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RESEARCH

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Evaluation of the effects of curcumin on chronic obstructive pulmonary disease with a bio-computational approach

Mohammad Maboudian[1,2,3†], Elham Amjad[1†], Solmaz Asnaashari[1], Siavoush Dastmalchi[1,3], Babak Sokouti[1*] and Yousef Javadzadeh[1,3*]

Abstract

Background According to the increasing trend of COPD, the timely diagnosis and treatment of the disease can reduce the high costs to the health systems. Therefore, by biological calculation methods, signaling pathways and genes involved in this disease can be obtained and used to design drugs and other treatment methods. By using biological calculations, we determined that curcumin can affect this disease and its genes and signaling pathways. Our goal in this study was to find the genes by which curcumin exerts its effect and can maintain the function of corticosteroids against oxidizing agents.

Results By finding the genes, it is possible to find precisely the pathways by which curcumin works, which can be used to design other drugs that cause these pathways and minimize their side effects. This study considers healthy samples (with/without curcumin) and oxygen-free radicals (with/without curcumin). Finally, statistical algorithms extract meaningful genes as effective biomarkers to investigate curcumin's effects and signaling pathways in COPD. The results show that the genes finally obtained as the most critical genes confirmed by the literature are effective in COPD. Finally, curcumin was input in SwissTargetPrediction to identify potential protein receptors. We used LigPlot+ software to visualize the receptor–ligand binding result provided by iGEMDOCK.

Conclusions The data showed that the most significant genes in each group have been confirmed in other studies to be effective in this disease, and protein–protein interaction networks can be established between them to investigate their roles.

Keywords Chronic obstructive pulmonary disease, Curcumin, Gene modules, Mathematical models, Biological pathways, Bio-computation

Introduction

Chronic bronchitis and pulmonary emphysema are two primary components of chronic obstructive pulmonary disease (COPD) [1], a significant global health burden ranks statistically third in terms of causes of death worldwide, and its incidence is steadily increasing [2]. The pathophysiology of this disease shows that airflow restriction is due to the destruction of small airways and the parenchyma of the lungs, which causes balance disorders between protease and antiprotease in the lung. The disease has four stages that are classified

†Mohammad Maboudian and Elham Amjad have contributed equally and should be considered joint first authors

*Correspondence:
Babak Sokouti
b.sokouti@gmail.com
Yousef Javadzadeh
javadzadehy@yahoo.com
[1] Biotechnology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[2] Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
[3] School of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran

from mild to severe. COPD patients commonly struggle with symptoms such as whooping cough, shortness of breath, and wheezing. Available approaches to controlling the disease include preventing illness progression, maintaining signs, and improving the exercise tolerance test (ETT). The essential and fundamental step is to quit smoking. This disease uses beta-agonists, anticholinergics, methylxanthines such as theophylline, and corticosteroids. One of the most critical challenges for controlling disease attacks is air pollution and lung infections [1]. The literature has ample evidence of the genetic role in the development of lung carcinoma. It is worth noting that the two diseases, lung cancer and COPD, share several genetic mechanisms; these include, i. inflammation, where both conditions involve chronic inflammation in the lungs, and it can lead to cellular damage and mutations; ii. transformed mesenchymal cells can contribute to the development of both lung cancer and COPD; iii. lung tissues are susceptible to oxidative stress, which can result in DNA damage and increase the risk of cancer and COPD; iv. the formation of new blood vessels in the lungs can promote the growth and spread of cancer cells, as well as contribute to the development of COPD; v. impaired DNA repair mechanisms can increase the risk of genetic mutations and cancer in both lung tissues; vi. cell proliferation can lead to the development of both lung cancer and COPD. These common genetic mechanisms highlight the close relationship between lung cancer and COPD, and suggest potential targets for therapeutic interventions. Considering the mechanism of inflammation, inhaling cigarette smoke or other carcinogens exposes the body to a weakened immune system associated with increased inflammation, all of which lead to the formation and progression of tumors, specifically COPD [3].

Increased oxidative stress through the generation of free radicals is one of the results of the smoking-related contributing factors; in other words, it, in turn, increases ROS production of ROS (reactive oxygen species) by lung epithelial cells [4]. Phytochemicals from the Curcuma longa roots include curcumin, which is naturally polyphenolic [5]. This plant belongs to the Zingiberaceae family and is native to Southeast Asia. Turmeric, with various pharmacological properties, contains a group of substances known as curcumin, including curcumin, dimethoxy curcumin, and methoxy-curcumin. Curcumin, with medicinal properties, is the main active ingredient in curcuminoids. The yellow color of turmeric and its therapeutic effects are related to the existence of curcumin [6]. Regarding the placement of curcumin in the pharmacological drug groups, it belongs to the group of anti-inflammatory substances with a non-steroidal structure. In addition to its non-inflammatory effects, curcumin has analgesic, antipyretic, and platelet inhibitory effects [7].

Curcumin has antioxidant activity that can reduce the body's ROS. This property of curcumin is due to its excellent electron transfer capacity due to its unique structure and various functional groups such as β-diketone and several π electrons. They can connect two phenyl rings [8]. Because genes are the potential source of many diseases, identifying and investigating significant biomarkers involved in chronic obstructive pulmonary disease using curcumin may increase the patient's chances of survival since early detection and treatment can benefit recurrence prevention. The use and analysis of gene expression data are essential in biomarker determination. Therefore, identifying genes with statistically significant expression values compared to other genes and assessing the signaling pathways are paramount. In this experiment, we want to find out the genes involved in COPD using different periods classified in other groups of samples by comparing them in the existence or absence of curcumin and taking into account the standard and high ROS levels. In the author's opinion, this work is a first, enabling further research and the development of effective treatments based on genes and pathways associated with COPD to be addressed in further studies.

Methods

The flowchart of the process of answering the research question is summarized in Fig. 1.

Source of microarray data sets

In this study, we obtained gene expression data from the Gene Expression Omnibus database (GEO), a publicly accessible repository of gene expression information maintained by the National Center for Biotechnology Information (NCBI). Specifically, we retrieved GSE10896 with platform GPL570 Affymetrix Human Genome U133 Plus 2.0 Array-based microarray dataset, from the GEO database. This platform offers a comprehensive analysis of genome expression, allowing for the detection of subtle changes in gene expression levels across different samples. By leveraging the resources of the GSE and the Affymetrix platform, we aimed to generate valuable insights into the complex mechanisms underlying specific biological processes and diseases. To assess the effects of curcumin, 24 samples are divided into eight groups to compare the possible significant gene expression levels at different conditions. The eight groups include group 1, naive_untreated_4h versus naive_curcumin_4h, group 2, naive_untreated_4h versus ROS_curcumin_4h, group 3, naive_curcumin_4h versus ROS_untreated_4h, group 4, ROS_untreated_4h versus

