ORIGINAL ARTICLE

Multi-Target Mechanistic Evaluation of Tailaparna (*Eucalyptus globulus* Labill.) Against Chronic Obstructive Pulmonary Disease and COVID-19: A Network Pharmacology and Molecular Docking Study

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Abstract

Introduction: COVID-19 and chronic obstructive pulmonary disease (COPD) are two most important respiratory diseases associated with oxidative stress, inflammation, and metabolic dysregulation. The limitations and adverse effects of current treatment methods need the advance and safer multi-target therapeutic drugs. Tailaparna (*Eucalyptus globulus*) possesses several bioactive phytochemicals with anti-inflammatory, antioxidant, and immunomodulatory properties that may support with respiratory disorders. **Aims:** The aim of the study was to explore the therapeutic potential and molecular mechanisms of *E. globulus* against COPD and COVID-19 using Network Pharmacology and Molecular Docking methods. **Materials and Methods:** *E. globulus* phytochemicals were screened from Dr. Duke's and IMPPAT databases, and SwissADME was used to screen them according to Lipinski's rule, oral bioavailability, and GI absorption. BindingDB and UniProt databases were used to find potential targets. The GeneCards and Human Protein Atlas databases provided disease-related targets for COVID-19 and COPD. Kyoto encyclopedia of genes and genomes (KEGG) pathway enrichment analysis and the STRING database were used to analyse common targets. Phytochemical-target-pathway networks were built using Cytoscape 3.7.2. PyRx and BIOVIA Discovery Studio were used for molecular docking. **Results:** A total of 294 active phytochemicals and 91 related targets were identified. Between them, 55 overlapping targets for COPD and 57 for COVID-19 were detected. KEGG analysis revealed metabolic pathways, PI3K-Akt signaling pathway, Mitogen-activated protein kinase signaling pathway, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor resistance, and proteoglycans in cancer as important pathways involved in both diseases. Molecular docking proved that Ellagic acid showed the highest binding affinity with PRKACA in COPD (−10.8 kcal/mol) and IGF1R in COVID-19 (−8.4 kcal/mol). Quercetin and Luteolin also showed strong interactions with EGFR. **Conclusion:** *E. globulus* demonstrated promising multi-target therapeutic potential against COVID-19 and COPD by modifying metabolic, oxidative stress, and inflammatory pathways. Further experimental and clinical research is required to validate these findings.

Key words: *Eucalyptus globulus*, tailaparna, chronic obstructive pulmonary disease, COVID-19, network pharmacology, molecular docking

INTRODUCTION

Chronic respiratory diseases, including bronchial asthma, chronic obstructive pulmonary disease (COPD), COVID-19 and other chronic airway diseases, are increasingly significant causes of morbidity and mortality worldwide. The global burden is likely to increase further because of population ageing, urbanization, air pollution and other associated risk factors.[1] According to the World

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Health Organization (WHO), COPD is one of the important causes of death worldwide.[2] Estimated cases globally in 2016 were 251 million, according to the study of global burden of disease.[3] The mortality rate increased 35.4% from 2009 to 2019 and is predicted to be the third leading cause of death globally by 2030.[4] Although tobacco smoking is a major risk factor for COPD cases are caused by exposure to pollutants in the workplace.[5] The WHO declared the spread of severe acute respiratory syndrome coronavirus 2 (SARS-coV-2), the causative agent of COVID-19, a pandemic in March 14, 2020, WHO reported that COVID-19 had spread to 213 countries with 4.3 million cases and an estimated 2,93,494 deaths, showing its widespread prevalence and rapid transmission across the world.[6]

COPD is a complex lung disease characterized by structural obstruction of the respiratory system and persistent inflammation of the airways.[7] The main site of SARS-coV-2 replication is in the lung alveoli. The virus infects the cells by attaching its spike protein to the ACE-2 receptors on the surface of the Type II pneumocytes in the alveolar lining and releases its positive-sense RNA.[8]

Medications commonly used for COPD have prominent side effects: β_2-agonists may provoke tachycardia and arrhythmias, antimuscarinics dry mouth or urinary disturbances, and oral corticosteroids (with long-term use) increase the risk of osteoporosis and hyperglycemia. Tremors and tachycardia (which affects quality of life) are also potential side effects of combination therapy with β_2-agonists and inhaled corticosteroids, which could lead to increased exacerbations.[9] Treatment for COVID-19 is mainly symptomatic: There is no known cure. Although a number of Antivirals have been studied, there is still diminutive proof. The WHO solidarity trial evaluated drugs including remdesivir and hydroxychloroquine. Emerging active medications and vaccines take time. Safe treatment is needed, especially for comorbid patients.[10]

The Pranavaha sroto dushti has been described as per the features of advanced stages of Kasa and Tamaka Shwasa, which are diseases similar to COPD, in Ayurveda.[11] COVID-19 is known as abhyantara rogamarga, which affects the chest with Pranavaha sroto dushti. It is classified as Agantuja Sannipataja Jwara (Vata-Kapha predominant) with symptoms resembling Kasa and Tamaka shwasa (COPD - like conditions) due to aggravated kapha obstructing Prana and Udana vata.[12]

Tailaparna (*Eucalyptus globulus* Labill.) is a major source of many pharmacologically and medicinally important chemicals, such as essential oils and terpenoids, which have also been widely studied for a range of pharmacological activities, such as analgesics, antifungal, antibacterial, antimalarial, antidiabetic, anti-inflammatory, antioxidant, anti-plaque, antitumor, cytochrome p450 enzyme inhibitor and hepatoprotective aspects.[13]

Network pharmacology helps to assess the safety and effectiveness of drugs by studying complex relationships between drugs, targets, and diseases. It explains how diseases work and how drugs affect the body on a system level. This method works well for exploring herbal treatments that have multiple components and aims. A drug-target network enables a detailed look at *E. globulus* compounds and their targets related to COPD and COVID-19. Thus, this study uses network pharmacology to explore the therapeutic potential of *E. globulus* Labill for COPD and COVID-19.

MATERIALS AND METHODS

Screening of bioactive phytochemicals

The phytochemicals contents of *E. globulus* were obtained from databases such as Indian Medicinal Plants, Phytochemistry and Therapeutics[14] and Dr. Dukes[15] using the Latin name of the plant. The simple structured chemicals were then filtered for duplicate compounds and those with aliphatic chains, and those that might not be the first target of the drugs were removed. The phytochemicals oral bioavailability and drug-likeness were assessed using the SwissADME[16] database. Compounds were selected on the basis of high GI absorption, bioavailability ≥0.55 and compliance with Lipinski's Rule of five (≤1 violation).

Target identification

The canonical SMILES and the corresponding PubChem IDs of the phytochemicals were retrieved from the short-listed PubChem database.[17] The BindingDB[18], a similarity-based platform for ligand-protein interaction study, was then used to determine possible protein targets using these SMILES representations. To find compound- target, a similarity criterion of 0.7 was used. For better accuracy, targets with a higher similarity score of ≥0.85 were chosen. Gene names and UniProt IDs from the Uniprot database[19] were then added to protein targets. Tailaparna targets were found using BindingDB, and phytochemicals were evaluated for oral bioavailability and drug-likeness. All targets were standardized using UniProtKB to ensure uniformity.

