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Exploring Phytochemicals As Potential Inhibitors Targeting Sars-Cov-2

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ABSTRACT
SARS CoV 2 is part of a large group of viruses called coronaviruses. It is a positive-sense, single-stranded RNA virus with one linear RNA segment. Coronaviruses can infect humans, animals like cows and pigs (livestock), pets, and even birds. COVID-19, caused by SARS-CoV-2, has seriously affected more than 219 countries around the world. At present, there are no specific small-molecule drugs that directly fight this virus. Doctors have used different types of medicines to treat COVID-19. These include antibiotics, anti-inflammatory drugs, and antiviral drugs. However, the full effect of these drugs on the virus has not been fully tested. Sometimes, after treatment, the virus can change its genetic material. This can lead to the creation of new strains, making the disease even more dangerous and harder to control. There are also no approved synthetic drugs available to treat memory loss caused by long COVID, often called "brain fog." Because of this, researchers are looking at natural substances to help treat it. The way these natural plant-based compounds (called phytocomponents) work has been studied using a method called structure-based docking simulation. This helps predict how they might act in the body.
Keywords: *Corona Virus, SARS-COV-2, phytocomponents, Docking, Brain Fog.*

INTRODUCTION

In December 2019, elderly people in Wuhan, the capital of Hubei Province in China and a major transportation hub, began showing symptoms of severe pneumonia with an unknown cause. These cases were reported to nearby hospitals.

Initially, some of the first patients were linked to the Huanan Seafood Wholesale Market, which also sold live animals. After the previous SARS outbreak, monitoring systems had been set up in the area. Breath samples from patients were collected and sent to laboratories for further investigation. On December 31, 2019, China officially reported the outbreak to health authorities. As a precaution, the Huanan Seafood Market was shut down on January 1, 2020. By January 7, scientists had identified the virus as a new type of coronavirus. It shared more than 95% similarity with known coronaviruses and over 70% similarity with the original SARS-CoV virus. Environmental samples collected from the seafood market also tested positive for the virus, suggesting that the outbreak may have started there.

Soon after, more cases were reported in the region. Some of these were not related to animal markets, indicating that the virus was spreading from person to person.

The first death from the virus was reported on January 11, 2020. Over the next few weeks, the outbreak spread rapidly, fuelled by China's large population. Cases began to appear in other countries, including Thailand, Japan, and South Korea, among travellers returning from Wuhan [1].

On January 20, 2020, healthcare workers were reported to have been infected while caring for patients, further confirming human-to-human transmission. By January 23, Wuhan, a city of 11 million people, was placed under lockdown. Travel in and out of the city was restricted. Soon after, similar lockdowns were extended to other cities in Hubei Province. Cases of COVID-19 also began appearing in people with no travel history to China. This showed that local transmission was happening in other countries as well. Airports in several nations, including India, introduced screening measures to detect and isolate travellers from China. Around 444,400 travellers were screened. It was soon discovered that the virus could spread even from people who showed no symptoms. This led countries like India to evacuate their citizens from Wuhan using special flights. Those returning were quarantined for 14 days and tested for the virus. As cases continued to grow, studies showed a clear pattern of a fast-spreading epidemic. On February 12, 2020, China changed its definition of a "confirmed case." It now included patients diagnosed through medical imaging and symptoms, even if lab results were not yet available. This caused a sharp increase in reported cases—around 15,000 new cases were added in a single day [2]. By May 3, 2020, there were over 96,000 confirmed cases across 87 countries, with 14,444 international transmissions reported. Meanwhile, countries like South Korea, Iran, and Italy experienced a rapid rise in cases. Among those infected, about 20% developed severe symptoms. Around 25% recovered quickly without major illness. However, more than 310 people had died by that time.

SARS-COV-2

SARS-CoV-2 is the virus responsible for the severe and life-threatening illness known as COVID-19. It was first detected in Wuhan, China, in November 2019. The World Health Organization (WHO) officially reported the first case on December 31, 2019.

On March 11, 2020, the WHO declared COVID-19 a global pandemic. By May 30, 2020, the virus had spread worldwide. At that time, there were 5,899,866 confirmed cases and 364,891 recorded deaths. SARS-CoV-2 mainly affects the lungs. It enters the human body by binding to the ACE2 receptor found on certain cells. Common symptoms of COVID-19 include fever, shortness of breath, fatigue, and cough. Some people also experience less common symptoms, such as the loss of smell and taste. Around 20% of infected people become seriously ill and need hospital care. Of those, about one-third require treatment in intensive care units (ICU). The treatment for COVID-19 is mostly supportive. However, patients who need ventilators often face more difficult and frustrating challenges [3].

