energy was recognized as the most binding ligand.

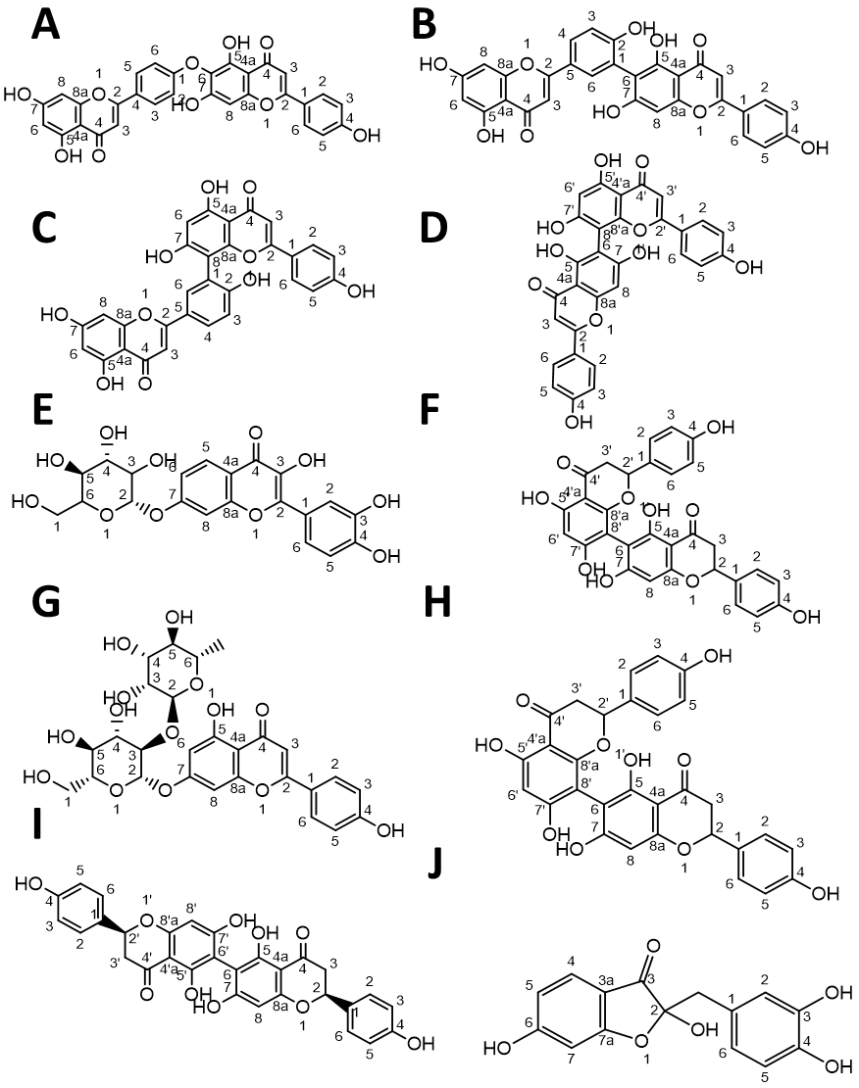

Figure 2. 2D structures of the ligands utilized in the study (A) Hinokiflavone, (B) Robustaflavone, (C) Amentoflavone, (D) Agathisflavone, (E) Fisetin_7-glucoside, (F) Rhusflavone, (G) Rhoifolin, (H) Rhusflavanone, (I) Succedaneaflavanone (J) 2,6,3',4'-Tetrahydroxy-2-benzylcoumaranone.

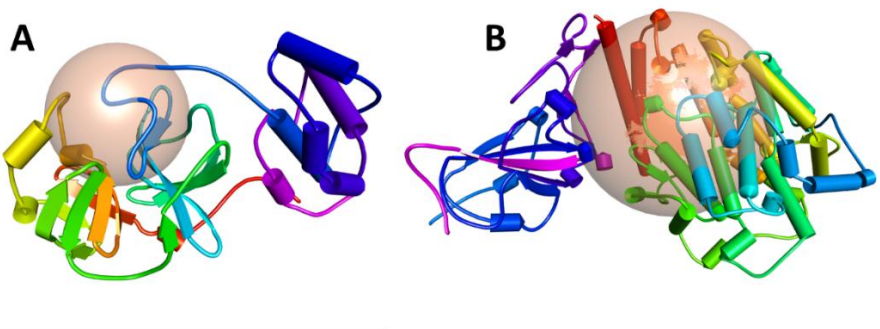

Figure 3. Prediction of Active sites by Drug Discovery Biovia 2020 (A) Main Protease (PDB ID: 6LU7) (B) Spike Protein (PDB ID: 6LZG).

2.6. Analysis and Visualization

Biovia Drug Discovery Studio 2020 was used to examine the docking site visually, and the results were confirmed with Autodock Vina [34, 35].

2.7. ADMET Analysis

The ligands ADMET with their pharmacokinetic properties must be investigated to establish their role within the body. The ADMET history of the ligands was studied, and admetSAR was used [36, 37].

3. Results and Discussion

3.1. Drug likeliness Properties

DataWarrior software was used to study the physicochemical properties of the selected ten active compounds. Except for three compounds, remaining all the compounds obeyed Lipinski's rule. (Table 1). The basic physicochemical properties of TPSA and AMR mainly include drug intake, distribution, and penetration functions [38].

3.2. Molecular Docking Studies

Molecular docking was conducted on ten phytoconstituents acquired from *Rhus succedanea* to discover a prospective SRAS Cov-2 candidate against the main protease and receptor-binding domain of spike protein (PDB ID: 6LU7 and 6LZG). Such ten compounds were bound to the target enzyme COVID-19 and rated based on their dock results. For a detailed review, refer to Tables 2 and 3 (Figure 4-8).

