Identification of Natural Compounds for Long COVID Based on Hub Gene Biomarkers and Repurposed Drugs

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Keywords: Long COVID; Symptoms; Natural Compounds; Hub Genes; Therapeutic Drug

Article

Identification of Natural Compounds for Long Covid Based on Hub Gene Biomarkers and Repurposed Drugs

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Abstract: Long COVID is a phenomenon in which individuals experience persistent symptoms after recovering from COVID-19. The symptoms are discovered to be unique for every individual and can affect multiple organs systems in the body. This study aimsto identify effective natural remedies for long COVID by analyzing hub genes associated with the symptoms of the condition and evaluating the repurposed drugs catered and used for treating the symptoms of long COVID. The most common and prevalent symptomsof long COVID were identified; Fatigue, Shortness of Breath, Loss of Smell, Headache, Brain Fog, Chest Pain, Insomnia, Heart Palpitations, Dizziness, Joint Pain, Depression, Anxiety, Tinnitus, Loss of Appetite. Hub genes for each of the symptoms provided an insight on the key biological pathways of the symptom. Repurposed drugs identified, provided the template to identify the natural compounds with similar structure as apotential therapeutic drug. The natural compounds were retrieved using fingerprint searchof the repurposed drugs from the NPASS Database. The findings of this study suggest several natural remedies for each symptom based on the molecular docking of the hub gene and natural compound using iGEMDOCK. The identified natural remedies may holdpromise in treating long COVID, but further research is required to explore the efficacy and effectiveness of the proposed natural compounds. The results of the study pose important implications for the development of effective treatments for long COVID.

Keywords: long covid; natural compounds; hub genes; therapeutic drug

Introduction

The Coronavirus disease 2019, which made its first appearance in 2019, is still active and spreading in many forms throughout the world. This disease has caused a greatimpact on the lives of humans as millions of people have fallen to the virus. Contrary to the previous years, the fight against this disease has decreased as COVID cases are being thought of and treated similar to common flu cases. This is plausible due to the improvements and advancement in treatment and prevention of COVID-19. The Severe Acute Respiratory Syndrome Coronavirus 2 (SAR-CoV-2) virus not only causes COVID-19 by infecting individuals but has found another way to instigate problems to people. This new problem goes by many names but is commonly referred to as "Long COVID" (Raveendran et al., 2021).

In the early days (2020), several clinical studies have identified that some symptoms of COVID-19 were found to remain in patients despite their recovery from the disease. This condition was initially referred as long COVID, post-acute sequelae of COVID (PASC), or post-acute COVID-19 syndrome (PACS) as it describes the persistence of the prolonged symptoms that presents after the acute SARS-CoV-2 infection (Deer et al., 2021). PCR tests conducted for the illness results negative, indicating that the syndrome is the delay between the microbial recovery and clinical recovery from the acute infection phase (Garg et al., 2021). The term "Long COVID" wasgenerally accepted to describe the illness where long COVID is defined as the wide rangeof symptoms that persists for over weeks and months experienced by COVID-19 survivors.

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Many reviews have documented the wide spectrum of persistent symptoms experienced by the patients (Akbarialiabad et al., 2021, Davis et al., 2023, Lopez-Leon et al., 2021, Crook et al., 2021). The common symptoms diagnosed under long COVID include fatigue, shortness of breath, heart palpitations, headache, joint pain, insomnia,loss of smell, chest pain and more (Sudre et al., 2021). The manifestation of the symptoms has been identified to be correlated to not a singular organ system but to

multiple organ systems, primarily the respiratory, neurological, cardiovascular and musculoskeletal systems. Classification of the condition poses a great challenge due to the wide range of symptoms and the symptom pattern that varies from individuals. Hence,two distinct categories were established for the symptoms: Post-acute COVID, where symptoms persist from more than three weeks but less than twelve weeks, and Chronic COVID, where the symptoms persist more than twelve weeks (Raveendran et al., 2021).

Treatment for long COVID remains undefined as no singular validated treatment strategy or drugs is available, providing coverage for all symptoms. Different types of symptoms are connected to different types of biological pathways (Davis et al., 2023). Thus, each treatment strategy for each symptom would be unique. A multidisciplinary approach involving assessment, symptomatic treatments, underlying problem treatment, physical therapy, occupational therapy, and psychological support is required to identify asuitable treatment plan for long COVID patients. Various synthetic drugs and repurposed drugs are being tested in clinical settings and are proposed as treatment for long COVID.

Similarly, natural products or compounds as natural remedies for long COVID is afield of research that could provide promising therapeutic drugs. Multiple studies have shown the use of natural remedies for COVID-19 such as herbal remedies and vitamin supplements. But there is limited research on the effectiveness of natural remedies for long COVID symptoms. Therefore, the study aims to explore the potential ability of the natural products and compounds as natural remedies designed for long COVID symptoms.

Methodology

The Identification of natural remedies for long COVID based on hub gene biomarkers and repurposed drugs involved various bioinformatics tools and databases; PubChem, NCBI, NPASS, Open Babel, AlphaFold database, UniProt, iGEMDOCK. The overall flow of the methodology is simplified and represented in a flowchart in Figure 1.1.

