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Structure-Activity Relationship of Phytochemicals for Combating Covid-19 Brain Fog

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ABSTRACT
The pandemic SARS-COV-2 caused by a strain of acute respiratory syndrome of corona virus has killed millions of people worldwide. The direct impact on the health economy of affected countries. More than 219 countries have been severely affected by COVID-19. There are no specific small molecule inhibitors against this virus. Section various anti-inflammatory drugs such as antibiotics, anti-inflammatory drugs, antiviral drugs and antiviral drugs are also used in the treatment of covid-19. The full effect of this drug against covid-19 targets has not been tested. After receiving treatment, the virus can change its genetic materials, more strains formed causing the dangerous epidemic. Covid-19 types of delta plus and omicron kill brain cells and cause long-term COVID-19 memory. There are currently no synthetic drugs available to treat the memory loss due to long COVID-19 brain fog. Therefore, an attempt has been made to treat COVID-19 associated brain fog using natural components. The biochemical mechanism of action of these phytocomponents has been predicted using structure-based docking simulation.
Keywords: *COVID-19, Acetyl cholinesterase enzyme, SARS-COV-2, phytocomponents.*

INTRODUCTION

The SARS-COV outbreak that occurred in China's Guangdong Province in 2003 was followed by the second MERS-COV outbreak that occurred in Saudi Arabia in 2012. December 2019, Chapter in December 2019, the Elderly in Wuhan, the capital of Hubei Province, and a major transportation hub in China, began sending Chapter cases of severe pneumonia of unknown cause to nearby hospitals. After the SARS epidemic, the monitoring device placed nearby was opened and the patient's breath was sent to laboratory for etiological investigations. On December 31 2019, China reported the outbreak to the Health authorities and closed the Humansea restaurant on January 1. On January 7 the virus was diagnosed as corona virus with> 95% identity to corona virus and >70% identity to SARS-COV-2 [1].
It is worth noting that while the number of patients has increased exponentially in other countries such as South Korea, Iran and Italy. 20 percent of those who got sick were in serious condition, 25 percent were healthy and 310 died. India is in critical condition, 25% have recovered, and 310 have died. India,

mentioned top 3 before May 3, 2020 and presently 29 cases; mostly Italian tourists and their residents in Delhi, Jaipur and Agra [4].

The novel coronavirus & severe acute respiratory syndrome corona virus 2s known as, has rapidly to the rest of the world from its source in Wuhan, Hubei province, China. As of the May 3, 2020, approximately 96,000 cases of corona virus 2019 and 3300 deaths have been reported. [5]

Over the years, there have been many cases of animal beta corona viruses infected human, causing serious illness. The first such event occurred in 2002-2003, when human were infected with a new bat-like virus of the Beta genus, an intermediate host for cats in Guangdong province, China. This disease, particularly pneumonia, infected 8,422 people in China and Hong Kong and caused 916 premature deaths [6]. About 10 years later, in 2012, MERS-COV also from bats, emerged in Saudi using dromedary camels' intermediate hosts, affecting 2494 people and causing 858 deaths [7].

Pollution is spread by large droplet produced by dromedary camels. Sometimes coughing and sneezing is helpful in symptomatic patients, but it can also happen in asymptomatic individual [8].

1. SARS-COV-2

SARS-COV-2 is the source responsible for the severe and threatening disease called COVID-19. It was first reported in Wuhan, China, in November 2019, and World Health Organization reported the first case on 31 December, 2019. It declared a global epidemic on 11 March, 2020, and spread worldwide on May 30, 2020. A total of 5,899,866 confirmed cases including 364,891 deaths were recorded. SARS-COV-2 mainly targets the lungs and enters the body via the ACE2 receptor. [10] The usual symptom of COVID-19 includes fever, shortness of breath, fatigue and cough, but there is also some unusual symptom such as loss of smell and taste. 20 percent of people are sick that they need to go to hospital and a third of them need intensive care. Treatment is usually supportive, but the frustrating for people who need ventilation. A trial continues to find effective vaccines and anti-inflammatory drugs. The aim of prevention strategies is to reduce the spread of infection through contact, hand washing, use of masks and effective control measures to reduce the risk of infection. [11,12]

Respiratory disease due to corona virus Type 2 a highly contagious disease that emerged in 2019, is as serious respiratory disease. It is known as the "2019 corona virus disease" and threatens people's health and public safety. [13]

