

Natural Compound against COVID-19 in Silico Screening by Attacking Mpro and ACE2 Using Molecular Docking

Dhiraj Kumar¹ and Sanjana Bhagat²

¹Student, Department of Pharm Sci. & Tech, B.I.T Mesra, Ranchi, INDIA

²Student, Department of Pharm Sci. & Tech, B.I.T Mesra, Ranchi, INDIA

¹Corresponding Author: dhirajk255@gmail.com

ABSTRACT

OBJECTIVE: At present, Coronavirus is spreading overall fastly and its control is troublesome on the grounds that there is no powerful antibody or medications accessible in blemish kets. This infection can taint the two creatures and people and cause diseases of the respiratory plot. WHO has pronounced Covid as pandemic and the entire world is battling against Covid. Worldwide, in excess of 199,478 individuals have been determined to have Coronavirus. As of Walk 18, 2020, in excess of 167 nations have been influenced and in excess of 8000 passings have been report-ed. The fundamental nation being influenced is China, followed by Italy, Iran, Spain, France and the USA.

MATERIALS AND TECHNIQUES: Since there are no powerful medications accessible against Covid, we directed virtual screening of phytochemicals to discover novel mixes against this infection. Thus, we made a phytochemical library of 19 phytochemicals from 19 plants, which have been accounted for as antiviral, antibacterial and antifungal action. The phytochemical library was exposed to virtual screening against sub-atomic targets, Principle protease (Mpro) and Angiotensin-Changing over Compound 2 (ACE2).

ENDS: In light of the coupling energy score, we recommend that these mixes can be tried against Covid and used to create successful antiviral medications.

Keywords- Covid, SARS-CoV-2, Coronavirus, Auto-docking, Phytochemicals, Mpro, ACE2.

patients. From that point forward, SARS-CoV-2 has influenced 6.22 million individuals and plagued in excess of 373,032 human patients (June 1, 2020).

Since the principal detailed cases in December 2019, Coronavirus Disease 2019 (COVID-19) has gotten a worldwide pandemic and a significant reason for morbidity & mortality. Because of increased susceptibility in the population & the absence of required therapeutics & vaccines in treating or preventing this developing infection, numerous medical care systems have been overpowered by a worldwide increase in cases. As of September 24, 2020, COVID-19 has caused 33 million confirmed infections and over 983,033 deaths worldwide (<https://www.worldometers.info/coronavirus/>). Numerous territories of the world have been in lockdown mode to check the viral transmission, however actually COVID-19 is setting down until a protected and effectual immunization opens up. The pandemic's disastrous financial effect is pushing governments to resume their economies, and this makes a general wellbeing situation. Depending on the examining of the RNA of the virus by the RT-PCR (Reverse transcription-polymerase chain reaction) technique, the only way to reduce the transmission of the virus is by maintaining social distancing & trace of any contact.

The evolution of plants, in the beginning, was a challenging prospect. They needed to get themselves protected from the herbivores that are dependent on plants for their survival, as well as various microorganisms. To survive in nature, they adopted a strategy to protect themselves; as a result, they began producing some natural products or a secondary metabolite that can be harmful to the animals.

Characterisation of more than 1 lakh (1, 00,000) plant steroidal metabolites was done. The primary structure was identified with nitrogen in its structure for e.g., amines, non-protein amino acids, alkaloids, cyanogenic glycosides, etc. Some of the important compounds without nitrogen included terpenoids and phenolic compounds.

This review indicates how different herbal constituents or plant metabolites can be effective against severe acute respiratory syndrome coronavirus (SARS-COV-2), which is responsible for causing COVID-19.

I. INTRODUCTION – PLANTS PRODUCING ANTIVIRAL ACTIVITY

By the end of 2019, the city of Wuhan in China was first reported with pneumonia-like symptoms because of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that's inflicting the Coronavirus Disease 2019(COVID-19). The underlying human-to-human spreading of the infection was noted in an epidemiological examination on January 20, 2020, where two patients were tested SARS-CoV-2 positive in Guangdong Province and who had no traveling history to Wuhan previously. In this manner, the suppositions of human-to-human transmission were reinforced by the report of COVID-19 out of 14 medical clinic staff from

Evidence of antiviral activities in herbal products

When compared with prokaryotic or eukaryotic cells, the structure of the viral particle is easy. All most all, the virus consists of a genetic material called the DNA/RNA, which may be sometimes complicated due to some proteins which bind to the genetic material forming

the nucleocapsid. A membrane envelope surrounds this capsid and the former is derived from the endoplasmic reticulum of the host cell. The viral proteins present in the membrane helps to bind with the potential receptor of the host cell.

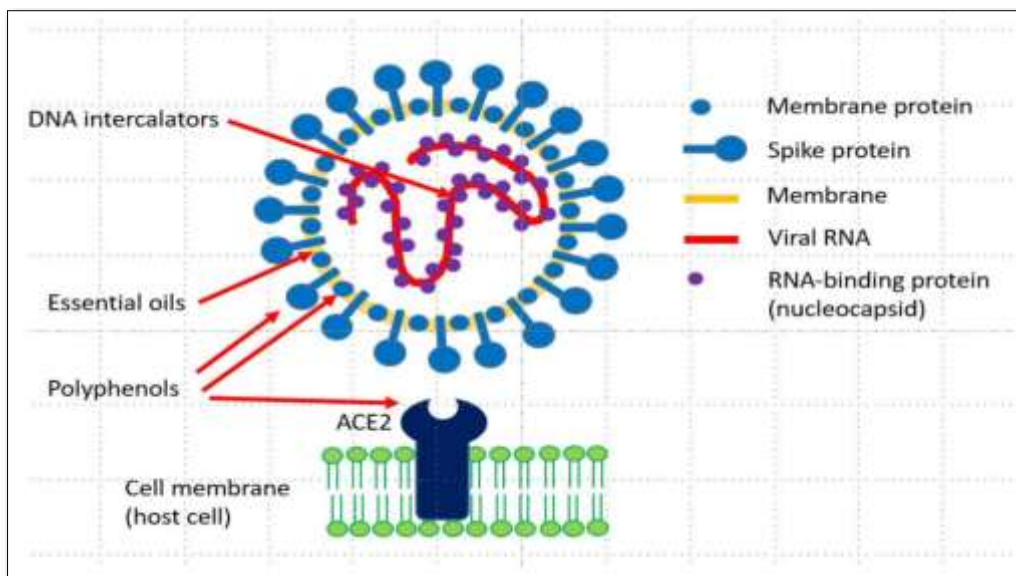


Figure 1: Schematic showing the virus attachment to receptor & activity of PSMs on SARS COV-2

Antiviral activities are derived from the herbal extract; they can act upon the viruses if both of them are stored or incubated together before being added to the cells. In case the host cells are previously infected, the herbal extracts or the PSMs are required to be added to the cell before the virus can attack it. Some of the herbal products are polar molecules; they cannot pass the membranes of the host cell freely due to low absorption into the cells. Tannins possessing some phenolic hydroxyl group are generally active towards the viral particles, which are free so that they can bind to the protein properly.

