

# COVID-19 Prevention Using *Michelia champaca* L. Extract by Blocking SARS-CoV-2 Main Protease Enzyme: an *In Silico* Analysis

Atasi Routray, Rakesh Kumar Gochhayat<sup>1</sup>, Faculty's name <sup>1</sup>, Dipankar Bhattacharyay<sup>1\*</sup>

<sup>1</sup> Centurion University of Technology and Management, Odisha, India

\*Corresponding author: email: dipankar.bhattacharyay@cutm.ac.in phone: +919007716604

## **Abstract:**

Coronavirus disease 2019 (COVID-19) is an infectious disease produced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease causes respiratory illness (like the flu) with symptoms such as a cough, fever, and in more severe cases, difficulty breathing. It has been a source of fright and anguish worldwide as an ongoing epidemic which is ensuing thousands of demises and affecting millions of people every day. To overcome these obstacles researchers are trying to come up with a traditional vaccine or preventive drugs. However, this study intentions to derive medicines from plant extract containing phytochemicals rather than synthesizing new chemicals which proved to be more expensive and unsafe compared to their organic counterpart. Phytochemicals are non-nutritive compounds obtained from plants. It has been reported that *Michelia champaca* L. plant extract is expected to cure COVID-19, which is caused by corona virus. The said virus contains (SARS -CoV- 2 main protease) enzyme which is reported to be very crucial for the survival of the organism. The molecular docking of the phytochemicals with the microbial enzyme was studied using Biovia Discovery Studio. The strength of the interaction was evaluated based on -CDocker energy and -CDocker interaction energy. High positive values for both the parameters indicated that out of different phytochemicals Beta-caryophyllene, beta-selinene, farnesol, gamma-cadinene, nerolidol, eugenol, gallic acid, quercetin can effectively deactivate the enzymatic metabolic activity thereby interrupting the life cycle of corona virus.

**Key words:** phytochemical, Biovia, Discovery studio, COVID-19, SARS-CoV-2

## **1. Introduction:**

Coronavirus disease 2019 (COVID-19) is a transmittable disease resulting in the ongoing 2019–20 coronavirus pandemic with serious fatal implications for countries with ageing populations. The World Health Organization (WHO) accredited the 2019–20 coronavirus outbreak a Public Health Emergency of International Concern (PHEIC) on 30 January 2020, and a pandemic on 11 March 2020.[1][2] Some of the first cases of the epidemic were reported in December 2019 at Wuhan, the capital of China's Hubei province, which has since escalated globally.[3][4] According to the statistics, the growth rate, at which the number of deaths is doubled, is only 7 days globally. Whereas 4600+ deaths adding on daily basis as per the time the article being written, sending the mortality graph skyward. The total number of confirmed cases has since touched the 1 million mark with 72000+ cases being reported daily. However, the total number of COVID-19 cases is not known. As World Health Organization (WHO) explains a confirmed case is “a person with laboratory confirmation of COVID-19 infection”. The total number of confirmed cases are lower than the number of total cases because not everyone is tested. Not all cases have a “laboratory confirmation”, testing is what makes the difference between the number of confirmed and total cases and also because for some of them, the disease has ended and they have either recovered or died from it. [5]. Unfortunately any kind of preventive or molecular drugs or vaccine couldn't been developed yet due to continuous mutation according to geographic regions in the virus.[6] However, rather than vaccinations, where attenuated antigenic materials are used to stimulate an individual's immune system, Anti-viral targeting may be approached where antiviral drug is designed to identify viral proteins, or parts of proteins, that can be disabled.

Nature has been a source of medicinal agents for thousands of years and an impressive number of modern drugs have been derived from natural source [7]. The medicinal value of the plants lies in some chemical substances that produce a definite physiological action on the human body, these substances are called phytochemicals, which can be used for therapeutic purpose. Plants based medicinal constituents can be derived from any part of plant like bark, leaves, flowers, roots, fruits, and seeds.[8] Various medicinal plants and their phytoextracts have shown numerous medicinal properties like anti-oxidant , anti-inflammatory , anti-cancer , anti-microbial, anti-diabetes action etc.[9]Among different sources of natural products, plants have been a source of novel chemical substance, which serves as starting materials for a number of old and new pharmaceutical products while proving to be safe and cost effective .

