ACCSCIENCE PUBLISHING

Eurasian Journal of Medicine and Oncology

ORIGINAL RESEARCH ARTICLE

Network pharmacology and *in silico* validation of sesamin targeting AR and MAPK1 in COVID-19 and malaria

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Citation: Khatun MT, Hossain MA, Hasan MI, *et al*. Network pharmacology and *in silico* validation of sesamin targeting AR and MAPK1 in COVID-19 and malaria. *Eurasian J Med Oncol*. doi: 10.36922/EJMO026190207

Received: May 8, 2026

Revised: July 15, 2026

Accepted: August 7, 2026

Published online: September 14, 2026

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Abstract

Introduction: COVID-19 and malaria may coexist in endemic regions, creating diagnostic and therapeutic challenges, while evidence-based strategies addressing their co-occurrence remain limited.

Objective: This study evaluates sesamin, a natural compound with reported antiviral, antioxidant, anti-inflammatory, and immunomodulatory activities, as a potential multitarget candidate for COVID-19 and malaria.

Methods: Network pharmacology and transcriptomic analyses were used to identify shared targets and pathways among sesamin, COVID-19, and malaria. Molecular docking; absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiling; 200-ns molecular dynamics simulations; and molecular mechanics/generalized Born surface area (MM-GBSA) binding free-energy calculations were performed to assess target interactions, dynamic stability, binding energetics, and predicted pharmacokinetic and toxicity properties.

Results: Seventy common differentially expressed genes were identified. Protein–protein interaction analysis highlighted AR, MAPK1, caspase-3, β-catenin, IL-6, HSP90α, and EGFR as key targets. Enrichment analysis linked the genes of these proteins mainly to apoptosis regulation and to FOXO and PI3K–AKT signaling. Sesamin showed favorable docking with MAPK1, AR, EGFR, CASP3, and β-catenin, with docking scores ranging from −10.0 to −8.6 kcal/mol, more favorable than those of the reference ligands. ADMET analysis indicated a potential Ames toxicity signal but no predicted hepatotoxicity or skin sensitization. During the simulations, sesamin remained stable with AR and MAPK1; the AR-bound system showed greater positional stability and lower solvent exposure, whereas the MAPK1-bound system

maintained more hydrogen bonds. MM-GBSA analysis showed favorable binding of sesamin to AR (−55.77 kcal/mol) and MAPK1 (−122.17 kcal/mol).
Conclusion: Sesamin may modulate shared immune and inflammatory pathways relevant to COVID-19 and malaria. Its stable interactions with AR and MAPK1 support further investigation, although experimental and clinical validation is required.

Keywords: Sesamin; Malaria; COVID-19; Androgen receptor; Mitogen-activated protein kinase 1; Molecular dynamics simulations; Phosphoinositide 3-kinase/Protein kinase B; Apoptosis

1. Introduction

SARS-CoV-2, an enveloped, positive-sense single-stranded RNA virus of the genus *Betacoronavirus*, emerged in Wuhan, China, in late 2019 and causes coronavirus disease 2019 (COVID-19).[1,2] The World Health Organization (WHO) declared COVID-19 a pandemic in March 2020. Since then, the virus has continued to evolve, producing multiple variants and Omicron-descendant lineages. Recent WHO monitoring classified JN.1 as a Variant of Interest, and XFG, NB.1.8.1, BA.3.2, and KP.3.1.1 as Variants Under Monitoring, highlighting the need for continued genomic and transcriptomic surveillance.[3,4] Therefore, continued genomic and transcriptomic surveillance remains important for understanding the biological and clinical consequences of emerging SARS-CoV-2 lineages. Several studies have demonstrated that COVID-19 severity is associated with dysregulated immune responses, particularly the overproduction of pro-inflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), IL-7, and IL-10.[5] The educational sector, economy, human health, and stress and anxiety levels have been adversely affected by COVID-19.[6] SARS-CoV-2 infection can result in acute respiratory distress syndrome (ARDS), mild symptoms at the infection site, lung failure, or patient death.[7]

