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RESEARCH ARTICLE

Computational Analysis of the Phytoligands From Bay Leaf (Laurus nobilis) Against COVID-19: Molecular Docking And ADME Analysis

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ABSTRACT

Objective: The objective of the study is to analyze the inhibitory activity or efficiency of selected phytoligands from the plant Bay Leaf using molecular docking in contrast to Covid-19 Main Protease. **Methodology:** In this study, all the computational or bioinformatics tools were employed to find out the capabilities of selected phytoligands as an acclamatory inhibitor for Novel Coronavirus. The 3-dimesnsional structures of the receptor were fetched from PDB (Protein Data bank) and of the phytoligands were retrieved from Pubchem databases. Molecular Docking analysis of the selected phytoligands was performed using AutoDock and Pyrx. Moreover, the Phytoligands were predicted or assumed using Lipinski filter and SwissADME online server. **Results**: All the compounds are non-violated according to the Lipinski's parameters and can serve as a good compound to treat or inhibit the Novel Coronavirus. As a result, all the phytoligands has highest binding affinity against COVID-19 Main Protease and expected to be effective in Covid-19 treatment.

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Keywords: SARS COV-2, Bay Leaf, ADME analysis, Molecular Docking

INTRODUCTION

COVID-19 pandemic has created a threat to human societies and a need of Novel Coronavirus vaccine is a must with different therapies and prevention methods also to be considered [1]. Nature is a big reservoir of anti-infectious compounds, which can be an effective source to produce therapies and products. The natural products have an immense potential to fight various infectious diseases mainly viral infections [2-4]. The bioactive compounds extracted from the plants with anti-microbial, anti-oxidant and various other properties act as potential ligand that helps in reducing the infection. The essential oils can directly interact with the viral membranes, so specific anti-viral compounds can be generated [5, 6].

One such small evergreen tree of lauraceae family with huge therapeutic properties is *Laurus nobilis* commonly known as Bay leaf. These are aromatic and fragrant plants which can yield essential oils in a good quantity [7-9]. It is a good source of minerals and dietary fibers. Bay leaf is used as one of the popular spice in India. It is even used as a food preservative. Bay leaf is always been a consistent ingredient in food habit of many Asian countries. Consumption of bay leaves is done in a variety of ways including frozen leaves, dry leaves, powdered leaves and extracted oil. Among all, extracted oil is considered as a high potential substance. Specified Extraction of oil is done by a chain of processes which are hydro distillation, gas chromatography and mass spectrometry (MS-GC), flame ionization detection for identifying the chemotypes. There are several other extraction methods, some of them are steam distillation, cohobation, maceration and effleurage [10-13].

Due to high pharmacological properties of *Laurus nobilis* plant, many useful phyto-chemical compounds can be isolated. The chemical constituents present in it have high medicinal value and can provide a traditional way of treating any human disease. The sharp and bitter taste of bay leaf is due to the presence of essential oils in plant parts. It is rich in 1; 8-cineole and other predominant components are alpha-terpinyl acetate, sabinene, limonene, alpha-pinene, linalool, terpinene-4-ol, alpha-terpinene, beta-pinene, alpha-terpineol, bornyl acetate, alpha-phellandrene, myrcene, camphene, p-cymene, and gama-terpinene. It also has flavanoids, citric acid, eugenol, alkaloids, steroids, carbohydrate, triterpenoids consecutively contributing to antioxidant, antiviral properties.

Its medicinal properties include Wound healing activity, Anti-oxidant activity eg. Metal chelating power, hydrogen peroxide and free radical scavenging, Anti-convulsant activity, Anti-inflammatory and Analgesic activity, Antimutagenic activity, Immunostimulant activity, Antiviral and Antimicrobial activity, Anticholinergic activity, Insect repellant and Acaricidal activity. It is also reported to have neuroprotective activity [14, 15].

Bay leaves are proved to be highly efficient in keeping up human health condition in a balance. Some properties such as rich source of Vitamin A, Vitamin C, iron, potassium, calcium and magnesium are considered as specified reasons for bay leaf's medicinal properties.

They show specificity for many fevers, cough, flu, bronchitis, asthma, influenza, cough, cold, lowering blood cholesterol level chicken pox, diarrhea, and anti-stress agents. It gives an effective medication for night blindness, sore eyes sore throat and constipation. It has been used to treat

epilepsy, neuralgia and Parkinsonism. It can even treat diabetes and migraine. It has been used for relieving hemorrhoid and rheumatic pains.