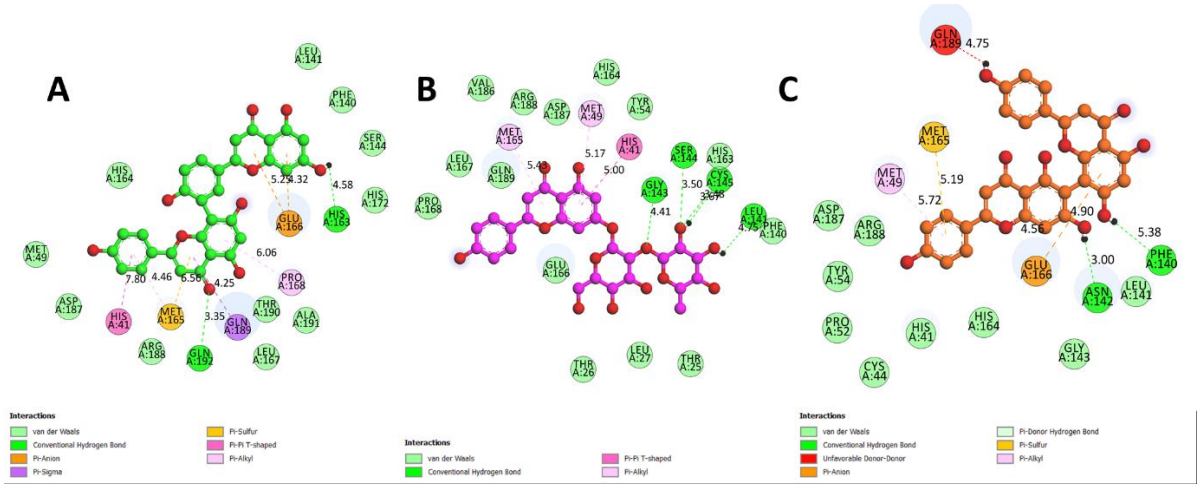

Figure 4. 2D Interactions of ligands with Main protease (6LU7). (A) Amentoflavone, (B) Rhoifolin, (C) Agathisflavone.

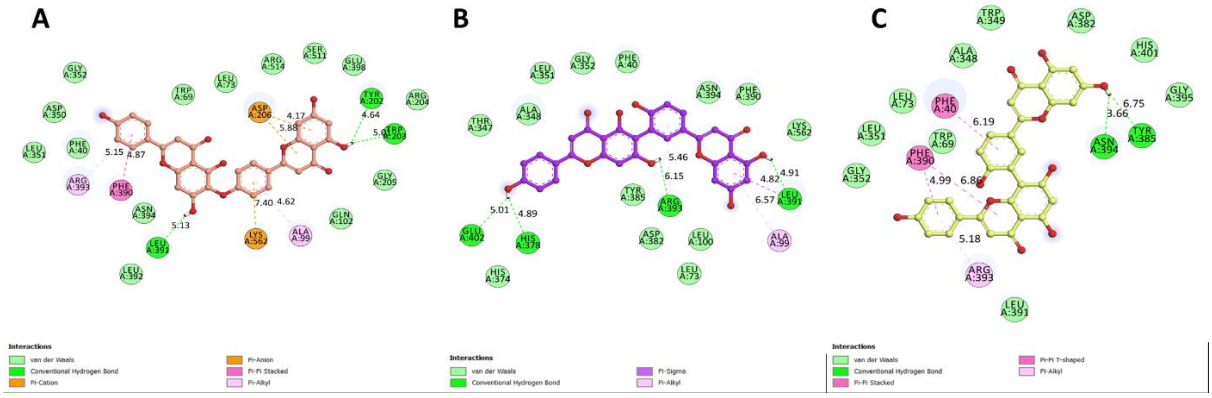

Figure 5. 2D Interactions of ligands with Spike Protein (6LZG). (A) Hinokiflavone, (B) Robustaflavone, (C) Amentoflavone.