Malaria is another lethal disease primarily seen in tropical and subtropical areas and is caused by protozoan parasites of the genus *Plasmodium*.[8] The WHO's World Malaria Report 2025 estimates that 282 million people worldwide were infected with malaria and 610,000 people died from malaria in 2024, representing approximately 9 million more infection cases than in 2023.[9] This indicates a continued high burden of disease, with cases showing an increase compared to previous years despite ongoing control and elimination efforts. At the molecular level, *Plasmodium falciparum* expresses *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) on infected erythrocytes, promoting cytoadherence to endothelial receptors such as endothelial protein C receptor (EPCR) and intercellular adhesion molecule 1 (ICAM-1), microvascular sequestration, and endothelial dysfunction.[10,11] In addition, parasite-induced hemolysis and heme-associated products promote oxidative stress and inflammation, contributing to anemia, vascular injury, organ dysfunction, and severe malaria.[12]

The coexistence of malaria-endemic regions and ongoing COVID-19 transmission has raised concerns regarding overlapping clinical presentations, including fever, fatigue, headache, respiratory complications, thrombocytopenia, and inflammatory abnormalities, which can complicate diagnosis and disease management in malaria-endemic regions. Emerging reports suggest that co-infections may contribute to worsened clinical outcomes and modify disease severity and immune responses. Nevertheless, the direction and magnitude of the interaction between COVID-19 and malaria remain incompletely understood and appear to vary according to disease severity, comorbidities, population characteristics, and study design.[13,14]

Furthermore, recent research shows that the frequency of potential combined effects of COVID-19 on malaria patients is increasing, resulting in the horrible condition of simultaneous co-epidemics.[15,16] Unfortunately, several cases of COVID-19 and malaria co-infections have previously been documented in Asia, such as in India[17] and Indonesia,[18] West Africa, such as in Nigeria,[19] and sub-Saharan Africa.[16] These co-infections highlight the need for enhanced surveillance and integrated disease management strategies. Recent evidence indicates that immune dysregulation, including elevated levels of cytokines such as IL-6 and TNF-α, may contribute to the pathogenesis of both malaria and COVID-19.[20] This suggests the presence of potential shared inflammatory pathways that could be targeted for therapeutic intervention. Besides, oxidative stress, immune-cell activation, coagulation, endothelial dysfunction, and metabolic regulation are also significant in both disease progressions.

Natural compounds have garnered attention as potential modulators of these pathways. Interestingly, sesamin, a lignan derived from *Sesamum indicum* and other plant sources, has been reported to exhibit antioxidant, anti-inflammatory, and anticancer properties.[21,22] Experimental studies have indicated that sesamin may modulate cell proliferation, apoptosis, angiogenesis, and inflammatory signaling pathways.[23] On the other hand, advances in high-throughput transcriptomics and bioinformatics provide opportunities to investigate common molecular mechanisms between the two diseases.[24] Although sesamin has been reported to have anti-inflammatory, antioxidant, and pharmacological activities, its shared molecular targets and multitarget mechanisms against COVID-19 and malaria remain poorly understood. Moreover, an integrated analysis combining network pharmacology, molecular docking, and molecular dynamics simulation (MDS) for these two diseases has not been adequately explored.

This study aims to identify shared molecular targets and pathways between COVID-19 and malaria, and to elucidate the potential multitarget therapeutic mechanisms of sesamin through an integrated approach combining network pharmacology, molecular docking, and MDS. Further *in vitro*, *in vivo*, and clinical investigations are required to validate the predicted targets, pathways, and therapeutic potential of sesamin against COVID-19 and malaria.

2. Materials and methods

The complete workflow of the study, from target identification and bioinformatics analyses to molecular docking; absorption, distribution, metabolism, excretion, and toxicity (ADMET) assessment; MDS; and molecular mechanics/generalized Born surface area (MM-GBSA) binding free-energy analysis, is summarized in Figure 1.

2.1. Identification of sesamin-related targets

To identify potential sesamin-related genes, we used several databases, including the Comparative Toxicogenomics Database (CTD), PharmMapper, SwissTargetPrediction, and Search Tool for Interacting Chemicals (STITCH), which provide various types of information on drug–gene interactions. Information on chemicals, gene products, phenotypes, diseases, and environmental exposures to human health is contextualized in CTD.[25] PharmMapper is a free online tool mainly used to identify potential therapeutic targets through reverse pharmacophore matching.[26] SwissTargetPrediction is an online program that uses similarity and change-based screening techniques to predict the most promising protein molecules.[27] STITCH is an online search tool for determining the interactions between proteins and small therapeutic agents.[28] These resources were selected because they provide complementary information based on curated chemical–gene associations, reverse pharmacophore mapping, ligand-similarity prediction, and chemical–protein interaction networks. Searches were restricted to *Homo sapiens*. The top 50 targets from each database were retained based on the database-native ranking or confidence score to standardize target contributions and minimize the impact of low-confidence predictions. All retrieved targets were converted to official gene symbols, merged, and de-duplicated before subsequent analysis.

