Original Article

# In Silico Analysis To Identify IL-6 Inhibitor From Antiviral Compounds Of Kabasurakudineer Extract Against COVID-19

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## Abstract

**Background:** Novel coronavirus (COVID-19) is an infectious disease which causes the outbreak as a pandemic and reiterated the call for countries to take immediate actions and proportion response to treat, detect and cut back transmission to save lots of people's lives. Several targeting specific functional proteins and ligands against coronavirus have been reported to prevent replication of virus RNA. **Aim:** The study was aimed to targetthe interleukin-6 protein, that may further block the binding of the virus to human cell receptor and signal transduction which activate the intracellular JAK-MAPK (Janus Kinase\Mitogen-activated protein kinase) and JAK- STAT3 (Janus Kinase/Signal Transducer and Activator of Transcription) signaling pathways. **Methods:** In this study, we selected 36 reported compounds and 2 standard anti-HIV drugs such as Abacavir and Hydroxychloroquine for the inhibition of IL-6 protein. It has been reportable with their antiviral efficacies against alternative virus-infected diseases. Molecular docking analyses were performed to identify the best affinity compound against IL-6. **Results:** Among 38 reported compounds, gallic acid and luteolin are the best binding affinity against Interleukin-6 protein. **Conclusion:** Therefore, the results suggest that gallic acid and luteolin has a potential inhibitory function against IL-6 protein, which inhibits the interaction and signal transduction of the virus with the host cell and it provide a potential lead molecule for the development of a new drug against COVID-19disease.

**Key words:** COVID-19, Kabasurakudineer, IL-6, Molecular Docking

## 1.INTRODUCTION

COVID-19 pandemic is the contemporary element of worriment across the world. It is a disease that is spread by Coronavirus whose vaccine is not yet discovered. Dread of COVID-19 outbreaks in December 2019. COVIDis a typical RNA virus, due to the presence of glycoprotein spikes on its envelope it said to be as Crown-like structure [1-3]. There are four genera of CoVs:
(I) α -coronavirus (alpha-CoV), (II) β -coronavirus (beta-CoV) probably present in bats and rodents, while (III) γ-

coronavirus (gamma-CoV), and (IV) δ -coronavirus (delta-CoV) probably represent avian species [4-6]. Symptoms of the novel coronavirus are quite similar to normal flu and we should seek medical advice if you develop fever cough runny nose sore throat difficulty in breathing and the infection starts with a simple upper respiratory tract infection [8]. The study reported by Jing Liu et al.[7] stated that COVID patients affected in severe cases show a sustained decrease in the proportion of lymphocytes compared with normal cases and the inflammatory cytokines (interleukin) increased in the peripheral blood. IL-6 binds with gp130 to initiate downstream signal transduction, gene expression, and intracellular signal transduction [9- 12].

On targeting the interleukin-6 proteins which may further block the binding of the virus to human cell receptors and signal transduction which activate the intracellular JAK-MAPK (Janus Kinase/ Mitogen-activated protein kinase), JAK-STAT3 (Janus Kinase/Signal Transducer and Activator of Transcription) signaling pathways, AKT-PI3K,RAS-RAF, and SRC-YAP-NOTCH, are leads to promotes proliferation, differentiation, oxidative stress, immune regulation[13- 20].IL-6 may play a critical role in the hyperactive inflammatory response in the lungs amongst with coronavirus disease 2019(COVID-19), the respiratory illness that is produced by COVID infection, multiple Food and Drug Administration (FDA) approved IL-6 inhibitors are now being repurposed to be used for the management of CoV-2 infection.

In this work, we found the potential drug targets and development of therapeutic strategies. All tools have either been developed explicitly for COVID research, have been extended or adapted to coronaviruses, or are of particular importance to study COVID epidemiology and pathogenesis through Bioinformatics workflow andtools.

## 2. Material andmethods

In silico procedures such as Molecular docking analysis was performed using the Maestro 11.4, Schrodinger 2017-4 [21-22].These Schrodinger software package were used to carry out the computational analysis.