As a unique beta corona virus, SARS-COV-2 shares 79 percent of its genome structure with beta corona viruses. The 6 open reads are arranged from 5 to 3: repeat, helix, envelop, membrane, and nucleocapsid. In addition, 7 putative ORFs were encoded by SARS-COV-2. [14]

According to the world health organization epidemiological update, 5 SARS-COV-2 VOC have been identified since beginning of epidemic:

- **Alpha (B.1.1.7):** 1st variant of concern in United Kingdom (UK) in late Dec 2020.
- **Beta (B.1.351):** 1st release in South Africa in Dec 2020.
- **Gamma (P.1):** first reported in Brazil in Jan 2021.
- **Delta (B.1.617.2):** first release in India in Dec 2020.
- **Omicron (B.1.1.529):** first introduced in South Africa in Nov 2021. [15,16]

2. **BRAIN FOG**

Brain Fog generally shows the confusion, memoryless, recognition lacking and brain readability. A situation in that you cannot suppose truly or take note of things in a high-quality manner. [17] Brain Fog is a symptom that may be as a result of stress, sleep modifications, medicines, and other elements. It could motive confusion, reminiscence issues, and a lack of awareness [18].

- Brain Fog itself isn't scientific situation however as a substitute a sign of different pharmaceutics situations. It is intellectual dysfunction regarding:
- Brain problems (memory less)
- Fuzziness
- Mindedness
- Confuse

"Brain fog" defines as a complication in mental functions. Although Learning disability is a neuropsychological symptom that is generally scientists explain as inhibition of intellectual functions e.g. thought, memorizing, and reasoning of intensity to interfere with daily activity [19–23].

So, as per the World Health organization (WHO), Brain Fog is a problem of intellectual activity in patients having post-acute COVID-19. To understand for Brain, fog an umbrella term used to explain as cluster of mental disability, such as confusion, Brain problem (Memory less), Fuzziness, and Mindedness [24].

As per current reports 20-30% of people show sign of brain fog approx. after three months from infection. And approx. 85% of people which infected with COVID long time brain fog also [25].

3. PATHOPHYSIOLOGY OF BRAIN FOG

Patients who cured from COVID-19 having neuropsychiatric sign, e.g. memory disfunction, drowsiness, tiredness, and insomnia. Long-time learning disability and neurodegeneration, with hippocampal atrophy [26], systemic inflammation problem with acute sepsis. Due to inhibition of nutrients and hypoxia or vascular injury may cause learning disability, generally patient infected with COVID-19 having acute illness which needed comprehensive treatment care and respiratory help [27]. Endothelial dysfunction leading to micro vascular damage has also been suggested [28-29]. However, cognitive problems also occur in patients with mild COVID-19 [30]. In this case, other mechanism has been proposed, including immunosuppression, chronic pain, or dysfunction in the body [31]. Other studies have linked cognitive problems with depression &anxiety [32].

The patients suffered from long COVID-19 complaint about the loss of memory. It has been a big issue word-wide. It has a major impact on the quality of life of survivors. Breathing difficulty was a great symptom of the dreadful disease. The novel corona virus disrupts transportation of nutrients and oxygen within the brain tissues and damage brain cells. In healthy brain, nerves get their supply from the surrounding 4,444 nerves. This connection is known as neurovascular junction.
The lack of oxygen and nutrient supply aggravate the immune response and systemic inflammatory response syndrome that encourage the generation of oxidative stress, free radicals which initiate brain inflammation due to releasing the pro inflammatory cytokines which badly affect peripheral nervous system and central nervous system. Another risk factor is long term mechanical pulmonary ventilation, hypoxia and sepsis, hallmarks of a severe SARS-COV-2 attack; cross the blood brain barrier and caused neurodegeneration [27-30]. There is no allopathy medicine.

ORIGINAL RESEARCH

Medicines to combat COVID-associated brain fog. Therefore, an attempt has been made to screen potential phytocomponents bearing the plants already reported in the literature. The structure based molecular docking simulation is an important tool used in the recent study for high through screening of phytoconstituents.

MATERIALS AND METHODS

1. Activity Data

The Five phytocomponents such as Bacosides, Carnosic Acid, Luteolin, Epigallocatechin Gallate, and Sitoindosideswere taken in the present study (Table 1). 2-D structures drawn by Chem draw 8.0 Software. These 2-D structures were transformed into 3-D files which are minimized using the MM2 force field. Molecular energy minimization was done using convergence criterion & dielectric constant of 0.01 Kcal/mol. and 1.0 using the Chem 3-D Ultra window, respectively. All 3-D optimized conformations were performed in addition to molecular docking analysis.