II. PATHOPHYSIOLOGY AND TRANSMISSION

COVID-19 infections results in inducing neutralizing antibody responses. The second variant rates in COVID-19 patients are 50% and 100% on the 7th and 14th day after the onset of post symptoms, respectively. Unknown number of asymptomatic contaminations has led to an urgent need for serological determination to decide the actual number of infected cases. While viral RNA-based testing for intense disease is the on-going process, looking over protection by an antibody is a vital aspect of going back to social normalisation.

Coronaviruses (CoVs) are an assembly of viruses which consist of an envelope & a positive single-stranded RNA genome, which is pathogenic in nature.

Coronavirus contamination is brought about by the SARS-CoV-2 is a more pathogenic structure in comparison with earlier recognized SARS-CoV (2002) and Middle East respiratory disorder coronavirus (MERS-CoV, 2013).

CoVs have a place in the Coronaviridae family of order Nidovirales. They have been grouped into four genera that incorporate α -, β -, γ -, and δ -Covids. Among them, α - and β -CoVs contaminate warm-blooded creatures, γ -Covids contaminate avian species, and δ -Covids contaminate the vertebrates and aves both. SARS-CoV, mouse hepatitis coronavirus (MHV), MERS-CoV, bovine coronavirus (BCoV), bat coronavirus HKU4, and human coronavirus OC43, such as SARS-CoV-2 all belong to the β - coronaviruses. SARS-CoV-2 is communicated through zoonotic transmission and spread among people through close contact. The essential propagation number (R_0) of the individual-to-individual spread of SARS-CoV-2 is about 2.6, which implies that the infected cases develop at an exponential rate.

Basically, SARS-CoV-2 contains four auxiliary proteins, that incorporate spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins. These proteins share high arrangement likeness to the sequence of the comparing protein of SARS-CoV and MERS-CoV.

SARS-CoV-2 identifies the ACE2 receptor to bind with the microorganism S protein. SARS-CoV-2 may be a single-stranded viral RNA. Spike protein (S) helps SARS-CoV-2 in integration and entering into cells. S1 subunit of S glycoprotein helps in strong binding to

the ACE2 receptor while as S2 subunit guarantees to combine with the host cell. Inside the respiratory tract of the host and gastrointestinal tract, epithelial cells can be

influenced. All in all, respiratory epithelial cells (pneumocytes) and enteric cells (enterocytes) are contaminated by CoVs, causing cytopathic changes.

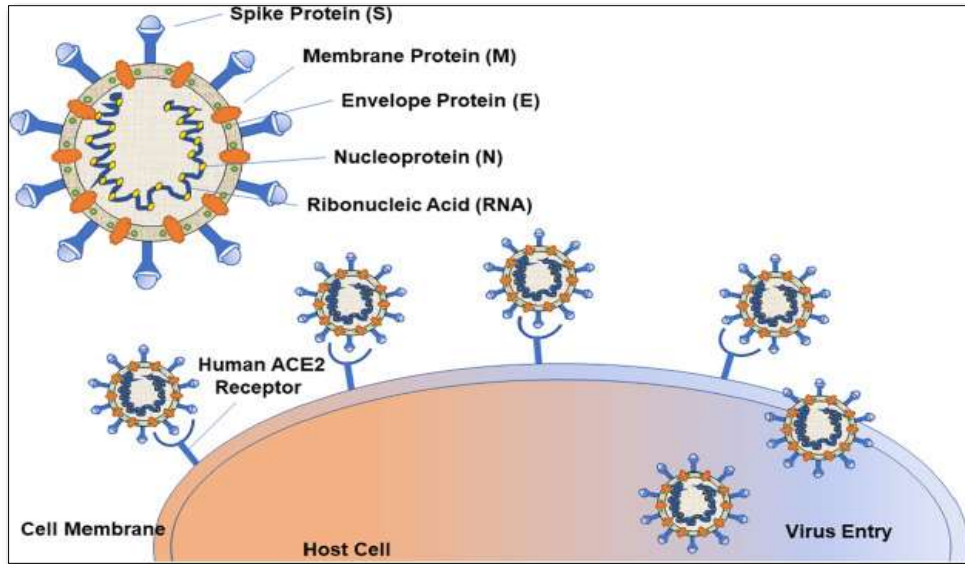


Figure 2: Schematic of COVID-19 and its mode of entry into the host cell

Applicability of Coronavirus SARS COV-2 & COVID-19

SARS COV-2 belongs to the Coronaviridae family. The genome of the virus is a single-stranded RNA (+sense), which can act as an mRNA. The binding protein which forms the nucleocapsid makes the mRNA more complex. This virus consists of a membrane envelop, which is obtained from the endoplasmic reticulum of the host cell. It consists of different proteins; Spike protein, which facilitates binding with the ACE2 receptor present in the host cell, also consists of the envelope proteins as

well as the membrane proteins (Fig 1). The virus enters the host/human cell, then it releases its genome. The viral polymerase copies the mRNA, which results in numerous new copies of the mRNA of the virus. Thus the copies of the mRNA results in translation at the ribosomes, which are attached with the ER such that the translated proteins (S protein, M protein, E protein) gets attached with the Endoplasmic Reticulum membrane (Fig2). Exocytosis facilitates the release of the several generated Golgi bodies.