2.2. Screening of common genes between COVID-19 and malaria

We searched for various datasets and selected two, GSE154998[29] and GSE152418,[30] based on the desired targets among the available COVID-19 transcriptomic RNA sequencing (RNA-seq) datasets in the National Center for Biotechnology Information. Dataset selection was based on the availability of clearly defined disease and control groups, sufficient sample annotation, and suitability for differential-expression analysis. We identified differentially expressed genes (DEGs) based on criteria including false discovery rate (FDR) < 0.05, adjusted $p < 0.05$, and |log2 fold change (FC)| ≥ 1. In addition, using CTD, the COVID-19 Host Gene Database (https://baillielab.net/), DISGENET, and PubChem, we identified human target genes for COVID-19. Similarly, we identified DEGs from two malaria transcriptomic RNA-seq datasets, GSE50957[31] and GSE86308,[32] based on an FDR < 0.05, adjusted $p <$ 0.05, and |log2FC| ≥ 1. Additionally, we searched for other datasets to obtain malaria-related target genes using CTD, DISGENET, and GeneCards.

For CTD and DISGENET, the top 500 human genes were retained based on their database-specific ranking scores to capture highly supported disease associations while excluding low-confidence entries. All targets were standardized to official gene symbols, and duplicate records were removed. The common targets among sesamin, COVID-19, and malaria were then identified using Venn diagram analysis and used in subsequent network pharmacology investigations.

2.3. Enrichment of Gene Ontology and KEGG pathway

Gene Ontology (GO) is the world's most widely used resource for humans and machines, providing information on the genome and gene products.[33] Based on genetic, chemical, and network data, the metabolic pathway was analyzed using the Kyoto Encyclopedia of Genes and Genomes (KEGG), a computational tool.[34] We obtained