Identifying goals that align with COPD and COVID-19 targets

Information on therapeutic targets associated with COPD and COVID-19 was obtained from the GeneCards[20] database and human protein atlas (HPA)[21] platforms. Disease-related targets were found by using the keyword "chronic obstructive pulmonary disease" and "COVID-19." Next, the potential targets of Tailaparna were compared with disease-associated targets of COPD and COVID-19. The common targets between the drugs and the disease were identified using Venny 2.1.0.

Generation of interactome network between proteins

To obtain information about the protein-protein interaction (PPI) network depending on the drug-protein relationship for significant bioactive chemicals in Tailaparna, a simple interface consisting of overlapping particular genes was created using STRING[22] version 11.0. To calculate the interaction of the protein with the species "Homo sapiens," a high-assurance level of 70% similarity (0.700) was used to increase the precision of the study.

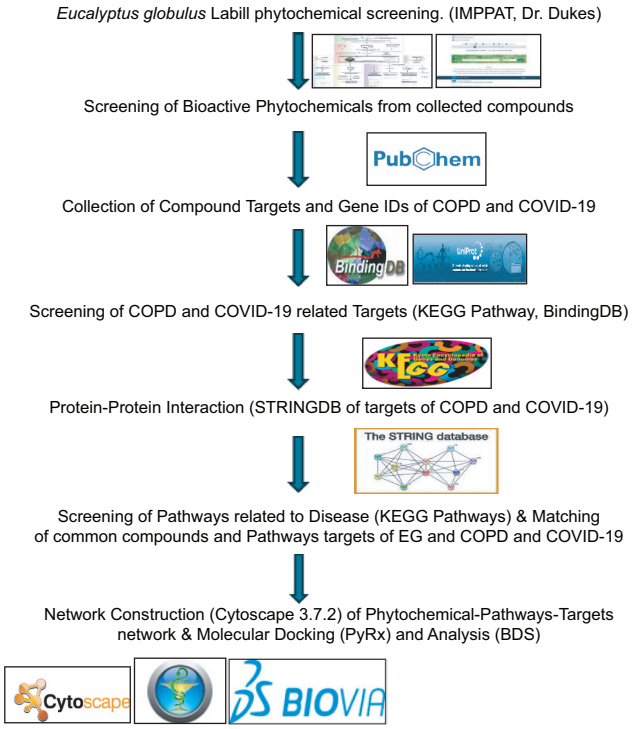

Figure 1: Workflow of the methodology utilized to construct the chemical-target-pathways network and molecular docking of EG in chronic obstructive pulmonary disease and COVID-19

Kyoto encyclopedia of genes and genomes (KEGG) pathway enrichment analysis

Homo sapiens was selected as species and FDR value was kept at 0.05 after intersecting targeted genes were included. The PPI network and top 10 KEGG pathways were obtained from the string database to ensure statistical importance and lower the false positive association. For KEGG pathway enrichment, an FDR threshold ≤0.05 was applied.

PPI network and key gene screening

The PPI network was constructed using the STRING database, which is a database of experimentally determined PPIs. The KEGG pathway was downloaded, and the pathways related to COPD and COVID-19 were screened. The overall workflow of the methodology utilized to construct the chemical-target-pathways network and molecular docking of EG in Chronic obstructive pulmonary disease and COVID-19 is illustrated in Figure 1.

Construction of "Herbal-Compound-Target" network

The COPD and COVID-19 related pathways in EG phytocompounds were catalogued, and the common targets of EG phytochemicals and COPD and COVID-19 were matched and sorted. The "Compound-Targets-Pathways" network was created using Cytoscape 3.7.2 software.[23]

Molecular docking

The crystal structures of the top three target proteins and the top five phytocompounds were obtained from the RSCB protein data bank[24] and PubChem databases, respectively. The Biovia DS program was used to remove water molecules and form polar connections in order to stabilize the protein

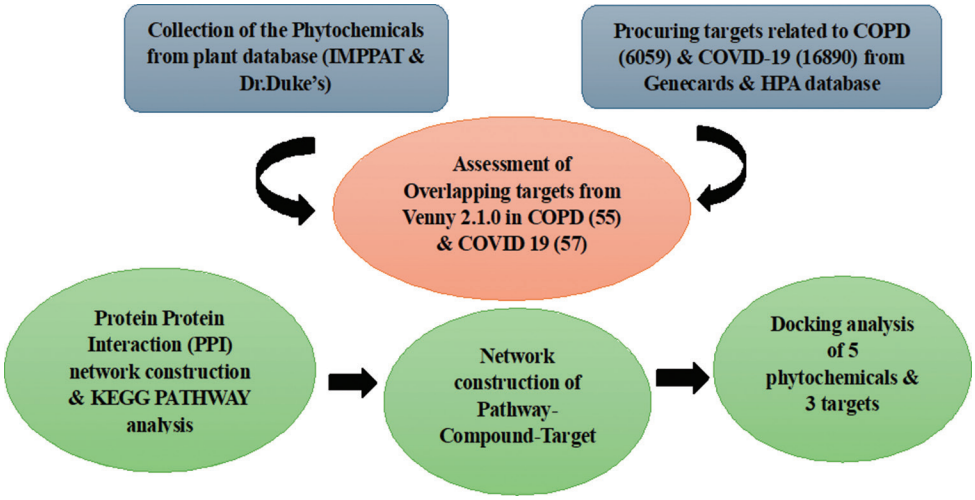

Figure 2: Step involved in Tailaparna, chronic obstructive pulmonary disease, and COVID-19 network construction and docking analysis

structures. The docking approach was utilized to predict the binding interaction of the top target proteins and ligands, and PyRx software[25] was utilized to automatically identify binding sites. The interaction with the best docking scores in two and three dimensions has been demonstrated using the Biovia Discovery Studio software.[26] The detailed workflow of Network construction and molecular docking analysis is presented in Figure 2.

RESULTS

Analysis of the collected phytochemicals from plant databases

A total of 363 phytochemicals were collected from two databases, IMPPAT and Dr. Duke's. After eliminating duplicate, 294 unique phytochemicals remained. These compounds were further screened for toxicity and ADME properties using the SwissADME and PubChem databases, and were carefully chosen based on criteria such as oral absorption, bioavailability, and Lipinski's violation. Later, by utilizing the BindingDB and UniProt databases, a total of 91 target genes related with these 294 active phytochemicals were identified.

Analysis of overlapping targets between phyto-targets and disease targets

The terms "COPD" and "COVID-19" were searched in the GeneCards and HPA databases, yielding a total of 6,059 and 16,890 disease-related targets, respectively, after removing duplicates. These disease targets were then interconnected with the phytochemical targets to identify common genes using Venny 2.1 software. Exactly, 91 targets associated with *E. globulus* were linked with the 6,059 COPD targets and 16,890 COVID-19 targets. As an outcome, 55 overlapping targets were identified for COPD and 57 overlapping targets for COVID-19. The overlapping targets of COPD are shown in Figure 3 and COVID-19 in Figure 4.

