# *In Silico* Computational Screening of Kabasura Kudineer - Official Siddha Formulation and JACOM - Novel Herbal Coded Formulation Against SARS-CoV-2 Spike protein

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**Abstract:**

Siddha Medicine is a valuable therapeutic choice which is classically used for treating viral respiratory infections, this principle of medicine is proven to contain antiviral compounds. In this study, we executed the molecular docking studies for Phytoconstituents of Siddha official formulation Kabasura Kudineer which is used in treating viral fever and respiratory diseases and a Novel Herbal Preparation - JACOM against the ongoing pandemic of novel coronavirus disease causative agent SARS-CoV-2 Spike protein. Further, we also conducted prediction studies on the pharmacokinetics (ADME) properties and the safety profile in order to identify the best drug candidates using pkCSM and SwissADME web servers. Totally 37 compounds were screened, of these 9 compounds showed high binding efficiency. Based on these, we proposed the new formulation called as "SNACK –V".

**Key words:**

COVID-19, SARS-CoV-2 Spike protein, Kabasura Kudineer, JACOM, Molecular docking, ADMET, Siddha Medicine, SNACK-V

**Introduction**

The novel Coronavirus disease-2019 (COVID-19) is an ongoing pandemic caused by Severe Acute Respiratory Syndrome Corona-Virus 2 (SARS-CoV-2) [1]. COVID-19 has been declared a pandemic disease by WHO which has severely affected the livelihood of the population. SARS-CoV-2 has spread across the continents, as of April 11, 2020, has led to a total of 16,99,676 cases with a mortality of 1,02,734 among the registered cases. Presently, quarantine and symptomatic treatment protocol for disease management exists and there are no specific antiviral drugs available to combat this virus. As per Ministry of Health and Family Welfare, Govt. of India, in India there are 7447 Active cases and 239 deaths as on April 11, 2020; these data commensurate the impending risk facing the country. This pandemic is still ongoing, hence there is an urgent need to find new preventive and therapeutic agents as soon as possible [2].

Knowledge of Microbes and their Disease spread is clearly mentioned in Siddha which is evinced by 'Kirumiyal vandha thodam perugavundu lines mentioned in Guru naadi"[3]. Siddha holistic approach will be helpful in combating COVID 19 using both therapeutic and non-therapeutic interventions. Siddhar's have advised evidence based treatment approach to understand a disease (Noi naadi), its etiology (Mudhal Naadi) based on those, fix a treatment (Athu Thanikka Vainaadi). As per basic Siddha

Concept Siddhar Theran has defined Vatham is responsible for creation, Pittam for prevention and Aiyam for destruction. Infections happen to a person when his immunity is challenged which could be related with reduction of Pitham. According to Siddha theory, in a Covid19 infection there is initial increase of body temperature, cough and throat pain which may subside if there is good amount of immunity and these symptoms subside when Pitta thathu (Humor) come into action. If not, it escalates to a phase of Kapha Dosham (Disorder) which is said as "Thanamulla sethumanthan ilagil veppu". If not treated at this stage it slowly moves to a Stage of Sanni (Severe Pneumonia- Respiratory failure). It has been unanimously agreed to have equated diagnosis as Kaphasuram in Siddha in early stages moving towards Sanni and which is also reassured through Delphi or other sources of FGD (Focus group discussion).

The control and treatment of a viral infection depends mainly on the availability of antiviral drugs, which are few in numbers and usually are not directly acting on virus but prevent replication in the host. The Siddha herbal formulations having medicinal importance have proved to be potentially active against a wide range of causative agents as Influenza, Dengue, Chikungunya, Tuberculosis, etc. [4,5,6]. Siddha medicines have been used effectively by human civilization over several centuries for treating various diseases and can be effectively employed to target the host response, like Kabasura Kudineer during influenza outbreaks [7]. Besides, during Dengue outbreak in India, a herbal formulation of Siddha medicine, Nilavembu Kudineer is used to prevent and control the morbidity level of public on contacting this viral fever [8].

Kabasura Kudineer, an official Siddha formulation described in Siddha manuscript Citta Vaittiyattirattu [9] is used for Aiyacuram (phlegmatic fevers) and is a dependable Siddha prescription for fever with flu-like symptom [9]. Further, we choose another herbal formulation called "JACOM" a coded novel drug due to its Neuraminidase inhibition potential against inactivated influenza virus H1N1(Patent no.201741016901 A, Dated 18.05.2018) [10].

Moreover, to screen out large number of herbs for compounds with antiviral activity against novel corona virus will be a challenge in very short period. Drug discovery is a time consuming, slow and challenging process [11, 12], so it is necessary to depend on computational tools (computer-aided drug design) to overcome these pitfalls to an extent. Of late, the impact on these tools for new drug development had made the

drug discovery process very cost effective and time efficient [11]. For searching compounds, this ligand-based virtual screening tool is used to identify most probable molecule with pharmacological activity [13] using Molecular docking [14]. Similarly, for studies pharmacokinetics, toxicity, and drug-likeness prediction many algorithms exist which makes the job easier [15]. There are lots of evidence which prove the application of computational tools in the discovery of natural-derived drugs [16–19]. Hence, the aim of the current study is to apply this incredible *in-silico* screening methodology for the official Siddha formulation Kaba Sura Kudineer and the novel formulation JACOM against SARS- CoV-2 Spike protein

**Materials and methods:**

**Ligand Preparation:**

The bioactive constituents used for docking were obtained from 15 herbs of Siddha formulation Kabasura Kudineer Chooranam are β-Sesquiphellandrene, β-Bisabolene, Geranial, Piperine, Piperlonguminine, Eugenol, β-Caryophyllene, Stigmosterol, 3-(2,4- dimethoxyphenyl)-6,7- dimethoxy-2,3- dihydrochromen-4-one, Squalene, γ-Sitosterol, Andrograpanin, 5-Hydroxy-7,8-dimethoxyflavanone, Lupeol, Betulin, Chebulagic acid, Gallic acid, Vasicinone, Carvacrol, Cirsimaritin, Chrysoeriol, 6-Methoxygenkwanin, Luteolin, Costunolide, Elemol, Tinosponone, Bharangin, Scutellarein, Magnoflorine, Cycleanine, Cyperene, β-Selinene. [20-22]. The bioactive constituents from JACOM are Vasicine, Andrographolide, Ursolic acid, Quercetin and Meliacine.

The 2D structures of ligands are summarized in Table S1. All the ligands were obtained from Pubchem and prepared a single .sdf file, further optimization and minimization of all ligands were done in Cresset Flare software with default settings. The ligands file read in Autodetect under full protonation mode.

**Protein Preparation:**

To investigate the phytochemical analogs of Siddha formulation Kaba Sura Kudineer Chooranam and JACOM against SARS-CoV-2 virus, we have selected novel spike glycoprotein (PDB ID: 6VSB), a key target for therapeutics, vaccines and diagnostics in SARS-CoV-2. This spike glycoprotein 2019-nCOV S protein is a single receptor-binding domain (RBD) which binds to ACE2 (Angiotensin converting Enzyme-2) receptor on the host cell with high affinity, which makes it a key target for the novel Coronavirus therapy development. The 3D structure of novel spike glycoprotein (PDB ID: 6VSB) were downloaded from Protein Data Bank

(https://www.rcsb.org/structure/6VSB). The target protein was downloaded in PDB format and protein preparation was carried out in Cresset module Flare software with default settings. Missing residues, Hydrogen's and 3D protonation were carried out on the target protein and minimized for the selected active residues. [23]

**Molecular docking studies:**

Molecular docking was carried for 32 phytochemical constituents of Siddha formulation Kaba Sura Kudineer Chooranam and 05 Phytoconstituents of JACOM. The phytochemical analogs were docked with Spike Protein SARS-CoV-2 (PDB ID: 6VSB) by using Cresset Flare Docking software [24,25] with default settings and the grid box was defined based on trial and error and carried out in normal mode. The crystal structure of protein was obtained from protein data bank. The structures of phytochemical constituents were downloaded from the Pubchem and the structures were converted into a single database file in sdf file format in Data warrior software. Best poses were generated and visualized in pose viewer and 3D images stored in storyboard. Analysis of docking results was done with Flare Software and the results are shown in **Table 1 & 2**. Best score generating Phytoconstituents in the largest cluster was analyzed for its interaction with the protein and 2D poses were obtained from Ligplus.

**Results:**

**Molecular Docking Studies:**

The molecular docking studies were carried out for the 32 phytochemical constituent's herbs Siddha formulation Kaba Sura Kudineer Chooranam and 05 phytochemical constituent's JACOM against Coronavirus Spike Protein to identify the molecular interactions between target protein with ligands. All the phytochemical analogs were docked with Spike Protein SARS-COV-2 (PDB ID: 6VSB) by using Cresset Flare Docking software.

The crystal structure of protein was obtained from pdb bank. The structures of phytochemical constituents were downloaded from the Pubchem and the structures converted into a single database file in sdf file format in Data warrior software. To fight against this deadly virus, many X-ray crystal structures of proteins were reposited in pdb bank for Receptor-binding protein (RBD, trimer) with PBD ID 6CRV and 6VSB; Heptad repeat 2(HR2) with PBD ID 2FXP.

The SARS-COV-2 virus binds to human cells through its spike glycoprotein, making this protein as key target to design potential therapeutics. In this regard, we have

selected potential phyto constituents with previously reported antiviral activity for carrying out the docking studies with the viral spike glycoprotein.

Binding affinities of phytocompounds of siddha formulation Kaba Sura Kudineer Chooranam and JACOM towards active site of Spike Protein SARS-CoV-2 was studied in detail. Biological interaction analyses of Phytoconstituents with spike protein SARS-COV2 were carried out to identify the compound having highest binding affinity with target protein. In the Flare software docking analysis,

The LF rank score is an indicator of the binding affinity of protein-ligand complex. The LF rank for each phytocompound is described in Table-1 & 2. The binding orientation for each phytocompounds into the active site of SAR-CoV-2 spike protein is identified based on the molecule having the least LF rank score. The more the negative LF rank score represent the better affinity of the phytocompound against target SARS-CoV2- spike protein.

Among the docking studies performed on phytocompound, all the analogs had effective binding interactions with SAR-COV-2 spike protein (LF rank score range from -5.75 to -11.03). From the results it reveals that Phytoconstituents with highest docking LF rank score were seen for Chrysoeriol and Luteolin from Kaba Sura Kudineer Chooranam and Quercetin from JACOM with LF rank score values -11.478, -11.392 and -11.159, respectively. Whereas, 5-Hydroxy-7,8-dimethoxyflavanone, Cirsimaritin, Scutellarein with LF rank score of -9.035, -9.228, and -10.277, show moderate binding affinity against the target protein. Remaining analogs also show lower binding affinity towards SARS-CoV2 spike protein. We further studied detailed binding orientation of top 11 phytocompounds in the active site of spike protein and best poses in 2D and 3D were generated.

The number of hydrogen bond and the number of amino acid residues of SARS-CoV-2 interacting with each phytocompounds are given in Table.2. From the detailed docking analysis, it is observed that Chrysoeriol, Luteolin and Scutellarein shows a high binding affinity with target protein SARS-CoV2 spike protein. It is found that, these three compounds have formed H-bond contact with more than four amino acid residues in spike protein showing that it forms more number of H-bonds resulting in increased binding affinity with target protein (**Fig.1,8 &10**).

The interaction analysis of Chrysoeriol, Cirsimaritin and magnoflorine-SARS-CoV2 spike protein complex reveals that amino acids Cys336, Asp364, Ser373, Asn343, Cys336, Gly339, Asp364, Arg346, Val341 and Thr345 have played

important role in the formation of H-bond network. The possible binding orientation of phytocompounds from Siddha formulation Kaba Sura Kudineer Chooranam and JACOM into the active site of SARS-CoV-2 spike protein and corresponding Hydrophobics interaction models, number of hydrogen bonds are shown in Table 1& 2 and Fig. 1-11. The Docking studies of all the phytochemicals from two formulations were compared with positive control Hydroxychloroquine and found that all docked ligands were interacting with the same amino acid residues. The validation docking and Hydrochloroquine has LF rank score -8.35 and forms two H-bond interactions with Phe342 and Asn343 (Fig 12**)**.