Medicinal plants are the foundation of many drugs prescribed today in modern medicinal system. About 25% of modern pharmaceutical drugs have botanical origins. Research needs in the field of medicinal plants are huge, but are balanced by the potential health benefits and the enormous size of the market. Research into the quality, safety, biological activity, and clinical efficacy of the numerous plants in common usage is required. Newly emerging scientific techniques and approaches have been used in the growing area of medicinal plant research, for the investigation of constituents and determination of biological activity of medicinal plants. Evidence for the beneficial effects of selected plants is generally based on experiments demonstrating a biological activity in a relevant in vitro bioassay or experiments using animal models.[10] Plants that demonstrated anticancer, antioxidant, anti-inflammatory, immunostimulatory, and antimicrobial properties have received research attention. *Michelia champaca L.* belongs to family Sterculiaceae. Champaca leaves extract is used to cure disease like diarrhea, cough, bronchitis, hypertension, dyspepsia, fever, rheumatism, abscesses, dysmenorrhoea and inflammation. It is also used as

purgative, expectorant, cardiogenic, digestive, carminative, stomachic, stimulant, diuretic, diaphoretic, antipyretic and astringent [16]. The plant is *Plumeria rubra* is a deciduous plant species belonging to the genus *Plumeria*. Originally native to Mexico, Central America, Colombia and Venezuela, it has been widely cultivated in subtropical and tropical climates worldwide and is a popular garden and park plant, as well as being used in temples and cemeteries.[17][18]. The plant is distributed in Eastern Himalaya, North East India and Western ghats. It is cultivated throughout India in gardens and near temple for fragrant flowers and handsome foliage[18]. *Michelia champaca* L. is known to contain phytochemicals like Beta-caryophyllene, beta-selinene, farnesol, gamma-cadinene, nerolidol, eugenol, gallic acid, quercetin etc. There is high possibility that these phytochemicals play a major role in curing COVID-19. However, there is no report identifying the specific phytochemical responsible to cure COVID - 19.

Coronavirus disease 2019 (COVID-19) is a transmittable disease instigated by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[11] Genetic analysis has revealed that the coronavirus genetically clusters with the genus Betacoronavirus, in subgenus Sarbecovirus (lineage B) together with two bat-derived strains. It is 96% identical at the whole genome level to other bat coronavirus samples (BatCov RaTG13).[12][13] Those infected with the virus may be asymptomatic or develop flu-like symptoms, including fever, cough, fatigue, and shortness of breath. Emergency symptoms include difficulty breathing, persistent chest pain or pressure, confusion, difficulty waking, and bluish face or lips; immediate medical attention is advised if these symptoms are present. Symptoms such as nausea, vomiting, and diarrhea have been observed in varying percentages [14][15]. It spreads much like a cold or the flu through the expelled airborne droplets from a person with infectious COVID-19 or through close/surface contact. When inhaled or came in contact with eyes, nose or mouth, the virus can settle in the lungs, where it begins to

grow which can be life-threatening. However, it is possible to control the disease by inhibiting the metabolic pathway of the microorganism.

This study focuses on the identification of the phytochemicals of beta-caryophyllene, beta-selinene, farnesol, gamma-cadinene, nerolidol, eugenol, gallic acid, quercetin responsible to cure COVID-19 caused by (SARS-CoV-2) by inhibiting the protein pathway.

## **2. Materials & methods:**

### **2.1 Software used:**

Discovery studio module of Biovia software (Dassault Systemes of France) was used for analysis. The software utilizes machine learning techniques to predict the level of molecular interaction

### **2.2 Methodology:**

**2.2.1 List of phytochemicals:** Phytochemicals are produced by plants as secondary metabolites to protect them from predators. The potential threats to plants include bacteria, viruses, fungi etc. When these plants or their parts are consumed by humans these phytochemicals fight off threats to health. Some phytochemicals have been used as poisons and others as traditional medicine. Published works showed that *Michelia champaca L.* contains beta-caryophyllene, beta-selinene, farnesol, gamma-cadinene, nerolidol, eugenol, gallic acid, quercetin. It has already been established that *Michelia champaca L.* plant belonging to Sterculiaceae family has potential to help controlling COVID-19. This work is focused on identification of the particular phytochemical responsible for inhibiting and controlling of COVID-19.

**2.2.2 Enzyme found in SARS -CoV-2 main protease:** It has been reported that COVID-19 can cause as a result of viral infestation. Various metabolic cycles have been seen in the viral life cycle

for its survival. These metabolic cycles are regulated by different enzymes. Brenda enzyme database was used to identify and list different enzymes found in (SARS-CoV- 2). It has been found that (SARS-CoV-2 main protease) enzyme (protein database code 6YB7) is involved in viral RNA synthesis which is found in extracellular matrix in order to survive.