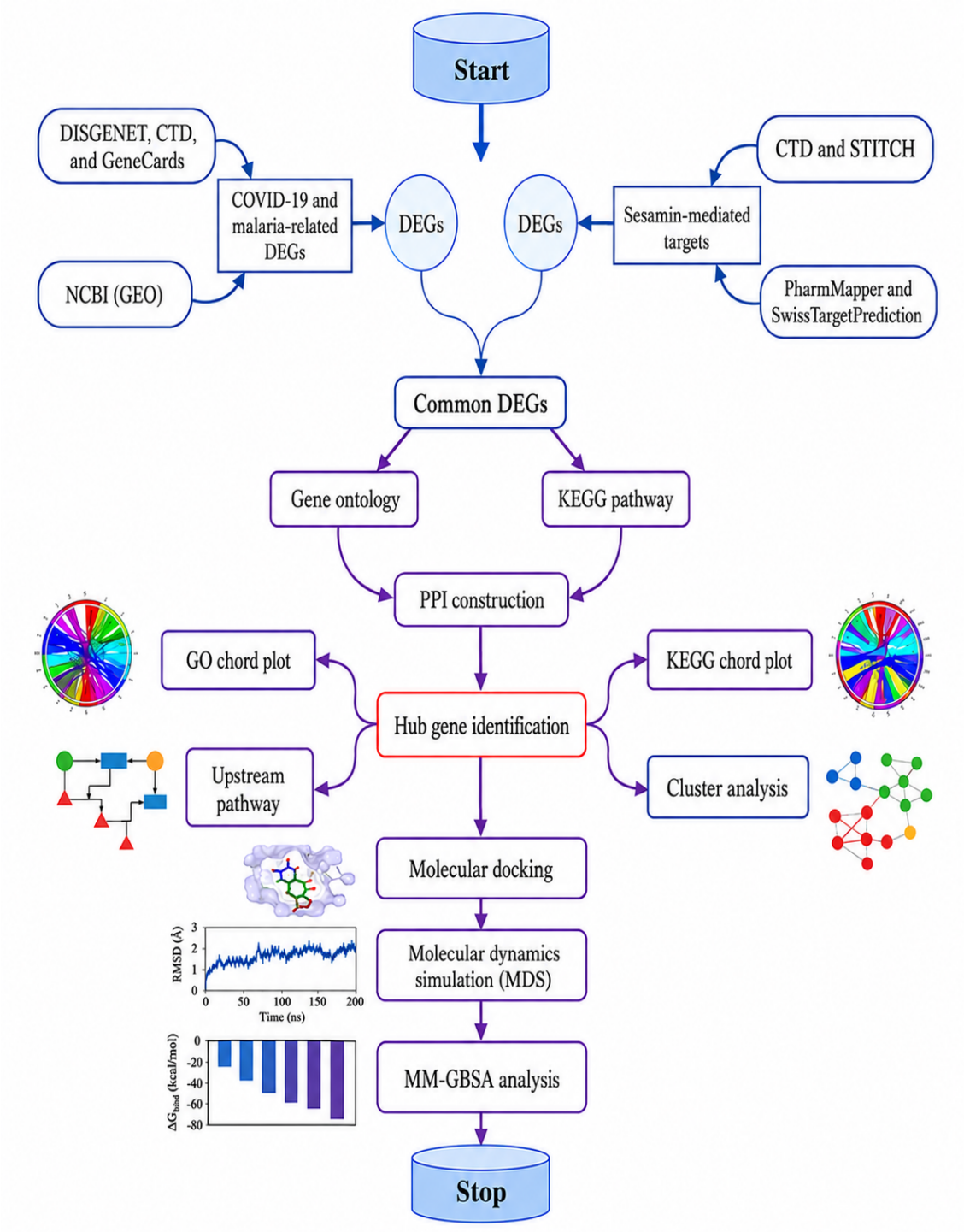


Figure 1. Schematic workflow of integrative network pharmacology and structure-based analysis. COVID-19-, malaria-, and sesamin-associated targets were identified from public databases and transcriptomic datasets, followed by the identification of common targets, GO and KEGG enrichment, PPI network construction, hub gene identification, upstream pathway and cluster analyses, molecular docking, molecular dynamics simulation, and MM-GBSA binding free energy analysis.

Abbreviations: CTD: Comparative Toxicogenomics Database; DEG: Differentially expressed gene; GO: Gene Ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes; MM-GBSA: Molecular mechanics/generalized Born surface area; NCBI: National Center for Biotechnology Information; PPI: Protein–protein interaction; STITCH: Search Tool for Interacting Chemicals.

all the GO terminology and enrichment pathways using the web-based tool Database for Annotation, Visualization and Integrated Discovery (DAVID), incorporating 70 shared DEGs among sesamin, COVID-19, and malaria. For GO enrichment analysis with $p < 0.05$, we selected three ontological terms: biological process (BP), cellular component (CC), and molecular function (MF). After obtaining the GO and KEGG pathways, we generated bar and bubble plots using the SRplot online tool.

2.4. Construction of protein–protein interaction network and analysis

We uploaded the identified common DEGs to generate a protein–protein interaction (PPI) network through the STRING database (version 11.5).[35] Cytoscape 3.9.1 (Cytoscape Consortium, United States of America [USA]) was used to analyze and visualize the resulting PPI network.[36] The identified nodes and edges of the PPI network indicate the number of proteins and protein interactions, respectively.

2.5. Protein module analysis and hub protein identification

The cluster findings are important for examining biological networks. For cluster analysis, we used the ClusterViz Cytoscape 3 plugin.[37] The Cytoscape cytoHubba plugin was used for topological network studies.[38] The top genes with the shortest paths and the key transformers in the formation of subnetworks were identified in this study using cytoHubba. Five cytoHubba plugin techniques were used, including two top algorithms: betweenness and closeness centrality. The other three methods include degree, maximum neighborhood component (MNC), and maximum clique centrality (MCC). Finally, by comparing the five cytoHubba approaches, we identified common hub proteins using the jvenn online server.[39]

2.6. Establishment of correlation between pathway enrichment and hub proteins

Common DEGs and their enriched GO and KEGG pathways, along with logFC values, were used to generate chord diagrams via the SRplot web portal. We generated a GO chord plot by uploading 12 GO terms isolated from the three BP, CC, and MF ontologies. Again, we generated a chord bubble plot using the KEGG pathway database, including 10 pathways, and shared DEGs to calculate logFC values.