Researchers are still conducting trials to find effective vaccines and anti-inflammatory medications. The main goal of prevention strategies is to stop the spread of the virus. This includes measures like avoiding close contact, frequent hand washing, wearing masks, and applying effective infection control practices. SARS-CoV-2 is classified as a beta coronavirus [4]. It shares 79% of its genetic structure with other known beta coronaviruses. The genome has six open reading frames (ORFs), which are arranged in the following order from 5' to 3': replicase, spike, envelope, membrane, and nucleocapsid's addition to these, SARS-CoV-2 also encodes seven possible (putative) ORFs [5].

According to recent updates from the World Health Organization, five variants of concern (VOCs) of SARS-CoV-2 have been identified since the start of the pandemic [6-7].

- **Alpha (B.1.1.7):** 1st variant of concern in United Kingdom (UK) in late Dec 2020[8].
- **Beta (B.1.351):** 1st release in South Africa in Dec 2020[9].
- **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.

Alpha Variant (B.1.1.7 -The SARS-CoV-2 Alpha variant is one of the earliest known mutant strains of the original SARS-CoV-2 virus. This variant was first identified in the United Kingdom in September 2020 [10]. The Alpha variant showed several important genetic changes. One of the key changes was in the receptor-binding domain (RBD), including the N501Y mutation. It also had the P681H mutation. Additionally, there were deletions at positions 69-70 and at position 144 in the N-terminal domain (NTD). Several other mutations were also found in this variant. These genetic variations made the Alpha variant more transmissible compared to the original strain. [11-12].

Beta Variant (B.1.351)- The Beta variant of SARS-CoV-2 was first identified in May 2020 in South Africa. As of July 2021, it had been officially recognized as a variant of concern.

The Beta variant contains several significant mutations, especially in the spike protein. It has a total of nine mutations in the spike region. Among these, three key mutations—N501Y, E484K, and K417N—are

located in the receptor-binding domain (RBD). In addition, there are deletions in the N-terminal domain (NTD) at specific positions. These mutations may affect how the virus binds to human cells and could impact immune response. [13].

Gamma Variation (P.1) - The gamma version changed into first observed in Brazil in January 2021 [14]. Through inheritable analysis of numerous traces from human being with the disorder, it changed into set up that the Gamma version registered greater than 22 mutations, of which about 12 were on the protein. [15].

Delta Variation (B.1.617.2) - The Delta variant was first spotted in India in 2020.There are 23 mutations in the delta mutation, the main mutation includes: spike protein E484Q and L452R RBD mutations and P681R cleavage site mutations. Examination of this variant revealed several mutations in ORF3, ORF7 [16]. Symptoms in patients with delta disease include: fever, headache, and shortness of breath, cough, vomiting, and anosmia, sore throat, loss of smell, fatigue [17].

Omicron (B.1.1.529) - This change was first seen in November 2021. Omicron is called a "variant of concern" because it caused some worries. People have different opinions about why this variant is different [18]. The first case of this variant was found in Botswana and South Africa. Some believe that people with this variant might live longer because of how the disease works [19-20]. Long COVID-19 can cause memory loss, brain damage, and swelling in the brain. This is known as "brain fog." It is a very serious and hard condition to treat [21-24].

ORIGINAL RESEARCH

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, 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. Endothelial dysfunction leading to micro vascular damage has also been suggested. However, cognitive problems also occur in patients with mild COVID-19. In this case, other mechanism has been proposed, including immunosuppression, chronic pain, or dysfunction in the body. Other studies have linked cognitive problems with depression &anxiety.

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.

There are no allopathy 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

In this study, six phytochemicals were selected: Asiatic acid, Ginsenosides, Carnosic acid, Quercetin, Curcumin, and Resveratrol (as shown in Table I). Their 2D chemical structures were drawn using ChemDraw 8.0 software. These 2D structures were then converted into 3D models and optimized using the MM2 force field.

Energy minimization of the molecules was carried out using a convergence criterion of 0.01 kcal/mol and a dielectric constant of 1.0 in the Chem3D Ultra software. After optimization, the 3D structures were used for further molecular docking analysis.

2. Molecular Docking

Molecular docking is a computer-based method used to study how a ligand (a small molecule) interacts with a receptor (usually a protein). It helps identify the active binding sites on the target protein and finds the most stable shape of the ligand-receptor complex. The goal is to achieve the lowest possible interaction energy, which is also shown as a docking score. This method also helps to find the key amino acids in the protein that interact with the ligand and may lead to biological effects. In this study, only 4 out of the 6 compounds were successfully docked into the active site of the target protein.