FIGURES

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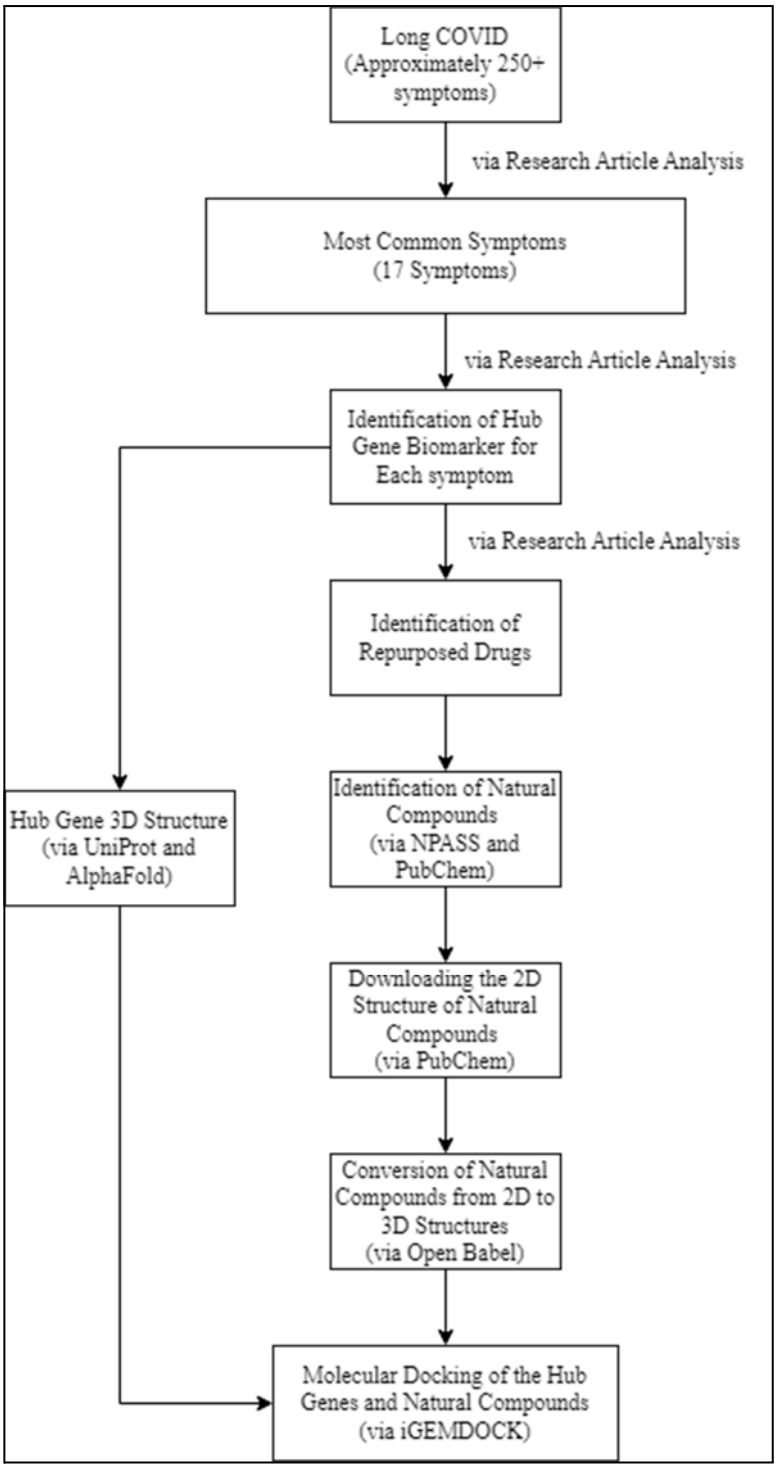

Figure 3.1. The overall workflow of the identification of natural remedies for the 17 common long COVID symptoms using the hub gene biomarkers and repurposed drugs.

Data Retrieval

The common symptoms of Long COVID were obtained based on publications thatreported for long COVID symptoms- systematic reviews, meta-analyses, and case study publications retrieved from public databases such as PubMed, LitCovid database and more. Over 250 symptoms were reported in journals and databases in relation to long COVID. However, only the most common and frequently appearing symptoms were subjected to the study.

A total of 17 symptoms were determined to be the most recurring symptoms experienced by patients in the case studies and review articles. Fatigue, shortness of breath, loss of smell, muscle

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pain, headache, brain fog, chest pain, difficulty sleeping, heart palpitations, dizziness, joint pain, depression, anxiety, tinnitus, diarrhea, loss of appetite and skin rash are the 17 identified symptoms. The hub gene list and FDA-approved drugs (for each hub gene) was created for each symptom, containing the top hub genes associated with each gene. Hub genes for each symptom serves as a biomarker that is thought to play a critical role in the regulation of the various biological processes of the symptom. Drugs targeting the hub genes affect the biological pathwaysof the gene, used in treating specific diseases and conditions. The hub genes that are associated with the 17 symptoms and the repurposed drugs for the hub genes wereobtained from a study conducted by Sanisha Das on long COVID G Protein-Coupled Receptors (Das & Kumar, 2022).

Identification of Natural Compounds

The presence of natural remedies for long COVID was to be determined byanalyzing the FDA approved repurposed drugs. This approach was utilized as over 50% of drugs that have been approved are either derived from natural products or are natural products themselves (Atanasov et al., 2021). Therefore, by using the Natural Product Activity and Species Source Database (NPASS), the natural compounds or their derivatives can be found from the repurposed drugs. For each symptom, there are a total of 10 hub genes and each gene has its respective FDA-approved repurposed drug. The FDA-approved drugs for each gene were taken individually and searched in the PubChemdatabase to identify their canonical SMILES, which were used to identify the natural compounds using the NPASS database. The natural compounds were retrieved using fingerprint search of the repurposed drugs from the NPASS database. The queries were searched by structure and the fingerprint type was set as PubChem-881 fp and with a threshold of >=0.80. These settings were used to at least identify one natural compound from the FDA drug. For the results with more than 10 compounds, the top 10 natural compounds that were identified will be taken into consideration. Hub genes and drugs that result in no natural compounds or natural products will be redundant. The remainder of natural compounds will advance to the next stage.

Hub Genes Data Collection (3D Structure)

The 3D structure of the hub gene (protein) provides an insight to their functions inmultiple biological pathways. Thus, the UniProt database was used to retrieve and download the 3D structure of the filtered list of hub genes based on the presence ofnatural compounds. Each hub gene was searched in the database individually and the following filters were applied in the search query; Organism: Homo sapiens and Status: Reviewed (Swiss-Prot). The AlphaFold structure was downloaded to obtain the 3D structure of the hub genes. As not all AlphaFold 3D structures are available, for hubgenes that do not have the AlphaFold structure, the SMR structure was obtained.

2. D Structure of Natural Compounds

The resulting prioritized natural compounds obtained from the structure of the FDA-approved drugs were recorded from the NPASS database and further studied its structure. The PubChem database, a public database containing information on millionsof chemical compounds, was utilized to extract the 2D structures of each natural compound. The secondary structures of each natural compound were downloaded in the SDF (Structure Data File) format from the PubChem database which would allow the analysis of the molecular structure of each compound in detail and to determine its properties.

Conversion of 2D structures to 3D structures (Natural Compounds)

The 3D structure of the natural compounds provides information on the physicochemical properties of the compound, such as solubility and toxicity, and tounderstand the interaction of the compound with target proteins. The 2D structures of the natural compounds were converted from a 2D SDF file format to 3D PDB, Mol or Mol2 formats. The OpenBabel cheminformatics online conversion tool

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(http://www.cheminfo.org/Chemistry/Cheminformatics/FormatConverter/index.html) was utilized for this process. The conversion process used the SDF file and some utilized the canonical SMILES for the 2D structures of the natural compounds to produce the 3D structures in either one of the applicable 3D structure formats; PDB, Mol and Mol2. The settings used in the conversion tools were set to convert the 2D structure into 3D structureand the rest were set to default.