PPI networks

A PPI network was constructed using the STRING database. A total of 55 and 57 common targets related with Tailaparna for COPD and COVID-19, similarly, were imported into the STRING database. The analysis was made by selecting "*Homo sapiens"* as the organism and fixing the confidence score to 0.50. Then, KEGG pathway enrichment data were obtained and analysed to identify the molecular pathways regulated by these targets. The PPI network of COPD is shown in Figure 5 and PPI of COVID-19 are shown in Figure 6.

KEGG pathway analysis

The STRING database and KEGG functional enrichment analysis were used to investigate the signaling pathways. To understand the mechanism of action of *E. globulus* leaves in the selected diseases, ten pathways associated with COPD and COVID-19 were identified and examined. The involved pathways of COPD are shown in Figure 7 and COVID-19 in Figure 8, and analysis of the COPD and COVID-19 disease process using Gene set enrichment is shown in Tables 1 and 2.

Merged network of target- phytochemical-pathway

The interaction network linking 10 KEGG pathways, 55 overlapping targets, and 8 active compounds for COPD, along with 10 significantly enriched KEGG pathways, 57 interconnecting targets, and 10 key active compounds for COVID-19, was created using Cytoscape 3.7.2 software. The network of COPD is shown in Figure 9, and COVID-19 is shown in Figure 10.

Docking analysis

Molecular docking was used to evaluate the binding affinities of specific phytochemicals produced from plants and the corresponding gene targets. Five phytochemicals

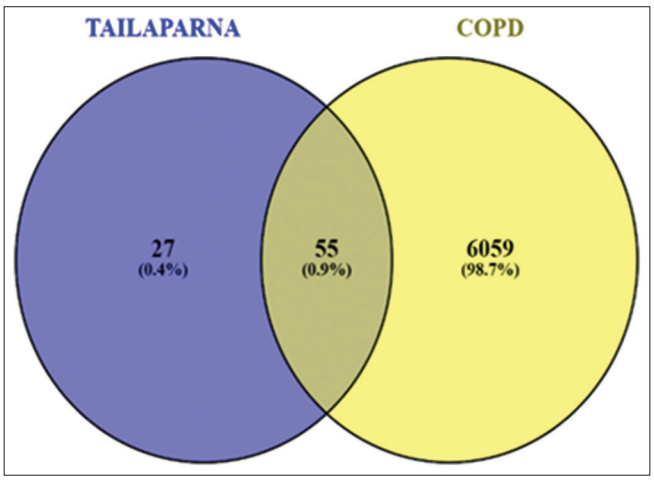

Figure 3: Overlapping Targets of EG with COPD

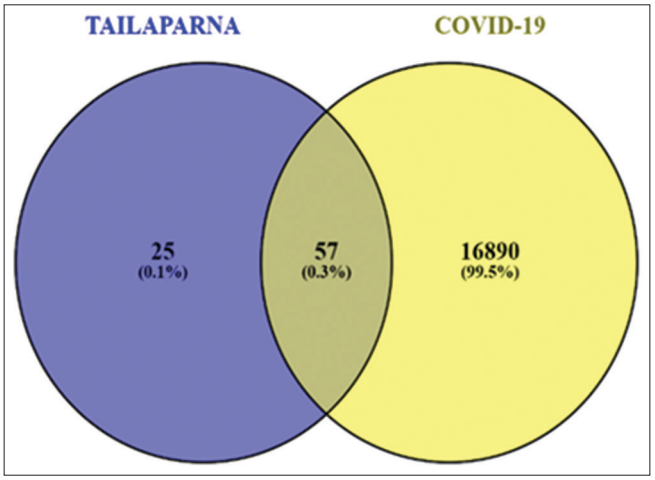

Figure 4: Overlapping Targets of EG with COVID-19

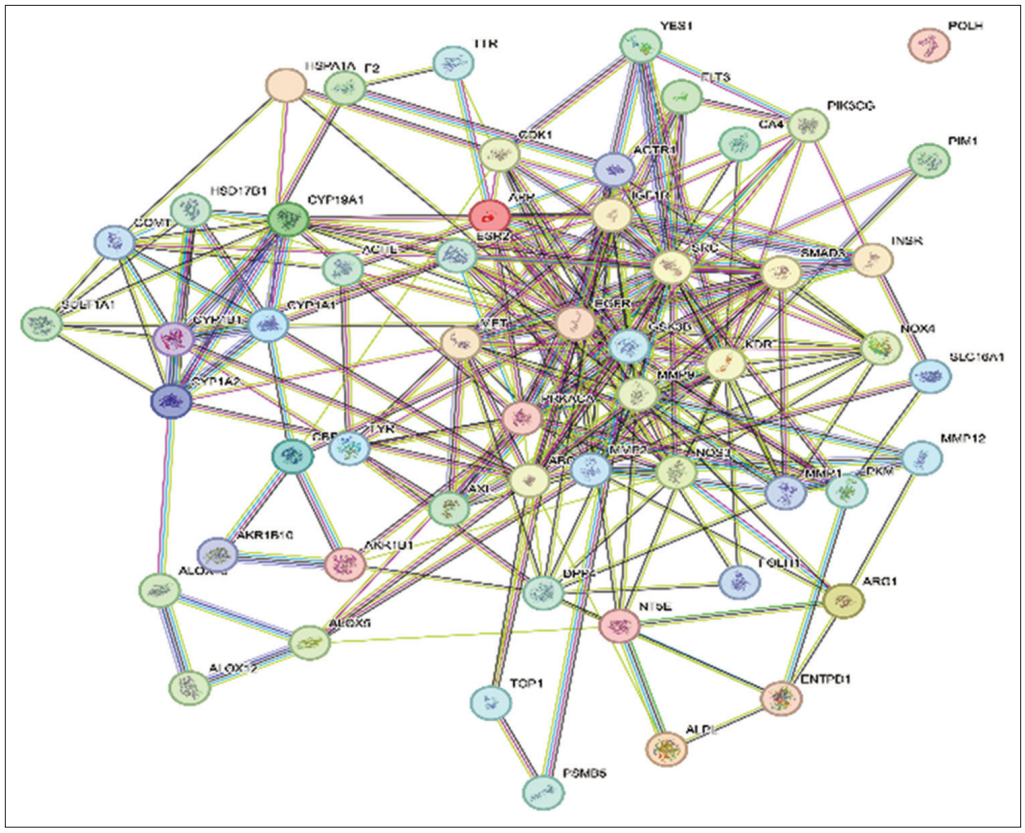

Figure 5: Protein-protein interaction network of chronic obstructive pulmonary disease