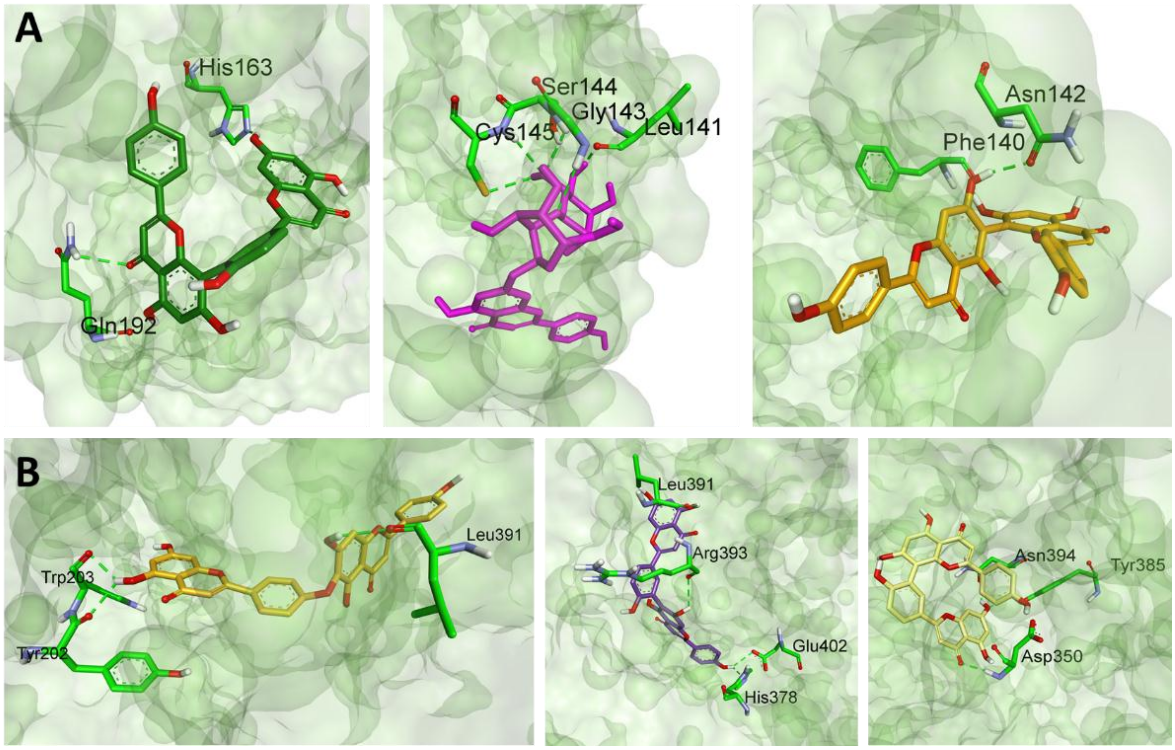

Figure 6. 3D picture of Hydrogen bond Interactions of (A) Amentoflavone, Rhoifolin, Agathisflavone with 6LU7 (B) Hinokiflavone, Robustaflavone, Amentoflavone with 6LZG.

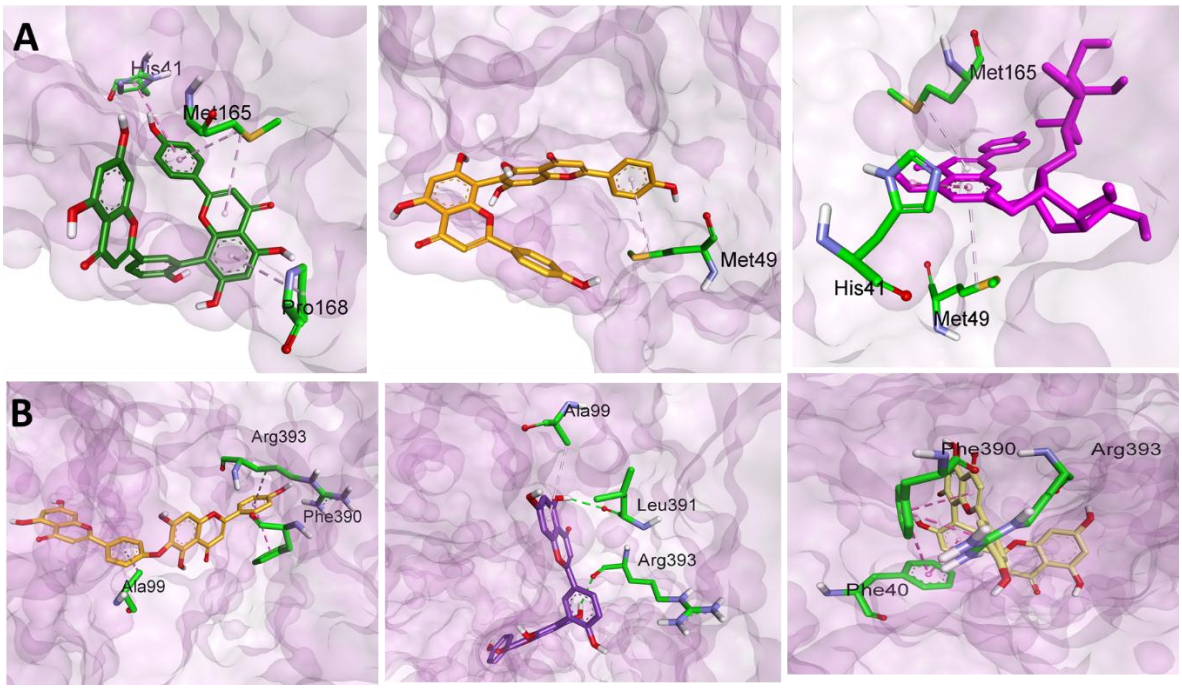

Figure 7. 3D picture of Hydrophobic Interactions of (A) Amentoflavone, Rhoifolin, Agathisflavone with 6LU7 (B) Hinokiflavone, Robustaflavone, Amentoflavone with 6LZG.