Flare was used to perform *in silico* computational studies, prediction of cavity, assigning bond orders, structure refinement, defining the active sites of the SARS-CoV-2 and structure preparation. The protein preparation was carried out with Flare and the chain was treated to add missing hydrogen, assign proper bond orders. The structure output format was set to pose viewer file so as to view the output of resulting docking studies and hydrogen bond interactions of different poses with the protein. The 2D and 3D interactions were generated with Ligplus and storyboard in Cresset. All the studied phytoconstitutents have showed good antiviral activity and excellent free energy of binding interactions with SARS-CoV-2.

***In Silico* Prediction of Drug likeliness, and Synthetic Accessibility:**

Rule of 5 by Lipinski is a significant criterion to evaluate drug likeliness and if a specific chemical compound with a certain biological activity has physio-chemical properties that would make it a likely orally active drug in humans. Lipinski's rule evaluates the different descriptors which are important for a drug design. 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) iv) O/W partition coefficient log P not greater than 5. If the molecule violates more than 3 descriptor parameters, it will not fit into the criteria of drug likeliness and it is not considered in order to proceed with drug discovery.

**Table 3 & 4** depicts the drug likeliness and various rules like Lipinski rule of five, Veber Ghose, Muegge and Egan rules were applied to all phytochemical constituents. From the data, most of the Phytoconstituents obeyed the rules only few analogs violated. The low value of synthetic accessibility indicates that all the Phytoconstituents could be synthesized. These results indicate the active ingredients

of two Siddha Formulations of Kabasura Kudineer Chooranam and JACOM have drug like properties.

***In Silico* Simulation of ADME and Pharmacokinetic Properties**

*In silico* pharmacokinetics properties of phytochemical constituents of Siddha formulation Kabasura kudineer chooranam and JACOM were carried out with online pkCSM webserver.

From the data of Pharmacokinetic Properties shows that Lupeol, Betulin, Cycleanine, β-selinene, Quercetin, Andrograpanin and Tinosponone have the highest gastrointestinal absorption, tissue distribution (Vd), and respectable total clearance (Table-5). The Lupeol and Betulin ingrediants of Kaba Sura kudineer chooranam formulation have 100% bioavailability and other ingredients also having oral bioavailability >80%. For JACOM formulation Ursolic acid has 100% bioavailability and other ingredients also having >80% bioavailability.

The Cytochrome P450 and P-glycoprotein simulation studies for substrate and inhibition were performed for all selected Phytoconstituents of two Siddha formulations by using online webserver. The results show that most of the Phytoconstituents has less CYP inducing and P-gp compatibility property (Table 6). Piperine, piperlonguminine, Stigmosterol, 3-(2,4-dimethoxyphenyl)-6,7-dimethoxy-2,3- dihydrochromen-4-one, Squalene, γ-sitosterol, Andrograpanin, 5-Hydroxy-7,8-dimethoxyflavanone, Lupeol, Betulin could undergoes metabolism via CYP3A4 enzyme (Table 6). Moreover, β-Sesquiphellandrene, β-Bisabolene, Geranial, Gallic acid, Carvacrol, Costunolide, and Elemol were free from drug-drug interaction via the inhibition of cytochrome-P (CYP) or P-glycoprotein (P-gp) I and II enzymes (Table 6).

***In Silico Toxicity Prediction:***

Toxicity assessment was performed for the selected Phytoconstituents of Siddha formulations and results show that very few analogs have deviated toxicity prediction. Overall the study indicates, the ingredients of these two formulations are free from carcinogenic, teratogenic and tumorigenic properties (Table 7).

**Discussion:**

In this work, we have chosen Official Siddha Formulation Kabasura kudineer chooranam and JACOM (patented formulation). Kabasura kudineer chooranam is a polyherbal formulation of fifteen herbs mixed in equal quantities from which a decoction is prepared. To prepare Kaba Sura kudineer from Kabasura kudineer

chooranam, all the fifteen ingredient drugs are coarsely powdered and mixed; 35 g of this powder is boiled with three liters of water and reduced to 1/12th the volume. This has to be taken 30 to 60 ml twice or thrice daily [9]. The ingredients in the above Siddha formulation are absorbable when administered orally.

Modern medicines focus on killing the virus but not on increasing the host immunity. In case of Siddha medicine, herbs like Amukkara, Nilavembu are immuno-modulator and having the capacity to inhibit the virus by enhancing and restoring immunity of human. So, we are utilizing this strength of Siddha medicine to arrive upon a potent formulation that is both anti-viral and Immuno-modulatory with minimum side effects on patients who are immuno compromised as well as those who have co-morbid conditions.

The Kabasura Kudineer increases the immunity and could act as immuno modulator as this virus is adversely affecting the immune response by effecting signaling pathway of TNF production as recent findings shows [26]. The formulation chosen are aimed at increasing Immunity and also to expel out the Kapham and reinstate respiratory health. Drugs in these formulations majorly possess Bitter taste or pungent taste. These drugs on Post digestive transformation get converted to Hot potency which increases and Normalizes Pitham and expel out excessive Kapham out of Lungs, which is the rationale behind selecting these formulations.

Based on the results, nine phyto compounds (6 plants) were found to be the best lead and drug candidates with good synthetic accessibility. These 6 plants interaction score is higher than the positive control Hydroxychloroquine. Based on these results, we proposed a novel herbal formulation called “SNACK -V” (*Sida acuta*, *Adhatoda vasica*, *Andrographis paniculata*, *Tinospora Cordifolia*, *Costus speciosus*, *Plectranthus ambonicus*) it may have high probability of directly inhibiting the novel coronavirus (2019-nCoV), possibly providing instant help in the prevention and treatment of the pneumonia that it can cause. This formulation having herbs that possess bitter taste increases pittam and expels out Kapham for their properties of Immunomodulation, expectorant and antipyretic. These effects reinstate Gaseous exchange normalizing trithodam and Sanni Symptoms are wiped away therby restoring Normal health.

*Tinospora Cordifolia* is a one of the drug of choice in conditions wherever pitta is diminished and Kapha dominates [27]. Due to its bitter taste in post Digestive transformation it turns into hot potency as a pungent active molecule and helps in

reinstating pitta to normalcy and eliminates kapha slowly out of the body. It is useful also in settling fever. Later studies had proved its efficacy as an Antiviral and an Immunomodulator. Its effect against HIV has been documented via clinical evaluation [28].

*Andrographis paniculata* by its bitter taste and hot potency helps in all fevers by precipitating diaphoresis [27], in Dengue out break and during other disaster Mitigation interventions it was the drug of choice even by public health authorities [5]. By possessing anti-inflammatory, Analgesic, Anti pyretic and Immuno - modulatory activity [29] this has also proven to inhibit Dengue virus [30].

*Adhatoda vasica* is bitter in taste and turns into hot potency. It is also an expectorant and very useful in kapha disorders [27]. Studies suggest that extracts have strong anti-influenza virus activity that can inhibit viral attachment and/or viral replication, and may be used as viral prophylaxis [31].

*Plectranthus ambonicus* is a plant having pungent taste and gets converted to hot potency post transformation, possess Diaphoretic and Expectorant property [27]. Many antimicrobial studies have established its effectiveness in Pneumonia and Proven to inhibit HIV1 Protease [32].

*Costus speciosus* is bitter in taste and turns into hot potency [27], indicated in fever and used as an expectorant. Studies have proved that it inhibits Herpes simplex and Varicella virus [33].

*Sida acuta* is bitter in taste and turns into hot potency. It is also an expectorant and very much useful in kapha disorders [27]. Studies show this herb inhibits the replication of Dengue viruses in cell cultures and protected mice against dengue infection. It also showed antipyretic and anti-inflammatory effects [34]. To summarize, these above mentioned 6 plants possess both anti viral and immuno-modulatory property, also all the bioactive compounds are non-toxic and non-carcinogenic. However, further experimental studies and clinical studies are required to validate the results.

**Conclusion:**

Siddha medicine is one of best way to control the COVID-19. The docking studies of bioactive compounds from Kabasura Kudineer and JACOM showed that stronger binding affinity with good ADMET properties. Further we propose a new formulation as SNACK-V. Given their binding affinity towards SARS-CoV-2 spike protein and *in*

*silico* safety studies, these two formulations qualify as a potential therapeutic for further *In vitro, In vivo* and Clinical studies.

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**Conflict of interest:**

The authors declare no Conflict of interest.

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**Table 1: In silico Docking studies of Phytoconstituents of Siddha formulation Kabasura Kudineer Chooranam and JACOM against Spike Protein SARS-COV-2 (PDB ID: 6VSB) Using Docking Software Cresset Flare**

| Plant Name | Compound name and Code | LF dG | LF VSscore | LF Rank Score | LF LE |
|---|---|---|---|---|---|
| **Kabasura Kudineer Chooranam** | | | | | |
| *Zingiber officinale* Rosc | β-sesquiphellandrene (**1**) | -6.638 | -6.846 | -2.658 | -0.443 |
| | β-bisabolene**(2)** | -6.562 | -6.713 | -2.8 | -0.437 |
| | Geranial**(3)** | -5.099 | -5.319 | -2.121 | -0.464 |
| *Piper longum* L | Piperine**(4)** | -6.768 | -7.445 | -4.143 | -0.322 |
| | Piperlonguminine**(5)** | -7.078 | -7.7 | -4.245 | -0.354 |
| *Syzygium aromaticum* | Eugenol**(6)** | -4.818 | -5.559 | -6.182 | -0.402 |
| | β-Caryophyllene**(7)** | -5.654 | -5.918 | -3.203 | -0.377 |
| *Tragia involucrata* L | Stigmosterol**(8)** | -9.724 | -10.39 | -7.466 | -0.324 |
| | 3-(2,4-dimethoxyphenyl)-6,7-dimethoxy-2,3-dihydrochromen-4-one**(9)** | -6.433 | -7.316 | -9.011 | -0.247 |
| *Anacyclus pyrethrum* | Squalene**(10)** | -9.722 | -10.187 | -1.389 | -0.324 |
| | γ–Sitosterol**(11)** | -9.956 | -10.521 | -7.679 | -0.332 |
| *Andrographis paniculata* | Andrograpanin**(12)** | -6.819 | -7.678 | -7.854 | -0.296 |
| | 5-Hydroxy-7,8-dimethoxyflavanone**(13)** | -7.356 | -7.966 | -9.035 | -0.334 |
| *Hygrophila auriculata* (Schum.)Heine | Lupeol**(14)** | -8.337 | -8.917 | -6.41 | -0.269 |
| | Betulin**(15)** | -7.984 | -9.117 | -7.02 | -0.249 |
| *Terminalia chebula* Retz. | Chebulagic acid**(16)** | -10.769 | -11.138 | -9.723 | -0.158 |
| | Gallic acid**(17)** | -5.549 | -6.602 | -6.916 | -0.462 |
| *Justicia adhatoda* L. | Vasicinone**(18)** | -5.753 | -6.272 | -8.164 | -0.384 |
| *Plectranthus amboinicus* (Lour) Spreng | Carvacrol**(19)** | -5.322 | -5.696 | -6.923 | -0.484 |
| | Cirsimaritin**(20)** | -6.42 | -7.227 | -9.228 | -0.279 |
| | Chrysoeriol**(21)** | -7.954 | -8.352 | -11.392 | -0.362 |
| | 6-Methoxygenkwanin**(22)** | -6.415 | -7.527 | -9.293 | -0.279 |
| *Saussurea lappa* (Falc.) Lipsh | Luteolin**(23)** | -8.149 | -8.584 | -11.159 | -0.388 |
| | Costunolide**(24)** | -6.081 | -6.607 | -3.799 | -0.358 |
| | Elemol**(25)** | -6.587 | -6.696 | -5.43 | -0.412 |
| *Tinospora cordifolia* (Willd.) Miers ex Hook.f&Thoms | Tinosponone**(26)** | -7.043 | -7.434 | -8.145 | -0.293 |
| *Clerodendrum serratum* | Bharangin**(27)** | -7.418 | -7.744 | -6.682 | -0.309 |

| | | | | | |
|---|---|---|---|---|---|
| L. | Scutellarein**(28)** | -7.805 | -9.148 | -10.277 | -0.372 |
| *Sida acuta* Burm. f. | Magnoflorine**(29)** | -7.635 | -8.527 | -9.762 | -0.305 |
| | Cycleanine**(30)** | -6.184 | -8.214 | -3.432 | -0.134 |
| *Cypreus rotundus* L. | Cyperene**(31)** | -6.024 | -6.225 | -3.558 | -0.402 |
| | β-selinene**(32)** | -6.33 | -6.587 | -3.412 | -0.422 |
| **JACOM Formulation** | | | | | |
| *Justicia adathoda* L. | Vasicine**(33)** | -5.19 | -6.1 | -7.67 | -0.37 |
| *Carica Papaya* | Quercetin**(34)** | -8.408 | -8.59 | -11.478 | -0.382 |
| *Andrographis paniculata* Burm.f.Nees | Andrographolide**(35)** | -7.74 | -8.45 | -7.85 | -0.31 |
| *Ocimum tenuiflorum* | Ursolic acid**(36)** | -7.08 | -7.71 | -5.1 | -0.21 |
| *Melia azedarach* | Meliacine**(37)** | -4.2 | -8.76 | -5.14 | -0.88 |