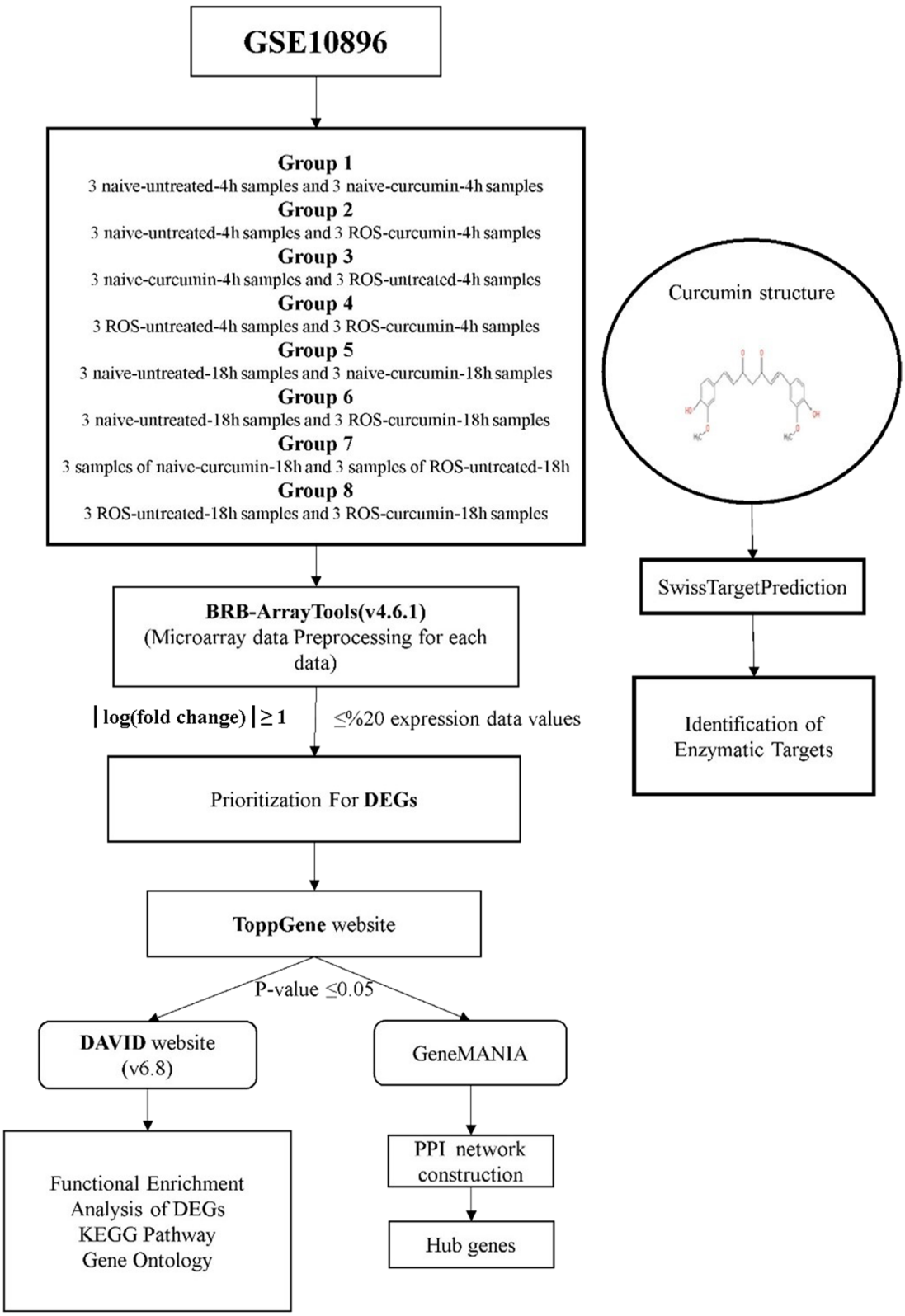

Fig. 1 The schematic flowchart of the research process starting from selection of the GEO microarray dataset to final post processing stages

ROS_curcumin_4h, group 5, naive_untreated_18h versus naive_curcumin_18h, group 6, naive_untreated_18h versus ROS_curcumin_18h, group 7, naive_curcumin_18h versus ROS_untreated_18h, group 8, ROS_untreated_18h versus ROS_curcumin_18h.

In the GSE10896 dataset, a specific cell line U937 was employed for investigative purposes. This cell line was allegedly derived from histiocytic lymphoma samples taken from a 37-year-old male individual and was intended to elucidate the behavior and differentiation of monocytes.

Different genes expressed between groups (DEG)

The BRB-Array Tools (version 4.6.1stable) development team, led by Dr. Richard Simon, has developed an analysis tool that can be used to identify noteworthy and differentially expressed genes. The steps in this tool included entering the GEO dataset, filtering genes by applying the $|\log(\text{fold change})| \geq 1$ option, normalizing with the quantile normalization option, and categorizing the most important DEGs. Due to inspecting even small changes of curcumin effects on gene expression levels, the cutoff for fold change was set to 1. This tool organized genes according to their intensity of expression using the MAS5 algorithm. The results obtained from DEGs were significant, considering $p < 0.05$.

DEGs priority

Based on evidence from the literature, the DEGs discussed in the previous section were ranked using the GeneCards [9] and ToPPGene [10] websites. Through 150 online sites and keywords, the GeneCards database (https://genecards.org) was used to find genes associated with a given disease, based on the training group's definitions. The terms "COPD" and "chronic obstructive pulmonary disease" were included in the keywords searched in this context. ToPPGene was used to rank the imported gene list and compare it with the train gene list to determine the gene(s) associated with COPD that was significantly differentially expressed (p-values less than 0.05). The test group was scored and ranked using the train group's similarity scores based on fuzzy and Pearson correlation measurement computations on the ToPPGene website.

Ontology and functional analysis of genes

In this section, we evaluate the ontology of genes through the DAVID version 6.8, a comprehensive information tool available for free at http://david.abcc.ncifcrf.gov/summary.jsp. It presents an extensive examination of differentially expressed genes (DEGs) and their involvement in KEGG signaling pathways, covering an assessment of their biological processes (BP) containing several chemical reactions, cellular components (CC) with various complex biomolecules, and molecular functions demonstrating activities of a target macromolecular with others (MF) [9, 10]. EASE score threshold was set to 0.1 by default.

Constructed network of protein–protein interactions

The constricted network of protein–protein interaction among the DEGs obtained from the previous steps helped find the interconnections among corresponding proteins through existing search tools. The search tool included STRING version 11.5 and GeneMANIA. In the STRING database, which contains data relating to protein–protein interactions, there are currently over 67 million proteins derived from nearly fourteen thousand distinct organisms. In August 2021, the database had accumulated over twenty million interactions between these proteins, representing a tremendous amount of data on protein–protein interactions. In the development of this tool, a comprehensive integration of GO, KEGG, Biocarta, and Reactome has been accomplished. With seamless information exchange between these databases, these pathways and networks can be identified more efficiently. IntAct, MINT, PID, BIND, DIP, GRID, HPRD, and IntAct are some of the prominent databases and initiatives that are affiliated with the tool. The tool can access a wealth of biological data and knowledge through these collaborations. In the protein–protein interaction network, the proteins obtained were represented by their nodes and the corresponding protein–protein relationships [11]. The GeneMANIA website at http://www.genemania.org was used to examine the functional possibilities of genes, analyze gene groups, and prioritize them for functional measurement. The website used genomics and proteomics information to link imported genes to similar genes in terms of functionality. Also, its search engine included a wealth of data on the functional roles of genes from the GEO, BioGRID, Pathway Commons, and I2D (Interlogous Interaction Database) databases. Additionally, the default cutoff score for STRING was 0.4, and no thresholds were available for GeneMANIA.