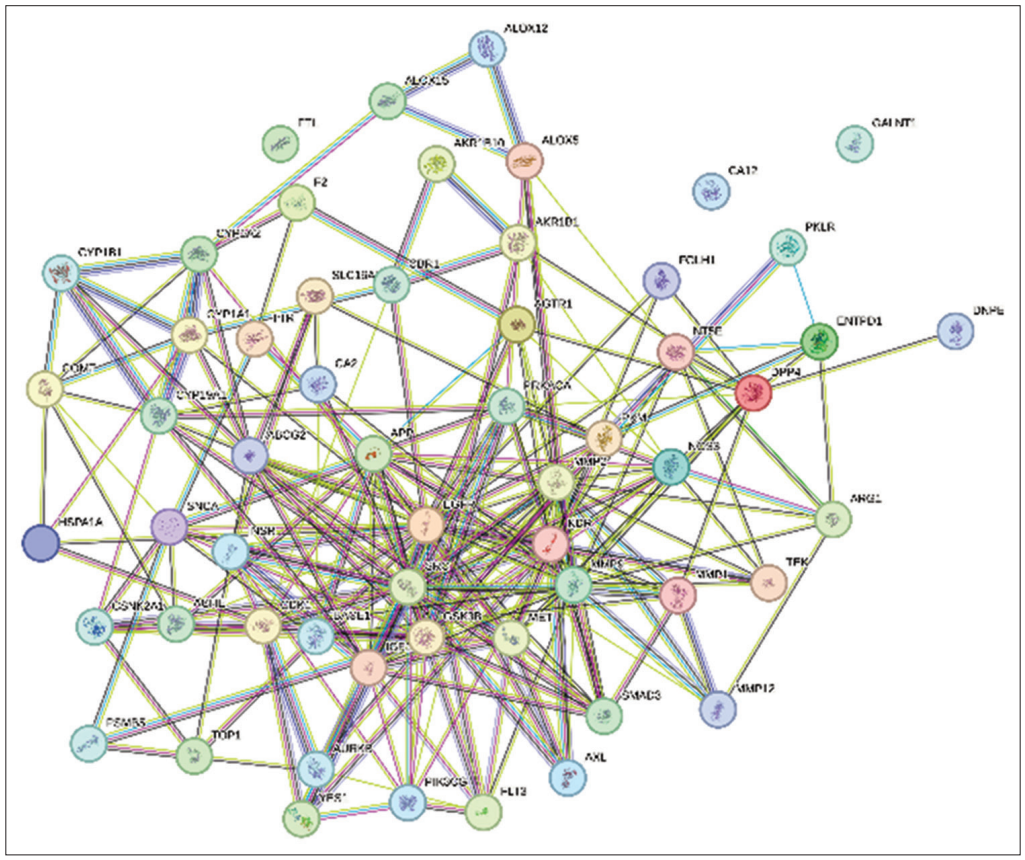

Figure 6: Protein-protein interaction network of COVID-19

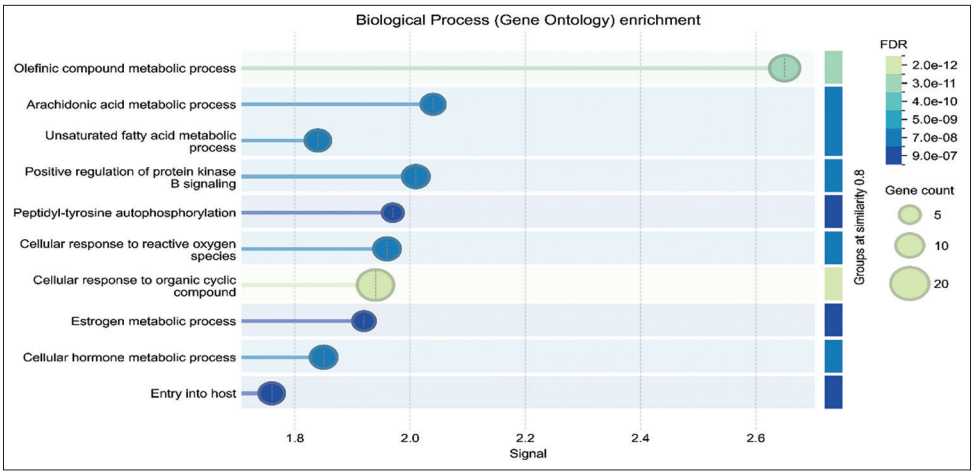

Figure 7: Involved pathways of chronic obstructive pulmonary disease

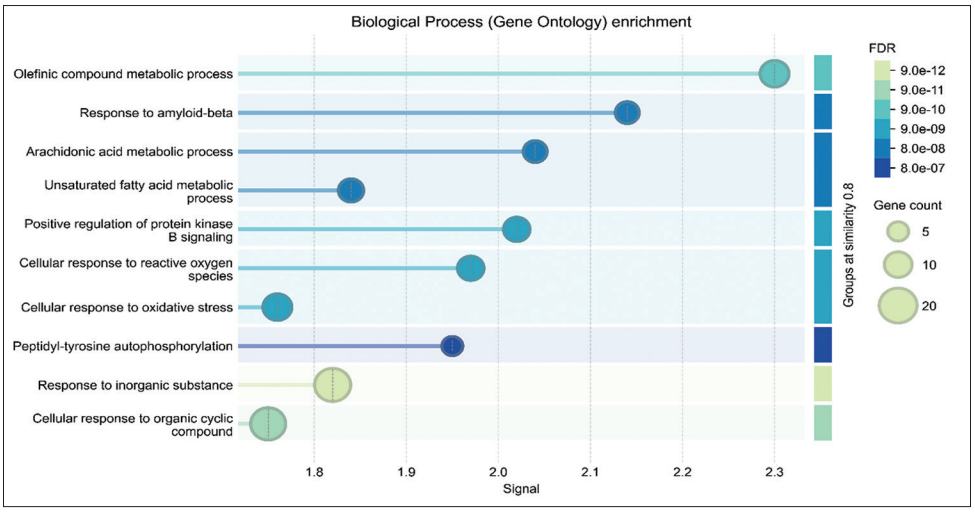

Figure 8: Involved pathways of COVID-19

with the greatest degree values in the network were selected for analysis under both conditions: Quercetin, Apigenin, Ellagic acid, Luteolin, and Chrysin. EGFR, PRKACA, and SRC were selected as targets for COPD, and EGFR, IGF1R, and MET were chosen for COVID-19 due to their notable interactions with the important phytochemicals. The selection was based on binding energy values of ≤−5 kcal/mol, which indicate strong and potentially important molecular interactions. The detailed molecular docking scores of the selected phytochemicals against COPD and COVID-19 targets proteins are presented in Tables 3 and 4, respectively.

Docking analysis of COPD targets

PRKACA with ellagic acid

PRKACA showed the strongest interaction with the chosen phytochemicals among the COPD-associated targets. With a docking score of −10.8 kcal/mol, Ellagic acid showed the highest binding affinity toward PRKACA, suggesting a very stable ligand-protein complex.

According to molecular docking and imaging experiments. The ligand improved complex stability by forming traditional hydrogen bonds with significant residues like ASP184, LYS72, and ARG18. The ligand-protein contact was reinforced by additional π-sigma, π-alkyl, and π-sulfur interactions. Ellagic acid was properly accommodated into the catalytic pocket without steric restriction, as confirmed by the 3D visualization. Ellagic acid may successfully control PRKACA activity and may have therapeutic potential against COPD-related pathways, according to the strong docking score and stable intermolecular contacts. Interaction of Ellagic acid with PRKACA, binding mode representation, and 2D representation of PRKACA is illustrated in Figure 11.