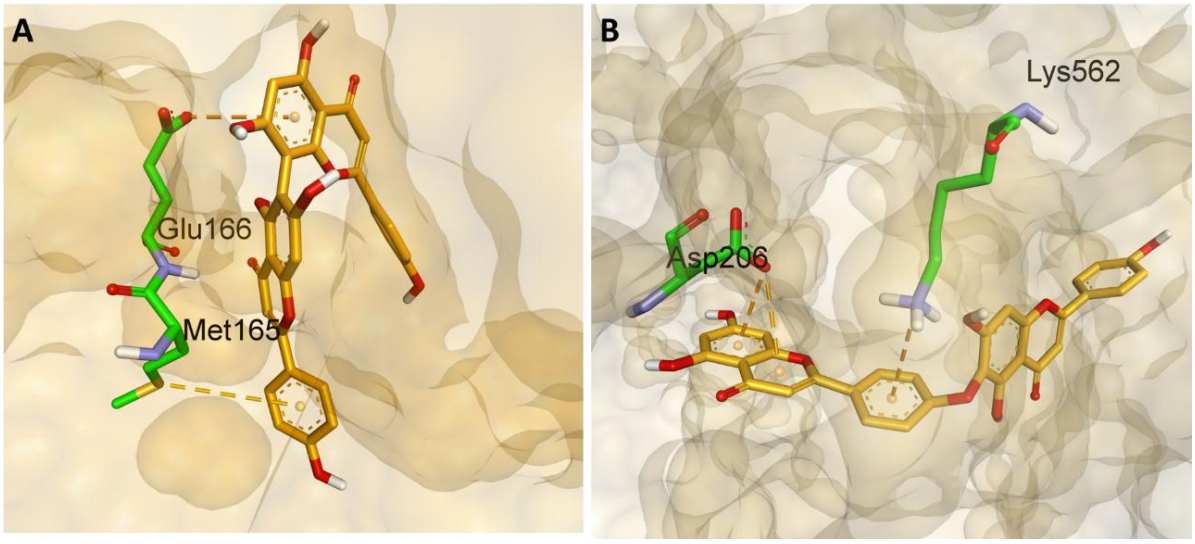

Figure 8. 3D picture of Electrostatic Interactions of (A) Agathisflavone with 6LU7 (B) Hinokiflavone, with 6LZG.

The rigid docking effects were foreseen utilizing Discovery Studio for communications assessment. Table 2 and Table 3 provided the best binding sites for protein-ligand interaction. The most strong connection was noticed in the Amentoflavone with the main protease (PDB: 6LU7) protein complex was -9.3 Kcal/mol. The main protease with Amentoflavone complex formed two hydrogen bond, i.e., HIS A:163 (4.58), GLN A:192 (3.35); four hydrophobic interaction with HIS A:41 (7.80), PRO A:168 (6.06), GLN A:189 (4.25), MET A:165 (4.46) and two electrostatic interactions with MET A:165 (6.56), GLU A:166 (4.32, 5.25). Rhoifolin -main protease complex has a docked score pf -8.6 kcal/mol, which formed four hydrogen bonds, i.e., LEU A:141 (4.75), CYS A:145 (3.48, 3.67), SER A:144 (3.50), GLY A:143 (4.41), and three hydrophobic interaction with HIS A:41 (5.00), MET A:49 (5.17), MET A:165 (5.43). All the ligands formed hydrogen bonding and hydrophobic interactions.

The best possible associate with Hinokiflavone (-10.5 kcal/mol) of the phytochemicals was identified to be the receptor-binding domain of spike protein (6LZG) of SARS Cov-2 (Table 3). The receptor-binding part of spike protein with Hinokiflavone complex formed three hydrogen bond, i.e., TYR A:202 (4.64), TRP A: 203 (5.01), LEU A:391 (5.13); three amino acids are involved in the formation of hydrophobic interactions ALA A:99 (4.62), PHE A:390 (4.87), ARG A:393 (5.15) and two amino acids involved in electrostatic interactions with ASP A:206 (4.17, 5.88), LYS A:562 (7.40).

3.3. ADME/T Evaluation by Using Admetsar

The ADMET attributes of the ligands have been tested using admetSAR. In the research study, ADMET properties for compounds are measured using admetSAR. All the substances demonstrated good human intestinal absorption (HIA) and penetration of the blood-brain barrier (BBB). No cancer-causing drug. All the

compounds displayed negative for AMES toxicity. Table 4 lists the tests of HIA, BBB, LD_{50} for the compounds.

3.4. Discussion

Coronaviruses have a long history of human and animal infection and diseases of the gastrointestinal, urinary, liver, and central nervous system [39]. A newly arrived SARS-CoV-2 now poses significant threats to human health [40]. The main focus was on clinical management that includes infection prevention, control, and help. No specific clinical treatments for SARS-CoV-2-mediated infections are currently available [41]. Therefore, new drug candidates must be identified and discovered to overcome the deprivation of health induced by SARS-CoV-2.

This recent discovery of M^{pro} in the viral agent of COVID-19 provided an excellent opportunity to recognize possible candidates for SARS-CoV-2 treatment. In this way, natural products have gained prominence in the last few years [42, 43]as successful anti-viral agents. We have screened Rhus succedanea phytoconstituents because of the urgent need for COVID-19 therapeutics and natural product facilities in medicines development. SARS-CoV-2 as novel drug molecules for discovering M^{pro} inhibitors for the availability of naturally occurring scaffolds for drug development.

Our examination majorly concentrated on exploring for nutraceutical valuable novel constituents from Rhus succedanea's herbal plant with suitable pharmacological efficiency with minimum toxicity. From this result, the nine selected phytoconstituents from *Rhus succedanea* is specifically chosen for further study.

Out of 10 candidates, three compounds had a higher binding affinity with lower energy binding to the main protease and receptor-binding domain of spike protein. Regarding the main protease, Amentoflavone has minimum binding energy of -9.3 kcal/mol and formed two hydrogen bond, i.e., HIS A:163 (4.58), GLN A:192 (3.35); four hydrophobic interaction with HIS A:41 (7.80), PRO A:168 (6.06), GLN A:189 (4.25), MET A:165 (4.46) and two electrostatic interactions with MET A:165 (6.56), GLU A:166 (4.32, 5.25). The bond length for hydrogen bonds is < 5 A °, meaning that the bond is more substantial and stable complexes are produced. Although Rhoifolin SARS-CoV-2-main protease complex has a docked score pf -8.6 kcal/mol, which formed four hydrogen bonds, i.e., LEU A:141 (4.75), CYS A:145 (3.48, 3.67), SER A:144 (3.50), GLY A:143 (4.41), and three hydrophobic interaction with HIS A:41 (5.00), MET A:49 (5.17), MET A:165 (5.43). Compared with other ligands, these three compounds are the least binding due to more hydrogen bonds with the proteins.