**Table 2: Amino acid residues of SARS COV2 Spike protein participated in H-Bond and Hydrophobic interactions with ligands**

| Compound Code | LF Rank Score | Interactions | |
|---|---|---|---|
| | | H-Bonding | Hydrophobic |
| β-sesquiphellandrene (**1**) | -2.65 | NHB | Ser373, Phe374 |
| β-bisabolene**(2)** | -2.8 | Phe342, Ser373, | Phe338, Gly339 |
| Geranial**(3)** | -2.12 | NHB | Ser373, Phe374, |
| Piperine**(4)** | -4.14 | Phe374, Trp436 | Phe338, Ser373, |
| Piperlonguminine**(5)** | -4.24 | Phe338 | Ser373, Phe342, Cys336, Leu335 , Val367 |
| Eugenol**(6)** | -6.18 | Asn343, Phe342, | Ser373 |
| β-Caryophyllene**(7)** | -3.20 | | Phe338, Gly337 |
| Stigmosterol**(8)** | -7.46 | Cys336, Gly336, | Phe342, Asn343, Ser373, |
| 3-(2,4-dimethoxyphenyl)-6,7-dimethoxy-2,3-dihydrochromen-4-one**(9)** | -9.01 | Arg509, Trp436, | Phe374, Phe342, Asn343, Thr345, Ala344, Leu441 |
| Squalene**(10)** | -1.38 | NHB | Thr345, Asn643, Phe342, Asn343, Phe338, Leu335 |
| γ–Sitosterol**(11)** | -7.67 | Cys336, Gly339 | Ser373, Phe374, Val510 |
| Andrograpanin**(12)** | -7.85 | Asn343 | Phe342, Leu335, Asp364 |
| 5-Hydroxy-7,8-dimethoxyflavanone**(13)** | -9.03 | Asp 364, Gly339 | Cys336, Phe337, Leu335, Phe342, Phe338, Leu368 |
| Lupeol**(14)** | -6.41 | Thr345 | Asn343, Ser373, Thr345, Arg509 |
| Betulin**(15)** | -7.02 | Thr345, Ser373 | Asn422, Val341, Arg509, Phe373, Thr345 |
| Chebulagic acid**(16)** | -9.72 | Tyr369, Asn370, Tyr369, Phe377, Cys379, Lys378 | Lys378, Phe337, Phe342, Cys336 |
| Gallic acid**(17)** | -6.91 | Lys356, Val341 | Ala397, Val341, Lys356 |
| Vasicinone**(18)** | -8.16 | Cys336, Gly339 | Val397, Cys336, Phe338, Leu335, Asp364 |
| Carvacrol**(19)** | -6.92 | Asp364 | Cys336, Leu335, Asp364 |
| Cirsimaritin**(20)** | -9.22 | Cys336, Asp364, Ser373, Asn343 | Phe338, Phe342, Phe374, Ser373 |
| Chrysoeriol**(21)** | -11.39 | Cys336, Gly339, Asp364, | Phe338, Phe342, Phe374, Leu335, Val367, Ser373 |

| | | | |
|---|---|---|---|
| 6-Methoxygenkwanin**(22)** | -9.29 | Cys336, Phe342 | Ser373, Phe342, Leu368, Phe338, Leu335 |
| Luteolin**(23)** | -11.15 | Asp364, Val367, Ser371, Ser373, Cys336, Val362 | Phe338, Gly339, Phe374, Phe342 |
| Costunolide**(24)** | -3.79 | Phe515, Gly431 | Val511, Phe515, Gly431 |
| Elemol**(25)** | -5.43 | Asp364, Asp364 | Phe374, Phe342, Asn343, |
| Tinosponone**(26)** | -8.14 | Phe342, Gly339 | Trp436, Asn343, Leu368, Val367 |
| Bharangin**(27)** | -6.68 | Phe338, Gly339, | Phe337, Phe342, Ser373 |
| Scutellarein**(28)** | -10.27 | Cys336, Phe338, Gly339, Asp364, Val362 | Ser373, Phe374, Leu335, Asn343 |
| Magnoflorine**(29)** | -9.76 | Arg346, Val341, Thr345 | Ala344, Lys356, Ala397 |
| Cycleanine**(30)** | -3.43 | Ser373 | Phe374, Trp436, |
| Cyperene**(31)** | -3.55 | NHB | Ser373 |
| β-selinene**(32)** | -3.41 | NHB | Phe342, Ser373 |
| **JACOM Formulation** | | | |
| Vasicine**(33)** | -7.67 | Phe 338, Asn343 | Gly339 |
| Quercetin**(34)** | -11.47 | Asp364 | Phe338, Leu335, Gly339, Leu368, cys336, he374 |
| Andrographolide**(35)** | -7.85 | Asp364, Phe368, Gly339, Asn343 | Cys336, Phe342, Leu368, Phe374 |
| Ursolic acid**(36)** | -5.1 | Val367 | Leu368 |
| Meliacine**(37)** | -5.14 | Phe338 | Val367, Ser371, Leu368, Phe338 |
| Hydroxychloroquine(**38)** | -8.35 | Phe342, Asn343 | Gly339, Phe338, Leu368, Trp436, Ser373, Phe374 |

*NHB: No Hydrogen Bond Interactions

**Table 3: Physiochemical and ADMET properties of Phytoconstituents of Siddha formulation Kabasura Kudineer Chooranam and JACOM**

| Code | Total Molwt | cLogP | cLogS | HBA | HBD | TSA | Mutagenic | Tumorigenic | Reprod Effective | Irritant | Shape Index |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | 204.4 | 5.1 | -3.6 | 0.0 | 0.0 | 190.8 | none | none | none | high | 0.7 |
| **2** | 204.4 | 5.5 | -3.5 | 0.0 | 0.0 | 190.3 | none | none | none | none | 0.7 |
| **3** | 152.2 | 3.3 | -2.1 | 1.0 | 0.0 | 146.8 | low | high | high | low | 0.8 |
| **4** | 285.3 | 3.6 | -3.6 | 4.0 | 0.0 | 229.9 | none | none | high | none | 0.7 |
| **5** | 273.3 | 3.3 | -3.7 | 4.0 | 1.0 | 226.5 | none | none | high | none | 0.7 |
| **6** | 164.2 | 2.3 | -2.1 | 2.0 | 1.0 | 140.2 | high | high | none | high | 0.7 |
| **7** | 204.4 | 5.5 | -3.7 | 0.0 | 0.0 | 175.0 | none | none | none | none | 0.5 |
| **8** | 412.7 | 7.6 | -6.4 | 1.0 | 1.0 | 335.3 | none | none | none | none | 0.5 |
| **9** | 360.4 | 2.1 | -3.2 | 7.0 | 1.0 | 267.7 | none | none | none | none | 0.5 |
| **10** | 410.7 | 13.1 | -6.3 | 0.0 | 0.0 | 397.4 | none | none | none | none | 0.8 |
| **11** | 414.7 | 7.9 | -6.7 | 1.0 | 1.0 | 336.3 | none | none | none | none | 0.5 |
| **12** | 318.5 | 3.6 | -3.8 | 3.0 | 1.0 | 248.7 | none | none | none | high | 0.5 |
| **13** | 300.3 | 2.7 | -3.3 | 5.0 | 1.0 | 224.4 | none | none | none | none | 0.5 |
| **14** | 426.7 | 7.6 | -6.8 | 1.0 | 1.0 | 325.6 | none | none | none | none | 0.4 |
| **15** | 442.7 | 6.7 | -6.3 | 2.0 | 2.0 | 333.4 | none | none | none | none | 0.4 |
| **16** | 954.7 | 0.5 | -4.5 | 27.0 | 13.0 | 602.9 | none | none | none | none | 0.3 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **17** | 170.1 | 0.1 | -0.7 | 5.0 | 4.0 | 116.4 | high | none | high | none | 0.6 |
| **18** | 202.2 | 0.4 | -1.7 | 4.0 | 1.0 | 143.7 | none | none | none | none | 0.5 |
| **19** | 150.2 | 2.8 | -2.5 | 1.0 | 1.0 | 128.9 | none | none | none | high | 0.6 |
| **20** | 314.3 | 2.5 | -3.2 | 6.0 | 2.0 | 229.2 | none | none | none | none | 0.6 |
| **21** | 300.3 | 2.3 | -2.9 | 6.0 | 3.0 | 213.3 | none | none | none | none | 0.5 |
| **22** | 314.3 | 2.5 | -3.2 | 6.0 | 2.0 | 229.2 | none | none | none | none | 0.6 |
| **23** | 286.2 | 2.0 | -2.6 | 6.0 | 4.0 | 197.4 | none | none | none | none | 0.5 |
| **24** | 232.3 | 4.2 | -3.1 | 2.0 | 0.0 | 191.0 | none | none | none | high | 0.5 |
| **25** | 222.4 | 4.1 | -3.3 | 1.0 | 1.0 | 189.8 | none | none | none | none | 0.5 |
| **26** | 330.4 | 1.7 | -3.3 | 5.0 | 1.0 | 237.4 | none | none | none | none | 0.4 |
| **27** | 328.4 | 2.8 | -3.2 | 4.0 | 1.0 | 244.0 | none | none | none | none | 0.5 |
| **28** | 286.2 | 2.0 | -2.6 | 6.0 | 4.0 | 197.4 | none | none | none | none | 0.6 |
| **29** | 342.4 | -0.3 | -2.9 | 5.0 | 2.0 | 247.4 | none | none | none | none | 0.4 |
| **30** | 622.8 | 6.5 | -7.3 | 8.0 | 0.0 | 473.8 | none | none | none | none | 0.4 |
| **31** | 204.4 | 4.2 | -3.6 | 0.0 | 0.0 | 159.6 | none | none | none | low | 0.4 |
| **32** | 204.4 | 4.7 | -3.8 | 0.0 | 0.0 | 174.5 | none | none | none | none | 0.5 |
| **33** | 188.2 | 0.2 | -1.5 | 3 | 1 | 139.6 | none | none | none | none | 0.4 |
| **34** | 302.2 | 1.5 | -2.5 | 7.0 | 5.0 | 201.9 | high | high | none | none | 0.5 |
| **35** | 350.4 | 1.8 | -2.9 | 5 | 3 | 258.9 | none | none | none | none | 0.3 |
| **36** | 456.7 | 6.0 | -6.1 | 3 | 2 | 337.8 | none | none | none | none | 0.3 |
| **37** | 666.7 | 0.70 | -4.7 | 12 | 3 | 441.1 | none | none | none | high | 0.4 |