## 2.2. Ligandpreparation

Totally 38 reported antiviral compounds [23-26] were chosen to perform the molecular docking contemplates and identify the potential antiviral compound for Coronavirus. PubChem and Drugbank information bases were utilized to remove out the 2D substance structures of the revealed atoms. LigPrep module (Schrodinger, LLC, NY, USA, 2009) was utilized from the Maestro developer board to plan ligand and create the 3D structure of the ligands by eliminating salt, adding hydrogen molecules, and ionizing at pH (7.0 +/- 2.0). Energy minimization was performed utilizing OPLS3 force field by utilizing the standard energy capacity of atomic mechanics and RMSD slice off 0.01 Å to create the low-energy ligand isomer.

| Plant Name | Compound name |
|---|---|
| Kabasura Kudineer Chooranam | |
| Kabasura Kudineer Chooranam<br>Zingiberofficinale Rosc | b-sesquiphellandrene |
| | b-bisabolene |
| | Geranial |
| PiperlongumL | Piperine |
| | Piperlonguminine |
| Syzygiumaromaticum | Eugenol |
| | b-Caryophyllene |
| TragiainvolucrataL | Stigmosterol |
| | 3-(2,4-dimethoxyphenyl)-6,7-dimethoxy-<br>2,3- dihydrochromen-4-one |
| Anacycluspyrethrum | Squalene |
| | γ-Sitosterol |
| Andrographispaniculata | Andrograpanin |
| | 5-Hydroxy-7,8-dimethoxyflavanone |
| Hygrophillaauriculata (Schum.)Heine | Lupeol |
| | Betulin |
| Terminaliachebula Retz. | Chebulagicacid |
| | Gallicacid |
| JusticiaadhatodaL. | Vasicinone |

| | |
|---|---|
| Plectranthusamboinicus(Lour)Spreng | Carvacrol |
| | Cirsimaritin |
| | Chrysoeriol |
| | 6-Methoxygenkwanin |
| Costusspeciosus | Luteolin |
| | Costunolide |
| | Elemol |
| Tinosporacordifolia(Willd.) MiersexHook.f&Thoms ClerodendrumserratumL. | Tinosponone |
| | Bharangin |
| | Scutellarein |
| Sidaacuta Burm.f. | Magnoflorine |
| | Cycleanine |
| CypreusrotundusL. | Cyperene |
| | b-selinene |
| JACOM Formulation | |
| JusticiaadathodaL. | Vasicine |
| Carica Papaya | Quercetin |
| Andrographispaniculata Burm.f.Nees | Andrographolide |
| Ocimumtenuiflorum | Ursolicacid |
| Standard antiviral compound | Hydroxychloroquine |
| | Abacavir |

**Table 1. List of antiviral agents docked against COVID-19**

## 2.3. Preparation of protein structures and gridgeneration

Protein structure of IL-6 (PDB IDs: 3L5I, having resolution < 1.90 Å, R-Value Free <0.222, R- Value Work <0.181) were selected and obtained from Protein Data Bank (http://www.rscb.org) with good resolutions [27]. In protein preparation wizard panel was used to prepare prote instructure, assigned Bonds orders and hydrogen atoms were added as well. Water molecules were removed within 3 Å of het groups [20]. Finally, the protein structure has minimized by OPLS3 force field in Schrodinger, LLC, NY, USA, 2009[28]. Further, a Site map was predicted and receptor grid boxes were generated using Glide's Receptor Grid Generation module at the active site (with the radius of 20 Å around the crystal structure) of co- crystallized ligand with the computing cubic box of 14.74 Å × 53.85 Å × 73.53Å.

## 2.4. Moleculardocking

The molecular docking approach is a structure-based drug design to identify the interactions between Target and ligands with minimum energy conformation [29]. The least binding energy of ligands is depicted by the best docking score which is used to prognosticate the binding affinity with the receptor. The GLIDE Extra precision (XP), docking convention was applied without smearing any constrain. Flexible docking with GLIDE Extra precision (XP) convention was performed to anticipate the binding affinity and ligand efficiency as an inhibitor of Coronavirus target [30]. Energy assessment was done with the dock score. Maestro interface (SchrodingerSuite,LLC,NY)wasalsousedastheVisualizationtoolfordockedligands[31].