Relationship between curcumin efficacy and its structural components

PubChem, a comprehensive public access chemical compendium maintained by NCBI, was searched for the structural formula and SMILES code of curcumin [12]. Generally, strings of SMILES code could be used to determine structural similarity obtained from PubChem and the ADME forecasting tool using SwissADME online websites [13–15] and SwissTargetPrediction [16]. By calculating numerous factors, such as physicochemical descriptors, ADME-relative parameters, and

pharmacokinetic properties and effects similar to medicines and studying the medicinal chemistry of SMILES structure, we employed the SwissADME web server for drug creation and detection. A general theory of similarity states that two molecules with similar properties (thresholds of similarity of 0.65 in 2D and 0.85 in 3D) are likely to be similar. We have statistically quantified that bioactive molecules with similar targets will likely share them under the SwissTargetPrediction. Subsequently, through the analysis of a dataset comprising 370,000 active molecules with known targets, the most closely related molecules were identified for a given query molecule. This was achieved by employing a sophisticated computational approach that enabled the identification of the most similar molecules based on their shared target proteins. Target molecules with the highest similarity to the query molecule are predicted targets. Moreover, in SwissTargetPrediction, those targets with similar binding properties to similar structure queries were selected with a probability criterion over 0.50 for molecular docking purposes.

Molecular docking

In the first step, probability values were used to determine which receptors are most likely to be targeted by curcumin in treating COPD. To validate the predicted targets, we employed molecular docking techniques. In this process, we utilized the protein data bank (PDB) or Research Coordination Center for Biological Systems accessible from https://www.rcsb.org/) to obtain the studied proteins structures, which provided a molecular framework for docking simulations. Water molecule was removed from the structure. With the help of OpenBabel (v.3.1.1) software (https://github.com/openbabel/openbabel), the verified curcumin structure obtained from ZINC15 (http://zinc15.docking.org/) was converted to.mol2 format. With default parameters, docking was done with iGEMDOCK (version 2.1) [17]. Using LigPlot+ software (version 2.2.8), the identified low-energy receptors were visualized.

Results

In the first phase of this research, the significant genes of the studied groups were obtained using BRB-ArrayTools. Different genes expressed between the samples in each group are obtained and labeled upregulation/downregulation based on fold change values. Since ignoring each gene can affect the final result, all genes with fold changes more significant than one in the microarray dataset are considered. For example, 67 different expressed genes are obtained between the two samples in group 6, of which 12 are upregulated and 55 are downregulated. The detailed results are summarized in Table 1.

Table 1 The number of DEGs obtained from analysis in BRB_Array tools

Group No.	DEGs	Upregulated	Downregulated
1	26	26	0
2	58	35	23
3	36	18	18
4	23	10	13
5	44	25	19
6	67	12	55
7	2	0	2
8	4	3	1

Table 2 The final number of DEGs after prioritization in TOPPGene website

Group No.	DEGs	Upregulated	Downregulated
1	25	25	0
2	52	30	22
3	35	18	17
4	19	10	9
5	38	21	17
6	55	8	47
7	2	0	2
8	4	3	1

Next, the effective genes found in the clinically published literature on COPD patients at GeneCards.org were compared with the significant genes derived by BRB-Array Tools, and their expressions were obtained between two comparing samples in each group. Then, the ToppGene prediction server ranked the input test dataset (i.e., genes obtained from BRB-Array Tools) based on the training dataset (i.e., the clinically confirmed genes from GeneCards.org) for all compared groups in each step; however, one of the groups did not contain a considerable number of essential genes. The p-value was considered lower than 0.05 to select significant genes at this stage. Among the DEGs identified at this stage for each group, groups one to six contain one, six, three, one, four, six, and twelve genes, respectively, as shown in Table 2. The gene list was reduced, and groups 7 and 8 remained unchanged.

Based on the output of the DAVID bioinformatics tool, eight groups of prioritized genes are analyzed biologically and functionally. The processes in which these molecules are involved can be divided into BP, CC, MF, and KEGG signaling pathways. We have inserted genes with a p-value below 0.05 into this website so that they can be analyzed. For example, genes with mRNA positive

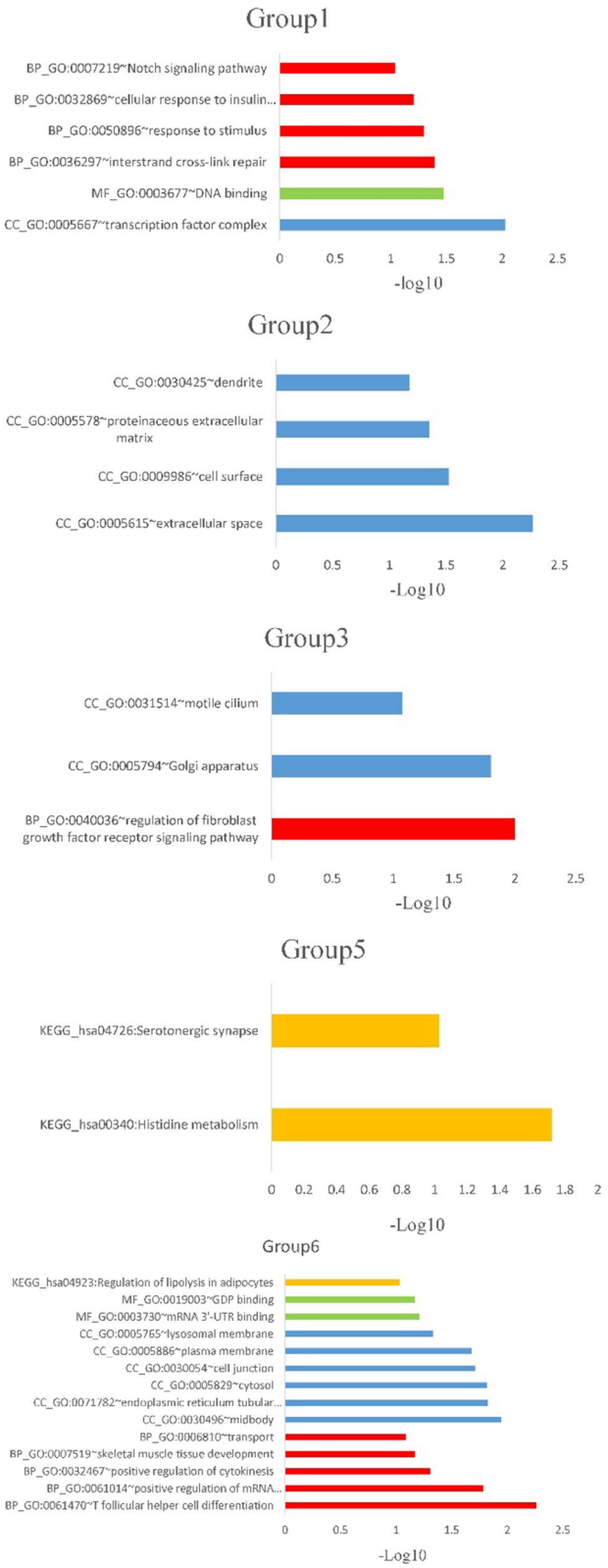

Fig. 2 The outcomes for BP (red), CC (blue), MF (green), KEGG signaling pathway (orange) enrichment analysis for target groups one, two, three, five, and six. The remaining groups four, seven, and eight did not present any enrichment analysis

regulation function in biological processing have practical expressions in catabolic processing, positive regulation of cytokine expression, and development of skeletal muscle tissue. Considering the cellular components, some genes affect extracellular space, the Golgi apparatus, and cell connections. In terms of molecular functions, there are genes with DNA binding activity, GDP binding, and 3'-UTR binding mRNA binding. The KEGG signaling pathway analysis shows that various genes play a role in histidine metabolism, serotonergic synapses, and the regulation of lipolysis in adipocytes (Fig. 2).