*HA- Hydrogen Bond Acceptor; HBD: Hydrogen Bond Donor; TSA- Total Surface area

**Table 4: The predicted lead likeness, Drug likeness, and synthetic accessibility score of phytochemical constituents Siddha formulation Kabasura Kudineer Chooranam and JACOM**

| Code | Lipinski rule of five[a] | Ghose filters[a] | Veberfilters[a] | Egan filters[a] | Muegge filters[a] | Lead likeness | Synthetic accessibility |
|---|---|---|---|---|---|---|---|
| **1** | Yes | Yes | Yes | Yes | No; 2 ( violations: XLOGP3>5, Heteroatoms<2) | No; (2 violations: MW<250, XLOGP3>3.5) | 4.42 |
| **2** | Yes | Yes | Yes | Yes | No; (2 violations: XLOGP3>5, Heteroatoms<2) | No; 2 violations: MW<250, XLOGP3>3.5 | 3.9 |
| **3** | Yes | No; 1 violation: MW<160 | Yes | Yes | No; 2 violations: MW<200, Heteroatoms<2 | No; 1 violation: MW<250 | 2.49 |
| **4** | Yes | Yes | Yes | Yes | Yes | Yes | 2.92 |
| **5** | Yes | Yes | Yes | Yes | Yes | No; 1 violation: XLOGP3>3.5 | 2.98 |
| **6** | Yes | Yes | Yes | Yes | No; 1 violation: MW<200 | No; 1 violation: MW<250 | 1.58 |
| **7** | Yes | Yes | Yes | Yes | No; 1 violation: Heteroatoms<2 | No; 2 violations: MW<250, XLOGP3>3. | 4.51 |
| **8** | Yes | 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 |
| **9** | Yes | Yes | Yes | Yes | Yes | No; 1 violation: MW>350 | 4.00 |
| **10** | Yes | No; 3 violations: WLOGP>5.6, | No; 1 violation: | No; 1 | No; 2 violations: XLOGP3>5, | No; 3 violations: MW>350, | 4.73 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | MR>130, #atoms>70 | Rotors>10 | violation: WLOGP>5.88 | Heteroatoms<2 | Rotors>7, XLOGP3>3.5 | |
| **11** | Yes | 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 | 6.30 |
| **12** | Yes | Yes | Yes | Yes | Yes | No; 1 violation: XLOGP3>3.5 | 4.63 |
| **13** | Yes | Yes | Yes | Yes | Yes | Yes | 3.31 |
| **14** | Yes | 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** | Yes | 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 | 5.68 |
| **16** | No; 3 violations: MW>500, NorO>10, NHorOH>5 | No; 3 violations: MW>480, MR>130, #atoms>70 | No; 1 violation: TPSA>140 | No; 1 violation: TPSA>131.6 | No; 5 violations: MW>600, TPSA>150, #rings>7, H-acc>10, H-don>5 | No; 1 violation: MW>350 | 7.92 |
| **17** | Yes | No; 2 violations: MR<40, #atoms<20 | Yes | Yes | No; 1 violation: MW<200 | No; 1 violation: MW<250 | 1.22 |
| **18** | Yes | Yes | Yes | Yes | Yes | No; 1 violation: MW<250 | 2.75 |
| **19** | Yes | No; 1 violation: MW<160 | Yes | Yes | No; 2 violations: MW<200, | No; 1 violation: MW<250 | 1.00 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | Heteroatoms<2 | | |
| **20** | Yes | Yes | Yes | Yes | Yes | Yes | 3.27 |
| **21** | Yes | Yes | Yes | Yes | Yes | Yes | 3.06 |
| **22** | Yes | Yes | Yes | Yes | Yes | Yes | 3.27 |
| **23** | Yes | Yes | Yes | Yes | Yes | Yes | 3.02 |
| **24** | Yes | Yes | Yes | Yes | Yes | No; 1 violation: MW<250 | 4.29 |
| **25** | Yes | Yes | Yes | Yes | No; 1 violation: Heteroatoms<2 | No; 2 violations: MW<250, XLOGP3>3.5 | 3.54 |
| **26** | Yes | Yes | Yes | Yes | Yes | Yes | 4.91 |
| **27** | Yes | Yes | Yes | Yes | Yes | Yes | 4.61 |
| **28** | Yes | Yes | Yes | Yes | Yes | Yes | 3.04 |
| **29** | Yes | Yes | Yes | Yes | Yes | Yes | 3.78 |
| **30** | Yes | No; 4 violations: MW>480, WLOGP>5.6, MR>130, #atoms>70 | Yes | Yes | No; 2 violations: MW>600, XLOGP3>5 | No; 2 violations: MW>350, XLOGP3>3.5 | 6.87 |
| **31** | Yes | Yes | Yes | Yes | No; 1 violation: Heteroatoms<2 | No; 2 violations: MW<250, XLOGP3>3.5 | 5.34 |
| **32** | Yes | Yes | Yes | Yes | No; 2 violations: XLOGP3>5, Heteroatoms<2 | No; 2 violations: MW<250, XLOGP3>3.5 | 3.42 |
| **33** | Yes | Yes | Yes | Yes | No; 1 violation: MW<200 | No; 1 violation: MW<250 | 3.36 |
| **34** | Yes | Yes | Yes | Yes | Yes | Yes | 3.23 |
| **35** | Yes | Yes | Yes | Yes | Yes | No; 1 violation: MW>350 | 5.06 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **36** | Yes | 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 | 6.21 |
| **37** | No; 2 violations: MW>500, NorO>1 | No; 3 violations: MW>480, MR>130, #atoms>70 | No; 1 violation: TPSA>140 | No; 1 violation: TPSA>131.6 | No; 4 violations: MW>600, TPSA>150, #rings>7, H-acc>10 | No; 1 violation: MW>350 | 7.76 |

Synthetic accessibility range from (0-1); 1 is very easy to synthesize & 10 is very difficult

[a]Lipinski rule of five, Ghose, Veber, Egan, and Muegge rules were applied to all phytochemical constituents

**Table 5: *In silico* pharmacokinetics properties of phytochemical constituents of Siddha formulation Kabasura Kudineer Chooranam and JACOM**

| Phytochemical Constituents | Intestinal absorption | BBB Permeability | Human Vd (L/kg) | Total clearance (mg/kg/day) | Renal OCT2 substrate |
|---|---|---|---|---|---|
| β-sesquiphellandrene **(1)** | 94.668 | 0.787 | 0.633 | 1.458 | No |
| β-bisabolene**(2)** | 95.232 | 0.788 | 0.634 | 1.458 | No |
| Geranial**(3)** | 95.317 | 0.626 | 0.166 | 0.376 | No |
| Piperine**(4)** | 94.444 | -0.102 | 0.158 | 0.232 | Yes |
| Piperlonguminine**(5)** | 94.721 | -0.334 | 0.008 | 0.229 | No |
| Eugenol**(6)** | 93.514 | 0.471 | 0.458 | 0.288 | No |
| β-Caryophyllene**(7)** | 94.827 | 0.74 | 0.645 | 1.088 | No |
| Stigmosterol**(8)** | 94.97 | 0.771 | 0.178 | 0.618 | No |

| | | | | | |
|---|---|---|---|---|---|
| 3-(2,4-dimethoxyphenyl)-6,7-dimethoxy-2,3-dihydrochromen-4-one**(9)** | 95.609 | -0.827 | -0.316 | 0.23 | No |
| Squalene**(10)** | 89.002 | 0.965 | 0.35 | 1.791 | No |
| γ–Sitosterol**(11)** | 94.464 | 0.781 | 0.193 | 0.628 | No |
| Andrograpanin**(12)** | 96.632 | -0.002 | 0.129 | 1.115 | No |
| 5-Hydroxy-7,8-dimethoxyflavanone**(13)** | 94.118 | 0.179 | -0.245 | 0.122 | No |
| Lupeol**(14)** | 100 | 0.738 | -0.088 | 0.153 | No |
| Betulin**(15)** | 100 | -0.428 | -0.403 | 0.236 | No |
| Chebulagic acid**(16)** | 95.704 | -3.708 | 0.017 | -2.638 | No |
| Gallic acid**(17)** | 43.374 | -1.102 | -1.855 | 0.518 | No |
| Vasicinone**(18)** | 75.52 | -0.164 | -0.145 | 0.623 | No |

| | | | | | |
|---|---|---|---|---|---|
| Carvacrol**(19)** | 93.694 | 0.427 | 0.438 | 0.219 | No |
| Cirsimaritin**(20)** | 94.112 | -0.317 | 0.053 | 0.671 | No |
| Chrysoeriol**(21)** | 82.048 | -1.11 | 0.072 | 0.717 | No |
| 6-Methoxygenkwanin**(22)** | 93.987 | -0.59 | 0.001 | 0.587 | No |
| Luteolin**(23)** | 84.392 | -1.151 | -0.103 | 0.662 | No |
| Costunolide**(24)** | 97.026 | 0.511 | 0.282 | 1.334 | No |
| Elemol**(25)** | 93.486 | 0.625 | 0.407 | 1.311 | No |
| Tinosponone**(26)** | 96.894 | -0.128 | 0.023 | 0.918 | Yes |
| Bharangin**(27)** | 94.384 | -0.17 | 0.189 | 0.847 | No |
| Scutellarein**(28)** | 70.092 | -1.267 | -0.046 | 0.625 | No |
| Magnoflorine**(29)** | 96.895 | 0.1 | 1.591 | 1.117 | No |

| | | | | | |
|---|---|---|---|---|---|
| Cycleanine**(30)** | 97.199 | 0.062 | -0.998 | 0.972 | No |
| Cyperene**(31)** | 94.425 | 0.812 | 0.757 | 0.97 | No |
| β-selinene**(32)** | 96.491 | 0.827 | 0.65 | 1.174 | No |
| Vasicine**(33)** | 86.22 | -0.127 | 0.08 | 0.58 | No |
| Quercetin**(34)** | 77.207 | -1.098 | 1.559 | 0.407 | No |
| Andrographolide**(35)** | 95.357 | -0.598 | -0.286 | 1.183 | No |
| Ursolic acid**(36)** | 100 | -0.141 | -1.088 | 0.083 | No |
| Meliacine**(37)** | 80.458 | -1.144 | 0.934 | -0.054 | No |

**Table 6: The Predicted Pharmacokinetics properties of phytochemical constituents for Cytochrome Inhibition and P-glycoprotein studies for two Siddha Formulations**

| Phytochemical Constituents | CYP2D6 and CYP3A4 Substrate | CYP enzymes inhibition | P-gp substrate | P-gp I or II inhibition |
|---|---|---|---|---|
| β-sesquiphellandrene (**1**) | No | -- | No | -- |
| β-bisabolene**(2)** | No | -- | No | -- |
| Geranial**(3)** | No | -- | No | -- |
| Piperine**(4)** | CYP3A4 | CYP2C19 | substrate | P-gp I |
| Piperlonguminine**(5)** | CYP3A4 | CYP2C19 | substrate | -- |
| Eugenol**(6)** | No | CYP1A2 | No | -- |
| β-Caryophyllene**(7)** | No | CYP2C9 | No | -- |
| Stigmosterol**(8)** | CYP3A4 | -- | No | P-gp I and II |
| 3-(2,4-dimethoxyphenyl)-6,7-dimethoxy-2,3-dihydrochromen-4-one**(9)** | CYP3A4 | -- | No | P-gp I |
| Squalene**(10)** | CYP3A4 | -- | No | P-gp II |

| | | | | |
|---|---|---|---|---|
| γ–Sitosterol**(11)** | CYP3A4 | -- | No | P-gp I and P-gp II |
| Andrograpanin**(12)** | CYP3A4 | CYP1A2 | No | P-gp I |
| 5-Hydroxy-7,8-dimethoxyflavanone**(13)** | CYP3A4 | CYP1A2, CYP2C19 | No | -- |
| Lupeol**(14)** | CYP3A4 | -- | No | P-gp I and P-gp II |
| Betulin**(15)** | CYP3A4 | -- | substrate | P-gp I and P-gp II |
| Chebulagic acid**(16)** | No | -- | substrate | -- |
| Gallic acid**(17)** | No | -- | No | -- |
| Vasicinone**(18)** | No | CYP1A2 | No | -- |
| Carvacrol**(19)** | No | -- | No | -- |
| Cirsimaritin**(20)** | No | CYP1A2, CYP2C19, CYP3A4 | substrate | P-gp II |
| Chrysoeriol**(21)** | No | CYP1A2, CYP2C19, CYP2C9 | substrate | -- |
| 6-Methoxygenkwanin**(22)** | CYP3A4 | CYP1A2, CYP2C19, CYP2C9 | substrate | -- |
| Luteolin**(23)** | No | CYP1A2, CYP3A4 | substrate | -- |

| | | | | |
|---|---|---|---|---|
| Costunolide**(24)** | No | -- | No | -- |
| Elemol**(25)** | No | -- | No | -- |
| Tinosponone**(26)** | CYP3A4 | -- | No | -- |
| Bharangin**(27)** | CYP3A4 | -- | No | P-gp I |
| Scutellarein**(28)** | No | CYP1A2, CYP2C9 | substrate | -- |
| Magnoflorine**(29)** | No | CYP1A2, CYP2D6 | substrate | -- |
| Cycleanine**(30)** | CYP3A4 | -- | substrate | P-gp I and P-gp II |
| Cyperene**(31)** | CYP3A4 | CYP1A2 | No | -- |
| β-selinene**(32)** | No | CYP1A2 | No | -- |
| Vasicine**(33)** | CYP3A4 | -- | No | -- |
| Quercetin**(34)** | No | CYP1A2 | substrate | -- |
| Andrographolide**(35)** | CYP3A4 | -- | No | -- |
| Ursolic acid**(36)** | CYP3A4 | -- | No | -- |
| Meliacine**(37)** | CYP3A4 | Non inhibitor | Substrate | P-gp I |