Concerning the receptor-binding domain of spike protein, Hinokiflavone has the lowest binding energy of -10,5 Kcal/mol and three bonds of hydrogen, i.e., TYR A:202 (4.64), TRP A: 203 (5.01), LEU A:391 (5.13); three amino acids are involved in the formation of hydrophobic interactions ALA A:99 (4.62), PHE A:390 (4.87), ARG A:393 (5.15) and two amino acids involved in electrostatic interactions with ASP A:206 (4.17, 5.88), LYS

A:562 (7.40). Robustaflavone established hydrogen bonding with LEU A:391 (4.91), ARG A:393 (6.15), HIS A:379 (4.89), GLU A:402 (5.01), and hydrophobic interactions with ALA A:99 (6.57), ARG A:393 (5.46).

Lipinski's five-rule is a primary standard for assessing drug likeliness. Lipinski's law specifies the molecular properties essential to medication pharmacokinetics in the human body, such as ADME. Lipinski's rule of five conditions for optimal medicines. The top three scored compounds don't obey Lipinski's rule, specifically in the number of H-bond donors and acceptors, as they were derived from natural origin. ADME analyses of selected ten compounds show that all met these ADME check screens (Table 3). This preliminary screening of possible molecules (anti-virals)[3] will provide rapid *in-silico* analysis for SARSCoV2 (COVID-19) therapy production.

Therefore, we expect that the use of *Rhus succedanea* would improve tolerance to fight infections with COVID-19.

4. Conclusion

In the research, we used bioinformatics tools; Autodock-Vina recognized the potent *Rhus succedanea* molecules against SRAS CoV-2 Main Proteases and the receptor-binding domain of spike protein part in the spread of coronavirus.[5] Our research suggests that the three phytoconstituents, including Amentoflavone, Rhoifolin, and Agathisflavone, should be used as potential inhibitors to COVID-19 Main Proteases; Hinokiflavone, Robustaflavone, and Amentoflavone displayed an excellent binding affinity with spike-proteins, which can also be discovered for *In vitro*, pre-clinical and even clinical trials against coronavirus (COVID-19).

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References

[1] Organization WH. Coronavirus disease 2019 (COVID-19): situation report, 70. (2020).

[2] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, and Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. (2020) 395: 507-13.

Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KS, Lau EH, and Wong JY. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. *N. Engl. J. Med.* (2020)

[4] Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, Bi Y, Ma X, Zhan F, Wang L, Hu T, Zhou H, Hu Z, Zhou W, Zhao L, Chen J, Meng Y, Wang J, Lin Y, Yuan J, Xie Z, Ma J, Liu WJ, Wang D, Xu W, Holmes EC, Gao GF, Wu G, Chen W, Shi W, and Tan W. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. (2020) 395: 565-74.

Jin Z, Du X, Xu Y, Deng Y, Liu M, Zhao Y, Zhang B, Li X, Zhang L, and Peng C. Structure of Mpro from COVID-19 virus and discovery of its inhibitors. bioRxiv. *Preprint*. (2020)

[6] Hui DS, Azhar EI, Madani TA, Ntoumi F, Kock R, Dar O, Ippolito G, Mchugh TD, Memish ZA, and Drosten C. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health—The latest

2019 novel coronavirus outbreak in Wuhan, China. *Int. J. Infect. Dis*. (2020) 91: 264-6.

[7] Veeramachaneni GK, Thunuguntla V, Bobbillapati J, and Bondili JS. Structural and simulation analysis of hotspot residues interactions of SARS-CoV 2 with human ACE2 receptor. *J. Biomol. Struct. Dyn.* (2020) 1-11.

[8] Murgueitio MS, Bermudez M, Mortier J, and Wolber G. In silico virtual screening approaches for anti-viral drug discovery. *Drug Discov. Today Technol*.[18] (2012) 9: e219-25.

[9] Castro T, Barbosa K, Albarello N, and Figueiredo S. Caracterização de pseudofrutos, frutos, sementes e plântulas obtidas a partir de germinação in vivo e in[19] vitro da espécie medicinal Hovenia dulcis (Rhamnaceae). *Rev. Cuba. de Plantas Medicinales.* (2005) 10: 1-16.

[10] Shen B. A New Golden Age of Natural[20] Products Drug Discovery. *Cell*. (2015) 163: 1297-300.

[11] Thomford NE, Senthebane DA, Rowe A, Munro D, Seele P, Maroyi A, and Dzobo K. Natural[21] Products for Drug Discovery in the 21st Century: Innovations for Novel Drug Discovery. *Int. J. Mol. Sci*. (2018) 19: 1578.

[12] Rastogi S, Pandey DN, and Singh RH. COVID-19 pandemic: A pragmatic plan for ayurveda[22] intervention. *J. Ayurveda Integr. Med*. (2020)

[13] Panyod S, Ho CT, and Sheen LY. Dietary therapy and herbal medicine for COVID-19 prevention: A review and perspective. *J. Tradit. Complement. Med*. (2020) 10: 420-7.

[14] Cao P, Wu S, Wu T, Deng Y, Zhang Q, Wang K, and Zhang Y. The important role of polysaccharides from a traditional Chinese medicine-Lung Cleansing and Detoxifying Decoction against the COVID-19 pandemic. *Carbohydr. Polym*. (2020) 240: 116346.