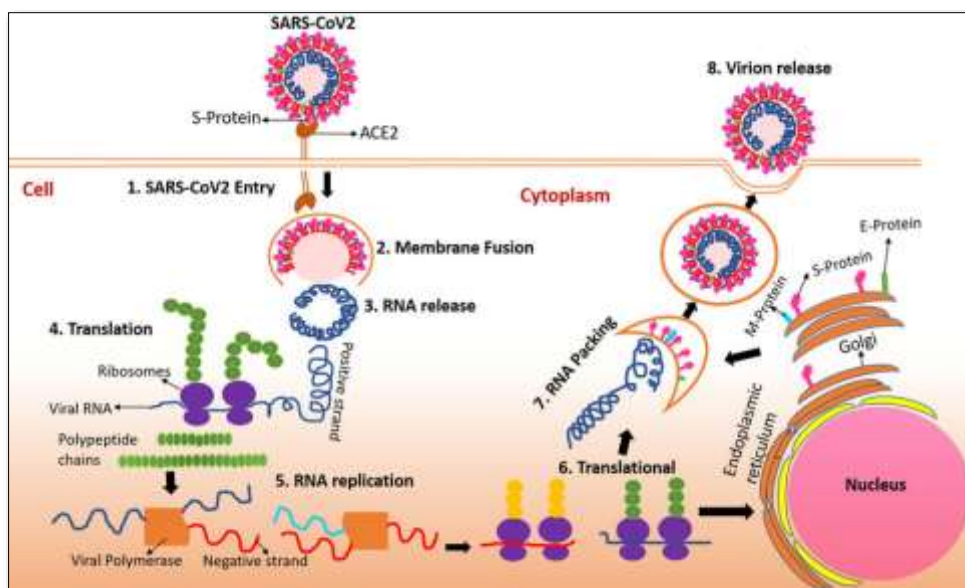


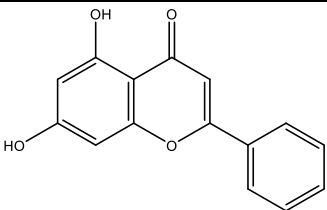
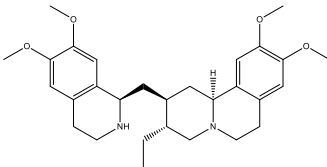
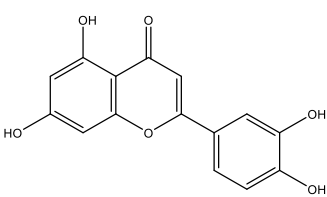
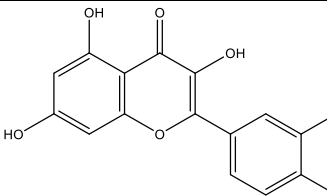
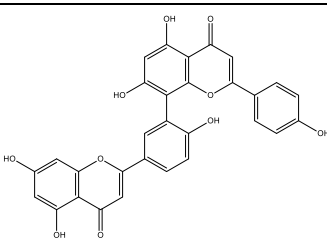
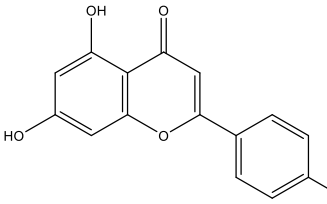
Figure 3: Schematic for replication of Coronavirus 2 into the host cell

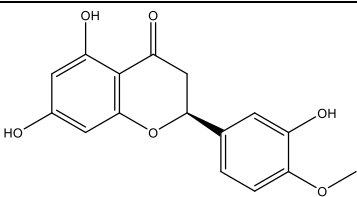
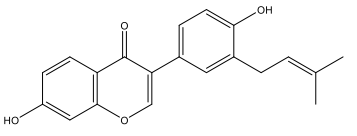
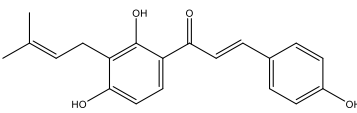
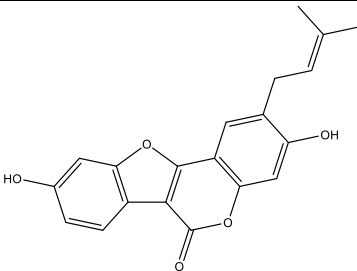
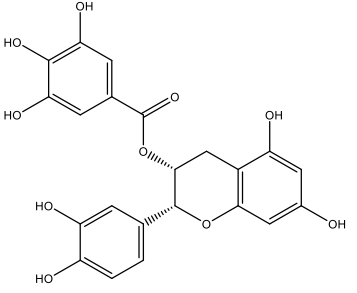
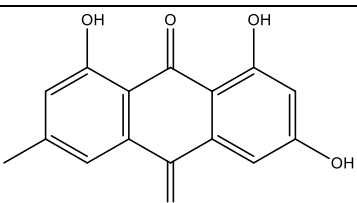
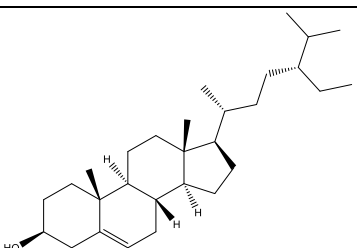
III. IN- SILICO STUDY

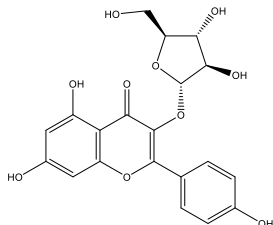
PDB ID: 7bz5

Protein: Protease N3 inhibitor (sourced from
www.rcsb.org)

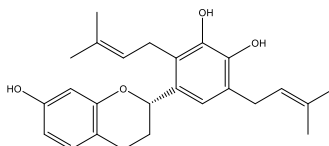
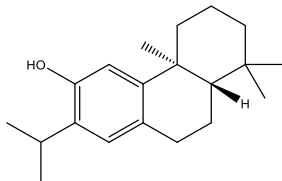
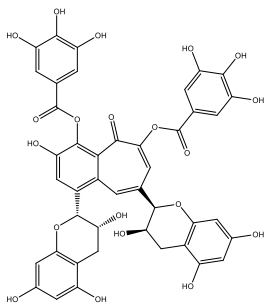
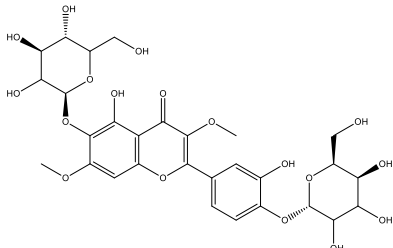
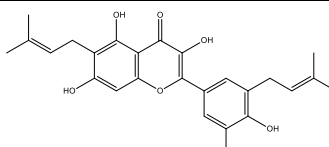
The molecular docking study of these following
natural products has been done on Auto dock version
1.5.7 and the interactions are viewed through the
discovery studio.

SL. No.	Natural Product	Natural source	Structure	Proposed Mechanism	kI:	Binding Energy :
1.	Chrysin	<i>Oroxylum indicum</i>		Inhibited interaction of SARS-CoV(S) protein and ACE2	14.76uM	-6.59
2.	Emetine	<i>Carapichea ipecacuanha</i>		Inhibited RNA, DNA and protein synthesis.	4.82uM	-7.25
3.	Luteolin	<i>Trifolium</i>		Blocking the viral entry.	21.88uM	-6.36
4.	Quercetin	<i>Torreya nucifera</i>		3CL protease inhibition.	9.27uM	-6.87
5.	Amentoflavone	<i>Torreya nucifera</i>		3CL protease inhibition	7.63uM	-6.98
6.	Apigenin	<i>Torreya nucifera</i>		3CL protease inhibition	21.25uM	-6.37

7.	Hesperetin	<i>Isatis indigotica</i>		3CL protease inhibition	12.61uM	-6.68
8.	Neobavaisoflavone	<i>Psoralea corylifolia</i>		Inhibitors of papain-like protease	6.97uM	-7.03
9.	Isobavachalcone	<i>Psoralea corylifolia</i>		Inhibitors of papain-like protease	32.12uM	-6.13
10.	Psoralidin	<i>Psoralea corylifolia</i>		Inhibitors of papain-like protease	6.8uM	-7.05
11.	Epicatechin gallate	<i>Camellia sinensis</i>		Inhibitors of papain-like protease	18.12uM	-6.47
12.	Emodin	<i>1,3,8-trihydroxy-6-methylantraquinone</i>		Inhibited interaction of SARS-CoV (S) protein and ACE2.	70.3uM	-5.67
13.	Beta sitosterol	<i>Isatis indigotica</i>		3CL protease inhibition	4.96uM	-7.24