2.7. Inference of upstream pathway activity

It is essential to infer signaling pathways from transcriptomic data to understand transcriptional dysregulation of a specific gene.[40] Therefore, using Signaling Pathway Enrichment using Experimental Data 2 (SPEED2), a signaling pathway enrichment analysis tool, we obtained signature candidate genes by inserting common DEGs among sesamin, COVID-19, and malaria.

2.8. Physicochemical properties, pharmacokinetics, and toxicity analysis of sesamin

The physicochemical properties, aqueous solubility, and drug-likeness of sesamin were evaluated using the SwissADME server. Its absorption, distribution, metabolism, and excretion profiles were also predicted using the pkCSM server, whereas major toxicity endpoints were assessed using the ProTox-3.0 server.[41,42]

2.9. Validation of potential hub proteins

2.9.1. Molecular docking

Several fields, including structural medicine architecture, lead optimization, and biochemical route analysis, utilize dynamic studies of molecular coupling.[43] The three-dimensional structures of sesamin and the COVID-19/malaria control drugs (nirmatrelvir/artemisinin) were obtained from the PubChem database.[44] Artemisinin was selected as the reference antimalarial compound due to its well-established clinical efficacy and its role as the core scaffold of current artemisinin-based combination therapies for malaria treatment.[45] Nirmatrelvir, the main protease inhibitor, was used as the reference antiviral compound for COVID-19 owing to its clinically validated efficacy against SARS-CoV-2 replication.[46] Receptor proteins, such as heat shock protein 90 alpha (HSP90α; Protein Data Bank [PDB] ID: 1BYQ) and caspase-3 (PDB ID: 1I3O), were obtained from the Research Collaboratory for Structural Bioinformatics (RCSB) PDB.[47] AutoDock Vina 1.2.0 (Scripps Research Institute, USA) was used to perform molecular docking.[48] Molecular Graphics Laboratory (MGL) Tools (version 1.5.6), including AutoDockTools, were used to remove heteroatoms, water molecules, and cofactors from the hub proteins and their ligands, preparing their structures in PDBQT format. BIOVIA Discovery Studio Visualizer (v20; Dassault Systèmes BIOVIA, USA) was used to visualize the 2D binding interaction of proteins and ligands.

2.9.2. Molecular dynamics simulation studies

A 200-ns MDS was performed to evaluate the binding stability of sesamin, artemisinin, and nirmatrelvir in complex with the androgen receptor (AR) and mitogen-activated protein kinase 1 (MAPK1) proteins. MDS was performed on a Linux-based system using Desmond within the Schrödinger Suite 2025-1 (Schrödinger, LLC, USA) with the Optimized Potentials for Liquid Simulations 4 (OPLS4) force field to evaluate the structural stability and dynamic

behavior of the selected protein–ligand complexes.[49] The three-point transferable intermolecular potential (TIP3P) water model was used to create a predefined orthorhombic periodic boundary box with a 10 Å water buffer, and 0.15 M Na^+ and Cl^- were added to neutralize the system. Electrostatic interactions were computed using a 12 Å cutoff distance to balance computational efficiency and accuracy. The solvated protein–ligand complex then underwent 100 ps (picoseconds) of energy minimization. The SHAKE algorithm was applied to constrain hydrogen bonds, and the system was heated to 310 K using the Nosé–Hoover thermostat[50] and a pressure of 1.01325 bar (1.01325×10^5 Pa) using the Martyna–Tobias–Klein barostat.[51] Finally, trajectory analyses were performed using the Simulation Interaction Diagram (SID) module of the Schrödinger suite, and snapshots were captured at 100 ps intervals. The stability of the protein–ligand complex was assessed by analyzing root mean square fluctuation (RMSF), root mean square deviation (RMSD), solvent-accessible surface area (SASA), and radius of gyration (Rg).