Utilizing the GeneMANIA website, the p-values less than 0.05 for the resulting genes in each protein–protein interaction network are illustrated (Fig. 3). In group 7, there are no data because there were no genes with p-value < 0.05. The images' purple, blue, yellow, and green lines (i.e., Fig. 3) mean coexpression, colocalization, shared protein domains, and genetic interactions.

PPI networks are generated for eight groups using Cytoscape software and the STRING database. Furthermore, genes with a p-value of less than 0.05 were entered into Cytoscape software to determine their interconnection relationships and identify genes using the cytohubba algorithm. The results show that in groups one to eight except seven, there are 16 nodes and one edge, 24 nodes and two edges, 22 nodes and one edge, eight nodes and no edge, 16 nodes and four edges, 25 nodes and four edges and two nodes and 0 edges; however, group 7 did not have results. Among the genes with higher interactions in PPI networks using eight groups, in group one, TCF3 and TCF7L1 were both upregulated with degree 1; in group two, SPON1, ADAMTS9, GABRA5 and NPTN were downregulated, and all had degree 1, in group three, TLE1 was upregulated, and ASCL1 was downregulated. Both had degree 1. In group five, HDC, SLC15A4 and HTR7 were downregulated, and MAOA was upregulated. In contrast, their degrees were 3, 1, 2 and 2, respectively, and in group six, UBE2A, RC3H1, HNRNPR, SLC1A2, GABRB2, ABHD5 and RAB18 were all downregulated, and their degrees were 1, 2, 1, 1, 1, 1 and 1, respectively (Table 3).

In biochemical networks, degrees 1, 2, 3, etc., classify the order in which protein–protein interactions occur: 1. First-degree interactions—Direct physical interactions between two proteins, such as enzymes and substrates. The proteins interact directly. Two proteins indirectly

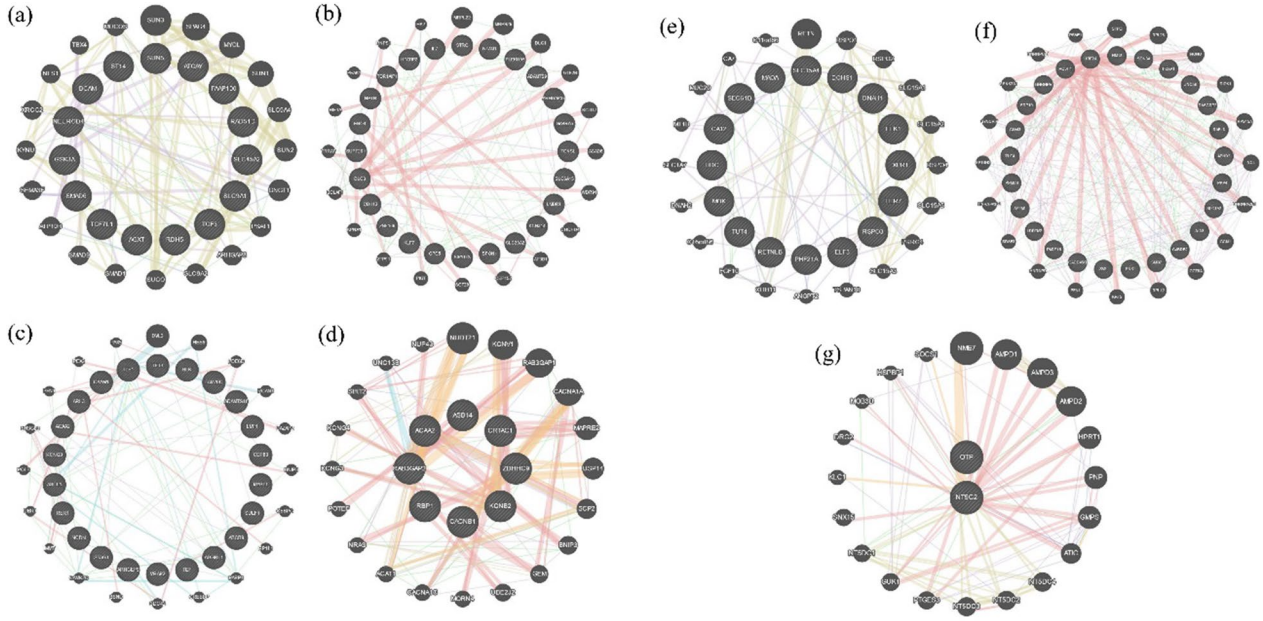

Fig. 3 The PPI networks constructed for **a** group 1, **b** group 2, **c** group 3, **d** group 4, **e** group 5, **f** group 6, and **g** group 8 propose the identified effected genes by other possible interacted genes

interact through an intermediate protein. For example, it is unclear whether protein A binds protein B or protein C directly. In addition, protein A indirectly affects the activity of protein C. 3. Third-degree interactions. In this case, two proteins (A and D) interact through a path involving two intermediate proteins (A–B, B–C, C–D). As a result, the functionally associated proteins A and D involve three steps. Two proteins that interact n-degrees indicate that they are linked by n-1 intermediate proteins, creating a chain of functional associations between the end proteins. In large protein functional networks within the cell, we can map the connectivity of indirect interactions and associations by analyzing these degrees of separation. To better understand information flow, network concepts like hubs, modules, and shortest paths take advantage of these interactions. They better understand how protein signaling has been interconnected and how signals propagate.

A molecular weight (MW) of 368.38 g/mol was observed by SwissADME, indicating curcumin's ability to absorb and distribute efficiently. The main feature of curcumin is that it forms hydrogen bonds with water molecules and accepts hydrogen bonds, which suggest that it enhances the solubility of water molecules through both donors and acceptors of hydrogen bonds. Approximately half of curcumin administered after oral administration reaches the systemic circulation, according to a study indicating 0.55 percent oral bioavailability. A lower topological polar surface area (TPSA) value indicates a low likelihood of curcumin interacting with membranes and moving across biological barriers. The absorption percentage of curcumin was impressively high at 93.06%, demonstrating the drug's excellent ability to penetrate the body. According to the findings presented, curcumin exhibits noteworthy oral bioavailability and solubility, rendering it a potentially valuable drug candidate. Studying the relationship between the effectiveness of curcumin and its structural components in the SwissTargetPrediction section, 101 curcumin target proteins were identified, among which enzymes, oxidoreductases, and isomerases had the highest probability values. Among 101 target proteins, monoamine oxidase A from the class of oxidoreductases, beta-amyloid A4 protein from the cell membrane category, histone acetyltransferase P300 from the Writer category, prostaglandin E synthase from the enzyme category, Toll-like receptor (TLR7/TLR9) from the toll-like and ll-1 receptors, beta-secretase one from the protease, and DNA topoisomerase II alpha from isomerase, with a probability of more than 50% were determined. This study also demonstrated curcumin's anti-inflammatory and antioxidant properties through the evidence from the literature presented in the next section.