**'—' Indicates Non Inhibition**

**Table 7: The predicted toxicity of phytochemical constituents of two Siddha Formulations**

| Code | AMES tox. | hERG I or II inhibition | Hepatotoxicity | Skin sensitization | Carcinogenicity | Human maximum tolerated dose (mg/kg/day) | Oral rat acute toxicity (mol/kg) | Oral rat chronictox. (mg/kg_bw/day) |
|---|---|---|---|---|---|---|---|---|
| **1** | No | No | No | Yes | No | 0.273 | 1.584 | 1.314 |
| **2** | No | No | No | Yes | No | 0.418 | 1.642 | 1.347 |
| **3** | No | No | No | Yes | No | 0.543 | 1.815 | 2.133 |
| **4** | No | No | Yes | No | No | -0.38 | 2.811 | 1.51 |
| **5** | No | No | Yes | No | No | -0.021 | 2.572 | 1.888 |
| **6** | No | No | No | Yes | No | 0.773 | 2.129 | 2.297 |
| **7** | No | No | No | Yes | No | 0.429 | 1.634 | 1.407 |
| **8** | No | hERG II | No | No | No | -0.664 | 2.54 | 0.872 |
| **9** | No | No | No | No | No | 0.944 | 2.244 | 1.453 |
| **10** | No | hERG II | No | No | No | -0.533 | 1.893 | 0.911 |
| **11** | No | hERG II | No | No | No | -0.621 | 2.552 | 0.855 |
| **12** | No | No | No | No | No | -0.973 | 2.157 | 1.994 |
| **13** | No | No | No | No | No | 0.303 | 2.41 | 1.562 |
| **14** | No | No | No | No | No | 0.042 | 2.925 | 1.756 |
| **15** | No | No | Yes | No | No | -0.372 | 4.228 | 2.256 |
| **16** | No | No | No | No | No | 0.438 | 2.482 | 9.246 |
| **17** | No | No | No | No | No | 0.7 | 2.218 | 3.06 |
| **18** | Yes | No | No | No | No | 0.15 | 1.956 | 2.564 |
| **19** | No | No | Yes | Yes | No | 0.994 | 1.9 | 2.301 |
| **20** | No | hERG II | No | No | No | 0.75 | 2.494 | 1.716 |
| **21** | No | No | No | No | No | 0.672 | 2.463 | 1.509 |
| **22** | No | No | No | No | No | 0.033 | 2.254 | 1.862 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **23** | No | hERG II | No | No | No | 0.982 | 2.178 | 2.259 |
| **24** | No | No | No | Yes | No | 0.539 | 1.869 | 1.826 |
| **25** | No | No | No | Yes | No | 0.283 | 1.686 | 1.229 |
| **26** | Yes | No | Yes | No | No | -0.005 | 2.855 | 1.021 |
| **27** | No | No | No | No | No | -0.028 | 2.155 | 1.791 |
| **28** | No | No | No | No | No | 0.902 | 2.299 | 3.078 |
| **29** | No | hERG II | No | No | No | 0.194 | 2.841 | 1.93 |
| **30** | Yes | hERG II | No | No | No | -0.001 | 2.723 | 0.675 |
| **31** | No | No | No | No | No | -0.204 | 1.56 | 1.319 |
| **32** | No | No | No | Yes | No | 0.211 | 1.632 | 1.543 |
| **33** | Yes | No | No | No | 1.86 | 0.204 | 2.697 | 1.427 |
| **34** | No | No | No | No | No | 0.499 | 2.471 | 2.612 |
| **35** | No | No | No | No | 1.37 | 0.128 | 2.162 | 1 |
| **36** | No | No | Yes | No | -0.787 | 0.199 | 2.346 | 2.054 |
| **37** | No | No | No | No | 0.997 | -1.197 | 2.877 | 3.539 |

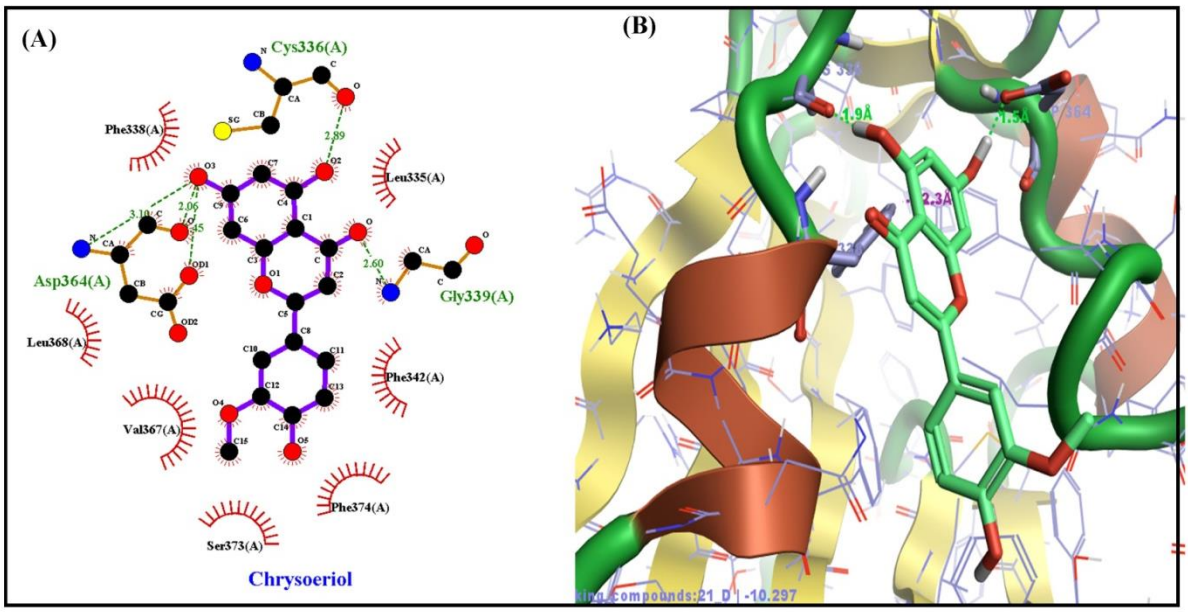



Fig.1. Molecular docking results of Chrysoeriol into SARS COV2 Spike protein. (A) Hydrophobic interaction of Chrysoeriol with SARS COV2 Spike protein (B) Binding mode of Chrysoeriol in SARS COV2 Spike protein. Amino acid residues involved in H-bond formation and H-bond networks are shown.

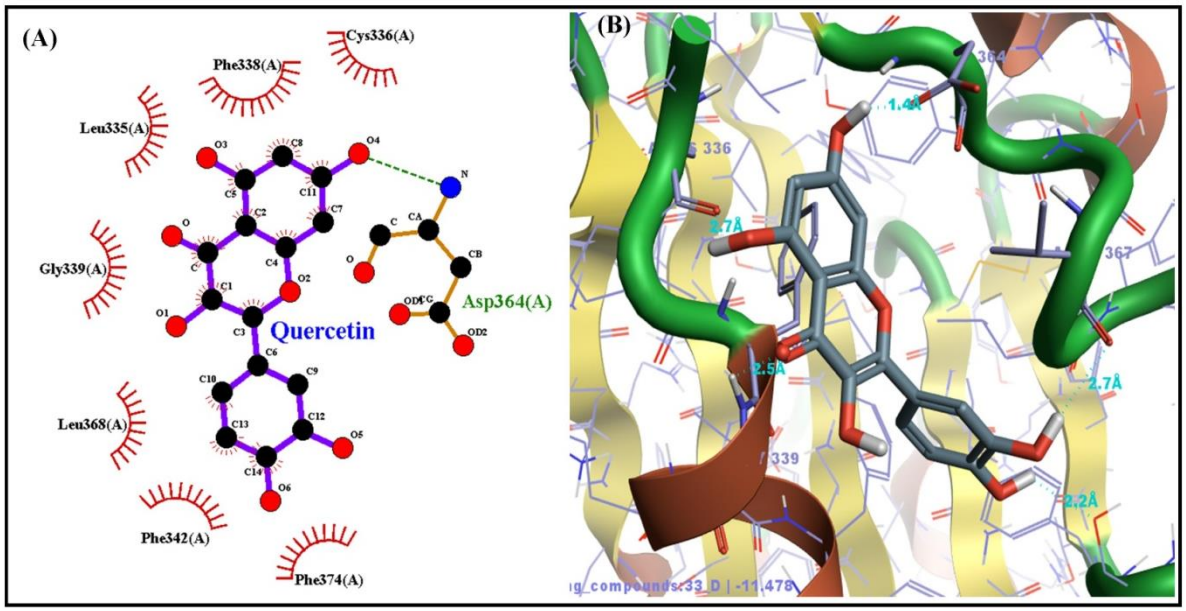



Fig.2. Molecular docking results of Quercetin into SARS COV2 Spike protein. (A) Hydrophobic interaction of Quercetin with SARS COV2 Spike protein (B) Binding mode of Quercetin in SARS COV2 Spike protein. Amino acid residues involved in H-bond formation and H-bond networks are shown.

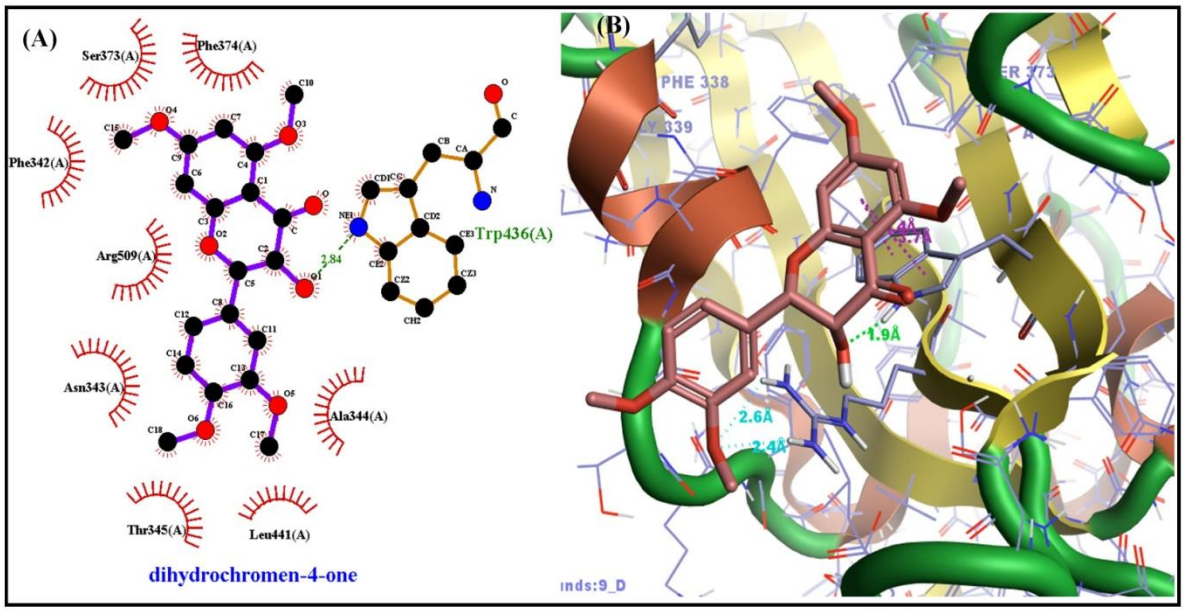



Fig.3. Molecular docking results of 3-(2,4- dimethoxyphenyl)-6,7- dimethoxy-2,3-dihydrochromen-4-oneinto SARS COV2 Spike protein. (A) Hydrophobic interaction of 3-(2,4-dimethoxyphenyl)-6,7- dimethoxy-2,3- dihydrochromen-4-one with SARS COV2 Spike protein (B) Binding mode of 53-(2,4- dimethoxyphenyl)-6,7- dimethoxy-2,3- dihydrochromen-4-onein SARS COV2 Spike protein. Amino acid residues involved in H-bond formation and H-bond networks are shown.