RESULTS AND DISCUSSION

In this study, six optimized plant-based compounds were docked into the active site of the acetylcholinesterase enzyme (AChE), which acts as a receptor enzyme. AChE is mainly responsible for breaking down the neurotransmitter acetylcholine and is commonly used in treatments for cognitive disorders.

The co-crystal structure of AChE with donepezil (PDB ID: 4EY7) was used for in-silico molecular docking studies. Grid points were created around the active site of this crystal structure to define the docking area. The co-crystallized molecule (Donepezil) was used as a reference to identify the binding site for other ligands. A flexible docking tool in Biovia Discovery Studio, powerful molecular simulation software, was used for these docking studies.

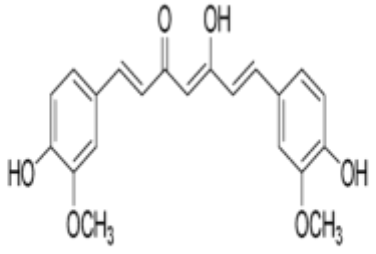
TABLE 1: INTERPRETATION OF PREDICTED MODE OF BINDING OF LIGANDS AFFINITY TOWARDS ACHE

S. NO.	COMPOUND NAME	AMINO ACID INTERACTION		DOCKING SCORE
		H-Bonding	Hydrophobic	
1.	QUERCETIN	PHE 295 GLY 121 GLY 122 SER 203	PHE 297 PHE 338	-10.6059 Kcal/mol
2.	CURCUMIN	GLY 121 SER 203	TYR 337 HIS 447 TRP 86	-12.1409 Kcal/mol
3.	ASIATIC ACID	NA	NA	NOT DOCKED
4.	GINSENOSIDES	NA	NA	NOT DOCKED
5.	RESVERATROL	HIS 980	TYR 870 PHE 871	-12.4294 Kcal/mol
6.	PIPERINE	TYR 337 TYR 341 SER 293 ARG 293	PHE 338 TYR 337 TRP 286	-11.3398 Kcal/mol

INTERPRETATION OF PREDICTED MODE OF BINDING OF LIGANDS AFFINITY TOWARDS ACHE

CURCUMIN

(1E, 6E) -1, 7-bis (4 hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione curcumin, also known as diferuloylmethane.



(1E,4Z,6E)-5-hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,4,6-trien-3-one

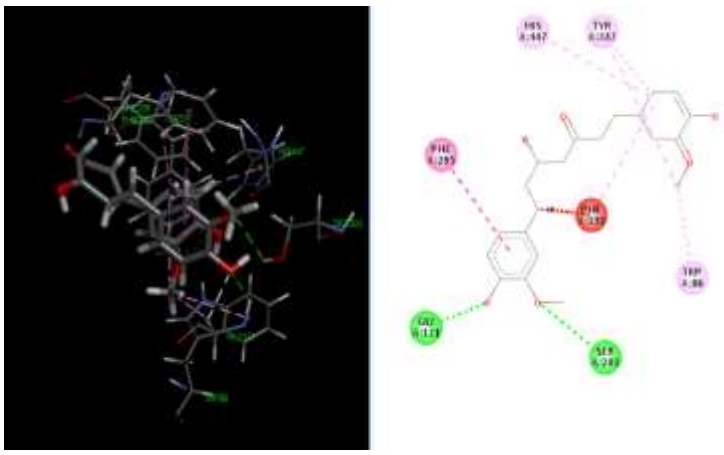
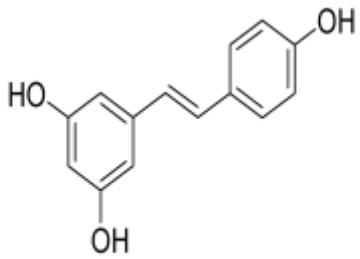


Figure I: 2D structure and best docked pose of Curcumin-AchE interaction

RESVERATROL

4 Hydroxy produce H Bond with HIS 980. Benzene associated to sterile moiety produced pi alkyl interaction with PHE 871 & TYR 870.