Corona virus infection has already increased the mortality rate to another extent proving it to be one of the deadliest viral infections across the globe. Vaccines are still in the clinical trial phases with high demand of naturally based anti-viral drugs. Different medicinal plants can provide different bioactive compounds hoping to treat this COVID-19 disease. In this breakthrough, bay leaves have proved to be an excellent source of antiviral compounds.

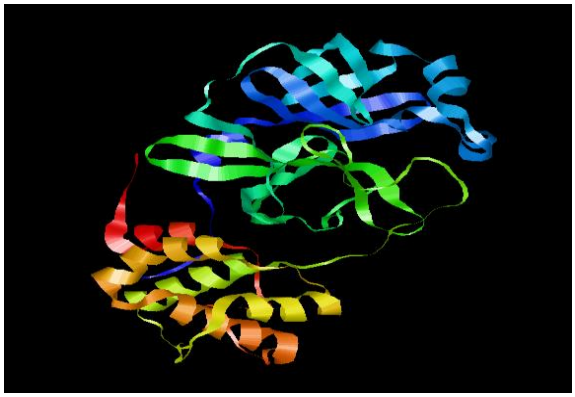
Methodology

Phytoligands Preparation

All the selected ligands were retrieved from the Pubchem database in SDF (Structured Data Format) format. And the entire file converted into PDB Format employing PyMol version 1.3 [16]. All the phytoligands such as Kaempferol, Quercetin, Apigenin, Luteolin were analyzed using Marvin view [17].

Receptor Selection

The three dimensional structure of COVID-19 main protease was fetched from Protein Data Bank (PDB ID: 6M03) [18].



Drug Likeness Analysis

The drug likeness prediction was carried out through Lipinski analysis and according to Lipinski filter, some main criteria must fulfill such as hydrogen donor and hydrogen acceptor, molecular mass, cLogP, and refractive index [19]. For best prediction of selected compounds was done using Lazar and virtual docking (http://lazar.in-silico.de/predict).

ADMET analysis

The physiological properties were investigated using SWISS ADME, which is known as best tool in drug designing [20]. ADME refers to adsorption, distribution, metabolism, excretion. The GI absorption and Brain barrier access are main pharmacological factors in drug designing.

BOILED-Egg

BOILED-Egg is used to assume or predict the gastrointestinal absorption as well as brain barrier for the development of drugs. In case of BOILED-Egg plot, if any compounds are successfully placed in white part of eggs, the probability of GI absorption is higher and in case of yellow region, the brain barrier is higher. In the present study, the analysis of the targeted compounds for BOILED-Egg was done employing SwissADME server [21].

Molecular Docking Simulation

The objective of the molecular docking process is to predict the binding modes of the respective ligands. According to Molecular docking, the binding energy and docking score of the respective molecule accordingly. Moreover, all the phytoligands were docked with the target receptors (PDB ID: 6M03) using AutoDock and Pyrx [22]

Results and Discussion

Ligands

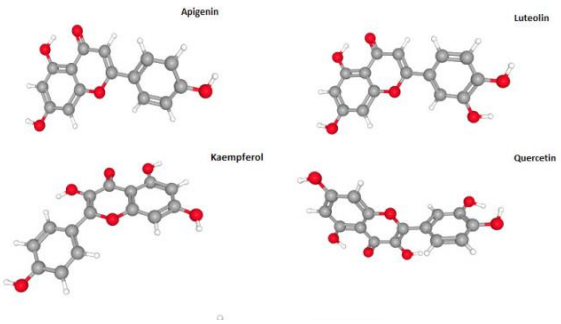


Figure 2. 3-D conformers of the selected ligands

Drug Likeness Analysis

In case of drug likeness, we were used Lipinski filter that explains the rigidity of all the selected compounds which can be considered for drug design.

BOILED-Egg Plot

BOILED-Egg Plot reveals that the physicochemical properties of all the compounds have high GI absorption like Kaempferol, Quercetin, Apigenin, and Luteolin

Table 1. Drug Likeness Analysis

Ligands	Molecular Weight	Hydrogen bond donor	Hydrogen bond acceptor	cLogP	Molar refractivity
Apigenin	270.24g/mol	3	5	2.11	73.99
Luteolin	286.24g/mol	4	6	1.73	76.01
Kaempferol	286.24g/mol	4	6	1.58	76.01
Quercetin	302.23g/mol	5	7	1.23	78.04

Table 2. ADME Analysis

Ligands	GI absorption	Blood Brain Barrier	p-GP substrate	Subcellular Localization
Apigenin	High	No	No	Mitochondria
Luteolin	High	No	No	Mitochondria
Kaempferol	High	No	No	Mitochondria
Quercetin	High	No	No	Mitochondria

All the selected ligands don't expose any type of toxicity which justifies considering all the compounds for next screening.