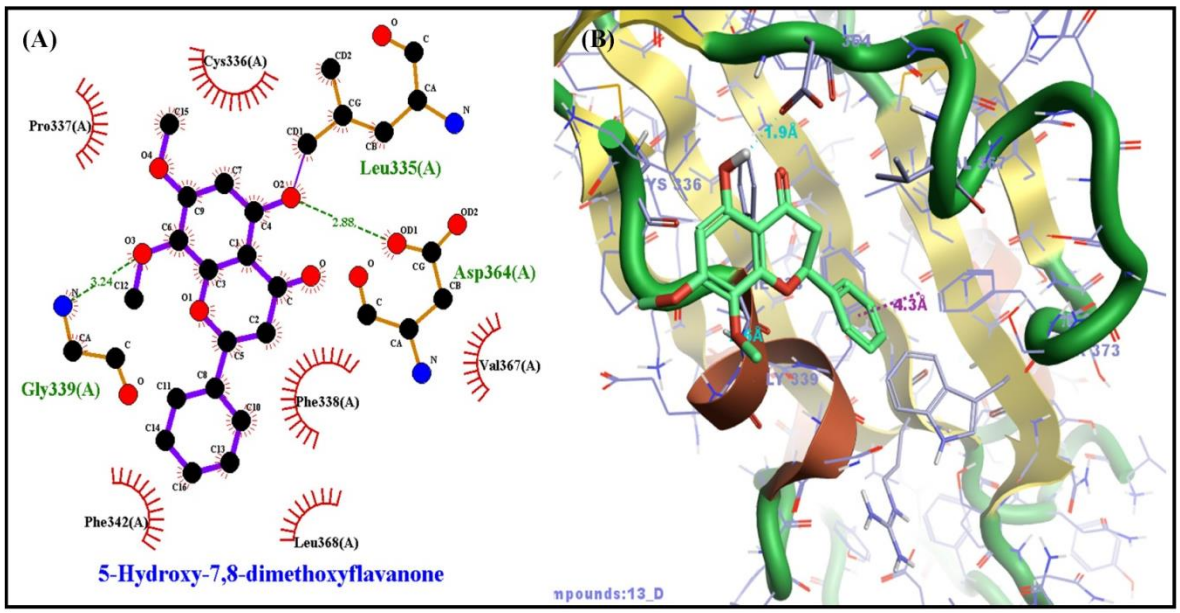



Fig.4. Molecular docking results of 35-hydroxy-7,8-dimethoxyflavonone-one into SARS COV2 Spike protein. (A) Hydrophobic interaction 5-hydroxy-7,8-dimethoxyflavonone with SARS COV2 Spike protein (B) Binding mode of 5-hydroxy-7,8-dimethoxyflavononein SARS COV2 Spike protein. Amino acid residues involved in H-bond formation and H-bond networks are shown.

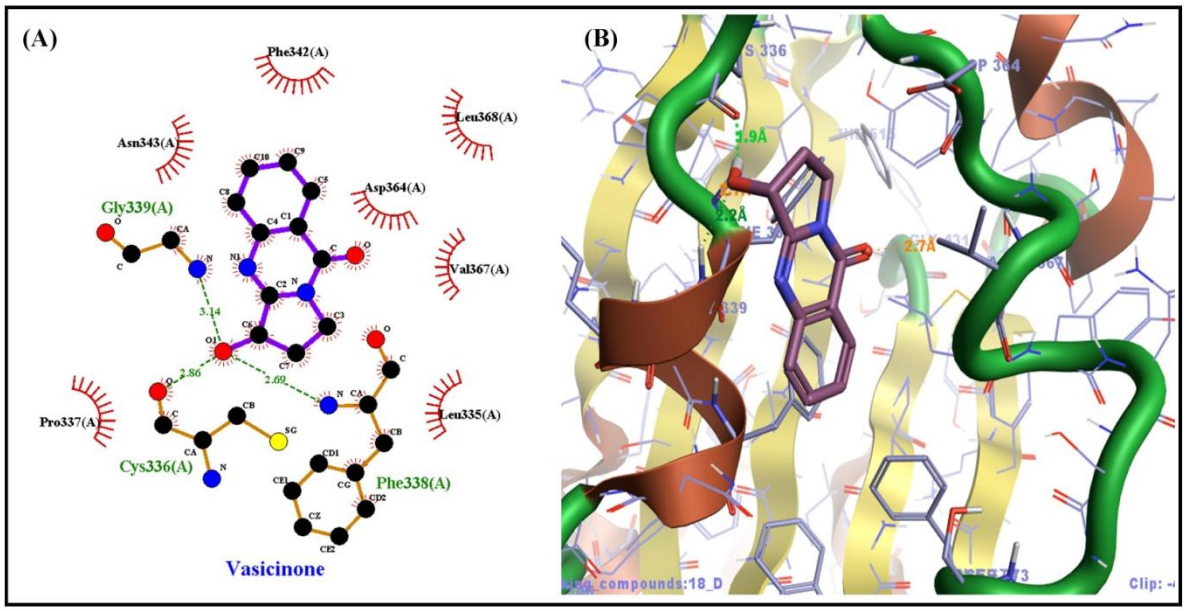



Fig.5. Molecular docking results of Vasicinone into SARS COV2 Spike protein. (A) Hydrophobic interaction of Vasicinonewith SARS COV2 Spike protein (B) Binding mode of Vasicinone in SARS COV2 Spike protein. Amino acid residues involved in H-bond formation and H-bond networks are shown

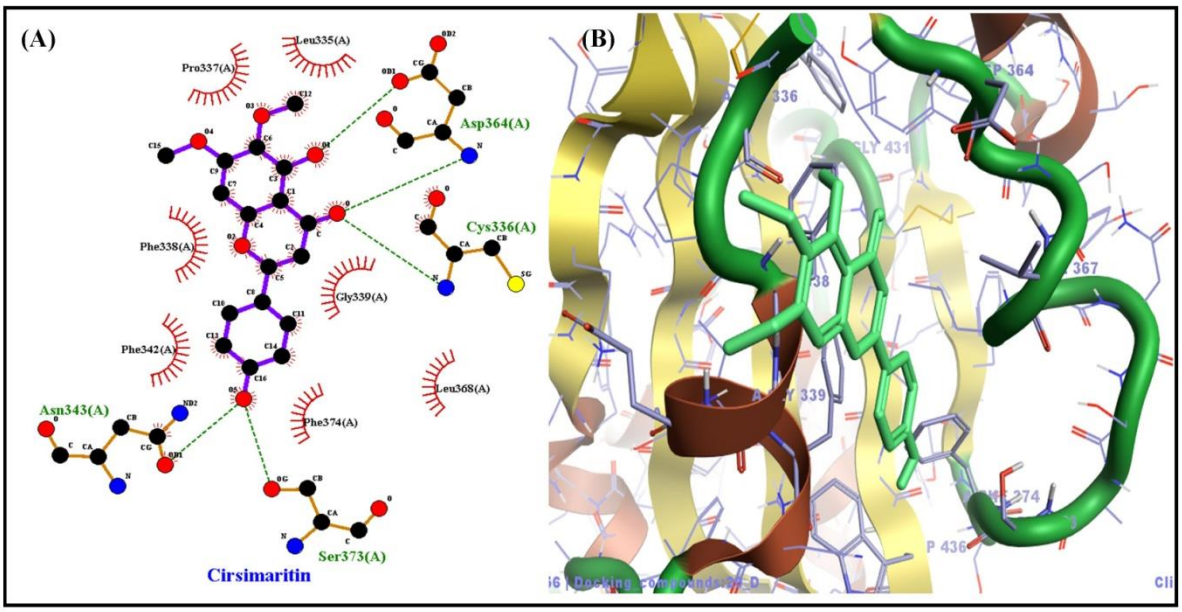



Fig.6. Molecular docking results of Cirsimaritin into SARS COV2 Spike protein. (A) Hydrophobic interaction of Cirsimaritin with SARS COV2 Spike protein (B) Binding mode of Cirsimaritin in SARS COV2 Spike protein. Amino acid residues involved in H-bond formation and H-bond networks are shown

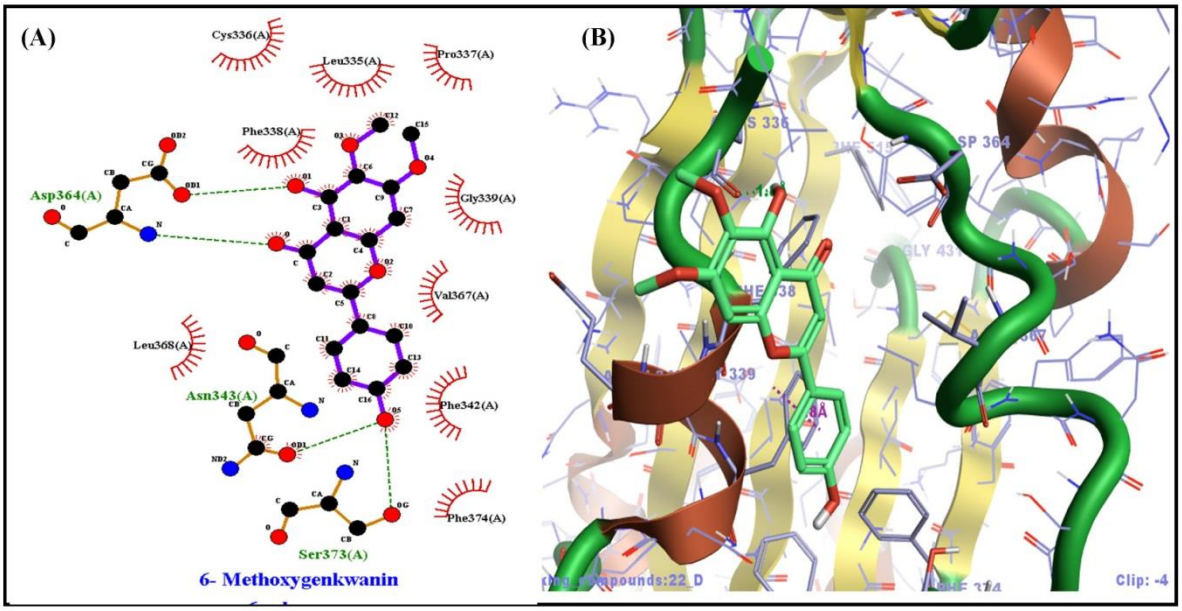



Fig.7. Molecular docking results of 6- Methoxygenkwanin into SARS COV2 Spike protein. (A) Hydrophobic interaction of 6- Methoxygenkwanin with SARS COV2 Spike protein (B) Binding mode of 6- Methoxygenkwanin in SARS COV2 Spike protein. Amino acid residues involved in H-bond formation and H-bond networks are shown

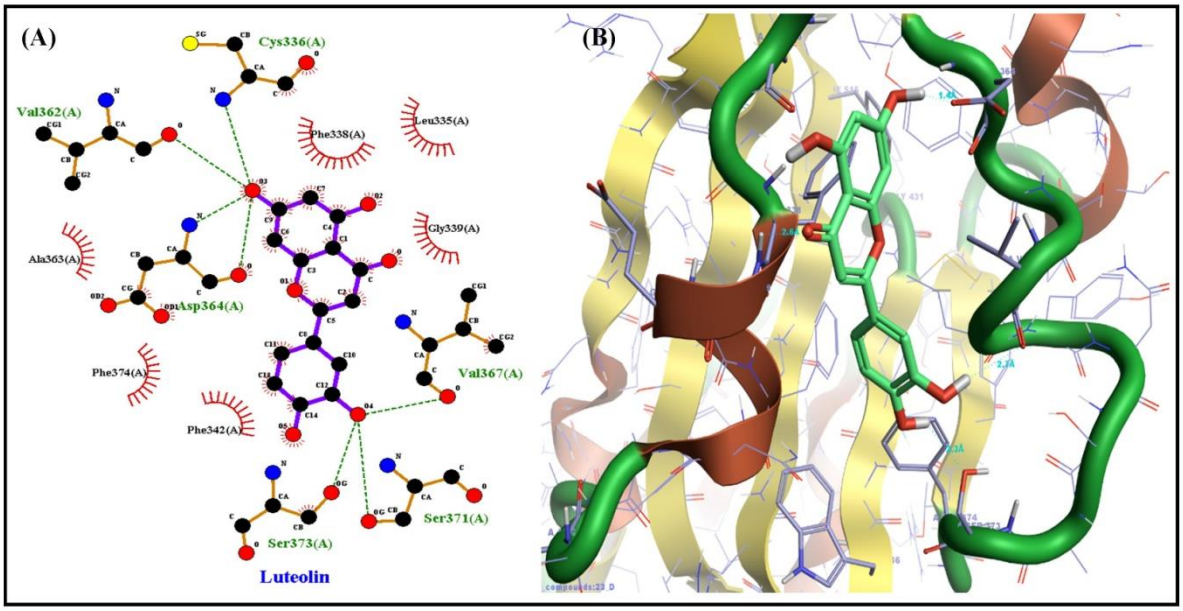



Fig.8. Molecular docking results of Luteolin into SARS COV2 Spike protein. (A) Hydrophobic interaction of Luteolin with SARS COV2 Spike protein (B) Binding mode of Luteolin in SARS COV2 Spike protein. Amino acid residues involved in H-bond formation and H-bond networks are shown