Docking analysis of covid-19 targets

IGF1R with ellagic acid

Molecular docking analysis revealed that Ellagic acid exhibited the highest binding affinity with IGF1R, with a docking score of −8.4 kcal/mol, indicating the formation of a stable ligand-protein complex. The strong negative binding

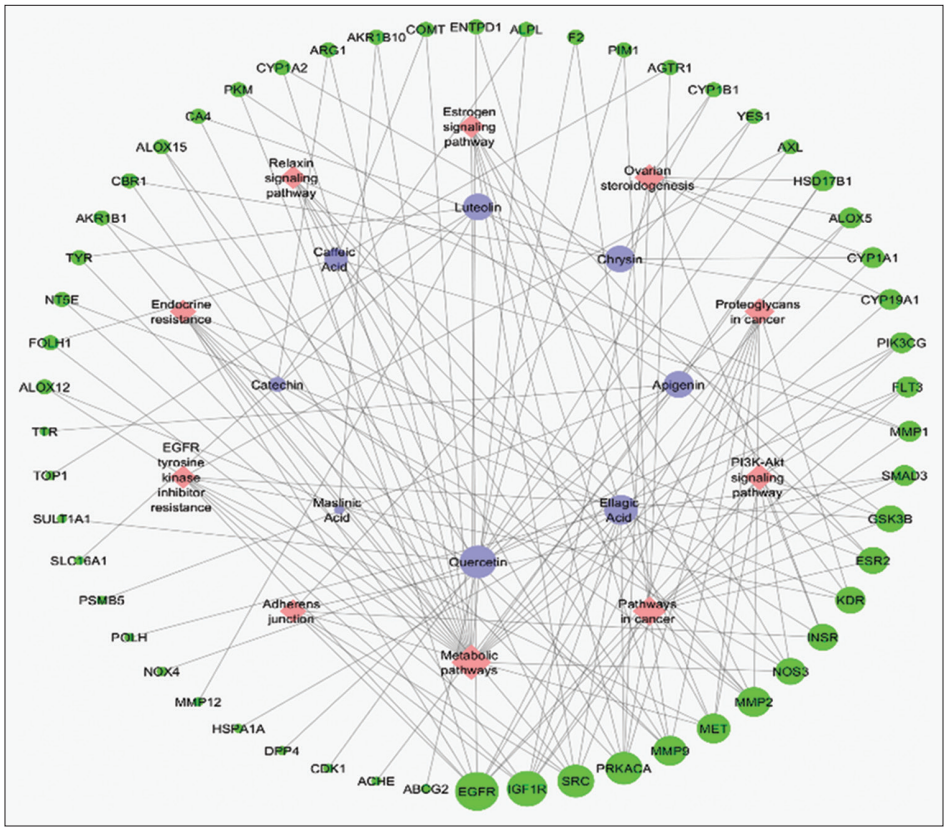

Figure 9: The interaction link between eight key active components, 55 overlapping targets, and ten significantly enriched Kyoto Encyclopedia of Genes and Genomes pathways was constructed using Cytoscape 3.7.2 software

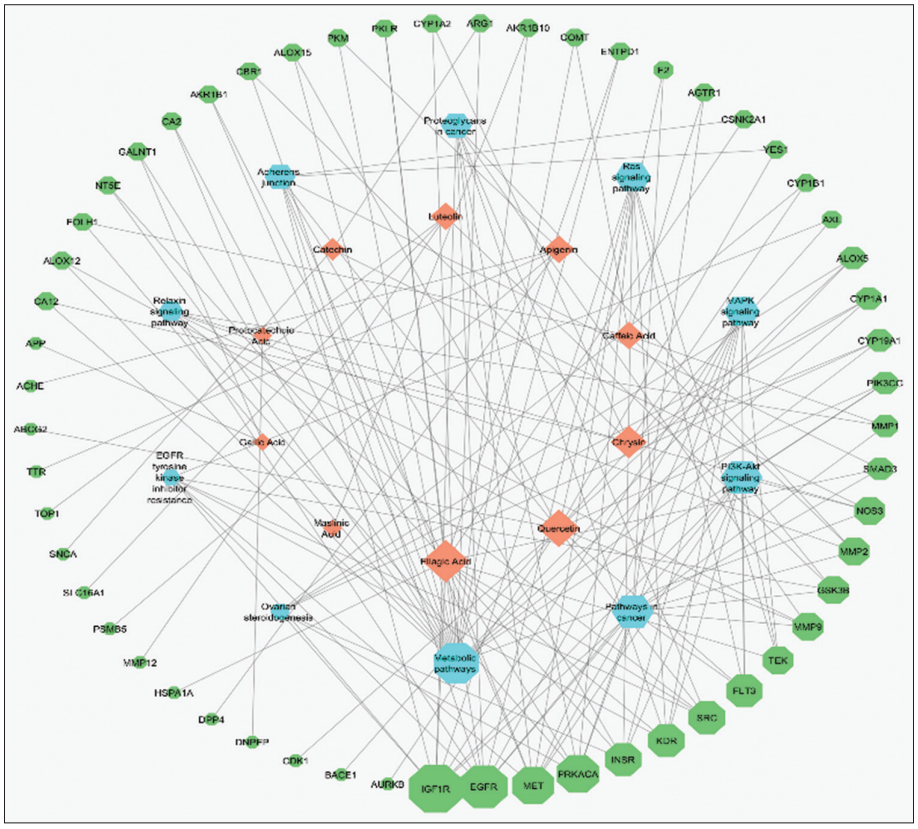

Figure 10: The interaction link between ten key active components, 57 overlapping targets, and ten significantly enriched Kyoto Encyclopedia of Genes and Genomes pathways was constructed using Cytoscape 3.7.2 software

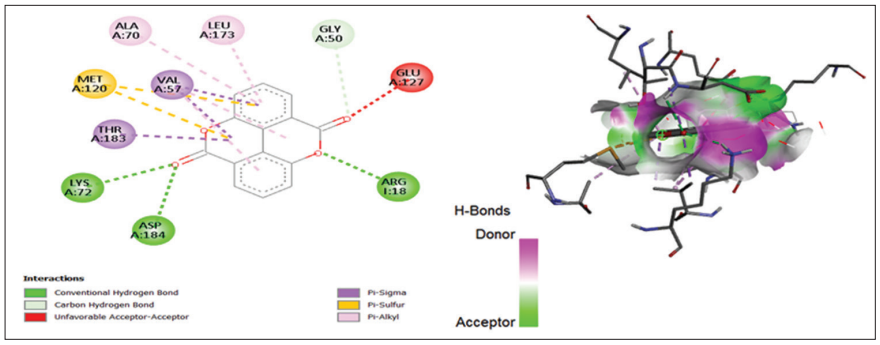

Figure 11: Interaction of Ellagic acid with PRKACA, binding mode representation, and 2D representation of PRKACA