In the SwissTargetPrediction analysis, the receptors mentioned earlier played a role in curcumin's impact on COPD. As listed in Table 4, we selected potential targets with their PDB IDs: 2BXR, 6UWP, 6GYR, 4BPM, 3WPF, 6ZJZ, 6OD6, 3QX3. Our next step involved docking eight

Table 3 The list of genes interacted with each other in PPI network from GeneMANIA

Groups	Gene symbol	Gene Name	Signaling pathways	References
Group 1	TCF3	Transcriptional factor 3	Wnt signaling pathway	[18]
	TCF7L1	Transcription Factor 7 Like 1	Wnt signaling pathway	[19]
	SUN5	Sad1 And UNC84 Domain Containing 5	–	[20]
	FAAP100	FA Core Complex Associated Protein 100	Fanconi anemia pathway (Repair of damaged DNA)	[21]
	AGXT	Alanine–Glyoxylate And Serine–Pyruvate Aminotransferase	Metabolic pathways	[22]
	SMAD6	SMAD Family Member 6	TGF-beta signaling pathway	[23]
	GSK3A	Glycogen Synthase Kinase 3 Alpha	Chemokine signaling pathway	[24]
	NEUROD4	Neuronal Differentiation 4	Notch signaling pathway	[25]
	ST14	ST14 Transmembrane Serine Protease Matriptase	Glycosaminoglycan biosynthesis—chondroitin sulfate / dermatan sulfate Pathway	[26]
Group 2	SPON1	Spondin 1	Apoptotic pathways in synovial fibroblasts and CREB pathway	[27]
	ADAMTS9	ADAM Metallopeptidase With Thrombospondin Type 1 Motif 9	Metabolism of proteins pathway	[28]
	GABRA5	Gamma-Aminobutyric Acid Type A Receptor Subunit Alpha5	Akt signaling	[29]
	SLC6A15	Solute Carrier Family 6 Member 15	Nuclear receptors meta-pathway	[30]
	SIPA1L3	Signal Induced Proliferation Associated 1 Like 3	Rap1 signaling pathway	[31]
	GPC5	Glypican 5	Glycosaminoglycan metabolism	[32]
	KLF7	Kruppel Like Factor 7	Adipogenesis pathway	[33]
	CDK12	Cyclin Dependent Kinase 12	Cell cycle	[34]
	ENO3	Enolase 3	Glycosaminoglycan metabolism	[35]
	NPTN	Neuroplastin	Akt Signaling	[36]
	HTATIP2	HIV-1 Tat Interactive Protein 2	Cytoskeletal signaling	[37]
	IL7	Interleukin 7	PI3K-Akt signaling pathway	[38]
			JAK-STAT signaling pathway	
Group 3	BLK	BLK Proto-Oncogene, Src Family Tyrosine Kinase	MAPK-Erk pathway	[39]
			NF-kappaB signaling	
	ADAMTS18	ADAM Metallopeptidase With Thrombospondin Type 1 Motif 18	Metabolism of proteins	[40]
	CEP89	Centrosomal Protein 89	Organelle biogenesis and maintenance	[41]
	SULF1	Sulfatase 1	–	[42]
	ABCB9	ATP Binding Cassette Subfamily B Member 9	Transport of inorganic cations/anions and amino acids/oligopeptides	[43]
	STAG3	Stromal Antigen 3	Cell cycle, mitotic	[44]
	RER1	Retention In Endoplasmic Reticulum Sorting Receptor 1	–	[45]
	ASCL1	Achaete-Scute Family BHLH Transcription Factor 1	Signal transduction	[46]
			Signaling by NTRKs	
	DAAM1	Dishevelled Associated Activator Of Morphogenesis 1	Wnt signaling pathway	[47]
			Signaling by Rho GTPases	
	TLE1	TLE Family Member 1, Transcriptional Corepressor	Wnt/Hedgehog/Notch signaling pathways	[48]
Group 4	ZDHHC9	Zinc Finger DHHC-Type Palmitoyltransferase 9	RAF/MAP kinase cascade	[49]
	ACAA2	Acetyl-CoA Acyltransferase 2	Metabolic pathways	[50]

Table 3 (continued)

Groups	Gene symbol	Gene Name	Signaling pathways	References
Group 5	SLC15A4	Solute Carrier Family 15 Member 4	Innate immune system	[51]
	HTR7	5-Hydroxytryptamine Receptor 7	Ras signaling pathway	[52]
	DNAH1	Dynein Axonemal Heavy Chain 1	–	[53]
	ELK1	ETS Transcription Factor ELK1	MAPK signaling pathway	[54]
			ErbB signaling pathway	
	RSPO3	R-Spondin 3	Wnt signaling pathway	[40]
			mTOR Signaling pathway	
	ELF3	E74 Like ETS Transcription Factor 3	Pre-NOTCH expression and Processing	[55]
	PHF21A	PHD Finger Protein 21A	Chromatin organization	[56]
	HDC	Histidine Decarboxylase	Histidine metabolism	[57]
	CA12	Carbonic Anhydrase 12	Reversible hydration of carbon dioxide	[58]
	SEC61B	SEC61 Translocon Subunit Beta	Phagosome	[59]
			Antigen processing-cross presentation	
	MAOA	Monoamine Oxidase A	Cytokine signaling in Immune system	[60]
	RC3H1	Ring Finger And CCCH-Type Domains 1	–	[61]
Group 6	HM13	Histocompatibility Minor 13	Cellular response to chemical stress	[62]
	HNRNPR	Heterogeneous Nuclear Ribonucleoprotein R	Translational control	[63]
	SLC1A2	Solute Carrier Family 1 Member 2	Glutamatergic synapse	[64]
	SCN3A	Sodium Voltage-Gated Channel Alpha Subunit 3	Activation of cAMP-Dependent PKA	[65]
	FOXP1	Forkhead Box P1	MicroRNAs in cancer	[66]
			Wnt/Hedgehog/Notch	
			Signaling pathways	
	UNC5B	Unc-5 Netrin Receptor B	Apoptosis signaling pathway	[67]
	RAB18	RAB18, Member RAS Oncogene Family	Innate immune system	[68]
	ABHD5	Abhydrolase Domain Containing 5, Lysophosphatidic Acid Acyltransferase	Lipid metabolism pathway	[69]
	GABRB2	Gamma-Aminobutyric Acid Type A Receptor Subunit Beta2	NF-kappaB pathway	[70]
			Akt pathway	
	SNX1	Sorting Nexin 1	Posttranslational regulation of adherens junction stability and disassembly	[71]
	SVIL	Supervillin	Coregulation of androgen receptor activity	[72]
	UBE2A	Ubiquitin Conjugating Enzyme E2 A	Ubiquitination cascade	[73]
Group 8	OTP	Orthopedia Homeobox	–	[74]
	NT5C2	5′-Nucleotidase, Cytosolic II	Metabolism of nucleotides	[75]

target proteins with curcumin, a potentially active molecule. Stable conformations have lower binding energies. Our assessment of the binding level was based on the quantitative fitness value. Predicted poses in a binding site are evaluated according to their fitness. In iGEMDOCK, fitness is computed as the product of van der Waal, hydrogen bonding, and electrostatic energy [17]. We used LigPlot+ to visualize protein–ligand interactions (Fig. 4) and the potential receptors along with their molecular docking results are proposed in Table 4.