## 3.RESULTS ANDDISCUSSION

To find a potential compound against IL-6, molecular docking studies were performed on over 38 natural and antiviral compounds on the binding site of IL-6. The potentialbinding residues are TYR, ALA, VAL,LYS, TRY, THR, and ASP. 38 molecules were ranked based on their dock score which docked against the target IL-6. Compounds having minimum energy of dock score are considered a best compound for inhibition of the IL-6. By the docking score analysis, the provisional analysis can be done. This table-2 describes that the list of active molecules obtained after docking studies and active molecules have a docking score value of -6.8 or lower. Therefore 2 compounds (Gallic acid and Luteolin) showed binding interactions withIL-6structures.

| Compound Name | Compound Id | Dockingscore | XpGScore | Hydrogen Bonds Interaction | Other Interaction |
|---|---|---|---|---|---|
| Gallic acid | CID_370 | -6.826 | -6.826 | VAL477,TRY478,ALA479 | LYS430 (Salt Bridge) |
| Luteolin | CID_5280445 | -6.604 | -6.621 | LYS429, THR393, TYR478, and ALA479 | LYS430 (pi-cation interaction) |
| Hydroxychloroquine | CID_ 3652 | -6.239 | -6.289 | ASP452 | ASP452 |

| | | | | | |
|---|---|---|---|---|---|
| Abacavir | CID_441300 | -5.053 | -5.058 | TRY478,THR393,AL<br><br>A389,VAL391 | - |

**Table2.Post-docking analysis of top two compounds along with 2 standard anti-viral compounds against IL-6.**

Compound 1 (Gallic acid) has one salt bridge interaction with LYS430 and three hydrogen bonding interactions with VAL477, TRY478, and ALA79 (Fig. 1.). It also has more lipophilic interactions and non-bonded interactions against IL-6. When comparing to other compounds including standard anti-HIV drugs, Gallic acid has a more binding affinity towards IL-6 and it showed besthydrogen bonding interactions. This studyclearlyindicates that involved in nonbonded interaction and few binding specificity against IL-6.

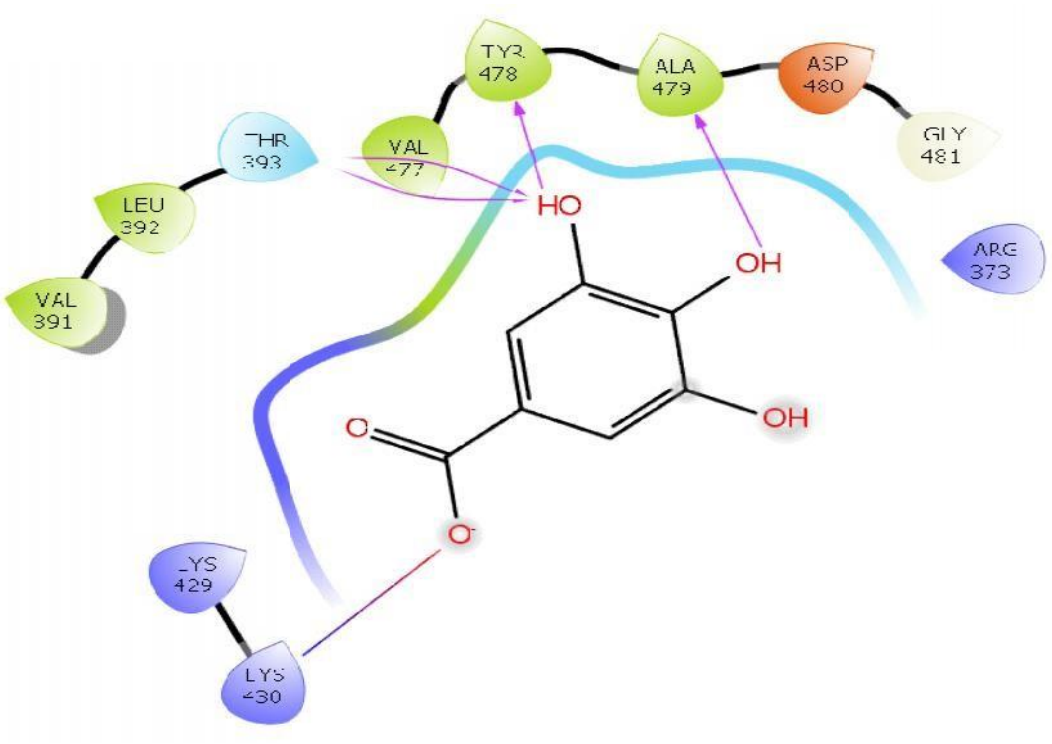


Fig.1.Docking interactions of Gallic acid(CID_370) with 3L5I.