.Molecular docking Simulation

The outcome observed from the molecular docking simulation of all selected phytoligands with targeted receptors exposing good docking score and binding affinity. The prediction of the selected compounds is better than co-crystal drugs and it leads us to believe that the compounds will effectively be suitable for cure.

Table 2. Docking score with Hydrogen bond residues.

Ligands	Docking score/ Binding Energy	Hydrogen Bond residues
Apigenin	-8.234	1 & Gln 256 & Thr 257
Luteolin	-9.221	2 & Ser2 & Phe 4
Kaempferol	-13.354	2 & Gln 299 & Arg 298
Quercetin	-7.346	2 & Mol 307 & Gly 2

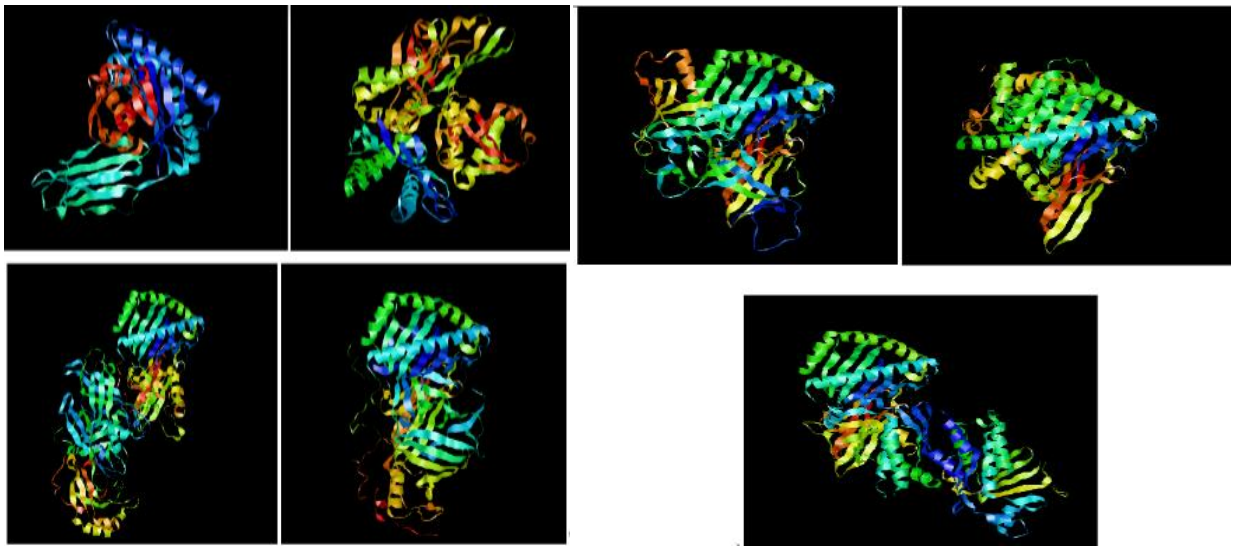


Figure 2. Molecular docking simulation of selected phytoligands with targeted receptor (COVID-19 main protease)

Conclusion

Nowadays, everyone is As the COVID-19 infection has become the global issue and caused many lives, yet to say millions of people are under treatment. This situation lightens up our need and urge for an effective vaccine. Along with introduction of vaccines, awareness about the uses and impacts should be provided to the public.

By comparing all the compounds interacted with COVID-19 Protease based on the binding score and energy criteria, knowing that Quercetin (-8.124) followed by Kaempferol (-8.254) have a good binding score.

According to Lipinski Filter and ADME analysis, all the compounds are active compounds for various models like P-glycogenic substrate, BBB penetration, and human intestinal absorption.

In this study, all the selected phytoligands showed better binding affinity in contrast to COVID-19 main protease. And it is concluded that some compounds are perfect

for inhibitory activity for Novel Coronavirus through computational biology or *insilico* study with special regarding to the molecular docking mechanisms.

Hence it has been assumed or predicted that all the selected phytoligands can possibly serves as a novel lead for the cure of COVID-19 and will be effective in future for *invivo* experiments.

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