Molecular Docking of the Hub Genes and Natural Compounds

Molecular docking is an in-silico structure-based method well established in the field of drug discovery (Pinzi & Rastelli, 2019). The molecular docking process utilized the iGEMDOCK docking tool to identify the binding affinity of each of the hub genes with their respective natural compounds. This tool is a Generic Evolutionary Method for molecular DOCKing. Thus, GEMDOCK. It is a software program that is commonly used for computing and analyzing the ligand conformation and orientation relative to the activesite of a particular target protein. The tool was downloaded from the official iGEMDOCKwebpage (http://gemdock.life.nctu.edu.tw/dock/igemdock.php). The hub genes were uploaded into the tool as the binding site and all the natural compounds for a specific gene were uploaded at the same time under compounds. Multiple compounds weredocked against a single binding site at the same time. The results produced were saved ina text file format where the binding energy, VDW, Hbond and Elec are recorded. The natural compounds were then analyzed to identify the best natural compound to be used as a therapeutic natural remedy/drug for symptoms of long COVID based on the bindingaffinity of the complexes.

Results

All the seventeen symptoms with ten hub genes and their corresponding FDA approved drug were analyzed and fourteen among the seventeen symptoms presented with at least one natural compound. The remaining three symptoms, muscle pain, diarrheaand skin rash symptoms resulted in no natural compounds. This was because of either the absence of canonical SMILES of the FDA approved drugs or the lack of identical or similar structured natural compounds for the particular drug.

For each symptom, the repurposed drugs for the different hub genes had provided a series of natural compounds but among the ten hub genes, not all genes resulted with a natural compound. Fatigue presented with four hub genes; NF1, SMAD4, RET andERBB4 genes. Shortness of breath symptoms resulted in three genes; CHRNE, CHRND and CHRNB1 genes. Loss of smell with two genes, GNRH1 and TAC3. Headaches presented with five genes where some of the genes were of those from fatigue; ESR1, NF1, SMAD4, RET and TERT. Brain fog includes KCNT1, GABRA1 and CACNA1B genes. Chest pain resulted in NF1, SMAD4 and RET genes, which are frequently seen amongst different symptoms. Insomnia was found with four genes; NR1H4, ABCB4, ABCB11 and SLC12A3. Heart palpitations showed two genes called SCN5A and GATA4. Dizziness shares the SCN5A with heart palpitation as well as CACNA1G, RYR2, SCN1A, NF1 and RET genes. Joint pain resulted in CR2 and FAS genes. Depression and anxiety presented with the same gene, CDH23. Tinnitus with NF1, RET genes again and TERT and CACNA1D genes. Finally, loss of appetite (anorexia) resultedwith SMAD4, MEN1 and PALB2 genes.

Among all genes, NF1, RET and SMAD4 were found to be associated with more than two symptoms. This shows that they contribute and play a major role in the biological pathway related to multiple symptoms of long COVID

Molecular docking conducted between the hub gene and natural compound provided the binding energy between the compounds. The binding energy of the complexes were tabulated, based on the symptoms, from the complex with the highest negative binding energy to the lowest (Supplementary Tables 1.2 to 1.13). The natural compound with the highest negative binding energy resulted with greater binding affinity towards the hub gene and as a promising therapeutic agent for the symptom.

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Discussion

The study identified a total of 250 hub gene-natural compound complexes fromthe molecular docking process which shows the potential therapeutic candidates for the seventeen long COVID symptoms. However, only the top binding energy complexes are to be selected as potential candidates due to the difference in the binding affinity and interaction between the complexes. Thus, only a certain number of complexes for each symptom were studied and found to provide promising data.

Fatigue is the feeling of exhaustion and weakness causing a reduction in the ability to perform physical and mental activities. It is found in over 64% of long COVID patients and is associated with the neuro and cardiovascular systems (Joli et al., 2022, Castanares-Zapatero et al., 2022). The mechanism of fatigue caused by long COVID remains unknown but is speculated to be due to the inflammation in the associated organ systems. NF1, SMAD4, RET and ERBB4 were the hub gene biomarkers linked to fatigue. Among the four genes and the identified natural compounds, three complexes with the highest binding affinity showed favorable results (Table 1.1): RET-NPC56271 (-94.65), ERBB4-NPC56271 (-94.29) and NF1-NPC117032 (-83.94). The natural compound Gefitinib (NPC56271), was found to interact with both RET and ERBB4 genes whereas Dehydroevidiamine (NPC117032) is the natural compound for the NF1 gene. The docking results have provided significant evidence that Gefitinib and Dehydroevidiamine can be used as a drug for their respective genes to reduce the significance of the neurologic symptom, fatigue.

Dyspnoea or shortness of breath is a distress symptom that induces breathing discomforts and is usually associated with lung disease, neurodegenerative diseases and chronic heart failure (Hentsch et al., 2021). The damage the SARS-CoV-2 virus causes to the respiratory system results in inflammation, scarring of lung tissues and damaged blood vessels leading to dyspnoea that is prolonged from six months to a year (Vijayakumar et al., 2022). The genes from the nicotinic acetylcholine receptor (nAChR) gene family, CHRNE, CHRND and CHRNB1, are the hub genes that play roles in the muscular and nerve cell signaling pathways. A total of five hub gene-natural compound complexes were determined for this symptom (Table 1.2). CHRNE-NPC108434(-106.33), CHRNB1-NPC10908 (-104.70), CHNRD-NPC11296 (-103.00), CHRNB1-NPC115284 (-102.98) and CHNRD-NPC10871 (-101.86), where

Lindoldhamine (NPC108434), Isotetrandrine (NPC10908), Daphnandrine (NPC11296), Fanchinin (NPC115284) and Tetrandrine (NPC10871) are the natural compounds. All five compounds are alkaloids, specifically, bisbenzylisoquinoline alkaloids, which are anti-cancer agents that possess anti-inflammatory, antiplasmodial and antiviral properties (Atanasov et al., 2015). The anti-inflammatory property of these compounds makes it an excellent candidate and natural remedy for shortness of breath.

Loss of smell is also known as anosmia and is a symptom that is experienced by 40% of long COVID patients. It is a symptom that is not harmful to the body but is found to negatively affect the quality of life. Anosmia is considered as a neurological symptom where the dysfunction in the olfactory system in the form of inflammation caused by SARS-CoV-2 virus results in prolonged loss of smell (Davis et al., 2023, Castanares-Zapatero et al., 2022, Park et al., 2022). The TAC3 and GRNH1 genes were the hub gene biomarkers for anosmia but have shown no evidence of association with the olfactory system. Regardless, the study had identified the genes as components involved in the biological pathway of the symptom. Hence, molecular docking was conducted and resulted in two main complexes from the GNRH1 gene (Table 1.3); GNRH1-NPC69843 (Tunicyclin D) with -105.95 binding energy and GNRH1-NPC322594 (Deoxyuridine triphosphate) with -100.52 binding energy. Similar to the hub gene, the natural compounds showed no relationship towards the symptom. Thus, our study hypothesized an unknown property in the genes and natural compounds that enables it to be a potential natural remedy for anosmia.