14.	Juglanin	<i>Polygonum aviculare</i>		Blocks the 3a channel	49.25uM	-5.88
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PDB ID: 6LU7

SL.No.	Natural Product	Natural source	Structure	Proposed mechanism	kI:	Binding Energy:
1.	Kazinol A	<i>Broussonetia papyrifera</i>		Protease inhibition	556.74uM	-6.44
2.	Ferruginol	<i>Sequoia sempervirens</i>		Inhibition of replication	265.3uM	-4.88
3.	Theaflavin-3,3'-digallate phenolic compound	Black tea		Inhibition of 3C-like protease (3CLPro)	109.04mM	-6.78
4.	Tomentin D flavanoids	<i>Paulownia tomentosa</i>		Inhibition of papain-like protease	4.14mM	-5.65
5.	Papyriflavonol A	<i>Broussonetia papyrifera</i>		Protease inhibition	54.27uM	-5.82

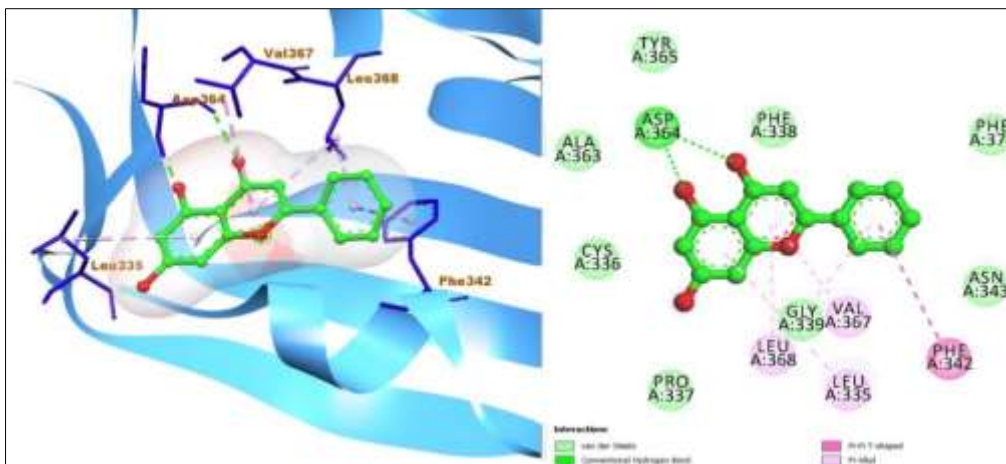
Visualization

The examination of 2D Hydrogen-bond communications of the intricate receptor-ligand structure was performed by BIOVIA Discovery Studio Visualizerto recognize the interaction of an amino acid of a receptor with a ligand. BIOVIA Discovery Studio

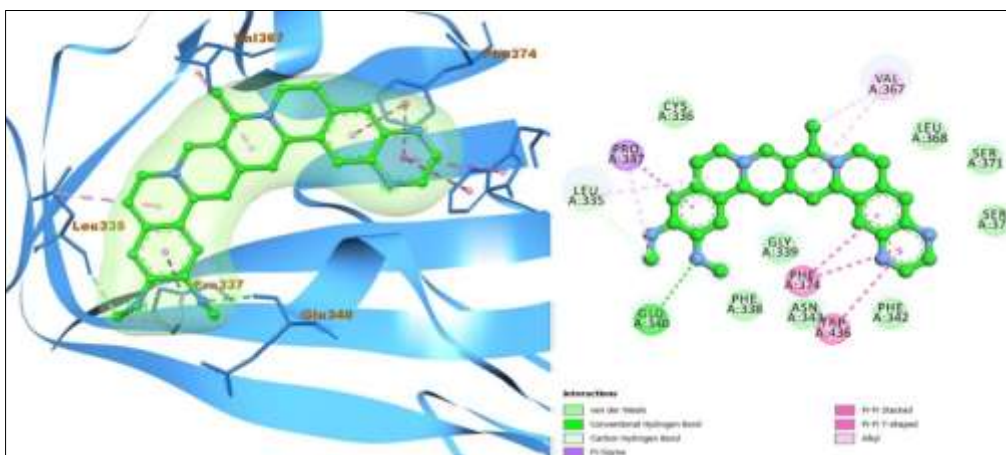
Visualizerportrays hydrophobic bonds, hydrogen bonds, and their bond lengths in each docking present as interaction portrayal.