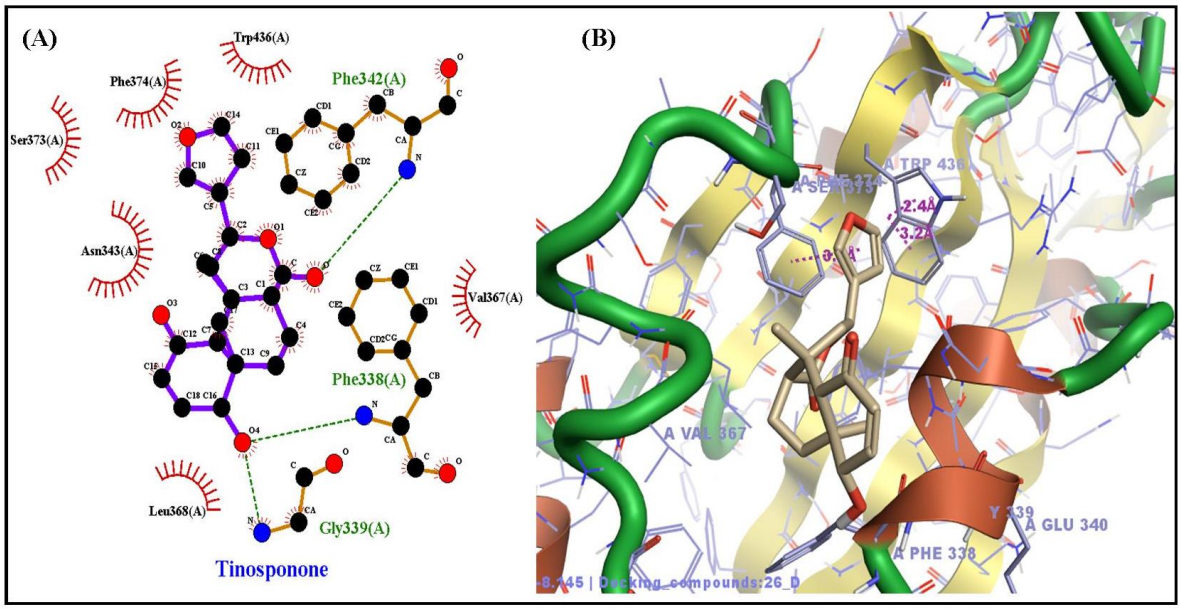



Fig.9. Molecular docking results of Tinosponone into SARS COV2 Spike protein. (A) Hydrophobic interaction of Tinosponone with SARS COV2 Spike protein (B) Binding mode of Tinosponone in SARS COV2 Spike protein. Amino acid residues involved in H-bond formation and H-bond networks are shown

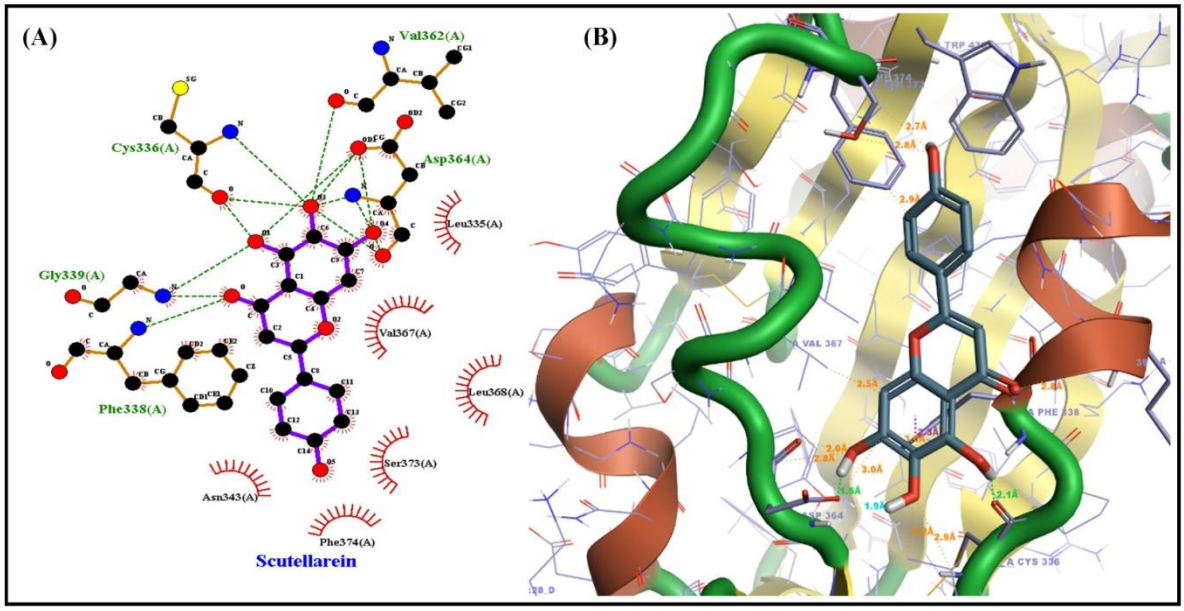



Fig.10. Molecular docking results of Scutellarein into SARS COV2 Spike protein. (A) Hydrophobic interaction of Scutellarein with SARS COV2 Spike protein (B) Binding mode of Scutellarein in SARS COV2 Spike protein. Amino acid residues involved in H-bond formation and H-bond networks are shown

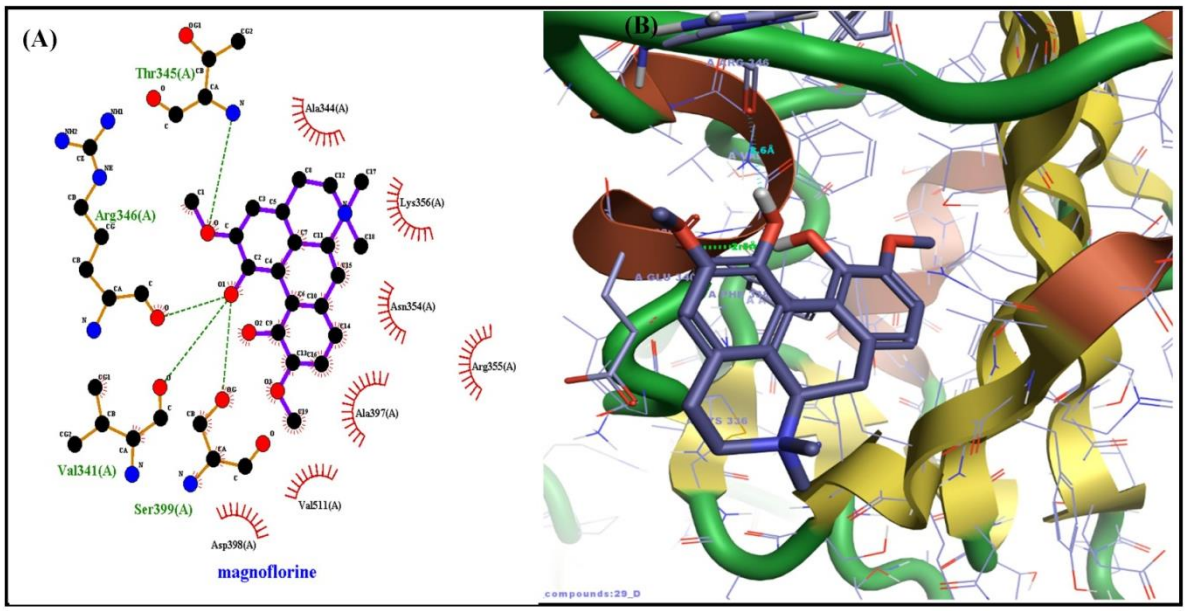



Fig.11. Molecular docking results of magnoflorine into SARS COV2 Spike protein. (A) Hydrophobic interaction of magnoflorine with SARS COV2 Spike protein (B) Binding mode of magnoflorine in SARS COV2 Spike protein. Amino acid residues involved in H-bond formation and H-bond networks are show