Discussion

Currently, the incidence and mortality of COPD, an inflammatory disease caused mainly by daily smoking, is continuously growing globally. COPD is a serious health problem and a danger to human life [76–78]. Studies on curcumin's pharmacological effects have gained momentum since its molecular structure (C21H20O6) was discovered as difluorocarbonyl methane in 1910 [79]. It has also been shown that curcumin,

Table 4 The list of potential receptors and molecular docking results of iGEMDOCK and LigPlot$^+$ using curcumin compound

Compound	PDB ID	Energy	VDW	Hbond	Amino acids
Monoamine oxidase A	2BXR	− 111.84	− 91.71	− 20.13	Gly214, Arg206, Ser209, Gln215, Glu216, Ile207, Trp441, Phe352, Tyr407, Tyr444
Beta amyloid A4 protein	6UWP	− 93.5364	− 65.1122	− 28.4242	Tyr198, Gly34, Asp32, Ser10, Ile226, Ile118, Asp228, Gly11, Tyr14, Ser229, Gly13, Gln12, Leu30, Gly230, Ile110
Histone acetyltransferase p300	6GYR	− 114.445	− 96.8397	− 17.6049	Trp1436, Tyr1446, Cys1438, Ser1396, Ile1395, Ser1400, Phe1467, His1402, Leu1398, Tyr1466, Tyr1414, Thr1411
Prostaglandin E synthase	4BPM	− 80.2304	− 63.7593	− 16.4711	Aln133, Gln34, Tyr130, Arg126
Toll-like receptor 9 (TLR9)	3WPF	− 78.7357	− 58.5542	− 20.1815	Lue707, Val731, Glu730, Thr754, Lys781, Leu756
Toll-like receptor 7 (TLR7)	6ZJZ	− 120.603	− 107.651	− 12.9516	Gly351, Pro498, Ile496, Gln519, Lys350, Phe495, Ala518, Tyr348, Val378, Tyr348, Gln525, Phe494, Phe568
Beta-secretase 1	6OD6	− 88.0633	− 76.9457	− 11.1176	Phe109, Lys107, Ile110, Phe108, Gln73, Tyr71, Gly230, Asp228, Gly34, Asp32
DNA topoisomerase II alpha	3QX3	− 91.0505	− 74.6289	− 16.4216	Glu777, Tyr821, Arg820, Gly776, Gln778, Arg503, Gly478, Asp479, Leu502

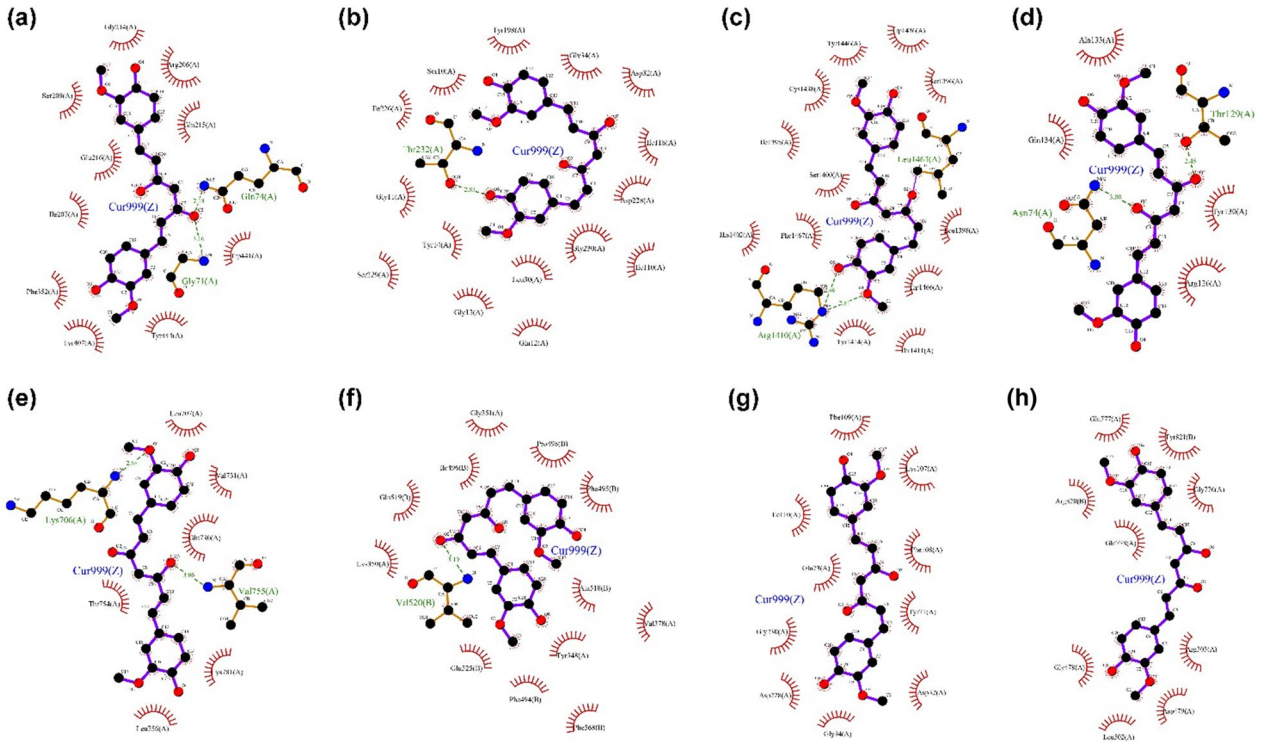

Fig. 4 Ligplot.$^+$ output of the interactions at the receptor–ligand (curcumin) interface in **a** 2BXR, **b** 6UWP, **c** 6GYR, **d** 4BPM, **e** 3WPF, **f** 6ZJZ, **g** 6OD6 and **h** 3QX3

an organic polyphenol produced from turmeric, a member of the ginger family, helps treat COPD [79].

Only 25% of people who smoke will get COPD, despite smoking being the leading cause of COPD cases [80]. Despite this, most smokers do not end up with COPD, and a significant number of people with COPD have never smoked. It suggests that COPD is a complex degenerative disease [81]. When compared with smokers who do not have COPD, those who have COPD and who smoke have an elevated risk of developing lung cancer that ranges from 1.3 to 4.9 times higher [80].

Further research findings demonstrated that curcumin alleviated emphysema and helped restore structural integrity to the alveolar epithelium of rats suffering from COPD [77, 81]. Individuals with chronic obstructive pulmonary disease (COPD) who received curcumin had more favorable body weight and respiratory rates than those who received a control treatment [81]. In a study

examining the effects of curcumin on COPD, the BALF total cell count was notably decreased without curcumin treatment [81]. On the other hand, it is yet uncertain whether oral curcumin may help with COPD-related mitochondrial dysfunction [77].

Patients with COPD can be restored to corticosteroid resistance with curcumin by inhibiting HDAC2 expression and revising histone modifications [82]. So, curcumin is an important regulator of chronic airway inflammation in COPD and inhibits an increase in pro-inflammatory chemokines in AEC II isolated from COPD rats [82].

As oral curcumin bioavailability is limited, more bioavailable curcumin may have a greater impact on COPD rats [77]. In COPD rats with skeletal muscle injury, curcumin treatment improved mitochondrial structure and increased mitochondrial enzyme activity [77].

Around 40% of people with COPD have mitering and dysfunction of their skeletal muscles [77].

Rats with COPD whose skeletal muscles were treated with curcumin had dramatically reduced levels of IL-6 and TNF-α [77]. Curcumin-treated COPD individuals showed a significant difference in their alveolar epithelial cell death rate from COPD model subjects in terms of apoptosis rates [81]. The reason for using curcumin as a preventive agent is that chronic inflammation and oxidative stress are involved in COPD [81].

The hypothesis is that Theracurmin®, a highly absorbable curcumin with increased bioavailability using a medication delivery method, reduces inflammation in people with moderate COPD [78]. According to the literature, curcumin may be beneficial in stopping arteriosclerosis by lowering AT-LDL levels, which have been shown to drop considerably after therapy with Theracurmin® [78].