[15] Lin YM, Anderson H, Flavin MT, Pai YH, Mata-Greenwood E, Pengsuparp T, Pezzuto JM, Schinazi RF, Hughes SH, and Chen FC. In vitro anti-HIV activity of biflavonoids isolated from Rhus succedanea and Garcinia multiflora. *J. Nat. Prod.* (1997) 60: 884-8.

[16] Shrestha S, Subaramaihha SR, Subbaiah SG, Eshwarappa RS, and Lakkappa DB. Evaluating the antimicrobial activity of methanolic extract of Rhus succedanea leaf gall. *Bioimpacts*. (2013) 3: 195-8.

[17] Pourahmad J, Eskandari MR, Shakibaei R, and Kamalinejad M. A search for hepatoprotective activity of aqueous extract of Rhus coriaria L. against oxidative stress cytotoxicity. *Food Chem. Toxicol.* (2010) 48: 854-8.

Lin Y-M, Chen F-C, and Lee K-H. Hinokiflavone, a Cytotoxic Principle from Rhus succedanea and the Cytotoxicity of the Related Biflavonoids1. *Planta Med.* (1989) 55: 166-8.

Wu P-L, Lin S-B, Huang C-P, and Chiou RY-Y. Antioxidative and Cytotoxic Compounds Extracted from the Sap of Rhus succedanea. *J. Nat. Prod.* (2002) 65: 1719-21.

Baheti J, Kumar V, Shah G, and Goyal R. Free radical scavenging activity of aqueous extract of Rhus succedanea galls. *J. Nat. Remedies* (2005) 5: 15-8.

Kang JS, Lee CW, Lee KH, Han MH, Lee H, Han S-B, Kim H-C, Lee K, Park S-K, and Kim HM. Anti-inflammatory Activity of Methanolic Extract Isolated from Immature Fruit of Rhus succedanea. *Lab. Anim. Res*. (2008) 24: 297-302.

Kumar V, Shah T, Shah G, and Parmar N. Anti-bacterial activity of Rhus succedanea galls. *J. Nat. Remedies* (2003) 3: 95-6.

[23] Mohanraj K, Karthikeyan BS, Vivek-Ananth R, Chand RB, Aparna S, Mangalapandi P, and Samal A. IMPPAT: A curated database of I Indian Medicinal Plants, Phytochemistry And therapeutics. *Sci. Rep.* (2018) 8: 1-17.

[24] Chaudhuri S, Symons JA, and Deval J. Innovation and trends in the development and approval of anti-viral medicines: 1987–2017 and beyond. *Anti-viral research*. (2018) 155: 76-88.

[25] Veeramachaneni GK, Thunuguntla V, Bhaswant M, Mathai ML, and Bondili JS. Pharmacophore Directed Screening of Agonistic Natural Molecules Showing Affinity to 5HT2C Receptor. *Biomolecules* (2019) 9: 556.

[26] Bokka CS, Veeramachaneni GK, Thunuguntla V, Bobbillapati J, and Bondili JS. Peptide Mapping, In Silico and In Vivo Analysis of Allergenic Sorghum Profilin Peptides. *Medicine (Kaunas)*. (2019) 55: 178.

[27] Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, and Olson AJ. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. *J. Comput. Chem*. (2009) 30: 2785-91.

[28] Satyanarayana SDV, Krishna MSR, Pavan Kumar P, and Jeereddy S. In silico structural homology modeling of nif A protein of rhizobial strains in selective legume plants. *J. Genet. Eng. Biotechnol.* (2018) 16: 731-7.

[29] O'Boyle NM, Banck M, James CA, Morley C, Vandermeersch T, and Hutchison GR. Open Babel: An open chemical toolbox. *J. Cheminform*. (2011) 3: 33.

[30] Pangastuti A, Amin IF, Amin AZ, and Amin M. Natural bioactive compound from Moringa oleiferaagainst cancer based on in silico screening. *Jurnal Teknologi*. (2016) 78:

[31] Eda SR, Veeramachaneni GK, Bondili JS, and Jinka R. Screening of caspase-3 inhibitors from natural molecule database using e-pharmacophore and docking studies. *Bioinformation* (2019) 15: 240-5.

[32] Bokka CS, Veeramachaneni GK, Thunuguntla VBSC, Manda NK, and Bondili JS. Specific panallergen peptide of Sorghum Polcalcin showing IgE response identified based on in silico and in vivo peptide mapping. *Biosci. Rep.* (2019) 39:

[33] Dallakyan S and Olson AJ, *Small-molecule library screening by docking with PyRx*, in *Chemical biolog;y* 2015, Springer. p. 243-50.

[34] Seeliger D and de Groot BL. Ligand docking and binding site analysis with PyMOL and Autodock/Vina. *J. Comput. Aided Mol. Des*. (2010) 24: 417-22.

[35] Eda SR and Jinka R. Combined e-pharmacophore based screening and docking of PI3 kinase with potential inhibitors from a database of natural compounds. *Bioinformation* (2019) 15: 709-15.

[36] Yang H, Lou C, Sun L, Li J, Cai Y, Wang Z, Li W, Liu G, and Tang Y. admetSAR 2.0: web-service for prediction and optimization of chemical ADMET properties. *Bioinformatics* (2019) 35: 1067-9.

[37] Cheng F, Li W, Zhou Y, Shen J, Wu Z, Liu G, Lee PW, and Tang Y, *admetSAR: a comprehensive source and free tool for assessment of chemical ADMET properties*. 2012, ACS Publications.