Interaction

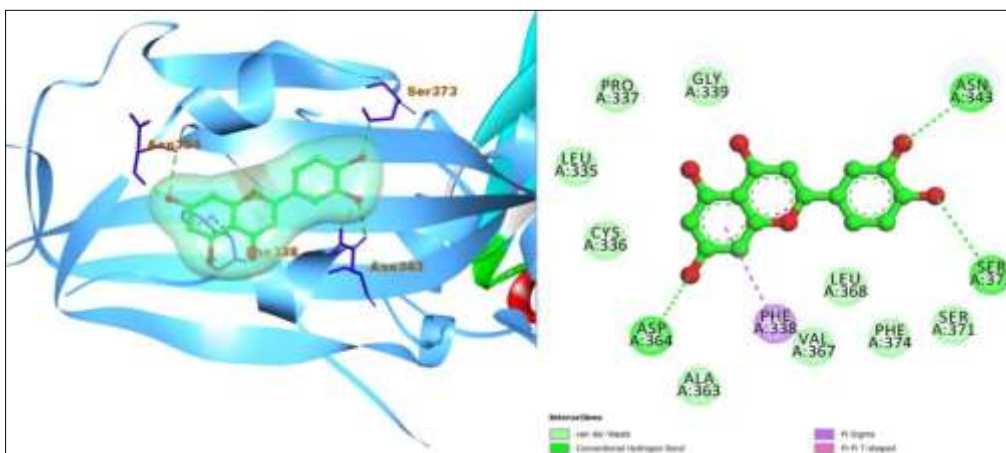
1. Alkaloids



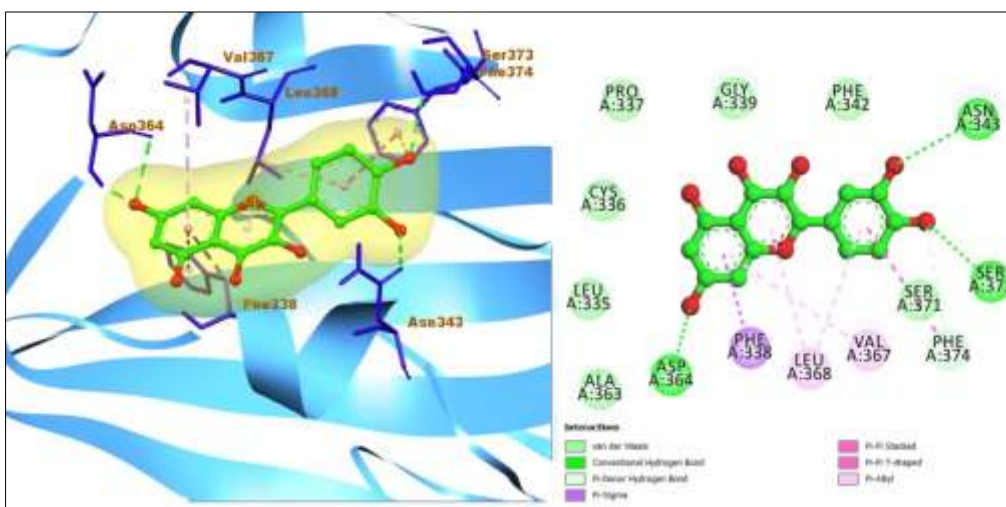
Chrysin



Emetine

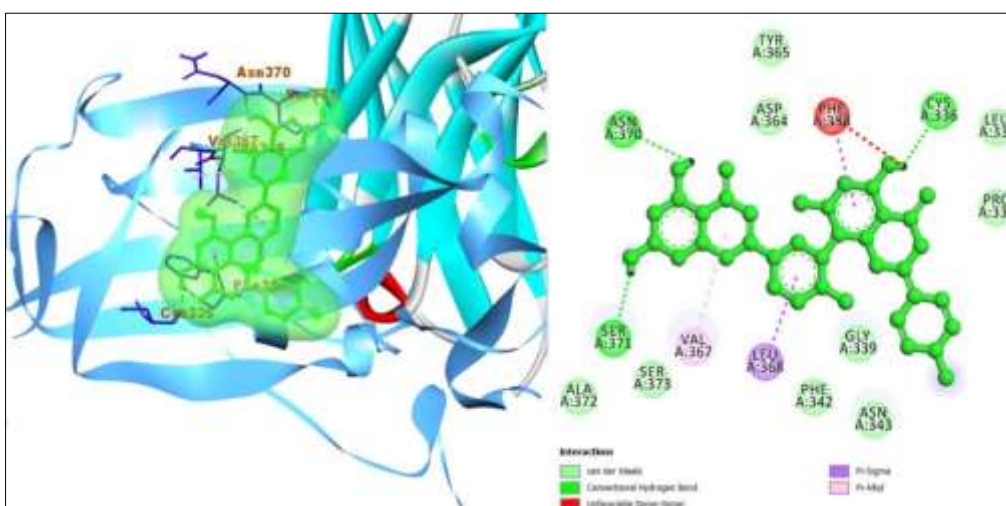


Luteolin

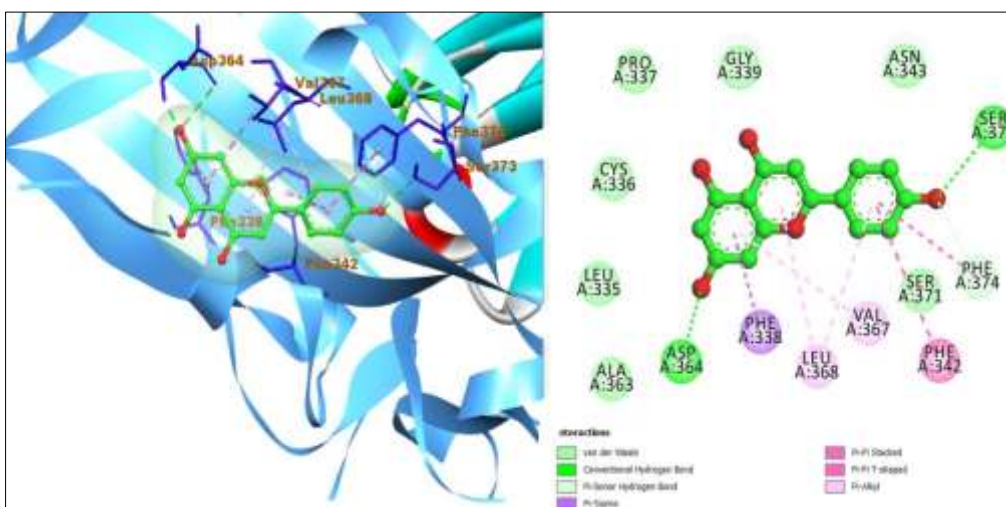


Quercetin

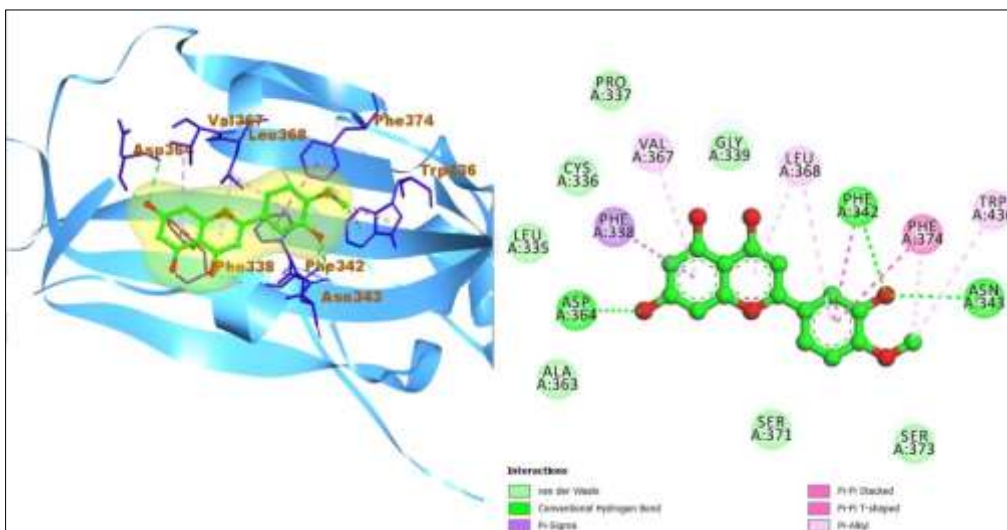
2. Flavonoids & Chalcones



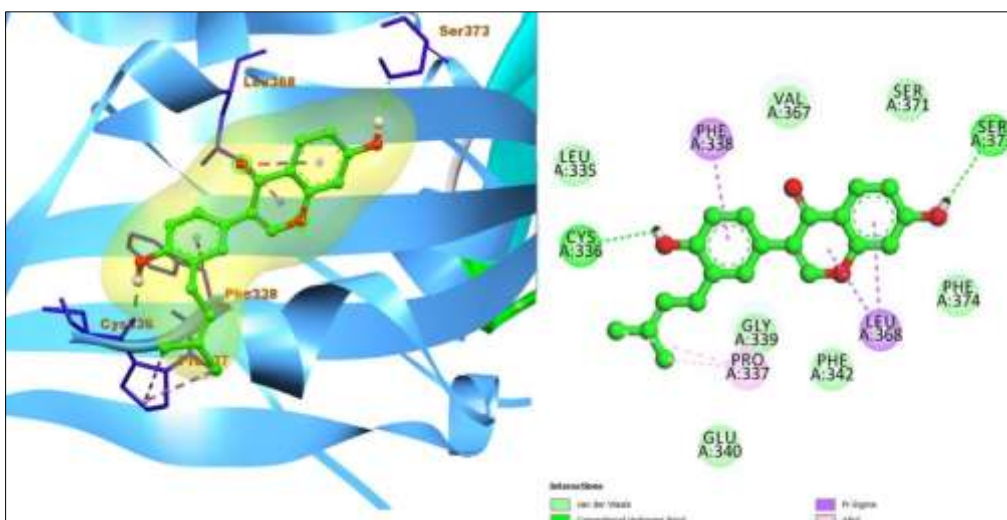
Amentoflavone



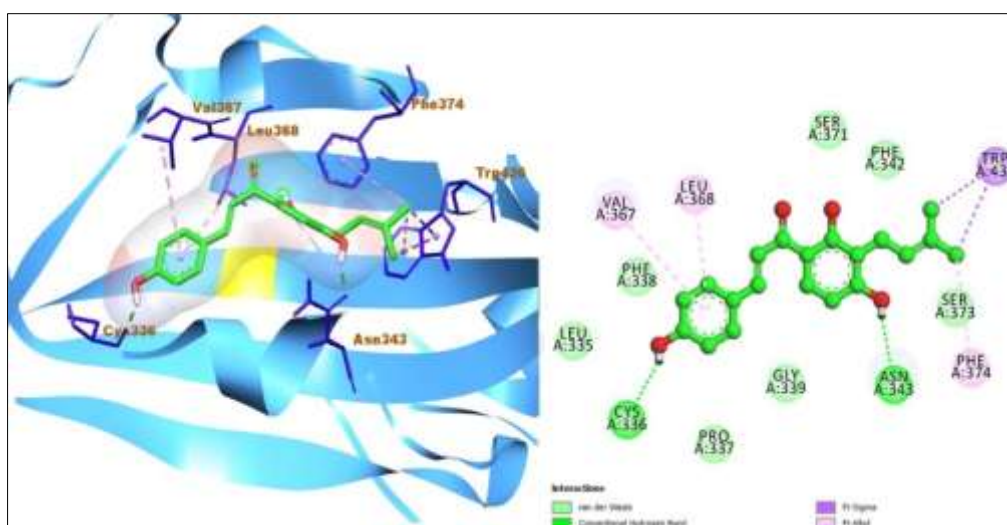
Apigenin



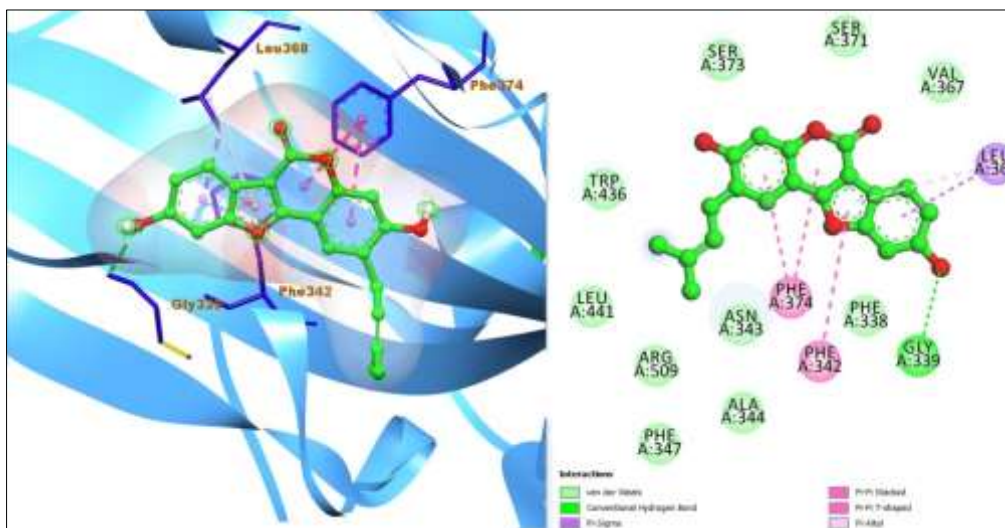
Hesperetin



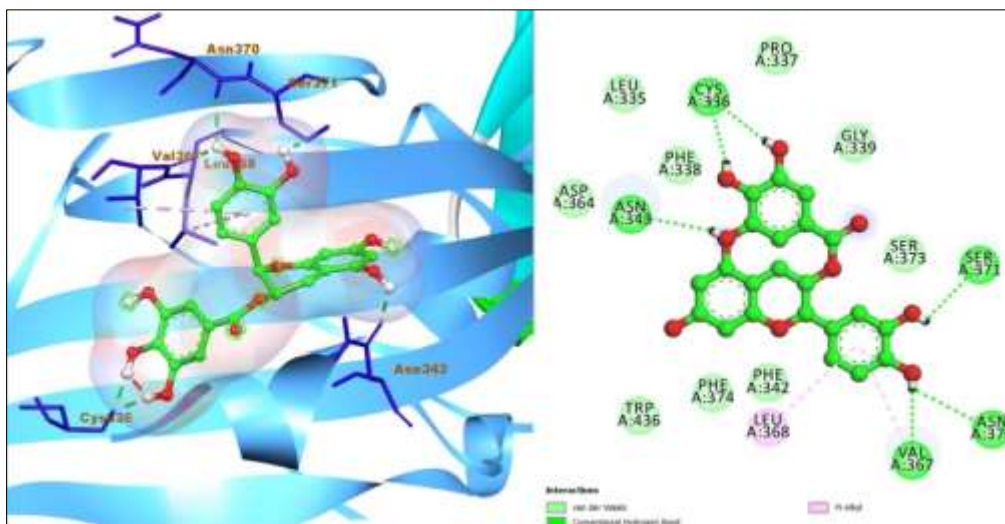
Neobavaisoflavone



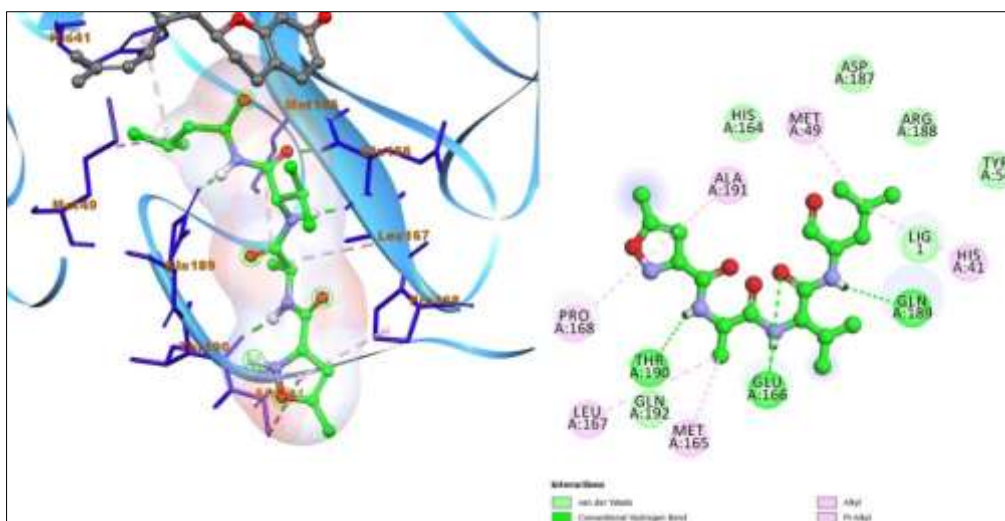
Isobavachalcone



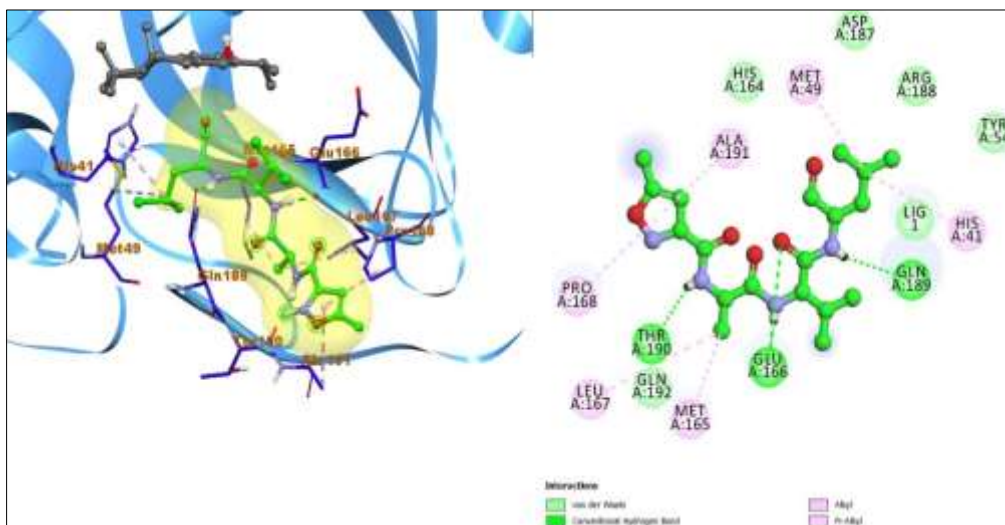
Psoralidin



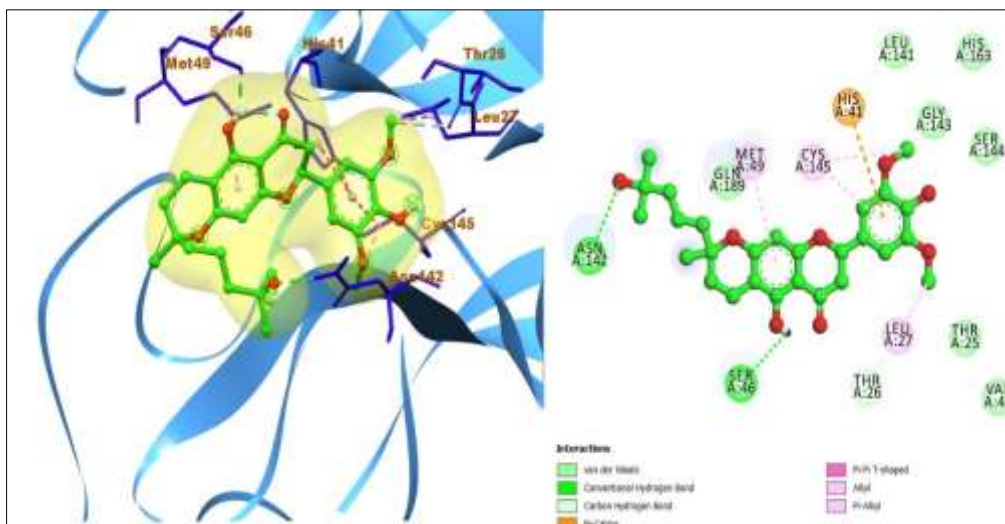
Epicatechin gallate



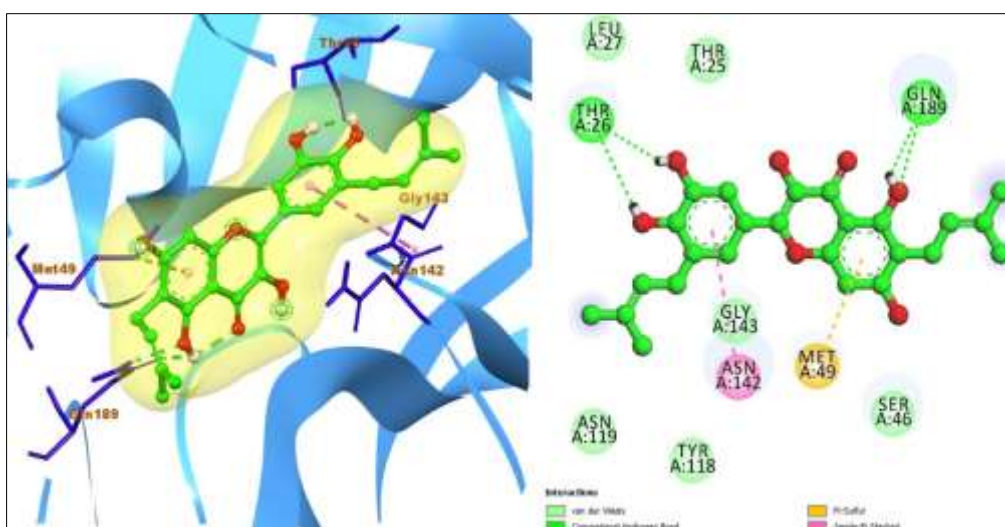