Research has shown that curcumin may reduce inflammation in the patients' airways through affecting the nuclear factor kappa-light-chain-enhancer of activated B cells and hence the gene expression values of cyclooxygenase-2 [76].

Curcumin can also slow lung cancer development in patients with high-risk COPD by prolonging the premalignant period [80]. These discoveries might lead to new therapeutic development approaches to treating COPD [76, 83].

Through a bio-computational approach, the study investigates how curcumin inhibits the progression of COPD by regulating genes and biological pathways. And COPD is a progressive chronic obstructive lung disease [1]. Patients with mild-to-moderate COPD are more likely to die of lung cancer; those with severe COPD are more likely to die of respiratory failure. According to studies, 46 to 60% of lung cancer patients also had COPD. According to current understanding, the growth of lung cancer is closely linked to a person's genetics [3]. It has already been discussed that COPD is a disease characterized by oxidative stress, and ROS has a significant role in that development and progression [4]. As a result, substances that contain antioxidants in their structure can be considered a treatment for this chronic disease. Curcumin can be an antioxidant and anticancer due to its structure and functional groups [8]. This study used a microarray dataset consisting of 24 samples divided into eight groups at two different time intervals of 4 and 18 h.

In addition, the 4-h and 18-h groups were compared using BRB-ArrayTools, where significant genes are identified through statistical analysis to obtain more accurate results. This study used several integrated groups, pre-processing algorithms, and normalization and filtering approaches to obtain differentially expressed genes (DEGs) for eight groups. To find effective genes in treating this disease with curcumin, the DEGs between the compared groups in which curcumin is present and the ROS enzyme is active are more important than those in healthy groups not treated with curcumin. In this study, it was determined that groups 2 and 6 experienced significant differences in gene expression over the period of 4 and 18 h, with particular differences observed in gene expression between those groups. The results show that these genes are significantly expressed and can be effective in the curcumin process in this disease. In the next stage, analyses on gene ontology and the KEGG pathway of DEGs were performed using the DAVID web server to determine the function of those genes involved in oxidative stress and carcinogenesis. In this stage, genes with a p-value < 0.05 were evaluated regarding BP, CC, MF and KEGG signaling pathways, and the results were presented in the results section. When the GeneMANIA and Cytoscape stages are performed, interconnections between genes are obtained; they indicate extensive connections between these genes, which may be involved in the effects of curcumin on gene expression levels in this disease. The STRING database also analyzed the PPI network and revealed several hub genes for eight groups. The clinical and experimental studies in the literature were used to validate gene biomarkers. Group 1 has two TCF3 and TCF7L1 genes; group 2 has four ADAMTS9, SPON1, GABRA5 and NPTN genes; group 3 has two TLE1 and ASCL1 genes; group 5 has four HDC, MAOA, HTR7 and SLC15A4 genes, group 6 has seven RC3H1, UBEPRA, HN genes, SLC1A2, GABRB2, ABHD5 and RAB18 were the most important among the target genes. No significant genes were found in groups 4, 7, and 8, possibly due to the proximity and lack of differences in the genes expressed. In the phase of curcumin efficacy with its structural components identified in the SwissTargetPrediction section, 101 proteins were obtained, of

which oxidoreductases and enzymes had the highest percentages (Fig. 5), and the rest of the proteins with similar rates were classified accordingly. For example, monoamine oxidase A and prostaglandin E synthase were present in the enzyme group with a probability of more than 50%, and the effect of these proteins on COPD has been shown in other articles (Table 5).

Curcumin may lower depression via interacting with serotonin and dopamine systems [101, 102]. Dopamine and serotonin release are affected by curcumin's monoamine oxidase inhibition [103]. Additionally, curcumin inhibits monoamine oxidases A and B, whereas Tetrabenazine reduces VMAT-2, which affects depressed motivation. Oral or intraventricular curcumin may reduce these effects. [104, 105].

Curcumin modulates cellular targets and effects, suggesting COPD therapy potential [106]. To prevent COPD, it regulates Th17 and Treg balance, inflammation, and anti-inflammatory factors [107]. For corticosteroid-resistant COPD patients, curcumin seems promising. Because of this novel advantage, curcumin may treat COPD by alleviating corticosteroid resistance symptoms [108]. Curcumin may directly affect beta-amyloid protein formation, which may affect Alzheimer's disease progression [109]. The reduction in plasma beta-amyloid protein levels suggests a connection between curcumin and the A4 receptor [109].

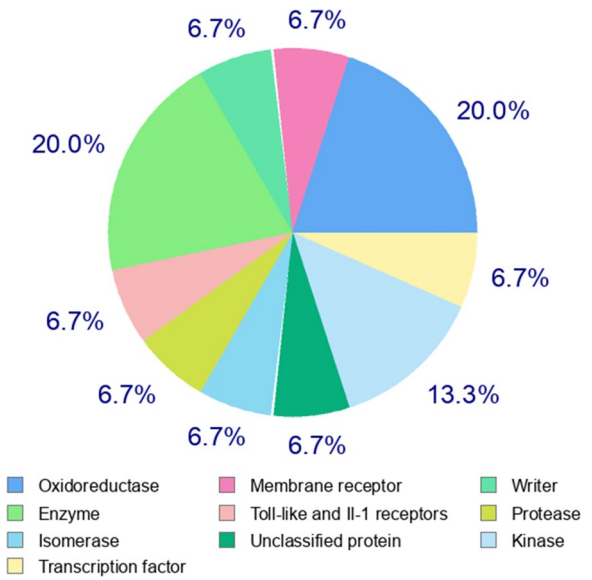

Fig. 5 The predicted potential receptors for the curcumin structure

Through altering COPD and Alzheimer's disorders, curcumin inhibited liver cancer and signaling pathways [110]. Curcumin inhibits breast cancer cell growth and induces death via modulating signaling pathways which makes scientists believe curcumin may cure cancer and COPD [111].

Curcumin also has an effect on the p300 receptor, which is a transcription factor that acetylates histones and transcription factors (HAT), including GATA4. This receptor is known to affect gene expression and cell function, including COPD [112–114]. Curcumin has been shown to decrease p300 HAT activity, which causes heart failure and hypertrophy by acetylating histones and GATA4 [112–114]. Additionally, curcumin was shown to reduce p300 HAT activity in animal models, reducing heart failure and cardiac hypertrophy [115, 116].

It was shown that curcumin inhibited the activity of p300 HAT in cancer and neuropathic pain models, which suggests that it has a wide range of potential therapeutic applications [117, 118]. In COPD, curcumin reduces p300 HAT activity, may affect major pathophysiological variables such as gene expression related to inflammation, tissue remodeling, corticosteroid resistance, and renal ischemia–reperfusion [119]. So, by targeting the p300 HAT receptor, researchers may overcome COPD corticosteroid resistance and reduce inflammation and fibrosis [119].