**2.2.3 Molecular docking:** Molecular docking method has been used to identify the phytochemical from the plant extract, that act as a ligand and form a strong covalent bond with the bacterial protein to successfully inhibit the microbe. The Discovery studio module of Biovia software was used for identifying molecular interaction and perform molecular docking. In this process first the sdf files for the phytochemicals found in the *Michelia champacaplant* were downloaded from the website. The protein database code of the enzymewas identified from the website. The active site of the enzyme was identified via “receptor cavity” protocol found under "receptor-ligand interaction" menu. Molecular docking was done using the CDocker protocol of Biovia software under “receptor-ligand interaction”. The enzyme molecule was treated as the receptor molecule and the phytochemical was treated as the ligand. The “-CDOCKER\_ENERGY” and “-CDOCKER\_INTERACTION\_ENERGY” were used as indicator for the quality of molecular docking. The high positive value of those indicators presented a good interaction between the ligand and the receptor. Thus, the interactions with high values might indicate the major phytochemical responsible for curing the disease.

### **3. Results and discussion:**

Fig. 1 shows the active site of the(SARS-CoV-2 main protease) enzyme. It appears as light green color. CDOCK is a molecular dynamics (MD) simulated-annealing-based algorithm. It is a grid-

based molecular docking method and optimized for accuracy. The ligand conformations were obtained by Molecular Dynamic methods.

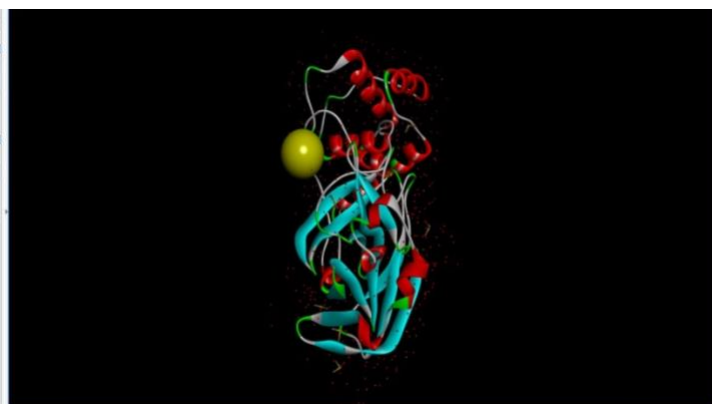


Figure 1. Active site of (SARS-CoV-2 main protease) enzyme

- CDOCKER energy was calculated based on the internal ligand strain energy and receptor-ligand interaction energy. - CDOCKER interaction signifies the energy of the nonbonded interaction that exists between the protein and the ligand. The criteria for best interaction was chosen based on a) high positive value of -CDOCKER energy and b) small difference between -CDOCKER energy and -CDOCKER interaction energy.

Table 1 shows that Gallic acid interaction has the highest positive value of -CDOCKER energy 13.9109 and minimum value of the difference 1.835 between - C DOCKER interaction energy and - C DOCKER energy followed by quercetin and eugenol . Thus, the results indicated that gallic acid and quercetin can effectively deactivate (SARS-CoV-2 main protease) enzyme thereby interrupting the metabolic pathway of the virus. Higher positive values for gallic acid indicated that it was the most active ingredient against corona virus. On the other hand, beta-caryophyllene,

beta-selinene, nerolidol, eugenol, farnesol can deactivate the enzyme to a small extent (negative -CDocker energy but positive -CDocker interaction energy). Thus, the key phytochemicals preventing COVID-19 caused by corona virus is gallic acid.

Table 1. Results of CDocking of phytochemicals with (xxxxx) (receptor)

SL NO	LIGAND	- C DOCKER ENERGY	- C DOCKER INTERACTION ENERGY	Difference between - C DOCKER interaction energy and - C DOCKER energy
1	Gallic acid	13.9109	12.0759	1.835
2	Quercetin	7.64282	10.2481	2.60528
3	Eugenol	-1. 21806	8.34884	9.5669
4	Beta-selinene	-29. 289	10.3821	39.6711
5	Beta-caryophyllene	-32. 1822	10.2574	42.4396
6	(-)-gamma-cadinene	-36. 9196	8.02721	44. 26876
7	Nerolidol	-43. 6565	8.27006	51.92656
8	Farnesol	-55. 8006	9.46816	65.26876

#### 4. Conclusions:

It was previously known that *Michelia champacaplant* has medicinal action against COVID-19. COVID-19 is caused by corona virus. This study was carried out to provide the theoretical basis of this observation. Using Discovery studio module of Biovia software, molecular docking operation was performed to identify the phytochemical Beta-caryophyllene, beta-selinene, farnesol, gamma-cadinene, nerolidol, eugenol, gallicacid, quercetin which can have a significant interaction with the vital enzyme (SARS-CoV-2 main protease) of the microbe. It was found that gallic acid and quercetin can form strong bond with the enzyme followed by quercetin and eugenol, successfully inhibiting the lipid metabolic cycle of the microbe. This study could explain



that the presence of gallic acid provided the medicinal values to *Michelia Champaca L.* against COVID-19 caused by coronaSARS-CoV-2 main protease.