With a prevalence of 13 to 74% and persists for over more than three months, headache is determined as one of the common long COVID symptoms (Membrilla et al., 2021). It is theorized that the damages as a result of the acute infection in different organssystems to be the underlying

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mechanism of the occurrence of headaches (Tana et al., 2022). The potential natural remedies for headaches revolve around the natural compounds associated with the five hub genes; ESR1, RET, SMAD4, NF1 and TERT. However, the top identified hub gene-natural compound complex involves only the TERT, ESR1 and RET genes. TERT-NPC230098 (unidentified gene based from PubChem and ChEMBL), ESR1-NPC136948 (Norselic Acid D) and RET-NPC56271 (Gefitinib) are the top 3 complexes with -97.62, -96.97 and -94.65 binding energy respectively (Table 1.4). As an unidentified compound, the TERT gene complex's properties remained a mystery whereas Norselic Acid D presented with antimicrobial activity that is not fully understood in relation to the cause of headache (Sheung et al., 2009). Gefitinib, on the other hand, revealed its ability to relieve headaches in erlotinib-induced liver injury (Nakatomi et al., 2011). This mechanism of the Gefitinib compound may provide an insight to combat the headache caused by long COVID.

Brain fog is a cognitive impairment that causes mental confusion, forgetfulness, concentration difficulties, intellectual functions and short-term memory loss. It was identified with a prevalence of 31 to 69% in long COVID patients (Nouraeinejad, 2022). Dysfunction in the brain is proposed to be the mechanism behind the symptom. The hub gene biomarkers (KCNT1, GABRA1 and CACNA1B) for the symptoms are intertwined with the neurological pathways that may provide an understanding of brain fog. But the potential natural remedy and therapeutic drug resulted from the CACNA1B gene (Table 1.5): CACNA1B-NPC198254 (-119.29) and CACNA1B-NPC473404 (-115-68). The

NPC198254 is also referred to as Micropeptin B and NPC473404 as Anabaenopeptin F. Both natural compounds were derived from a form of cyanobacteria that is effective in reducing neuroinflammation (Kirk et al., 2021), providing probable cause to conduct further studies on the association of the natural compounds and brain fog in long COVID patients.

Chest pain, a form of cardiac anomaly, is experienced by 58% of long COVID patients and is related to the respiratory and cardiovascular systems (Roca-Fernandez et al., 2022). The inflammation by the virus in the myocardium and the inflammation by the immune response in the lungs are suspected to be the causes of chest pain. The SMAD4, NF1 and RET gene, also known as the commonly recurring gene in multiple symptoms, are found to be linked to the biological pathways of chest pain. Similar to the results from fatigue, the natural compounds, Gefitinib and Dehydroevidiamine were identified aspotential remedies as the NF1 and RET gene complex (RET-NPC56271 (-94.65) and NF1-NPC117032 (-83.94)) posed to have higher binding energy compared to the SMAD4gene complex (Table 1.6). Gefitinib, with its anti-inflammatory effects, is able to provide relief to chest pain symptoms present in non-small cell lung cancer and is assumed to playa role in improving cardiac conditions and symptoms (Natale, 2004). Dehydroevidiamine is speculated to have anti-inflammatory properties (Amaravathi et al., 2021) as well, providing evidence to study the compound to identify its properties and as a potential natural remedy.

Stress caused by the COVID-19 pandemic is one of the factors impacting thesleep cycle of an individual leading to insomnia, a sleep disorder. Environmental stressors and persistent inflammatory responses have been associated with insomnia in long COVID patients. The dysregulation of neurotransmitters in the brainstem caused by the virus is responsible for the human body sleep cycle (Yong, 2021). This leads to a broad range of neurological disorders including insomnia. Interestingly, the four hub genes for insomnia have been found to be primarily associated with the renal system/pathways. However, the implications of the renal system towards insomnia enables us to hypothesize the hub genes, ABCB4, ABCB11, NR1H4 and SLC12A3 to affect the renal system in a manner which causes insomnia to long COVID patients. A singular natural compound interrelated with two hub genes was identified as the potential natural remedy/therapeutic drug (Table 1.7). ABCB11-NPC100366 (-107.98) and NR1H4-NPC100366 (-97.79) are the two complexes associated with the same natural compound, Ethyl(4R,20S,24R)-Epoxy-4,25,28-Trihydroxy-3,4-Secodammar-3-Oate. Isolated from the stem bark of the *dysoxylum binecteriferum*, the natural compound is assumed to possess cytotoxic and anti-inflammatory activity (Huijiao et al., 2014). The link between the natural compound and the hub gene and the symptoms is lacking. Thus, additional

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studies are required to understand the implications of the hub genes and the natural remedies proposed for long COVID insomnia.

Heart palpitation is the fluttering and pounding feelings in the chest that is caused by an irregular heartbeat. It not only is associated with the neuro-cardiovascular system and is found in 20% of long COVID patients (DePace & DePace, 2022). Myocardial injuries and inflammations (due to autonomic dysfunctions) result in the persistent cardiac symptoms including an abnormal heartbeat. The SCN5A gene and GATA4 genes were found to be linked to the heart and have a main role in the biological pathwayrelated to heart palpitations. The top two hub gene-natural compound complexes from molecular docking with more than -100 energy were identified to have high binding energies towards the gene (Table 1.8). Both complexes are from the GATA4 gene; GATA4-NPC101636 (Apigenin 7-O-Alpha-L-3-O-Acetyl Rhamnopyranosyl-(1->6)-Beta-D-Glucopyranoside) and GATA4-NPC100818 (Asphodelin A-4'-O-beta-glucoside). No link was identified for the

Apigenin 7-O-Alpha-L-3-O-Acetyl Rhamnopyranosyl-(1->6)-Beta-D-Glucopyranoside compound in relation to the GATA4 gene and heart palpitations. However, asphodelin A-4'-O-beta-glucoside expresses moderate antimicrobial activity against certain species ofbacteria and fungi (El-Seedi, 2007). This allows the speculation of the potential of the natural compound to reduce and provide relief for the inflammation of the heart caused bySARS-CoV-2 virus.

Dizziness is one of the common long COVID symptoms that causes disturbed impaired spatial orientation with a distorted sense of motion. It was assumed to be only the manifestation of neurological elements but factors such as inner ear problems, low blood sugar, low blood pressure, side effects of medications and other nonspecific common neurological symptoms were found to cause dizziness as well (Korres et al., 2022). The RYR2, SCN1B, SCN5A, NF1, RET and CACNA1G genes were found to be associated with the biological pathway related to the symptom. Molecular docking resulted in the RET-NPC56271 complex and RYR2-NPC122235 with the top two highest binding energies (Table 1.9). The RET gene natural compound, Gefitinib, showed evidence of association with dizziness where the use of the compound for non-small cell lung cancer alleviates a number of symptoms including dizziness (Z. Gao et al., 2012). The RYR2 gene's natural compound, Linalyl anthranilate, is commonly found in plants that exhibit antimicrobial activities (S. Yang et al., 2021). This compound also induces oxidative stress that is likely to be related to dizziness (S. Yang et al., 2021). However, thestudy was conducted on bacterial cells and not animal cells. Thus, the effects of Linalyl anthranilate must be extensively studied to understand the potential association between dizziness and Linalyl anthranilate.