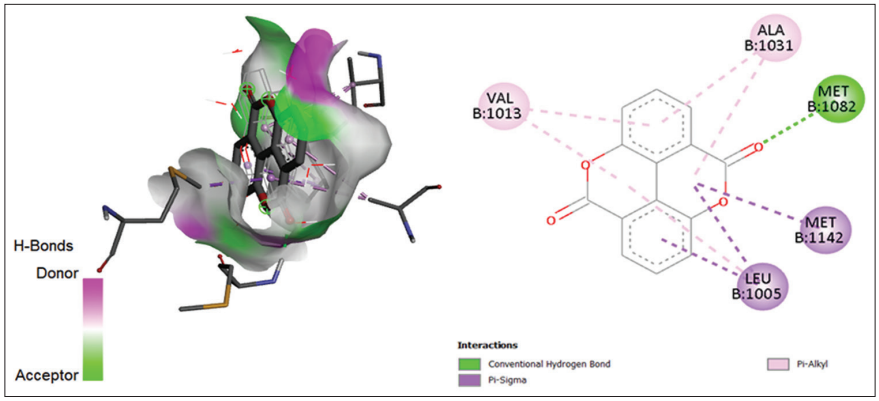

Figure 12: Interaction of Ellagic acid with IGF1R, binding mode representation and 2D representation of IGF1R

Table 1: Analysis of the chronic obstructive pulmonary disease process using Gene set enrichment

Term ID	Term description	Observed gene count	Background gene count	False discovery rate	Proteins
hsa01100	Metabolic pathway	21	1435	1.78E−08	HSD17B1, ALOX12, FOLH1, NT5E, TYR, AKR1B1, CBR1, ALOX15, NOS3, CA4, PKM, CYP1A2, ARG1, AKR1B10, COMT, ENTPD1, ALOX5, ALPL, CYP1A1, CYP19A1, PIK3CG
hsa05200	Pathways in cancer	14	515	1.78E−08	MMP2, FLT3, EGFR, F2, PRKACA, MET, MMP1, GSK3B, SMAD3, ESR2, MMP9, PIM1, AGTR1, IGF1R
hsa04151	PI3K-Akt signaling pathway	9	349	1.50E−05	FLT3, KDR, EGFR, NOS3, INSR, MET, GSK3B, PIK3CG, IGF1R
hsa04913	Ovarian steroidogenesis	8	50	1.23E−09	HSD17B1, INSR, PRKACA, ALOX5, CYP1A1, CYP19A1, CYP1B1, IGF1R
hsa05205	Proteoglycans in cancer	8	194	3.48E−06	MMP2, KDR, EGFR, PRKACA, MET, MMP9, SRC, IGF1R
hsa04520	Adherens junction	7	69	1.38E−07	EGFR, INSR, MET, SMAD3, SRC, YES1, IGF1R
hsa01521	EGFR tyrosine kinase inhibitor resistance	7	77	2.25E−07	KDR, EGFR, AXL, MET, GSK3B, SRC, IGF1R
hsa01522	Endocrine resistance	7	94	6.88E−07	MMP2, EGFR, PRKACA, ESR2, MMP9, SRC, IGF1R
hsa04926	Relaxin signaling pathway	7	126	3.48E−06	MMP2, EGFR, NOS3, PRKACA, MMP1, MMP9, SRC
hsa04915	Estrogen signaling pathway	7	133	3.96E−06	MMP2, EGFR, NOS3, PRKACA, ESR2, MMP9, SRC

EGFR: Epidermal growth factor receptor

Table 2: Analysis of the COVID-19 disease process using Gene set enrichment

Term ID	Term description	Observed gene count	Background gene count	False discovery rate	Proteins
hsa01100	Metabolic pathway	21	1435	3.89E−08	CA12, ALOX12, FOLH1, NT5E, GALNT1, CA2, AKR1B1, CBR1, ALOX15, NOS3, PKM, PKLR, CYP1A2, ARG1, AKR1B10, COMT, ENTPD1, ALOX5, CYP1A1, CYP19A1, PIK3CG
hsa05200	Pathways in cancer	14	515	1.83E−06	MMP2, FLT3, EGFR, F2, PRKACA, MET, MMP1, GSK3B, SMAD3, MMP9, AGTR1, IGF1R
hsa04151	PI3K-Akt signaling pathway	10	349	3.92E−06	FLT3, KDR, EGFR, NOS3, INSR, MET, GSK3B, TEK, PIK3CG, IGF1R
hsa04520	Adherens junction	8	69	1.75E−08	CSNK2A1, EGFR, INSR, MET, SMAD3, SRC, YES1, IGF1R
hsa05205	Proteoglycans in cancer	8	194	5.13E−06	MMP2, KDR, EGFR, PRKACA, MET, MMP9, SRC, IGF1R
hsa04014	Ras signaling pathway	8	225	1.12E−05	FLT3, KDR, EGFR, INSR, PRKACA, MET, TEK, IGF1R
hsa04010	MAPK signaling pathway	8	286	4.96E−05	FLT3, KDR, EGFR, INSR, PRKACA, MET, TEK, IGF1R
hsa04913	Ovarian steroidogenesis	7	50	3.89E−08	INSR, PRKACA, ALOX5, CYP1A1, CYP19A1, CYP1B1, IGF1R
hsa01521	EGFR tyrosine kinase inhibitor resistance	7	77	3.64E−07	KDR, EGFR, AXL, MET, GSK3B, SRC, IGF1R
hsa04926	Relaxin signaling pathway	7	126	5.13E−06	MMP2, EGFR, NOS3, PRKACA, MMP1, MMP9, SRC

EGFR: Epidermal growth factor receptor

Table 3: Protein docking of *Eucalyptus globulus* in chronic obstructive pulmonary disease

Phytochemicals	Binding affinity		
	EGFR (4HJO)	PRKACA (4WB5)	SRC (4MXO)
Quercetin	−9	−9.4	−8.5
Apigenin	−8.6	−9.5	−8.2
Luteolin	−8.8	−10	−8.2
Chrysin	−8.7	−9.7	−8.2
Ellagic-acid	−9.1	−10.8	−8.6

EGFR: Epidermal growth factor receptor

Table 4: Protein docking of *Eucalyptus globulus* in COVID-19

Phytochemicals	Binding affinity		
	EGFR (4WKQ)	IGF1R (1JQH)	MET (3KDF)
Quercetin	−8.4	−7.4	−7.5
Apigenin	−8.1	−7.5	−8.2
Luteolin	−8.4	−7.5	−8.2
Chrysin	−8	−7.6	−8.1
Ellagic-acid	−8	−8.4	−7.7

EGFR: Epidermal growth factor receptor

energy suggests favorable interaction of Ellagic acid within the active binding pocket of IGF1R.

Visualization studies further confirmed the stable accommodation of ellagic acid inside the catalytic cavity of IGF1R. The ligand formed a conventional hydrogen bond with MET1082, while additional π-sigma and π-alkyl interactions with residues LEU1005, VAL1013, ALA1031, and MET1142 enhanced the overall stability of the complex. The 3D surface visualization demonstrated proper fitting of the ligand without steric hindrance, suggesting favorable conformational orientation and effective interaction with the active site residues of IGF1R. Interaction of Ellagic acid with IGF1R, binding mode representation and 2D representation of IGF1R is illustrated in Figure 12.

Even though Ellagic acid had the highest binding affinity for IGF1R, the visualization analysis also showed the presence of persistent hydrogen bond connections, indicating strong ligand–protein stability and effective binding into the active area.