[38] Ertl P, Rohde B, and Selzer P. Fast calculation of molecular polar surface area as a sum of fragment-based contributions and its application to the prediction of drug transport properties. *J. Med. Chem.* (2000) 43: 3714-7.

[39] To KK, Hung IF, Chan JF, and Yuen KY. From SARS coronavirus to novel animal and human coronaviruses. *J. Thorac. Dis*. (2013) 5 Suppl 2: S103-8.

[40] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W, China Novel Coronavirus I, and Research T. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N. Engl. J. Med*. (2020) 382: 727-33.

[41] Zhou Y, Hou Y, Shen J, Huang Y, Martin W, and Cheng F. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. *Cell Discov*. (2020) 6: 14.

[42] Lin LT, Hsu WC, and Lin CC. Anti-viral natural products and herbal medicines. *J. Tradit. Complement. Med*. (2014) 4: 24-35.

[43] Martinez JP, Sasse F, Bronstrup M, Diez J, and Meyerhans A. Anti-viral drug discovery: broad-spectrum drugs from nature. *Nat. Prod. Rep*. (2015) 32: 29-48.

Tables:

Table 1. Physicochemical properties of active compounds and accordance with the rule of Drug-likeliness.

Ligand	MW	Logp	Alogp	HBA	HBD	TPSA	AMR	nRB	nAtom	nAcidic	RC	nRigidB	nAromRing	nHB
Agathisflavone	519.95	1.6	-3.598	0	0	60.42	29.32	3	40	0	6	42	6	0
Amentoflavone	519.95	1.6	-3.598	0	0	60.42	29.32	3	40	0	6	42	6	0
Hinokiflavone	519.95	2.487	-3.291	0	0	69.65	28.37	4	40	0	6	41	6	0
Robustaflavone	519.95	1.6	-3.598	0	0	60.42	29.32	3	40	0	6	42	6	0
Rhoifolin	558.01	-0.726	-4.793	9	0	67.13	78.11	6	51	0	5	39	3	9
Fisetin 7-glucoside	432.98	0.336	-4.006	5	0	48.67	49.64	4	37	0	4	31	3	5
Succedaneaflavanone	521.96	0.962	-3.629	2	0	52.6	45.21	3	42	0	6	42	4	2
Rhusflavone	520.96	1.281	-3.61	1	0	56.51	37.26	3	41	0	6	42	5	1
Rhusflavanone	521.96	0.962	-3.629	2	0	52.6	45.21	3	42	0	6	42	4	2
2,6,3',4'-Tetrahydroxy-2-benzylcoumaranone	275.97	1.136	-2.177	2	0	26.3	24.39	2	21	0	3	21	2	2

Table 2. Interactions of COVID-19 Main Protease (PDB ID:6LU7) amino acid residues with ligands at receptor sites.

Ligands	Binding Affinity, ΔG (Kcal/mol)\	Amino acids involved and Distance (A°)		
		Hydrogen Binding Interactions	Hydrophobic Interactions	Electrostatic Interactions
Amentoflavone	-9.3	HIS A:163 (4.58), GLN A:192 (3.35)	HIS A:41 (7.80), PRO A:168 (6.06), GLN A:189 (4.25), MET A:165 (4.46)	MET A:165 (6.56), GLU A:166 (4.32, 5.25)
Rhoifolin	-8.6	LEU A:141 (4.75), CYS A:145 (3.48, 3.67), SER A:144 (3.50), GLY A:143 (4.41),	HIS A:41 (5.00), MET A:49 (5.17), MET A:165 (5.43),	-
Agathisflavone	-8.4	PHE A:140 (5.38), ASN A:142 (3.00)	MET A:49 (5.72)	MET A:165 (5.19), GLU A:166 (4.90)
Rhusflavone	-8.2	SER A:144 (4.34), CYS A:145 (4.63), GLU A:166 (3.72, 4.08)	MET A:49 (6.81)	CYS A:145 (7.74)
Rhusflavanone	-7.9	PHE A:140 (4.73), GLU A:166 (3.78), LEU A:141 (6.18), CYS A:145 (3.81), GLY A:143 (3.55), ASN A:142 (3.70)	MET A:49 (6.55)	-
2,6,3',4'-Tetrahydroxy-2-benzylcoumaranone	-7.8	LEU A:141 (6.24), SER A:144 (3.34), CYS A:145 (4.01)	HIS A:41 (7.62), MET A:165 (4.62), CYS A:145 (6.85)	-
Robustaflavone	-7.4	GLU A:166 (4.84),	GLN A:189 (4.76), PRO A:168 (5.61), HIS A:41 (7.84), MET A:165 (5.07), CYS A:145 (5.56)	MET A:165 (8.00)
Fisetin_7-glucoside	-7.3	GLY A:143 (3.62), THR A:190 (5.14)	MET A:165 (4.53), HIS A:41 (6.53), MET A:49 (5.94), CYS A:145 (6.60), GLN A:189 (4.37)	MET A:49 (6.64)
Hinokiflavone	-6.2	ASN A:142 (5.30), GLN A:189 (4.26)	MET A:49 (6.27)	-

Table 3. Interactions of COVID-19 Spike Protein (PDB ID:6LZG) amino acid residues with ligands at receptor sites.