Kazinol A



Ferruginol

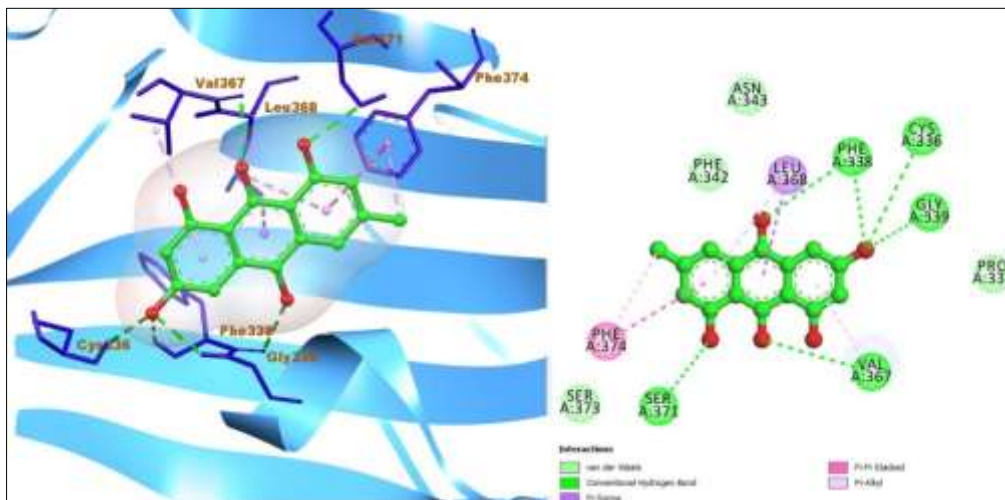


Tomentin D

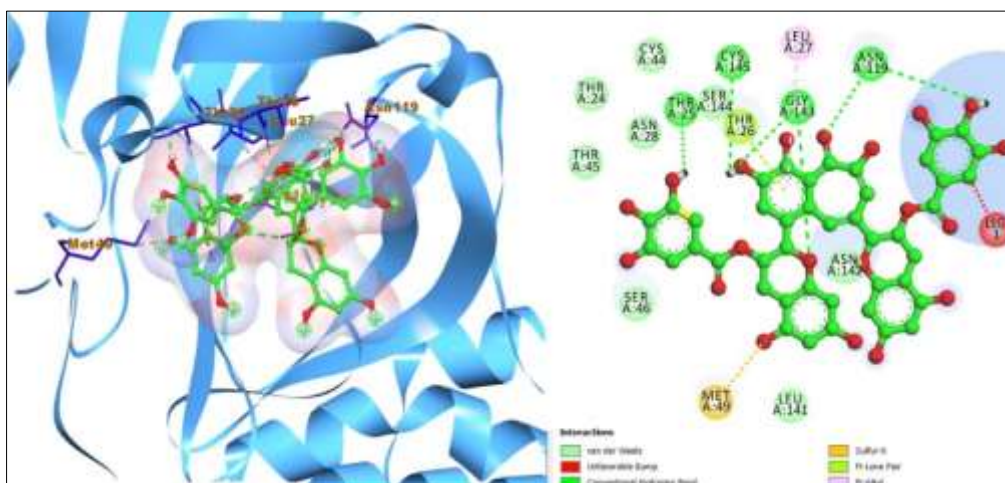


Papyriflavonol A

3. Phenolic Compounds

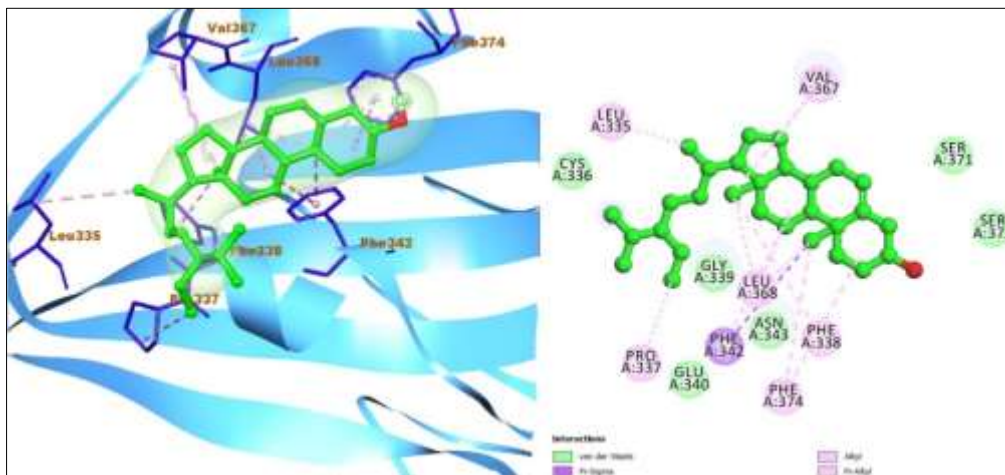


Emodin



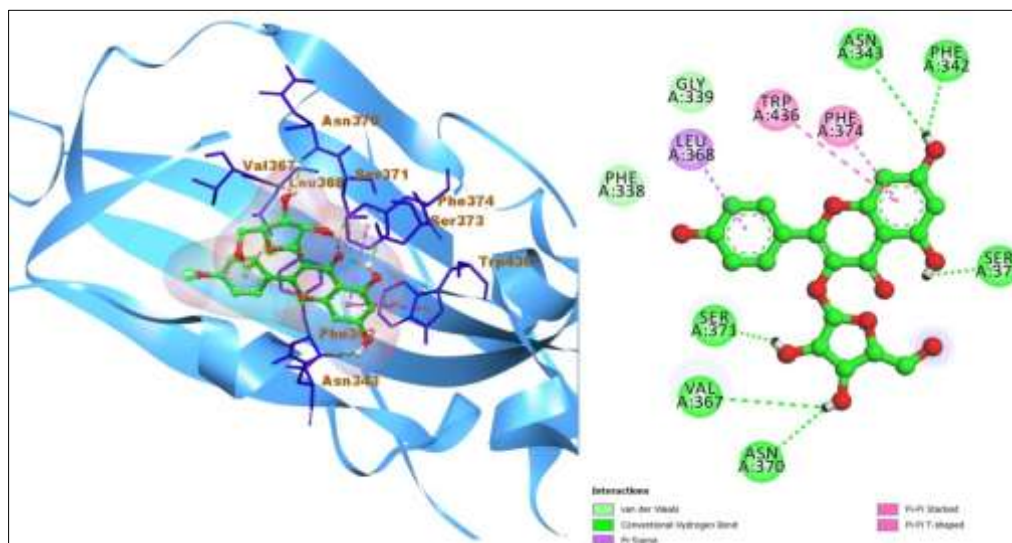
Theaflavin-3,3'-digallate phenolic compound

4. Steroids



Beta sitosterol

5. Glycosides



Juglanin

IV. CONCLUSION

Herbal plant life offers a huge style of vital and opportunity remedy, which might also additionally help to remedy the various puzzles in the back of many viral diseases. Herbal treatments consisting of plant extract, plant-derived hybrid (phytoconstituents) natural plant extract from precise elements of the plant (stem, roots, seed, barks, meals and