A symptom that is more prevalent in females than males and is known to affectthe joints in the body is the joint pain long COVID symptom. The pathophysiology of the symptoms is considered to be either due to the excessive release of cytokines and tumor necrosis or tissue inflammation causing rheumatic/musculoskeletal symptoms. Inaddition, as a hub gene biomarker for joint pain, the CR2 and FAS genes were also the causative agent of an autoimmune disorder (systemic lupus erythematosus (SLE)) which presents joint pain as a common symptom. The natural compounds identified via molecular docking (Table 1.9) were FAS-NPC115624 (4'-Demethyl Deoxypodophyllotoxin beta-D-glucopyranoside) and FAS-NPC116759 (4-Demethyl-Epipodophyllotoxin-7'-O-Beta-D-Glucopyranoside) where both natural components are identified to be isolated from the plant species, *Podophyllum hexandrum*.

The natural compounds extracted from *Podophyllum hexandrum* the plant species showedno relation to the symptom as they exhibit anti-cancer properties (Zilla et al., 2014). Though it remains curious on how a compound associated with the cancer cell pathways can be determined as a potential natural remedy to joint pain. Thus, further investigation of the natural compounds is required to reveal its hidden properties.

The long COVID psychological symptoms are anxiety and depression that are hypothesized to appear due to the impact of the COVID-19 virus on the central nervous system (CNS). External environmental stressors too, influence the severity and durationof both mental health disorders. The CDH23 gene (cadherin-related 23 gene) belonging tothe cadherin superfamily, was identified as

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the single gene associated with both anxiety and depression. Long-term conditions such as hearing impairment and balance disorders are linked to the gene where they cause psychological issues including anxiety and depression. The natural compound, (2S)-2-(methylazaniumyl)-3-phenylpropanoate(NPC67043), and CD23 gene interaction resulted in the binding affinity of -53.12 (Table 1.10). The lack of another complex to make a comparison makes the CDH23-NPC67043 to be the potential therapeutic candidate and natural remedy targeted for both longCOVID symptoms.

Table 1.1: Molecular Docking results for Fatigue. Table showing hub genes and natural compounds derived from NPASS database.

Hub Gene & Natural Component	Energy	VDW	HBond	Elec
RET-NPC56271	-94.65	-85.16	-9.49	0.00
ERBB4-NPC56271	-94.29	-85.58	-8.71	0.00
NF1-NPC117032	-83.94	-80.65	-2.74	-0.55
SMAD4-NPC189301	-73.85	-53.31	-21.34	0.80
SMAD4-NPC176164	-73.26	-47.26	-26.00	0.00
SMAD4-NPC226027	-70.85	-56.50	-13.59	-0.75
SMAD4-NPC174246	-69.07	-55.26	-15.09	1.28
SMAD4-NPC183845	-67.90	-31.13	-36.77	0.00
SMAD4-NPC112890	-65.48	-31.35	-32.29	-1.84
SMAD4-NPC140872	-64.27	-46.55	-17.72	0.00
SMAD4-NPC118459	-59.74	-38.78	-20.96	0.00
SMAD4-NPC245027	-55.96	-44.00	-10.50	-1.46
SMAD4-NPC162620	-54.80	-47.63	-7.17	0.00

Table 1.2: Molecular Docking results for Shortness of Breath. Table showing hub genes and natural compounds derived from NPASS database

Hub Gene & Natural Component	Energy	VDW	HBond	Elec
CHRNE-NPC108434	-106.33	-93.35	-12.99	0.00
CHRNB1-NPC10908	-104.70	-92.98	-11.72	0.00
CHNRD-NPC11296	-103.00	-83.34	-19.66	0.00
CHRNB1-NPC115284	-102.98	-94.69	-8.29	0.00
CHNRD-NPC10871	-101.86	-78.73	-23.43	0.29
CHRNB1-NPC108434	-98.10	-89.39	-8.72	0.00
CHRND-NPC108434	-97.35	-78.84	-18.50	0.00

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CHRNE-NPC10871	-96.64	-84.54	-12.10	0.00
CHRNB1-NPC116465	-94.42	-81.36	-13.06	0.00
CHNRD-NPC115284	-94.09	-93.60	-0.49	0.00
CHRNE-NPC11296	-93.10	-74.49	-18.61	0.00
CHRNB1-NPC10871	-93.05	-90.87	-2.90	0.73
CHRNB1-NPC11296	-93.02	-88.30	-4.72	0.00
CHNRD-NPC13916	-92.25	-74.21	-18.04	0.00
CHRNB1-NPC13916	-92.22	-81.32	-10.89	0.00
CHRNB1-NPC104196	-91.30	-87.10	-4.20	0.00
CHRND-NPC104196	-88.75	-71.78	-16.98	0.00
CHRNE-NPC106295	-86.51	-84.75	-1.76	0.00
CHNRD-NPC106295	-84.77	-83.12	-1.65	0.00
CHRNE-NPC10908	-84.70	-74.68	-10.02	0.00
CHNRD-NPC116465	-83.01	-68.36	-14.65	0.00
CHRNE-NPC115284	-82.07	-79.57	-2.50	0.00
CHRNB1-NPC106295	-81.97	-81.97	0.00	0.00
CHRNB1-NPC114124	-81.78	-65.48	-16.30	0.00
CHRNB1-NPC103379	-81.66	-60.92	-20.74	0.00
CHRNE-NPC13916	-81.21	-65.30	-15.91	0.00
CHRND-NPC10908	-79.41	-79.41	0.00	0.00
CHRNE-NPC116465	-79.33	-73.68	-5.65	0.00
CHRNE-NPC114124	-78.43	-60.67	-17.77	0.00
CHNRD-NPC103379	-78.37	-70.02	-8.35	0.00
CHRNE-NPC104196	-78.19	-73.19	-5.00	0.00
CHNRD-NPC114124	-77.32	-65.32	-12.00	0.00
CHNRD-NPC123323	-76.01	-73.71	-2.30	0.00
CHRNB1-NPC123323	-74.20	-66.93	-7.27	0.00
CHRNE-NPC123323	-73.07	-73.07	0.00	0.00
CHRNE-NPC103379	-72.46	-59.26	-13.20	0.00

Table 1.3: Molecular Docking results for Loss of Smell. Table showing hub genes and natural compounds derived from NPASS database