5-(4-hydroxystyryl)benzene-1,3-diol

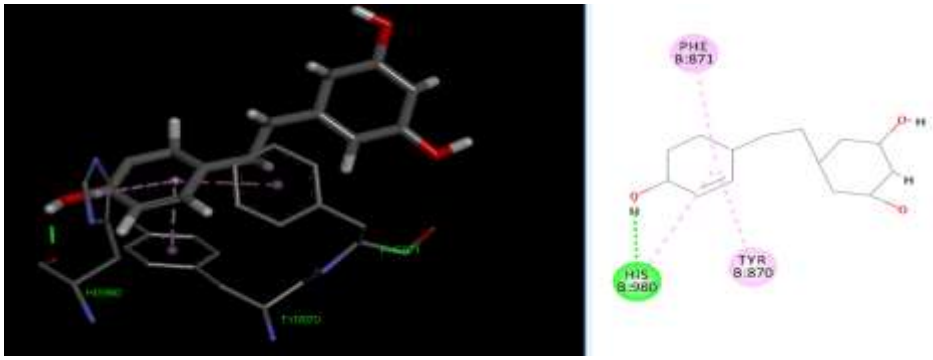
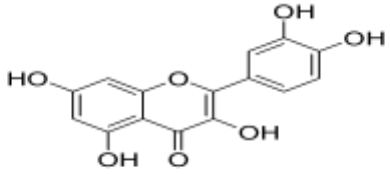


Figure II: 2D structure and best docked pose of Resveratrol-AchE interaction

1. QUERCETIN

Chromen interaction with GLY 122 & 121, SER 203& 202. 3-4 Dihydroxy interaction with TYR.



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

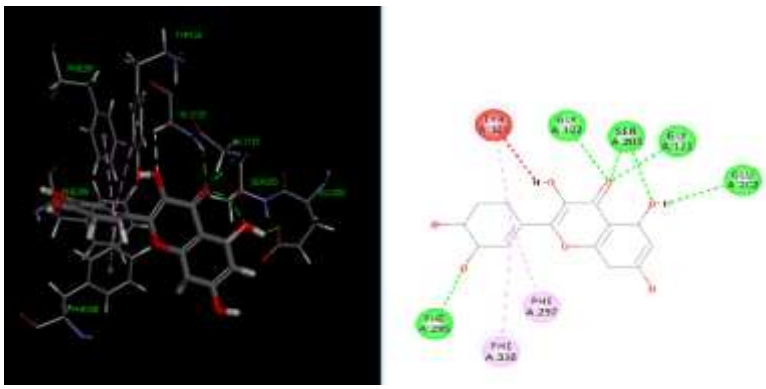
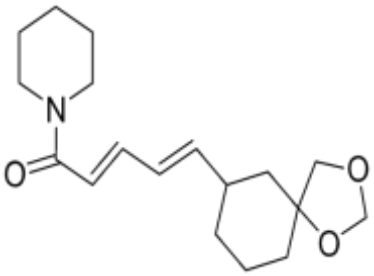


Figure III: 2D structure and best docked pose of Quercetin-AchE interaction

4. **PIPERINE**

Benzene ring of 5- (1, 3 benzodioxol) ring produce hydrophobic interaction with PHE 338 and TYR 337. C-4 dioxol produce H Bonding with TYR 337. Piperidine ring produce hydrophobic interaction with TRP 286 and Hat position of piperidine produce H Bonding with TYR 341 and SER 293. Carbonyl group at 1 position of Penta 2, 4 dienes produce H bonding with ARG 296.



(2E,4E)-5-(1,3-benzodioxol-5-yl)-1-piperidin-1-ylpenta-2,4-dien-1-one

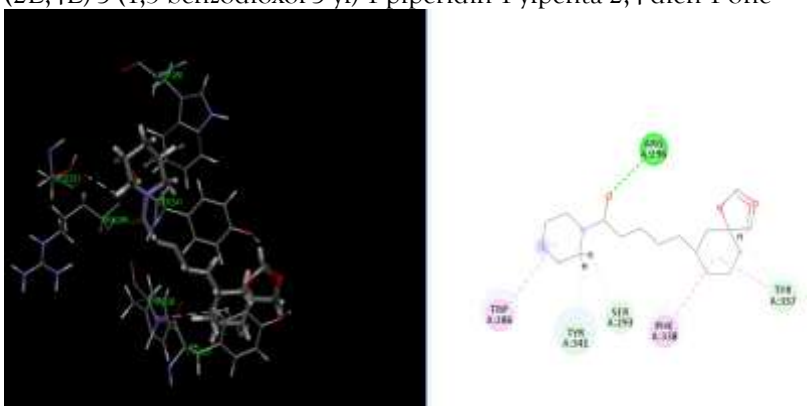


Figure IV: 2D structure and best docked pose of Piperine-AchE interaction

CONCLUSION

If a person is infected with SARS-CoV-2, they should consider using natural remedies to help prevent neurological problems. Patients can also manage this issue by doing physical exercise, practicing meditation, and getting enough sleep. This study found that curcumin (from turmeric), resveratrol (found in berries), quercetin (from onions and lettuce), and piperine (from black pepper) can strongly bind to brain acetylcholine receptors. Because of this, these plant-based compounds might be useful as treatments to fight brain fog caused by long COVID-19.

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