flower), nutraceuticals in addition to dietary supplements have a look at programs in treating disorder range from common to uncommon infectious and non-infectious ailments. A record of the World Health Organization (WHO), 80% of the man or women in growing international locations relies upon on conventional plant life for fitness requirements. Many types of research have evidenced approximately plant life derived merchandise and their promising arrangements device in opposition to many viral infectious outbreaks. Considering the low toxicity screening of natural remedies, they may be hired notably to goal COVID-19. Since we've got already investigated in-silico anti-COVID-19 pastime of a few capability drug candidates, in this mini-review, we summarize the potential phytoconstituents like alkaloids, flavonoids and chalcones, steroids and phenolic compounds that might goal the principle protease for the remedy of nCoV-2019 via way of means of using molecular docking tool. We proposed a few herbal products including Chrysin, Emetine, Luteolin, Quercetin, Amentoflavone, Apigenin, Hesperetin, Neobavaisoflavone, Isobavachalcone, Psoralidin, Epicatechin gallate, Emodin, Beta-sitosterol, Juglanin, Kazinol A, Ferruginol, Theaflavin-3,3'-digallate phenolic compound, Tomentin D, Papyriflavonol A as a capacity candidate for exerting the antiviral hobby in opposition to SARS-CoV-2 contamination the usage of molecular docking study.

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