Table 5 The potential receptors functional for curcumin predicted by SwissTargetPrediction

Receptors	Function	Probability	References
Monoamine oxidase A	Functional in cell signaling and oxidative injury	1.00	[84, 85]
Beta amyloid A4 protein	Transition metal ion binding and inflammation	1.00	[86]
Histon acetyltransferase P300	Reduces pro-inflammatory gene expression and inhibits histone deacetylases	1.00	[87, 88]
Prostaglandin E synthase	Ameliorates acute lung injury in mice	1.00	[89, 90]
Toll-like receptor (TLR7/TLR9)	Protective self-defense mechanisms	1.00	[91, 92]
Beta-secretase 1	Formation of amyloid-β	0.80	[93]
DNA topoisomerase II alpha	Cell cycle progression	0.50	[94, 95]
Glyoxalase I	Reduces oxidative stress and inflammation	0.24	[96]
Nuclear factor erythroid 2-related factor 2	Protective role against apoptosis	0.22	[97, 98]
Arachidonate 5lipoxygenase	Reduces inflammation	0.22	[99, 100]

On the other hand, in patients with COPD, interacting with the prostaglandin E synthase (PGES) receptor may result in inhibiting microsomal prostaglandin E synthase-1, secreting pro-inflammatory prostaglandin E2 (PGE2). As a result, inhibition of mPGES-1 enhances its anti-inflammatory capabilities and possible treatment against cancer and chronic inflammation [89].

Curcumin inhibits IL-1β, reducing mPGES-1 production, a crucial enzyme in the inflammatory response. This is done by inhibiting Egr-1 and other signaling pathways. Thus, curcumin may modulate mPGES enzyme expression and activity [120]. Curcumin has been studied further in relation to the prostaglandin E receptor EP4, which is implicated in PGE2 activity [121]. Both the prostaglandin E synthase and the PGE2 signaling pathways, which are both regulated by curcumin, may be attributable to inflammation and tissue damage.

According to the sources, curcumin may treat COPD via Toll-like receptors 9 and 7. For decades, TLR activation has been recognized to initiate innate immune responses [122]. In asthma and COPD-related chronic inflammation, TLR9 and TLR7 may inappropriately trigger immunological responses [123].

In numerous diseases, curcumin regulates TLR expression and activation. TLR4 downregulation by curcumin decreases inflammatory cytokines and adhesion molecules in atherosclerotic plaques [124]. Curcumin also reduces TLR4 expression while increasing TLR2 expression in resting microglia [125] and may contribute to its anti-atherosclerosis activities [126].

TLRs, including as TLR9 and TLR7, have been implicated in the immunopathology of stable COPD [127]. Furthermore, in COPD, TLR2 gene expression is highly related to the amount of neutrophils in sputum [128]. TLR4 has also been linked to COPD-induced inflammation [129]. In addition, the researchers reported TLR4 polymorphisms have been linked to both tuberculosis and COPD [130].

Curcumin, the principal active element in turmeric, has been demonstrated in several studies to have anti-inflammatory and antioxidant effects. However, it is challenging to link curcumin's interactions with a variety of protein targets to its possible therapeutic benefits which might be important for treating COPD; (i) the enzyme CA12, which guards the body from free radical damage, may be activated by curcumin. Patients with COPD may have less lung tissue damage from damaging oxidative stress if CA12 activation is present, (ii) this compound may reduce COPD-related lung inflammation by controlling pro-inflammatory cytokines and enhance lung function by modifying NF-κB activity, reducing excessive inflammation. (iii) Histone deacetylases (HDACs), which affect chromatin structure and inflammation, were downregulated by curcumin. By inhibiting HDAC, corticosteroids may cure COPD longer, while curcumin may slow lung fibrosis. On the other hand, MicroRNAs regulate a wide range of gene networks, which has a significant impact on COPD severity.

To understand the intricate relationship between genetic predisposition and COPD progression/treatment, one must analyze the patient's genetic profile. By doing so, one may better understand COPD development processes and therapy effectiveness. This information may help personalize treatment and improve patient outcomes by adjusting therapies to genetics. Numerous genetic investigations have found COPD susceptibility genes, such as α1-antitrypsin deficiency, smoking-induced CFTR failure, and newly discovered genes [131–133]. Genes linked to the pathophysiology of COPD have been linked to the condition's possible association and provide unique insights into the development and severity of the disease [132]. Additionally, the prevention and treatment of COPD depend on the identification and prioritization of COPD candidate genes [134]. Immune-related gene research has also revealed putative COPD mechanisms and diagnostic biomarkers, resulting in a better knowledge of the disease's management [135].

In the research, there were significant variations in the expression of genes linked to stress response, inflammation, and cell death [136]. Biological medicines targeting particular pathological characteristics and disease endotypes may be used to treat COPD [137]. Studying the genetic overlap between COPD and asthma has discovered SNPs linked to their development or therapy [138].

In addition, there has been debate over the role of individual susceptibility or genetic variables in the development of COPD, which shows that the disease may be affected by genetic polymorphisms and interactions between genes and the environment [139]. Furthermore, it has been shown that certain genetic variants are associated with the severity of the advancement of COPD illness. This finding provides evidence of the possible effect that genetic differences might have on the progression of the disease [140, 141].

Natural polyphenol curcumin from Curcuma may treat COPD due to its anti-inflammatory characteristics. By suppressing NLRP3, a key component of the NLRP3 inflammasome, IL-1β release is decreased and inflammation is avoided [142]. Curcumin suppresses NF-κB signaling and COX-2, reducing lung remodeling and inflammation in mice with cigarette-induced COPD [76]. Moreover, curcumin regulates SIRT1 to modify autophagy and endoplasmic reticulum stress in rats, improving COPD [107]. Additionally, curcumin inhibits oxidative stress in human nasal fibroblasts via activating the Nrf2/HO-1 pathway by preventing its

oxidation [143]. Curcumin may be beneficial for respiratory diseases, according to some research. It may also lower blood levels of low-density lipoprotein, a sign of atherosclerosis, which may help with COPD symptoms [144].

In summary, curcumin targets COPD-related anti-inflammatory and antioxidant protein factors. More clinical studies are needed to prove curcumin's effectiveness and understand how it activates its main pathways in COPD patients. Lung cell protein indicators affected by curcumin may help optimize future therapies.

Conclusions

Chronic obstructive pulmonary disease (COPD) imposes a growing health and economic burden globally. Finding better prevention and treatment options is important. Curcumin is a natural compound with anti-inflammatory and antioxidant properties that may have therapeutic potential for treating COPD. This study used a bioinformatics approach to analyze gene expression data and identify genes and pathways affected by curcumin treatment in COPD model cell lines. Several differentially expressed genes and pathways were identified previously implicated in COPD pathogenesis or shown to be modulated by curcumin. Protein–protein interaction network analysis revealed connections between the identified genes and highlighted some hub genes that may be key targets of curcumin. Literature mining provided evidence to support the roles of some of the identified genes and pathways in COPD and as targets of curcumin. Molecular docking analysis indicated potential binding interactions between curcumin and some protein targets involved in inflammation and oxidative stress pathways underlying COPD. Further clinical research is needed to confirm curcumin's therapeutic efficacy and mechanisms in COPD patients. This bioinformatics study concludes that curcumin modulates multiple genes and pathways involved in COPD pathogenesis, warranting further investigation of its therapeutic potential.

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Author contributions
SA, YJ and BS conceived the study. SA, SD, and BS designed the experiment and developed the methodology. EA and MM performed in silico experiments. EA, SA, BS, SD and YJ analyzed data. All authors contributed to experimental design and data analysis. All authors wrote the manuscript. BS and YJ reviewed and supervised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The initial dataset for analysis is available from PubMed in the following link: https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE10896. And, all data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
As this study is solely based on computational and publicly available microarray dataset, i.e., GSE10896, so the article does not contain any studies with human participants or animals performed by authors in this research.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no conflict of interest.

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