2.9.3. MM-GBSA–based binding free energy analysis

The binding free energies of sesamin, artemisinin, and nirmatrelvir with AR (PDB ID: 1E3G) and MAPK1 (PDB ID: 6SLG) were estimated using the Prime MM-GBSA module of the Schrödinger Suite 2025-1. Representative frames were extracted at regular intervals from the equilibrated portions of the 200-ns Desmond molecular dynamics trajectories and subjected to MM-GBSA analysis. The conformational entropy term was not included; therefore, the calculated values represent relative binding free-energy estimates. The energy values obtained from the selected trajectory frames were averaged, and more negative ΔG_{bind} values were interpreted as indicating more favorable predicted ligand–protein interactions.[52]

3. Results

3.1. Screening of target genes for sesamin, COVID-19 and malaria

We identified 431 genes as sesamin targets from a variety of sources, including CTD (14), STITCH (26), PharmMapper (291), and SwissTarget (100); 386 of these were selected as unique targets with no overlap. Similarly, we identified 2,544 unique genes related to COVID-19 after removing duplicate genes from the various sources, including 1,305 from GSE154998, 2,459 from GSE152418, and the top 500 genes from CTD (7,246 genes), DisGeNET (1,843 genes), PubChem (653 genes), and the COVID-19 host genes database (500 genes). After removing duplicate genes from the malaria datasets using multiple sources, including GSE86308 (681 genes), GSE50957 (533 genes), DISGENET (133 genes), and the top 500 genes from CTD (12,802 genes) and GeneCards (767 genes), we identified 1,932 genes. The R language was used to generate volcano plots showing upregulated and downregulated genes (Figure 2A–D). Figure 2E shows a Venn diagram of sesamin, COVID-19, and malaria co-infection generated using the free online Venn diagram tool. Malaria and COVID-19 shared 449 genes; COVID-19 and sesamin shared 159 genes; malaria and sesamin shared 111 genes; and sesamin, COVID-19, and malaria shared 70 genes. These 70 common genes were used for PPI and network analysis.

3.2. COVID-19/ malaria GO enrichment and molecular pathway analysis

A total of 407 GO pathways were identified, including 298 BP, 40 CC, and 69 MF. The top 10 biological pathways in each category with $p < 0.05$ were examined. Figure 3 illustrates the enrichment of the GO network. The BP category included responses to medication, negative apoptotic processes, extrinsic apoptotic signaling pathways in the absence of ligands, and positive control of nitric oxide biosynthesis. The cytosol, extracellular region, extracellular space, cell surface, and extracellular exosomes were included in the CC category. Meanwhile, enzymes, identical proteins, and oxygen binding were significantly involved in the MF category. Additionally, we used KEGG pathway enrichment analysis to identify more precise pathways associated with sesamin, COVID-19, and malaria. Of the 88 pathways identified, we selected the top 30 KEGG pathways based on $p < 0.05$ from the data analysis. The main pathways involved are cancer, phosphoinositide 3-kinase (PI3K)–protein kinase B (AKT) signaling, proteoglycans in cancer, prostate cancer, hepatitis B virus, hypoxia-inducible factor-1 (HIF-1) signaling, forkhead box O (FOXO) signaling, nucleotide-binding oligomerization domain (NOD)-like receptor signaling, microRNA in cancer, tuberculosis, and focal adhesion. Figure 4 shows the KEGG molecular pathway.

3.3. Establishment of protein–protein interaction network

Systems biology relies heavily on PPIs, which link biological processes, molecular functions, and cellular components to identify signaling pathways and protein complexes under certain circumstances. Because PPIs are fundamental to organismal interactomics, aberrant PPIs can cause various health complications. The sharing of various protein sub-networks suggests that the two diseases are associated. This study used the 70 DEGs shared among malaria, COVID-19, and sesamin to construct a PPI network comprising 59 nodes and 147 edges. The core targets are indicated by the nodes of the network. The edge thickness depends on the type of connection and network, reflecting node