## 5. References:

- [1] Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV)". World Health Organization (WHO). Archived from the original on 31 January 2020. Retrieved 11 February 2020.
- [2] Mahtani, S.; Berger, M.; O'Grady, S.; Iati, M. (6 February 2020). "Hundreds of evacuees to be held on bases in California; Hong Kong and Taiwan restrict travel from mainland China". The Washington Post. Archived from the original on 7 February 2020. Retrieved 11 February 2020.
- [3] Naming the coronavirus disease (COVID-19) and the virus that causes it". World Health Organization (WHO). Archived from the original on 28 February 2020. Retrieved 28 February 2020.
- [4] Hui, D. S.; I. Azhar E.; Madani, T. A.; Ntoumi, F.; Kock, R.; Dar, O.; Ippolito, G.; Mchugh, T. D.; Memish, Z. A.; Drosten, Christian; Zumla, A.; Petersen, E. (February 2020). "The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health—The latest 2019 novel coronavirus outbreak in Wuhan, China". *Int J Infect Dis.* 91: 264–66. doi:10.1016/j.ijid.2020.01.009. PMID 31953166.
- [5] Max Roser, Hannah Ritchie and Esteban Ortiz-Ospina (2020) - "Coronavirus Disease (COVID-19) – Statistics and Research". Published online at OurWorldInData.org. Retrieved from: '<https://ourworldindata.org/coronavirus>' [Online Resource]

- [6] Sardar, Rahila, et al. "Comparative analyses of SAR-CoV2 genomes from different geographical locations and other coronavirus family genomes reveals unique features potentially consequential to host-virus interaction and pathogenesis." *bioRxiv* (2020).
- [7] Henrich J, Heine S, Norenzayan A. The weirdest people in the world? *Behavioral and Brain Sciences*. 2010;33(2-3):61-83. DOI:10.1017/S0140525X0999152X.
- [8] Srivastava Praveen Kumar. *Achyranthes aspera*: A potent immunostimulating plant for traditional medicine. *International Journal of Pharmaceutical Sciences and Research*. 2014;5(5):1601-1611.
- [9] Hussain Iqbal, Ullah Ria, Ullah Rooh, Khurram Muhammad, Ullah Naseem, Abdul Basee, Khan Farhat, Khattak Muhammad, Zahoor Muhammad, Khan, Jehangir, Khan Dr. Naeem. Phytochemical analysis of selected medicinal plant. *African Journal of Biotechnology*. 2011;10: 7487-7492.
- [10] Wachtel-Galor S, Benzie IFF. Herbal Medicine: An introduction to its history, usage, regulation, current trends, and research needs. In: Benzie IFF, WachtelGalor S, editors. *Herbal Medicine: Biomolecular and Clinical Aspects*. 2nd Edition. Boca Raton (FL): CRC Press/Taylor & Francis. 2011;Chapter 1.  
Available:<https://www.ncbi.nlm.nih.gov/books/NBK92773/>
- [11] "Naming the coronavirus disease (COVID-19) and the virus that causes it". World Health Organization (WHO). Archived from the original on 28 February 2020. Retrieved 28 February 2020.
- [12] Hu, Ben et al. "Bat origin of human coronaviruses." *Virology journal* vol. 12 221. 22 Dec. 2015, doi:10.1186/s12985-015-0422-1

- [13] Lu, Roujian, et al. "Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding." *The Lancet* 395.10224 (2020): 565-574.
- [14] "Coronavirus Disease 2019 (COVID-19) Symptoms". Centers for Disease Control and Prevention. United States. 10 February 2020. Archived from the original on 30 January 2020.
- [15] Chen, N.; Zhou, M.; Dong, X.; Qu, J.; Gong, F.; Han, Y.; Qiu, Y.; Wang, J.; Liu, Y.; Wei, Y.; Xia, J.; Yu, T.; Zhang, X.; Zhang, L. (February 2020). "Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study". *Lancet*. 395 (10223): 507–513. doi:10.1016/S0140-6736(20)30211-7. PMID 32007143.
- [16] Minter, S. "Fragrant Plants." in Prance, G. and M. Nesbitt. (2005). *The Cultural History of Plants*. London: Routledge. 242. This is great
- [17] <http://wizzley.com/sri-lankan-brown-palm-civets-paradoxurus-montanus-non-ringtails-of-sri-lanka/>
- [18] FRISCH, J.D. & FRISCH, C.D. - *Aves Brasileiras e Plantas que as atraem*, São Paulo, Dalgas Ecotec, 3rd. edition, 2005, ISBN 85-85015-07-1, page 374