2. Molecular Docking

Molecular docking is an in silico computational method which helps to study the ligand–receptor interaction for identifying the active binding sites of the target protein and also to obtain the most energetically stable conformation of ligand–receptor complex so that the energy of interactions, also represents a score, between ligand and receptor would be minimal. It helps to find the important amino acid residues of the target which could bind with the ligand moiety and produce biological activity. It was shown that all only 6 out of 11 components have successfully been docked inside the active site of the target. The mode of binding along has been detailed in the next Results and Discussion section.

RESULTS AND DISCUSSION

In acetyl cholinesterase enzyme (AChE) which is a receptor enzyme 6 optimized phytocomponents were docked into the active binding cavity of the receptor enzyme. Acetyl cholinesterase enzyme (AChE) is mainly responsible for the hydrolysis of the neurotransmitter acetylcholine and is mainly used in the treatment of cognitive disorder.

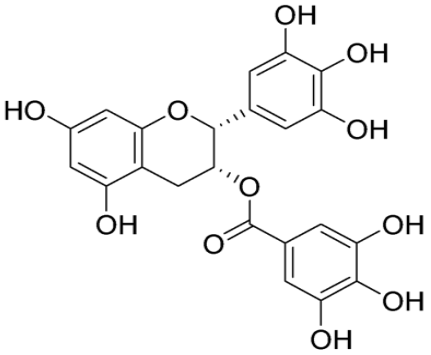
Co-crystal of Complex structure with donepezil and acetyl cholinesterase enzyme (AChE) (PDB ID: 4EY7) selected for in-silico molecular docking studies. In surrounding of crystal complex bound Grid points were generated with the active cavity of the target. This co-crystallized molecule is considered as a reference to assign the binding site for the ligand X-ray group. A flexible docking module was incorporated in Argus Lab 4.0.1 which is very powerful docking simulation software.

TABLE 1: INTERPRETATION OF PREDICTED MODE OF BINDING OF LIGANDS AFFINITY TOWARDS ACHE

S. NO.	COMPOUND NAME	AMINO ACID INTERACTION		DOCKING SCORE
		H-Bonding	Hydrophobic	
1.	BACOSIDES	NA	NA	NOT DOCKED
2.	CARNOSIC ACID	NA	NA	NOT DOCKED
3.	LUTEOLIN	TYR 124 PHE 338 PHE 337	TRP 286	-9.448 Kcal/mol
4.	EPIGALLOCATECHIN GALLATE	GLY 122 HIS 447 SER 203	TYR 341 PHE 297 PHE 338	-11.6264 Kcal/mol
5.	SITOINDOSIDES	NA	NA	NOT DOCKED

1.EPIGALLOCATECHIN GALLATE

Tri hydroxyl Phenyl produces H Bond with SER 203. 3' hydroxy of 3, 4-5 tri hydroxy benzoate produce Hydrogen bonding with HIS 447. 3, 4-5 tri hydroxy benzoate produce pi alkyl interact hydrophobic with TRP 236 & ALA 204. Chromen produce pi alkyl hydrophobic interaction with PHE 297 & 338, TYR 341. Carboxylate moiety produce H bonding interaction with GLY 122 &TYR 124.



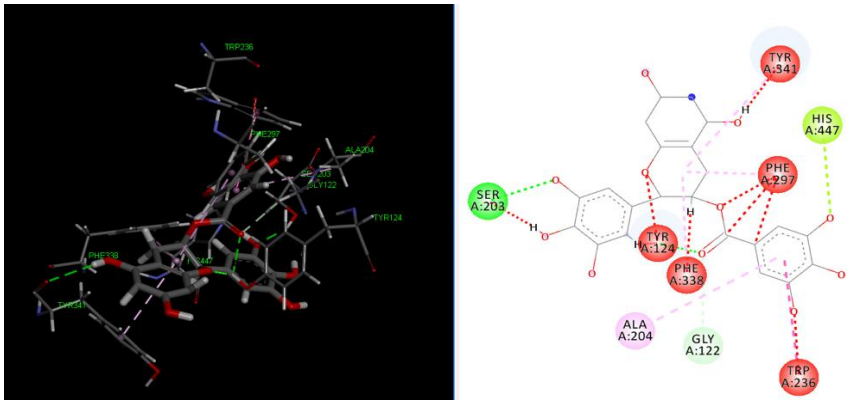
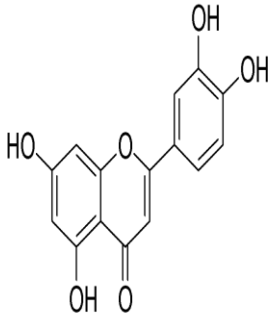