Luteolin (−8.4 kcal/mol) and (Quercetin −8.4 kcal/mol) also confirmed comparable binding affinities and substantial

hydrogen bond interactions with EGFR, suggesting a stable binding orientation and potential inhibitory efficacy against the target. These findings demonstrate that, in addition to docking score, hydrogen bonding is crucial for maintaining the phytochemical-target complexes.

DISCUSSION

The current study used network pharmacology and molecular docking to investigate the therapeutic potential of *E. globulus* against COVID-19 and COPD. The results showed that *E. globulus* phytochemicals relate with several disease-associated sites and signaling pathways, indicating a multi-target therapeutic approach.

The results of network pharmacology were further verified by molecular docking studies. Ellagic acid showed the highest binding affinity among the chosen phytochemicals toward IGF1R in COVID-19 (−8.4 kcal/mol) and PRKACA in COPD (−10.8 kcal/mol). The strong binding interactions and stable ligand–protein complexes were supported by multiple hydrogen bonds and hydrophobic interactions.

E. globulus may have synergistic therapeutic effects because Quercetin and Luteolin also shown significant binding affinities with EGFR. By lowering oxidative stress and inflammatory cytokines, Ellagic acid confirmed notable anti-inflammatory and antioxidant benefits.

Ellagic acid in COPD

Ellagic acid showed significant anti-inflammatory and antioxidant effects by reducing neutrophils infiltration, vascular permeability, edema and proinflammatory cytokine interleukin (IL)-6 and increasing anti-inflammatory IL-10 levels. Its activity was independent of AP-1 and nuclear factor kappa B (NF-κB) pathways, as compared to dexamethasone, indicating fewer immunosuppressive effects.

Ellagic acid has shown therapeutic potential in problems associated with COPD, by decreasing oxidative stress, pulmonary hypertension, and accumulation of inflammatory cells in models of COPD and emphysema. It also improved heart function, prevented oxidative damage and restored the activity of antioxidant enzymes.[27]

Ellagic acid in covid-19

Ellagic acid and its metabolites show strong antioxidant and anti-inflammatory properties. During chronic inflammation, they aid in lowering oxidative stress, fibrosis, tissue damage, and excessive immune cell infiltration.

In addition, Ellagic acid shields endothelial cells by reducing inflammatory molecules, including ICAM1 and VCAM1. The NF-κB pathway is activated by elevated cytokines such as tumor necrosis factor-α, IL-1β, and IL-6 in COVID-19, resulting in severe inflammation. These proinflammatory cytokines can be decreased and NF-κB signaling suppressed by Ellagic acid, pomegranate polyphenols, and particularly urolithin A. As a result, they might act as protective natural agents against oxidative stress, lung fibrosis, neuroinflammation, and inflammation brought on by SARS-CoV-2 infection.[28,29]

PRKACA in COPD

PRKACA regulates significantly the cAMP/PKA signaling pathway, which is involved in inflammation, bronchodilation, oxidative stress and apoptosis in COPD. Dysregulation of PRKACA can worsen chronic airway inflammation by triggering inflammatory transcription factors, including NF-κB and CREB. Another effect of impaired signaling that leads to airflow restriction is reduced airway smooth muscle relaxation.

In addition, changes in PRKACA action stimulate the growth of emphysema by increasing oxidative stress and epithelial cell damage. Respiratory pathogens may use this route to damage immune responses, resulting in serious infections and exacerbations of COPD. Overall, PRKACA is a key player in the pathophysiology of COPD.[30]

IGF1R in covid-19

IGF1R plays a defensive role in tissue repair and immunological parameter during COVID-19. The greater levels of IL-6 and lower levels of insulin-like growth factor-1 in individuals with severe COVID-19 suggested increased inflammation and reduced IGF1R signaling. The severity of the disease, cytokine storm, and lung damage may all be impacted by this imbalance. Therefore, a possible target for COVID-19 treatment could be the IGF1R pathway.[31]

IGF1R uses the PI3K/AKT and MAPK signaling pathways to control inflammation, cell survival, and tissue repair. Abnormal IGF1R activity may exacerbate ARDS, lung inflammation, fibrosis, and cytokine storm in severe COVID-19. In addition, it is linked to neurological issues, comorbidities, and age-related vulnerability, all of which exacerbate the severity of the illness.[32]

The pharmacological effects of *E. globulus* against COVID-19 and COPD were linked to the top ten signaling pathways, according to KEGG pathway analysis. The metabolic pathway was shown to be the common mechanism involved in both disorders.

Metabolic pathways in COPD and COVID-19

Metabolic pathway disturbances involving mitochondrial dysfunction, modified glycolysis, and anomalies in lipid,

amino acid, glucose, nucleotide, and microbial metabolism are closely linked to the pathophysiology of COPD.[33] Through pathways like mTOR, AMPK, and NAD^+/SIRT1, these changes promote oxidative stress, chronic inflammation, immunological dysregulation, and disturbed energy balance. In COPD, the ensuing immune-metabolic imbalance causes weariness, muscular atrophy, airway remodeling, emphysema progression, and general systemic weakness.[34]

SARS-CoV-2-induced metabolic reprogramming, which involves disruptions in glucose, amino acid, lipid, nucleotide, and mitochondrial pathways, is closely associated with COVID-19 pathogenesis. The virus causes ROS generation, oxidative stress, compromised antiviral responses, immunological dysregulation, and cytokine storm by suppressing oxidative phosphorylation and increasing glycolysis. Metabolic pathways are crucial therapeutic targets because of the interrelated metabolic and mitochondrial changes that lead to inflammation, multi-organ damage, and increased disease severity.[35]

CONCLUSION

In the present study, the therapeutic potential of Tailaparna (*E. globulus* Labill.) against COVID-19 and COPD was demonstrated by network pharmacology and molecular docking. The multi-component and multi-target pharmacological activities of *E. globulus* are ascribed to the identification of several bioactive phytochemicals and their related targets, according to the study.

Network pharmacology analysis revealed that the metabolic pathways, PI3K-Akt signaling pathway, MAPK signaling pathway, EGFR tyrosine kinase inhibitor resistance, and proteoglycans in cancer were significantly involved in the pathophysiology of both COVID-19 and COPD. Among them, metabolic pathways were identified as the common mechanism pathway between the two disorders.

The molecular docking and visualization studies using BIOVIA Discovery Studio were undertaken to validate the therapeutic potential of the selected phytochemicals. Among the compounds analysed, ellagic acid showed the highest binding affinity with IGF1R in COVID-19 and PRKACA in COPD, indicating a prolonged ligand-protein interaction and a potential regulatory influence on oxidative stress and inflammatory pathways. The strong binding affinities of Quercetin and Luteolin to EGFR also show the synergistic therapeutic potentials of *E. globulus* phytochemicals.

The results suggest that *E. globulus* might be a possible choice to treat COVID-19 and COPD in a natural approach by modulating immunological, metabolic, oxidative stress and inflammatory pathways. These computational findings need to be confirmed by further *in vitro*, *in vivo,* and clinical research to find their safety and efficacy in clinical practice.

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DECLARATION ON THE USE OF AI TOOLS

AI tools were used for improvising language and manuscripts.