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Hub Gene & Natural Component	Energy	VDW	HBond	Elec
GNRH1-NPC69843	-105.95	-91.90	-12.60	-1.46
GNRH1-NPC322594	-100.52	-82.39	-18.12	0.00
GNRH1-NPC328779	-95.88	-46.03	-49.85	0.00
GNRH1-NPC120887	-92.41	-70.14	-22.27	0.00
GNRH1-NPC17892	-88.11	-63.65	-24.47	0.00
GNRH1-NPC320249	-82.83	-55.55	-27.28	0.00
GNRH1-NPC324390	-77.60	-56.91	-20.69	0.00
GNRH1-NPC226769	-73.68	-44.94	-28.74	0.00
TAC3-NPC17760	-70.87	-64.87	-6.00	0.00
GNRH1-NPC474926	-70.68	-48.60	-22.08	0.00
GNRH1-NPC229249	-70.02	-70.02	0.00	0.00
TAC3-NPC241086	-69.42	-59.93	-9.49	0.00
TAC3-NPC197239	-68.37	-61.77	-6.61	0.00
TAC3-NPC282087	-67.22	-51.77	-15.45	0.00
GNRH1-NPC106780	-66.35	-66.35	0.00	0.00
TAC3-NPC259800	-66.01	-50.62	-15.39	0.00
GNRH1-4-NPC107135	-58.84	-36.30	-22.54	0.00
TAC3-NPC142638	-58.49	-38.96	-19.54	0.00
TAC3-NPC106551	-57.96	-45.84	-12.78	0.66
TAC3-NPC281686	-57.96	-44.77	-13.83	0.64
GNRH1-NPC43655	-55.76	-47.40	-8.36	0.00
TAC3-NPC188867	-54.67	-33.17	-21.51	0.00
TAC3-NPC239697	-52.34	-39.72	-12.62	0.00

Table 1.4: Molecular Docking results for Headache. Table showing hub genes and natural compounds derived from NPASS database

Hub Gene & Natural Component	Energy	VDW	HBond	Elec
TERT-NPC230098	-97.62	-85.53	-12.09	0.00
ESR1-NPC136948	-96.97	-78.32	-18.65	0.00
RET-NPC56271	-94.65	-85.16	-9.49	0.00

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TERT-NPC474324	-92.79	-82.29	-10.50	0.00
ESR1-NPC123319	-92.16	-77.78	-14.38	0.00
TERT-NPC319549	-91.83	-71.07	-20.76	0.00
TERT-NPC33256	-85.58	-69.20	-16.38	0.00
ESR1-NPC1015	-85.42	-70.77	-14.64	0.00
TERT-NPC237044	-85.10	-75.60	-9.50	0.00
ESR1-NPC139397	-84.00	-80.50	-3.50	0.00
NF1-NPC117032	-83.94	-80.65	-2.74	-0.55
TERT-NPC474325	-83.26	-62.39	-20.87	0.00
TERT-NPC298186	-83.22	-72.58	-10.94	0.30
ESR1-NPC255253	-82.47	-71.97	-10.50	0.00
TERT-NPC304675	-81.06	-65.27	-15.79	0.00
ESR1-NPC144258	-80.38	-74.17	-6.21	0.00
TERT-NPC301189	-80.12	-69.50	-10.61	0.00
TERT-NPC165797	-78.17	-69.69	-8.47	0.00
ESR1-NPC126993	-76.15	-73.83	-2.33	0.00
ESR1-NPC136548	-74.01	-61.01	-13.00	0.00
SMAD4-NPC189301	-73.85	-53.31	-21.34	0.80
SMAD4-NPC176164	-73.26	-47.26	-26.00	0.00
ESR1-NPC129913	-73.01	-64.51	-8.50	0.00
SMAD4-NPC226027	-70.85	-56.50	-13.59	-0.75
SMAD4-NPC174246	-69.07	-55.26	-15.09	1.28
SMAD4-NPC183845	-67.90	-31.13	-36.77	0.00
SMAD4-NPC112890	-65.48	-31.35	-32.29	-1.84
SMAD4-NPC140872	-64.27	-46.55	-17.72	0.00
SMAD4-NPC118459	-59.74	-38.78	-20.96	0.00
SMAD4-NPC245027	-55.96	-44.00	-10.50	-1.46
SMAD4-NPC162620	-54.80	-47.63	-7.17	0.00

Table 1.5: Molecular Docking results for Brain Fog. Table showing hub genes and natural compounds derived from NPASS database

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Hub Gene & Natural Component	Energy	VDW	HBond	Elec
CACNA1B-NPC198254	-119.29	-90.52	-28.77	0.00
CACNA1B-NPC473404	-115.68	-86.02	-33.71	4.05
CACNA1B-NPC153554	-109.71	-85.83	-23.88	0.00
CACNA1B-NPC240130	-104.61	-70.44	-31.19	-2.99
CACNA1B-NPC274198	-100.59	-76.19	-24.98	0.58
KCNT1-NPC329708	-85.81	-77.31	-8.50	0.00
KCNT1-NPC193238	-85.17	-70.08	-15.09	0.00
KCNT1-NPC274291	-84.64	-70.82	-13.82	0.00
GABRA1-NPC317054	-83.96	-77.67	-6.30	0.00
KCNT1-NPC47059	-80.67	-73.67	-7.00	0.00
KCNT1-NPC203754	-78.36	-72.36	-6.00	0.00
KCNT1-NPC165349	-76.72	-72.59	-4.13	0.00
KCNT1-NPC264166	-74.93	-72.43	-2.50	0.00
KCNT1-NPC118832	-70.83	-62.29	-8.54	0.00
KCNT1-NPC150048	-70.42	-65.85	-4.57	0.00
KCNT1-NPC231986	-69.20	-65.70	-3.50	0.00

Table 1.6: Molecular Docking results for Chest Pain. Table showing hub genes and natural compounds derived from NPASS database

Hub Gene & Natural Component	Energy	VDW	HBond	Elec
RET-NPC56271	-94.65	-85.16	-9.49	0.00
NF1-NPC117032	-83.94	-80.65	-2.74	-0.55
SMAD4-NPC189301	-73.85	-53.31	-21.34	0.80
SMAD4-NPC176164	-73.26	-47.26	-26.00	0.00
SMAD4-NPC226027	-70.85	-56.50	-13.59	-0.75
SMAD4-NPC174246	-69.07	-55.26	-15.09	1.28
SMAD4-NPC183845	-67.90	-31.13	-36.77	0.00
SMAD4-NPC112890	-65.48	-31.35	-32.29	-1.84
SMAD4-NPC140872	-64.27	-46.55	-17.72	0.00
SMAD4-NPC118459	-59.74	-38.78	-20.96	0.00

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SMAD4-NPC245027	-55.96	-44.00	-10.50	-1.46
SMAD4-NPC162620	-54.80	-47.63	-7.17	0.00

Table 1.7: Molecular Docking results for Insomnia. Table showing hub genes and natural compounds derived from NPASS database