Figure I: 2D structure and best docked pose of Epigallocatechin Gallate-AchE interaction

2. **LUTEOLIN**

04 atom of Chromen produce H Bond interaction with TYR 124.Chromen 4 one produce H bond interaction with PHE 338 & TYR 337. 7 Hydroxy group produce H bond interaction with GLY 122 & GLY 121. 3 OH group produce H bonding with SER 293. Phenyl ring can produce Pi alkyl interaction with TRP 286 & PHE 297.



5,7-dihydroxy-2-(3,4-dihydroxyphenyl)-4*H*-chromen-4-one

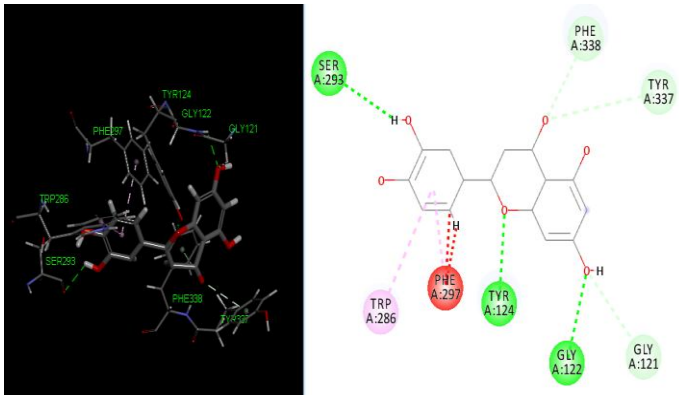


Figure II: 2D structure and best docked pose of Luteolin-AchE interaction

CONCLUSION

If person suffering from SARS-CoV-2 infection, Patient should take these natural drugs to avoid neurological complications. The patients can control this problem by physical exercises and meditation, to get enough sleep. The present study showed that, Epigallocatechin (Tea), Luteolin (Parsley, Thyme) have strong affinity to bind the brain acetylcholine receptor. Therefore, these Phyto drugs may be used as potential therapeutics to combat long COVID-19 associated brain fog.

REFERENCES

1. Xinhua. China's CDC detects a large number of new coronaviruses in the South China seafood market in Wuhan. Available at: https://www.xinhuanet.com/2020-01/27/c_1125504355.htm. Accessed 20 Feb 2020.
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506. doi: 10.1016/S0140-6736(20)30183-5. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