AUTHORS CONTRIBUTION

1st Author: Conceptualization and Methodology, Writing, Network Pharmacology, and Molecular Docking analysis. 2nd Author: Review and Editing. 3rd Author: Data analysis.

REFERENCES

1. Adeloye D, Song P, Zhu Y, Campbell H, Sheikh A, Rudan I, *et al*. Global, regional, and national prevalence of, and risk factors for, chronic obstructive pulmonary disease (COPD) in 2019: A systematic review and modelling analysis. Lancet Respir Med 2022;10:447-58.
2. The Top 10 Causes of Death - World Health Organization (WHO). Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of/death [Last accessed on 2022 Nov 09].
3. López-Campos JL, Tan W, Soriano JB. Global burden of COPD. Respirology 2016;21:14-23.
4. Indian Institute of Metrology and Health Assessment; 2020. Available from: https://www.healthdata.org/india [Last accessed on 2022 Nov 09].
5. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. Lancet 2009;374:733–43.
6. World Health Organization. Timeline- COVID-19: Available from: https://www.who.int/news/item/29-06-2020-covidtimeline [Last accessed on 2021 Jun 01].
7. Celli B, Fabbri L, Criner G, Martinez FJ, Mannino D, Vogelmeier C, *et al*. Definition and nomenclature of chronic obstructive pulmonary disease: Time for its revision. Am J Respir Crit Care Med 2022;206:1317-25.
8. Du L, He Y, Zhou Y, Liu S, Zheng BJ. The spike protein of SARS-CoV--atarget for vaccine and therapeutic development. Nat Rev Microbiol 2009;7:226-36.
9. Fahmi MZ, Karuniawati H, Ismail WI. Drug-related problems in chronic obstructive pulmonary disease: Literature review. J Pharm Sci 2025;8:1916-22.
10. Borse S, Joshi M, Saggam A, Bhat V, Walia S, Marathe A, *et al*. Ayurveda botanicals in COVID-19 management: An *in silico* multi-target approach. PLoS One 2021;16:e0248479.

11. Aswathy M, Jithesh M. Ayurvedic management of chronic obstructive pulmonary disease using the treatment principles of tamaka swasa -a case report. Kerala J Ayurveda 2024;3:10-3.
12. Girija PLT, Sivan N. Ayurvedic treatment of COVID19/ SARS-CoV-2: A case report. J Ayurveda Integr Med 2020:2-6.
13. Ahmad MI, Ali N, Feroz F, Faizan M, Usman M, Farman M, *et al*. Phytochemical and pharmacological profile of *Eucalyptus globulus*. Asian Pac J Trop Biomed 2014;4 Suppl 1:S169-76.
14. Karthikeyan M, Bagavathy SK, Vivek-Ananth RP, Bharath Chand RP, Aparna SR, Mangalapandi P, *et al*. IMPPAT: A curated database of Indian medicinal plants, phytochemistry and therapeutics. Sci Rep 2018;8:4329.
15. Dr. Duke's Phytochemical and Ethnobotanical Databases. U.S. Department of Agriculture, Agricultural Research Service. 1992 2016. Available from: https://phytochem.nal.usda.gov [Last accessed on 2022 Aug 20].
16. Daina A, Michielin O, Zoete V. SwissADME. A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep 2017;7:42717.
17. Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, *et al*. PubChem 2019 update: Improved access to chemical data. Nucleic Acids Res 2019;47:D1102-9.
18. Liu T, Lin Y, Wen X, Jorissen RN, Gilson MK. BindingDB: A web accessible database of experimentally determined protein-ligand binding affinities. Nucleic Acids Res 2007;35:D198-201.
19. Wang Y, Wang Q, Huang H, Huang W, Chen Y, McGarvey PB, *et al*. A crowdsourcing open platform for literature curation. Uni Prot PLoS Biol 2021;19:e3001464.
20. Stelzer G, Rosen N, Plaschkes I, Zimmerman S, Twik M, Fishilevich S, *et al*. The GeneCards suite: From gene data mining to disease genome sequence analyses. Curr Protoc Bioinformatics 2016;54:1.30.1-33.
21. The Human Protein Atlas. Human Protein Atlas; 2019. Available from: Available from: https://www.proteinatlas.org
22. Szklarczyk D, Kirsch R, Koutrouli M, Nastou K, Mehryary F, Hachilif R, *et al*. The STRING database in 2023: Protein-protein association networks and functional enrichment analyses for any sequenced genome of interest. Nucleic Acids Res 2023;51:D638-646
23. Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, *et al*. Cytoscape: A software environment for integrated models of biomolecular interaction networks. Genome Res 2003;13:2498-504.
24. Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, *et al*. The protein data bank. Nucleic Acids Res 2000;28:235-42.
25. Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. Methods Mol Biol 2015;1263; 243 250.
26. Kemmish H, Fasnacht M, Yan L. Fully automated antibody structure prediction using BIOVIA tools: Validation study. PLoS One 2017;12:e0177923.
27. Gupta A, Singh AK, Kumar R, Jamieson S, Pandey AK, Bishayee A. Neuroprotective potential of ellagic acid: A critical review. Adv Nutr. 2021;12(4):1211-8.
28. Aleksandrova S, Alexova R, Tancheva L, Kalfin R. The anti-COVID19 potential of the ellagic acid and the pomegranate polyphenols. Trakia J Sci 2021;19 Suppl 2:38-44.
29. Aleksandrova S, Alexova R, Tancheva L, Kalfin R. Anti-COVID-19 potential of ellagic acid and polyphenols of *Punica granatum* L. Molecules 2023;28:3772.
30. Online Mendelian Inheritance in Man, OMIM®. PRKACA, Protein Kinase, cAMP-Dependent, Catalytic, Alpha; OMIM Entry 601639. Baltimore, MD: Johns Hopkins University; 1966-2026. Available from: https://www.omim.org/entry/601639 [Last accessed on 2026 May 20].
31. Feizollahi P, Matin S, Roghani SA, Mostafaei S, Safarzadeh E, Taghadosi M. Evaluation serum levels of insulin growth factor-1 (IGF-1) and its association with clinical parameters in severe COVID-19. Inflammopharmacology 2022;30:199-205.
32. Al-Kuraishy HM, Al-Gareeb AI, Al-Hussaniy HA, Al-Buhadily AK, Al-Harcan NA, Alotaibi AM, *et al*. The effect of IGF-1 plasma concentration on COVID-19 severity. Microb Pathog 2022;165:105420.
33. Wu W, Li Z, Wang Y, Huang C, Zhang T, Zhao H. Advances in metabolomics of chronic obstructive pulmonary disease. Chin Med J Pulm Crit Care Med 2023;136:2371-82.
34. 34. Chen W, Huang S, He L, Zhou X, Li R, Wang G. Immune-metabolic positive feedback model in COPD: Cross-mechanisms and potential intervention strategies. Front Cell Dev Biol 2026;14:730727.
35. Singh KK, Chaubey G, Chen JY, Suravajhala P. SARS-CoV-2 mitochondrial metabolic and epigenomic reprogramming in COVID-19. Free Radic Biol Med 2024;188:107170.

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