Hub Gene & Natural Component	Energy	VDW	HBond	Elec
ABCB11-NPC100366	-107.98	-85.27	-22.72	0.00
NR1H4-NPC100366	-97.79	-87.37	-10.42	0.00
ABCB4-NPC213206	-96.30	-79.94	-16.35	0.00
ABCB4-NPC187022	-96.10	-85.42	-10.68	0.00
ABCB4-NPC208890	-94.01	-79.52	-14.49	0.00
ABCB4-NPC169387	-92.86	-90.86	-2.00	0.00
ABCB4-NPC136860	-88.28	-79.85	-8.43	0.00
ABCB4-NPC222524	-86.16	-78.11	-8.05	0.00
SLC12A3-NPC321053	-81.71	-47.62	-34.09	0.00
ABCB4-NPC188163	-81.18	-71.92	-9.26	0.00
ABCB4-NPC128019	-71.50	-61.79	-9.71	0.00

Table 1.8: Molecular Docking results for Heart Palpitations. Table showing hub genes and natural compounds derived from NPASS database

Hub Gene & Natural Component	Energy	VDW	HBond	Elec
GATA4-NPC101636	-107.59	-90.62	-16.97	0.00
GATA4-NPC100818	-103.25	-67.84	-35.40	0.00
GATA4-NPC100887	-98.92	-67.75	-31.18	0.00
GATA4-NPC10097	-89.52	-56.87	-32.65	0.00
GATA4-NPC100985	-84.82	-62.35	-22.47	0.00
SCN5A-NPC162417	-83.58	-73.08	-10.50	0.00
SCN5A-NPC64436	-82.21	-74.38	-7.83	0.00
SCN5A-NPC470971	-81.67	-71.48	-10.19	0.00
GATA4-NPC101366	-79.21	-54.46	-24.75	0.00
SCN5A-NPC322433	-78.26	-60.08	-18.18	0.00
SCN5A-NPC265100	-77.86	-70.08	-7.78	0.00

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SCN5A-NPC136112	-77.71	-66.44	-11.27	0.00
GATA4-NPC101294	-76.70	-69.70	-7.00	0.00
SCN5A-NPC26285	-76.27	-73.59	-2.68	0.00
SCN5A-NPC242933	-75.49	-60.87	-14.62	0.00
GATA4-NPC10027	-74.31	-65.03	-9.28	0.00
SCN5A-NPC319645	-72.42	-64.05	-8.37	0.00
SCN5A-NPC226143	-72.40	-68.95	-3.45	0.00
GATA4-NPC100986	-71.88	-55.38	-16.50	0.00
SCN5A-NPC248462	-71.41	-58.66	-12.75	0.00
SCN5A-NPC70406	-70.84	-52.41	-18.43	0.00
SCN5A-NPC141739	-70.80	-65.80	-5.00	0.00
SCN5A-NPC26524	-68.43	-63.12	-5.30	0.00
SCN5A-NPC173295	-63.42	-55.17	-8.26	0.00
SCN5A-NPC57051	-63.00	-60.62	-2.38	0.00
SCN5A-NPC42383	-61.93	-56.37	-5.56	0.00
SCN5A-NPC65408	-61.57	-55.44	-6.13	0.00
SCN5A-NPC97811	-58.36	-55.41	-2.94	0.00
SCN5A-NPC24777	-57.83	-50.23	-7.60	0.00

Table 1.9: Molecular Docking results for Dizziness. Table showing hub genes and natural compounds derived from NPASS database

Hub Gene & Natural Component	Energy	VDW	HBond	Elec
RET-NPC56271	-94.65	-85.16	-9.49	0.00
RYR2-NPC122235	-85.94	-78.79	-7.15	0.00
NF1-NPC117032	-83.94	-80.65	-2.74	-0.55
SCN5A-NPC162417	-83.58	-73.08	-10.50	0.00
SCN5A-NPC64436	-82.21	-74.38	-7.83	0.00
SCN5A-NPC470971	-81.67	-71.48	-10.19	0.00
SCN5A-NPC322433	-78.26	-60.08	-18.18	0.00
SCN5A-NPC265100	-77.86	-70.08	-7.78	0.00
SCN5A-NPC136112	-77.71	-66.44	-11.27	0.00

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SCN5A-NPC26285	-76.27	-73.59	-2.68	0.00
SCN5A-NPC242933	-75.49	-60.87	-14.62	0.00
CACNA1G-NPC264400	-74.95	-58.77	-16.18	0.00
CACNA1G-NPC55529	-73.98	-62.68	-11.30	0.00
RYR2-NPC150323	-73.75	-47.76	-26.00	0.00
CACNA1G-NPC470926	-73.59	-71.09	-2.50	0.00
SCN5A-NPC319645	-72.42	-64.05	-8.37	0.00
SCN5A-NPC226143	-72.40	-68.95	-3.45	0.00
CACNA1G-NPC256452	-71.53	-61.21	-10.32	0.00
SCN5A-NPC248462	-71.41	-58.66	-12.75	0.00
SCN5A-NPC70406	-70.84	-52.41	-18.43	0.00
SCN5A-NPC141739	-70.80	-65.80	-5.00	0.00
SCN5A-NPC26524	-68.43	-63.12	-5.30	0.00
RYR2-NPC319645	-68.19	-57.69	-10.50	0.00
CACNA1G-NPC71140	-66.84	-59.10	-7.75	0.00
SCN5A-NPC173295	-63.42	-55.17	-8.26	0.00
RYR2-NPC226794	-63.12	-47.87	-15.24	0.00
SCN5A-NPC57051	-63.00	-60.62	-2.38	0.00
SCN5A-NPC42383	-61.93	-56.37	-5.56	0.00
SCN1B-NPC264400	-61.81	-41.42	-20.39	0.00
SCN5A-NPC65408	-61.57	-55.44	-6.13	0.00
SCN5A-NPC97811	-58.36	-55.41	-2.94	0.00
SCN5A-NPC24777	-57.83	-50.23	-7.60	0.00

Table 1.10: Molecular Docking results for Joint Pain. Table showing hub genes and natural compounds derived from NPASS database

Hub Gene & Natural Component	Energy	VDW	HBond	Elec
FAS-NPC115624	-115.52	-84.27	-31.25	0.00
FAS-NPC116759	-115.52	-77.79	-37.72	0.00
FAS-NPC103197	-110.38	-97.35	-13.03	0.00
FAS-NPC152424	-108.06	-81.95	-26.11	0.00
FAS-NPC100465	-103.29	-71.46	-31.83	0.00

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FAS-NPC119910	-103.26	-89.55	-13.71	0.00
FAS-NPC14294	-102.40	-73.18	-29.22	0.00
FAS-NPC150943	-97.35	-71.67	-25.68	0.00
FAS-NPC115281	-95.30	-76.80	-18.51	0.00
FAS-NPC163527	-91.19	-70.10	-21.08	0.00
CR2-NPC139397	-70.48	-63.87	-6.61	0.00