Compound 2 (Luteolin) has one pi-stacking interaction with LYS430 and four hydrogen-bonding Interactions with LYS429, THR393, TYR478, and ALA479(Fig.2). It also has more lipophilic Interactions and non-bonded interactions against IL-6. When comparing to other compounds including standard anti-HIV drugs, Luteolin has a second-most binding affinity, hydrogen bond towards IL-6 and it showed best hydrogen bonding interactions. Resultsofthe present study clearly show that that they are involved in nonbonded interaction and few binding specificity against IL-6

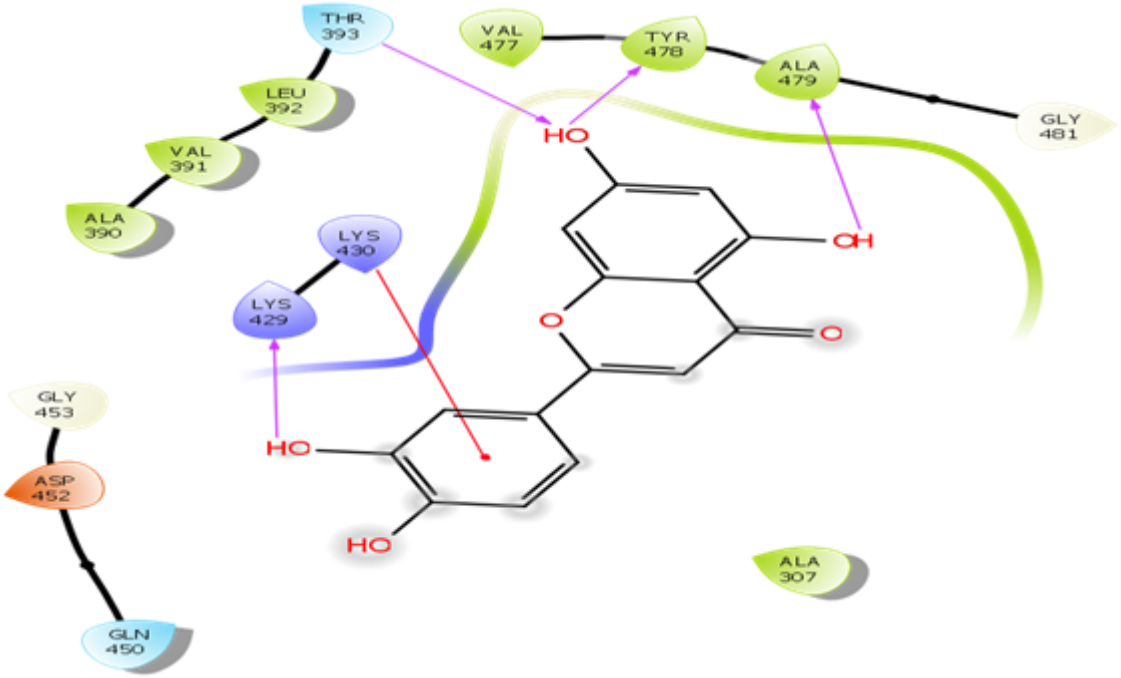


Fig.2. Docking interactions of Luteolin (CID_5280445) with 3L5I.

## 4. CONCLUSION

The IL-6 mechanism has multiple beneficial actions and supports the growth of Bcells. It is antagonistic to regulatory T cells. The docking score observed and active amino acid residues Were obtained in docking analysis. Among 38 reported compounds, gallic acid and luteolin are The best binding affinity against interleukin-6 protein. The best hit compounds were studies in a Special case to explore their dynamic property and interaction pattern. The structural stability and conformational analysis provide detailed data on the identification of potential lead compounds. The identified compounds such as gallic acid and luteolin bind with the target protein of IL-6. Hence, it is concluded that kabasurakuduneer extract containing gallic acid and luteolin could be therapeutic natural drug target for the treatment of COVID-19.

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