Ligands	Binding Affinity, ΔG (Kcal/mol)	Amino acids involved and Distance (A°)		
		Hydrogen Interactions	Hydrophobic Interactions	Electrostatic Interactions
Hinokiflavone	-10.5	TYR A:202 (4.64), 1TRP A: 203 (5.01), LEU A:391 (5.13)	ALA A:99 (4.62), PHE A:390 (4.87), ARG A:393 (5.15)	ASP A:206 (4.17, 5.88), LYS A:562 (7.40)
Robustaflavone	-10.4	LEU A:391 (4.91), ARG A:393 (6.15), HIS A:379 (4.89), GLU A:402 (5.01)	ALA A:99 (6.57), ARG A:393 (5.46)	-
Amentoflavone	-10.1	TYR A:385 (6.75), ASN A:394 (3.66)	PHE A:40 (6.19), PHE A:390 (4.99, 6.86), ARG A:393 (5.18)	-
Agathisflavone	-9.7	TYR A:196 (6.22), LYS A:562 (5.69)	GLY A:205 (5.09, 6.90)	ASP A:206 (3.88), GLU A:398 (6.66)
Fisetin_7-glucoside	-9.5	ALA A:396 (4.07), TRP A:566 (4.79), LYS A:562 (5.27), TYR A:196 (6.36), TYR A:202 (3.01)	GLY A:205 (4.47, 6.19), TRP A:203 (6.42)	ASP A:206 (4.26)
Rhusflavone	-9.4	ALA A:348 (4.28), ARG A:393 (6.95)	PHE A:40 (5.95), LEU A:391 (5.12), LEU A:73 (6.66)	-
Rhoifolin	-9.3	ASP A:206 (3.87, 4.40), TYR A:202 (3.58, 5.08), GLY A:205 (4.11), GLN A:102 (4.62), SER A:70 (4.67)	ALA A:99 (4.77), LEU A:73 (4.44)	-
Rhusflavanone	-9.1	GLU A:375 (5.25), PRO A:346 (5.07)	PHE A:40 (6.15), HIS A:378 (4.37), ALA A:348 (4.97)	-
Succedaneaflavanone	-9.1	HIS A:345 (4.50), PRO A:346 (4.58), ARG A:514 (5.06), GLU A:398 (3.86), ASN A:397 (5.06), ASN A:394 (4.13)	HIS A:401 (5.02), HIS A:378 (5.67)	ASP A:206 (5.16), LYS A:562 (5.08)
2,6,3',4'-Tetrahydroxy-2-benzylcoumaranone	-7.6	TYR A:202 (3.98), GLN A:98 (5.28), LYS :562 (5.34, 3.38), GLU A:564 (5.70)	LEU A:95 (5.54), GLY A:205 (5.20)	-

Table 4. ADME / T Properties of *R. succedanea* compounds.

S. No	Ligand	Absorption					Distribution	Metabolism							Toxicity			
		BBB	HIA	Caco2	P-glyco protein Substrate	Renal Organic Cation Transporter	Subcellular localization	CYP450 2C9 Substrate	CYP450 2D6 Substrate	CYP450 3A4 Substrate	CYP450 1A2 Inhibitor	CYP450 2C9 Inhibitor	CYP450 2D6 Inhibitor	CYP450 2C19 Inhibitor	CYP450 3A4 Inhibitor	AMES Toxicity	Carcinogens	Fish Toxicity (mg/kg)	Rat Acute Toxicity (mol/kg)
1	Agathisflavone	0.6602	0.9739	0.5085	0.5	0.9197	0.8001	0.7931	0.9072	0.7154	0.6838	0.892	0.9322	0.6827	0.6172	0.9509	0.9307	0.442	3.1298
2	Amentoflavone	0.6602	0.9739	0.5085	0.5	0.9197	0.8001	0.7931	0.9072	0.7154	0.6838	0.892	0.9322	0.6827	0.6172	0.9509	0.9307	0.442	3.1298
3	Hinokiflavone	0.6585	0.9562	0.7307	0.5544	0.9184	0.6583	0.8116	0.9112	0.6822	0.6264	0.8318	0.9004	0.6307	0.5	0.9187	0.9367	0.4003	2.955
4	Robustaflavone	0.6602	0.9739	0.5085	0.5	0.9197	0.801	0.7931	0.9072	0.7154	0.6838	0.892	0.9322	0.6827	0.5157	0.9509	0.9307	0.442	3.1298
5	Rhoifolin	0.8364	0.8915	0.8986	0.652	0.8942	0.7093	0.7667	0.8872	0.5494	0.9095	0.939	0.9615	0.949	0.9373	0.8185	0.9503	1.0832	2.252
6	Fisetin 7-glucoside	0.6975	0.7855	0.9398	0.5905	0.8921	0.6068	0.8116	0.8923	0.6035	0.9084	0.9296	0.9513	0.9289	0.9193	0.5776	0.9589	1.0156	2.3869
7	Succedaneaflavanone	0.654	0.9416	0.5409	0.532	0.9081	0.7998	0.7705	0.8565	0.6436	0.5212	0.8963	0.8452	0.6398	0.6628	0.9375	0.9388	0.4821	3.6436
8	Rhusflavone	0.654	0.9416	0.5409	0.532	0.9081	0.7998	0.7705	0.8565	0.6436	0.5212	0.8963	0.8452	0.6398	0.6628	0.9375	0.9388	0.4821	3.6436
9	Rhusflavanone	0.654	0.9416	0.5409	0.532	0.9081	0.7998	0.7705	0.8565	0.6436	0.5212	0.8963	0.8452	0.6398	0.6628	0.9375	0.9388	0.4821	3.6436
10	2,6,3',4'-Tetrahydroxy-2-benzylcoumaranone	0.7924	0.8101	0.798	0.5939	0.9043	0.6752	0.7446	0.8517	0.5922	0.7878	0.8045	0.8767	0.8265	0.791	0.6664	0.9477	0.1761	0.2959

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