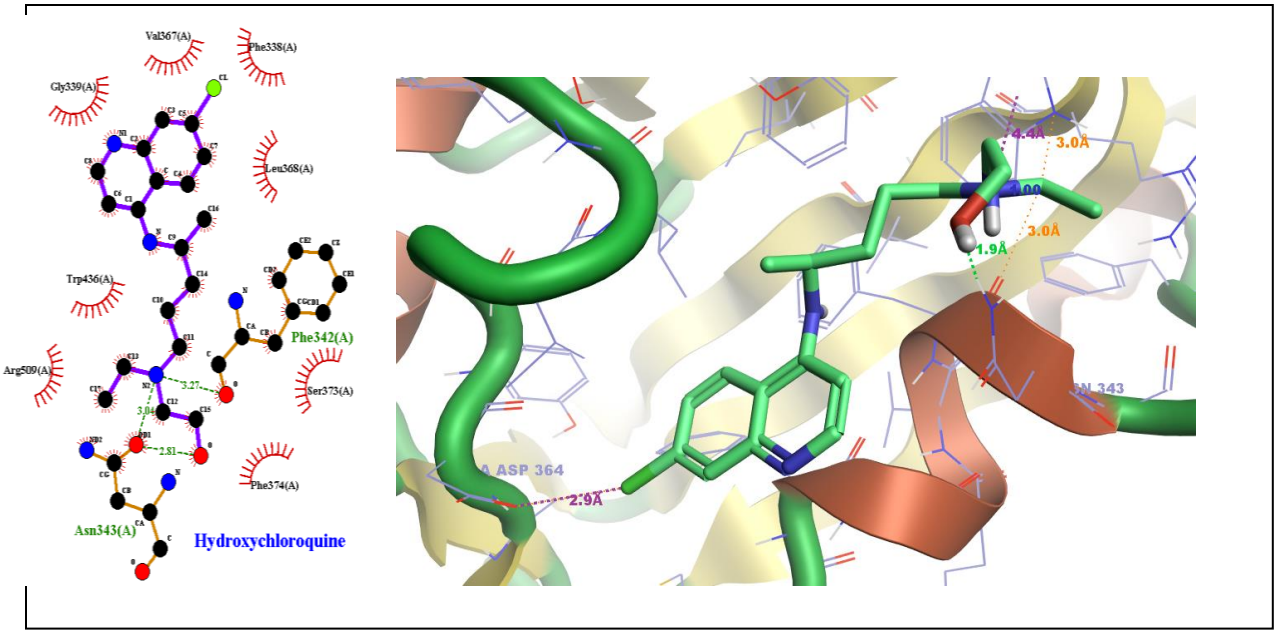
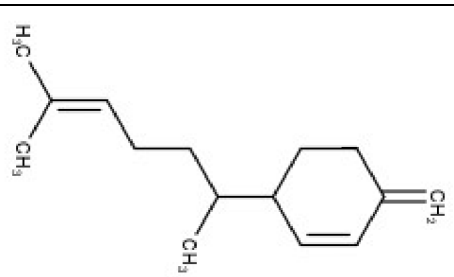
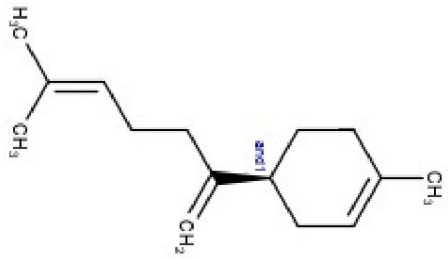
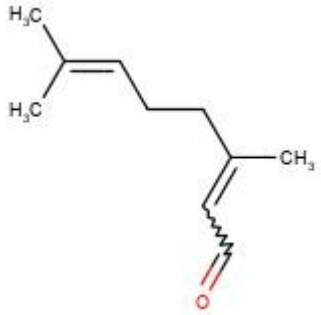
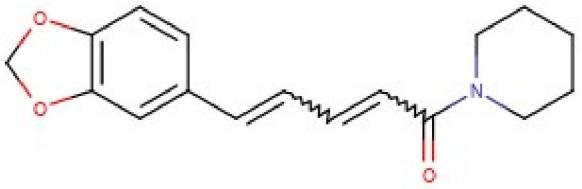
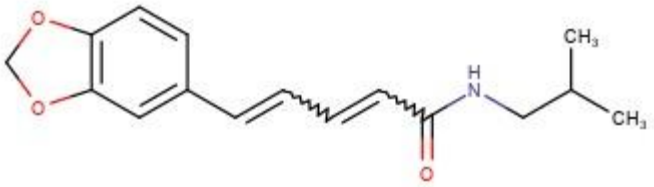
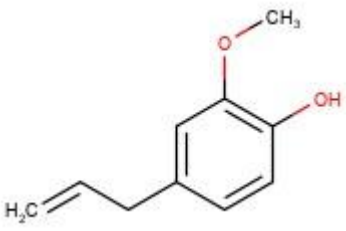
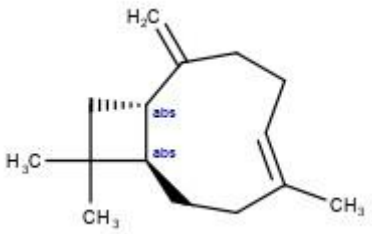
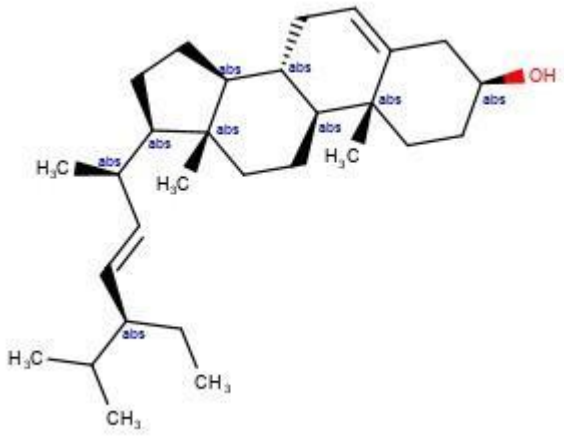
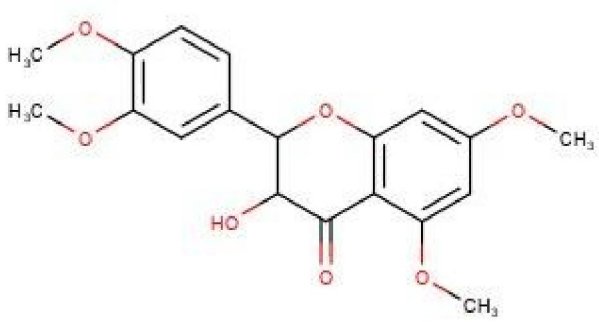
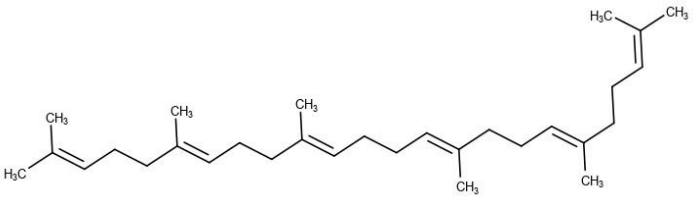
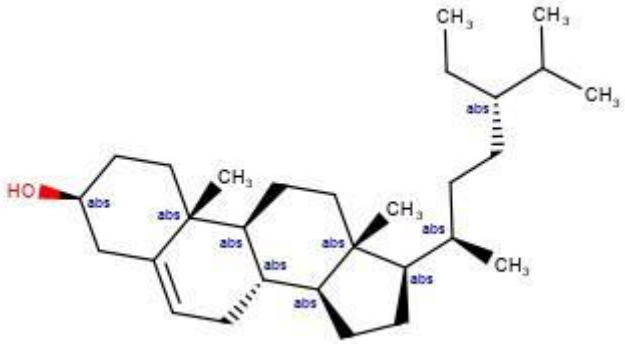
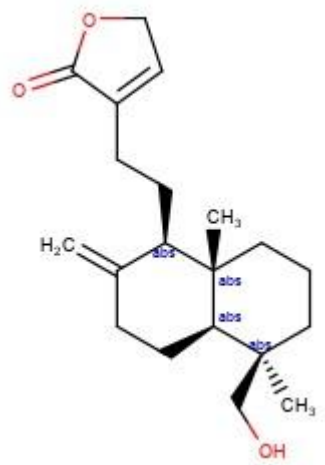
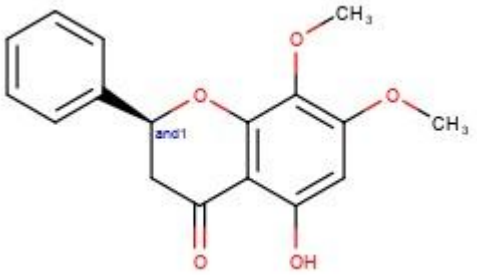
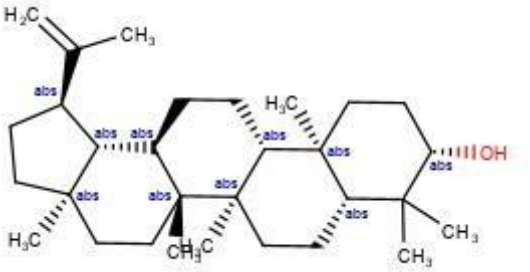
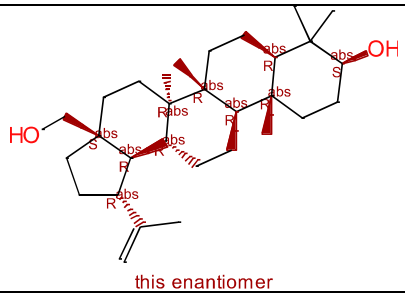
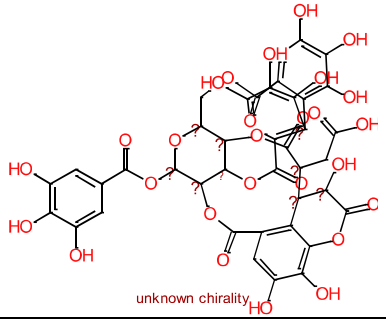
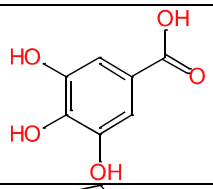
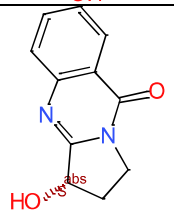
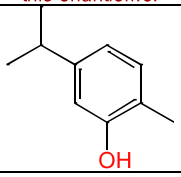
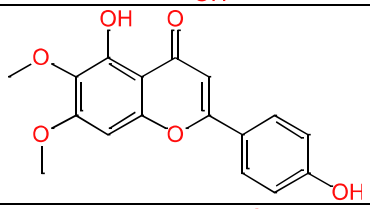
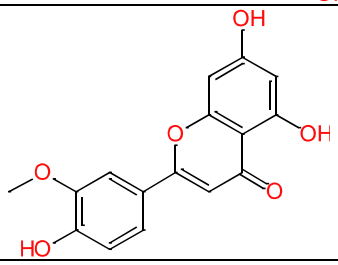
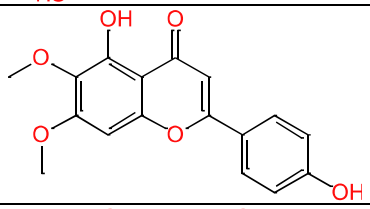
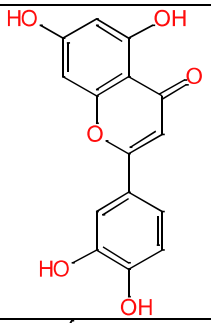
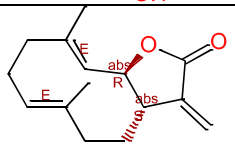



Fig.12. Molecular docking results of Hydroxychloroquine into SARS-COV-2 Spike protein. (A) Hydrophobic interaction of Hydroxychloroquine with SARS COV2 Spike protein (B) Binding mode of Hydroxychloroquine in SARS COV2 Spike protein. Amino acid residues involved in H-bond formation and H-bond networks are shown.

| Table S1: Phytochemical Constituents used for Molecular Docking studies against SARS-COV-2 | | |
|---|---|---|
| **S.No** | **Compound Name** | **Structure** |
| 01 | β-sesquiphellandrene |  |
| 02 | β-bisabolene |  |
| 03 | Geranial |  |
| 04 | piperine |  |
| 05 | piperlonguminine |  |
| 06 | Eugenol |  |

| | | |
|---|---|---|
| 07 | β-Caryophyllene |  |
| 08 | Stigmosterol |  |
| 09 | 3-(2,4-dimethoxyphenyl)-6,7- dimethoxy-2,3-dihydrochromen-4-one |  |
| 10 | Squalene |  |
| 11 | γ-sitosterol |  |

| | | |
|---|---|---|
| 12 | Andrograpanin |  |
| 13 | 5-Hydroxy-7,8-dimethoxyflavanone |  |
| 14 | Lupeol |  |
| 15 | Betulin |   |
| 16 | Chebulagic acid |   |

| | | |
|---|---|---|
| 17 | Gallic acid |  |
| 18 | Vasicinone |  this enantiomer |
| 19 | Carvacrol |  |
| 20 | Cirsimaritin |  |
| 21 | Chrysoeriol |  |
| 22 | 6-Methoxygenkwanin |  |
| 23 | Luteolin |  |
| 24 | Costunolide |  this enantiomer |

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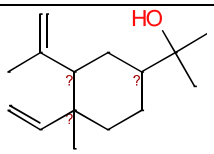
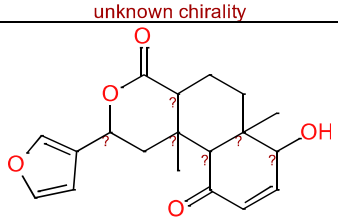
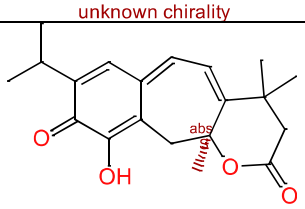
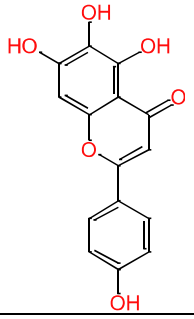
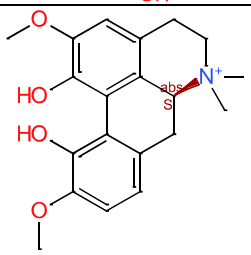
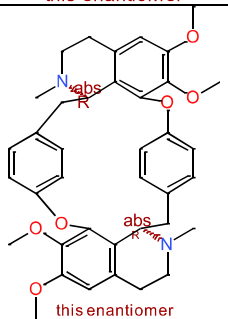
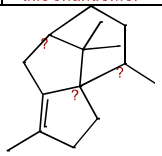
|---|---|---|
| 25 | Elemol |  unknown chirality |
| 26 | Tinosponone |  unknown chirality |
| 27 | Bharangin |  this enantiomer |
| 28 | Scutellarein |  |
| 29 | magnoflorine |  this enantiomer |
| 30 | cycleanine |  this enantiomer |
| 31 | Cyperene |  unknown chirality |

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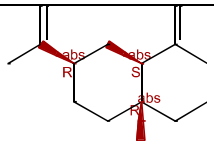
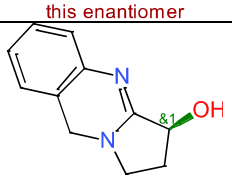
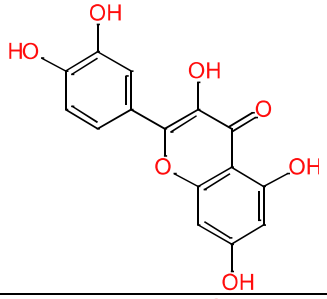
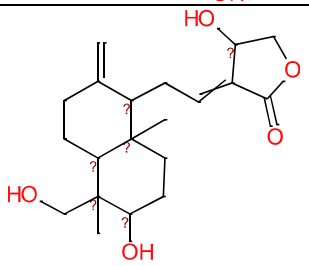
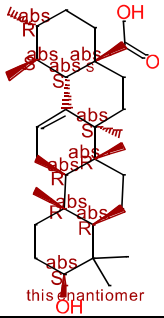
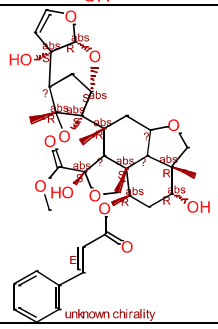
|---|---|---|
| 32 | beta-selinene |  this enantiomer |
| 33 | vasicine |  racemate |
| 34 | Quercetin |  |
| 35 | Andrographolide |  unknown chirality |
| 36 | Ursolic acid |  this enantiomer |
| 37 | Meliacine |  unknown chirality |