The condition where a person is hearing a buzzing or a ringing in the ears, phantom perception, without an external source creating the sound is referred to astinnitus. Tinnitus is a long COVID symptom where its prevalence among the general population ranges between 16 to 26% (Degen et al., 2022). Research on the pathophysiology of tinnitus resulted in two hypothetical mechanisms; hearing loss and theabnormal neural activity caused by inflammation induced by the virus. The previously discussed long COVID symptoms, depression and anxiety are emotional distress that potentially increases the duration of tinnitus in patients. The hub genes of tinnitus (CACNA1D, NF1, RET and TERT genes) presented with no direct link towards the symptom itself but showed an association to hearing loss, a condition that is a closely related symptom to tinnitus. The CACNA1D-NPC36836 complex and TERT-NPC230098 complex are the top two complexes proposed as prospective therapeutic targets candidatesfor tinnitus (Table 1.12). NPC36836 is the calcium channel blocker called Nicardipine, usually employed in vascular disorders and as an anti-inflammatory agent as it is found tobe more selective for the blood vessels in the nervous and cardiac systems (B. Huang et al., 2014). NPC230098, as examined in the headache symptom, is an unknown natural compound with unknown properties in relation to its hub gene, TERT. As both natural compounds provide a suitable link to tinnitus, further examinations are needed to investigate the properties and therapeutic benefits of both natural compounds as they are determined viable targets for managing tinnitus.

Anorexia is an eating disorder, also known as, loss of appetite has an overall negative impact in life by causing malnutrition and sudden weight-loss. It is a long COVID symptom where the SARS-CoV-2 virus invades the gastrointestinal system. This causes several complications including the increased production of leptin, the hormone that provides satiety sensations resulting in the loss of appetite (Van Der Voort et al., 2020). Furthermore, pandemic-induced fear and stress also influences the eating habits of an individual. The hub gene biomarkers (SMAD4 and MEN1) for anorexia were found to have no direct relationship with the symptom. A faint and indirect link was identified for the MEN1 gene as this gene is known to cause hyperparathyroidism, which then induces hypoglycemia, leading to a range of symptoms including anorexia. The exact mechanism for both genes however remains unidentified. The MEN1-NPC474814 complex wasinitially analyzed as a natural remedy with the binding energy of -114.41 (Table 1.13).But the origin and the properties of the natural compound was unidentified. Thus, the second-best complex, MEN1-NPC199737 was investigated. The natural compound is known as Lavendustin B, a weak inhibitor and is majorly used as a negative control analogue among other compounds of the Lavendustin family. The relationship of both compounds to anorexia is not well understood as no evidence is present linking both together. Further research is required to analyze the properties of these natural components as both are found to be associated with the biological pathway of anorexia based on our study.

Table 1.11: Molecular Docking results for Depression and Anxiety. Table showing hub genes and natural compounds derived from NPASS database.

Hub Gene & Natural Component	**Energy**	**VDW**	**HBond**	**Elec**
CDH23-NPC67043	-53.12	-42.68	-10.44	0.00

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Table 1.12: Molecular Docking results for Tinnitus. Table showing hub genes and natural compounds derived from NPASS database.

Hub Gene & Natural Component	Energy	VDW	HBond	Elec
CACNA1D-NPC36836	-109.75	-94.82	-16.40	1.47
TERT-NPC230098	-97.62	-85.53	-12.09	0.00
RET-NPC56271	-94.65	-85.16	-9.49	0.00
TERT-NPC474324	-92.79	-82.29	-10.50	0.00
CACNA1D-NPC63370	-92.73	-85.36	-8.25	0.88
TERT-NPC319549	-91.83	-71.07	-20.76	0.00
TERT-NPC33256	-85.58	-69.20	-16.38	0.00
TERT-NPC237044	-85.10	-75.60	-9.50	0.00
NF1-NPC117032	-83.94	-80.65	-2.74	-0.55
TERT-NPC474325	-83.26	-62.39	-20.87	0.00
TERT-NPC298186	-83.22	-72.58	-10.94	0.30
TERT-NPC304675	-81.06	-65.27	-15.79	0.00
TERT-NPC301189	-80.12	-69.50	-10.61	0.00
CACNA1D-NPC190945	-79.50	-61.18	-18.10	-0.22
TERT-NPC165797	-78.17	-69.69	-8.47	0.00

Table 1.13: Molecular Docking results for Anorexia (Loss of Appetite). Table showing hub genes and natural compounds derived from NPASS database.

Hub Gene & Natural Component	Energy	VDW	HBond	Elec
MEN1-NPC474814	-114.41	-96.24	-18.17	0.00
MEN1-NPC199737	-95.91	-61.68	-34.24	0.00
MEN1-NPC471778	-94.89	-77.62	-17.27	0.00
MEN1-NPC112336	-90.02	-69.56	-20.45	0.00
MEN1-NPC301702	-82.55	-47.69	-34.86	0.00
MEN1-NPC181526	-74.30	-46.46	-27.84	0.00
SMAD4-NPC189301	-73.85	-53.31	-21.34	0.80
MEN1-NPC323798	-73.31	-50.23	-23.08	0.00
SMAD4-NPC176164	-73.26	-47.26	-26.00	0.00
SMAD4-NPC226027	-70.85	-56.50	-13.59	-0.75

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SMAD4-NPC174246	-69.07	-55.26	-15.09	1.28
SMAD4-NPC183845	-67.90	-31.13	-36.77	0.00
MEN1-NPC316574	-67.29	-39.65	-27.64	0.00
SMAD4-NPC112890	-65.48	-31.35	-32.29	-1.84
SMAD4-NPC140872	-64.27	-46.55	-17.72	0.00
SMAD4-NPC118459	-59.74	-38.78	-20.96	0.00
SMAD4-NPC245027	-55.96	-44.00	-10.50	-1.46
SMAD4-NPC162620	-54.80	-47.63	-7.17	0.00

The limitations of the study include the unavailability of specific literature on the natural compounds as they prevented us from further analyzing the properties of the natural compounds as a natural remedy against long COVID. Furthermore, as a field of research that is not fully understood, the exact mechanism behind the underlying conditions of long COVID are undetermined. Regardless, as per the objective of the study, the potentialnatural remedies and therapeutic drugs for the symptoms of long COVID have been identified and studied based on the interaction between the hub gene and natural compounds via molecular docking.

Conclusion

Long COVID has been determined as a major worldwide health concern but the research on the syndrome/condition is still lacking and the mechanism of the condition is currently unknown. The identification of natural compounds for long COVID as natural remedies based on hub gene biomarkers and repurposed drugs shows promising potential for improving the symptoms caused by the condition. The identified natural remedies for the fourteen common symptoms, provides an insight and a stable foundation of research on the undiscovered potential of the natural compounds and the unidentified mechanisms of long COVID symptoms. The results from this study also aids in the development of effective therapeutic drugs and interventions catering to each individual symptom based on the hub gene biomarkers and repurposed drugs associated.

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