3. Richman DD, Whitley RJ, Hayden FG. Clinical Virology, 4th ed. Washington: ASM Press; 2016.
4. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020. 10.1056/NEJMoa2001316. [PMC free article] [PubMed]
5. World Health Organization. Situation reports. Available at:https://www.who.int/ emergencies/diseases/novel-coronavirus-2019/situation-reports/. Accessed 22 Feb 2020.
6. Chan-Yeung M, Xu RH. SARS: epidemiology. Respirology. 2003; 8:S9–14. doi: 10.1046/j.1440-1843.2003.00518.x. [PMCfreearticle] [PubMed] [CrossRef][Google Scholar]Middle East Respiratory Syndrome Coronavirus. Accessed 16 Feb 2020.
7. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. N Engl J Med. 2020. 10.1056/NEJMc2001737. [PMC free article] [PubMed]
8. Luo CH, Morris CP, Sachithanandham J, Amadi A, et al. (2021). Infection with the SARS-CoV-2 Delta Variant is Associated with Higher Infectious Virus Loads Compared to the Alpha Variant in both Unvaccinated and Vaccinated Individuals. medRxiv, doi: 10.1101/2021.08.15.21262077. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
9. Tao K, Tzou PL, Nouhin J, et al. (2021). The biological and clinical significance of emerging SARS-CoV-2 variants. Nat Rev Genet, 22(12): 757–773. [PMC free article] [PubMed] [Google Scholar]
10. Volz E, Mishra S, Chand M, et al. (2021). Assessing transmissibility of SARS-CoV-2 lineage B.1.1.7 in England. Nature, 593(7858): 266–269. [PubMed] [Google Scholar]
11. Choi JY, Smith DM. (2021). SARS-CoV-2 Variants of Concern. Yonsei Med J, 62(11): 961–968. [PMC free article] [PubMed] [Google Scholar]
12. Cascella M, Rajnik M, Aleem A, et al. (2022). Features, Evaluation, and Treatment of Coronavirus (COVID-19). StatPearls. Treasure Island (FL).P.:11–12 [PubMed] [Google Scholar]
13. Ramesh S, Govindarajulu M, Parise RS, et al. (2021). Emerging SARS-CoV-2 variants: A review of its mutations, its implications and vaccine efficacy. Vaccines (Basel), 9(10):1195. [PMC free article] [PubMed] [Google Scholar]
14. Cascella M, Rajnik M, Aleem A, et al. (2022). Features, Evaluation, and Treatment of Coronavirus (COVID-19). StatPearls. Treasure Island (FL).P.:11–12 [PubMed] [Google Scholar]
15. Ramesh S, Govindarajulu M, Parise RS, et al. (2021). Emerging SARS-CoV-2 variants: A review of its mutations, its implications and vaccine efficacy. Vaccines (Basel), 9(10):1195. [PMC free article] [PubMed] [Google Scholar]
16. Cao Y, Wang J, Jian F, et al. (2022). Omicron escapes the majority of existing SARS-CoV-2 neutralizing antibodies. Nature, 602(7898):657–663. [PMC free article] [PubMed] [Google Scholar]
17. Bhattacharyya RP, Hanage WP. (2022). Challenges in inferring intrinsic severity of the SARS-CoV-2 Omicron variant. N Engl J Med, 386(7):e14. [PubMed] [Google Scholar]
18. Abbasi J. (2021). Researchers tie severe immunosuppression to chronic COVID-19 and virus variants. JAMA, 325(20):2033–2035. [PubMed] [Google Scholar]
19. Nouraeinejad A. Differential diagnosis in optometry and ophthalmology. 2nd ed. Iran: Noruzi Publication; 2017
20. Nouraeinejad A. Neuro-Optometry, Neuro-optometrist, and neuro-optometric rehabilitative implications. J Mod Rehabil. 2018;12(2):77–84. [Google Scholar]
21. Krishnan K, Lin Y, Prewitt KM, et al. Multidisciplinary approach to brain fogand related persisting symptoms post COVID-19. J Health Serv Psychol. 2022;48(1)
22. Lindlau A, Widmann CN, Putensen C, et al. Predictors of hippocampal atrophy in criticallyill patients. EurNeurol. 2015;22(2):410–415.doi: 10.1111/ene.12443. [PubMed] [CrossRef] [Google Scholar]
23. Alonso-Lana S, Marquié M, Ruiz A, et al. Cognitive and neuropsychiatric manifestations of COVID-19 and effects on elderly individuals with dementia. Front Aging Neurosci. 2020;26(12):588872. doi: 10.3389/fnagi.2020.588872. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
24. Zhou H, Lu S, Chen J, et al. The landscape of cognitive function in recovered COVID-19patients. JPsychiatrRes. 2020; 129:98–102. doi: 10.1016/ j.jpsychires. 2020.06.022. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
25. Martynov MY, Bogolepova AN, Yasamanova AN. Endotelial'nayadisfunktsiyapri COVID-19 ikognitivnyenarusheniya [Endothelial dysfunction in COVID- 19 and cognitive impairment]. ZhNevrolPsikhiatrIm S SKorsakova. 2021;121(6):93–99. Russian. 10.17116/jnevro202112106193. [PubMed]
26. Bliddal S, Banasik K, Pedersen OB, et al. Acute and persistent symptoms in non-hospitalized PCR-confirmed COVID-19 patients. Sci Rep. 2021;11(1):13153. doi: 10.1038/s41598-021-92045-x. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
27. Moghimi N, Di Napoli M, Biller J, et al. The neurological manifestations of post-acute sequelae of SARS-CoV-2 infection. CurrNeurolNeurosci Rep. 2021;21(9):44. doi: 10.1007/s11910-021-01130-1. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
28. Almeria M, Cejudo JC, Sotoca J, et al. Cognitive profile following COVID-19 infection: clinical predictors leading to neuropsychological impairment. Brain BehavImmun Health. 2020; 9:100163. doi: 10.1016/j.bbih.2020.100163. [PMC free article] [PubMed] [CrossRef] [Google Scholar]