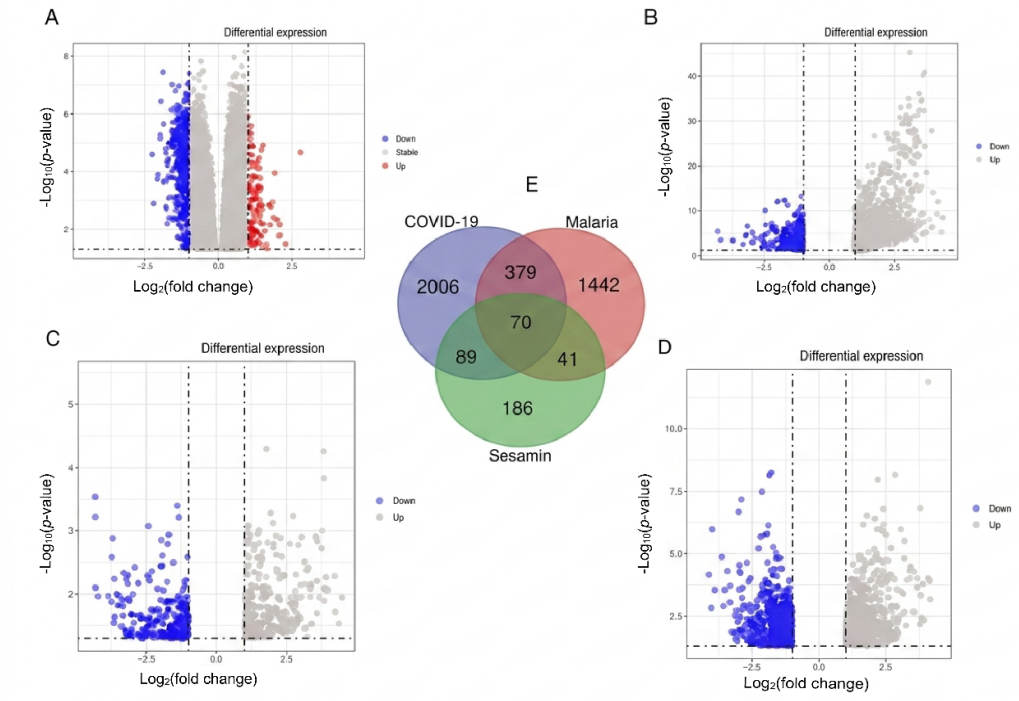


Figure 2. Volcano plots of (A) malaria from GSE86308, (B) COVID-19 from GSE152418, (C) malaria from GSE50957, and (D) COVID-19 from GSE154998. (E) A Venn diagram shows the common targets (70 differentially expressed genes) among sesamin, COVID-19, and malaria.

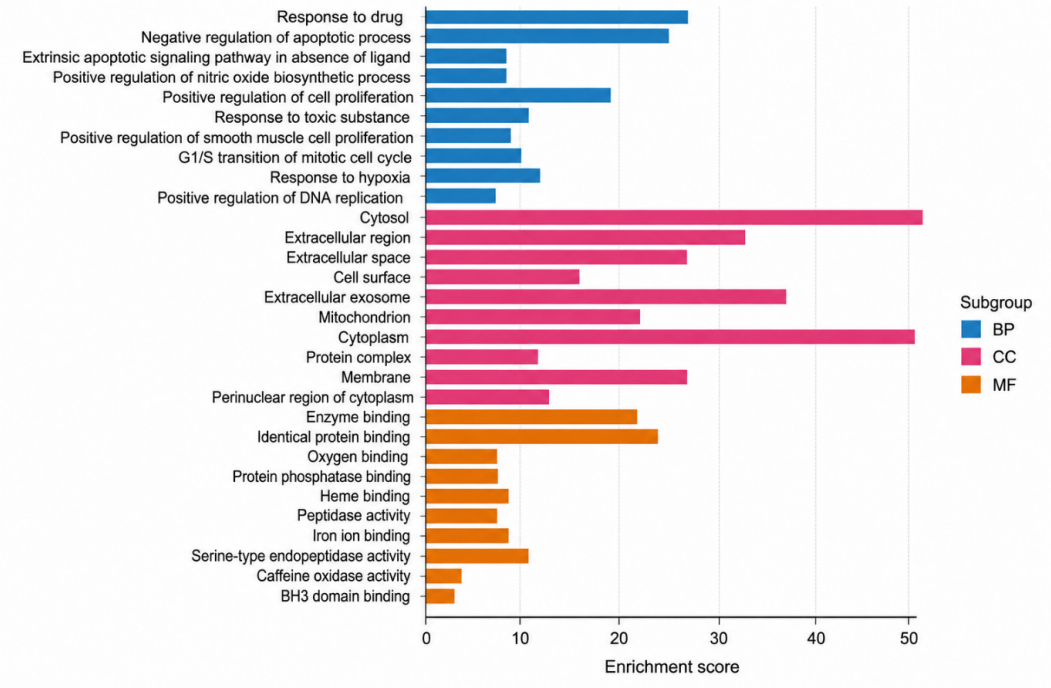


Figure 3. Gene Ontology analysis using three biological terms: biological process (BP), cellular component (CC), and molecular function (MF). The results of the pathway analysis are sorted using combined scores (based on *p*-value).

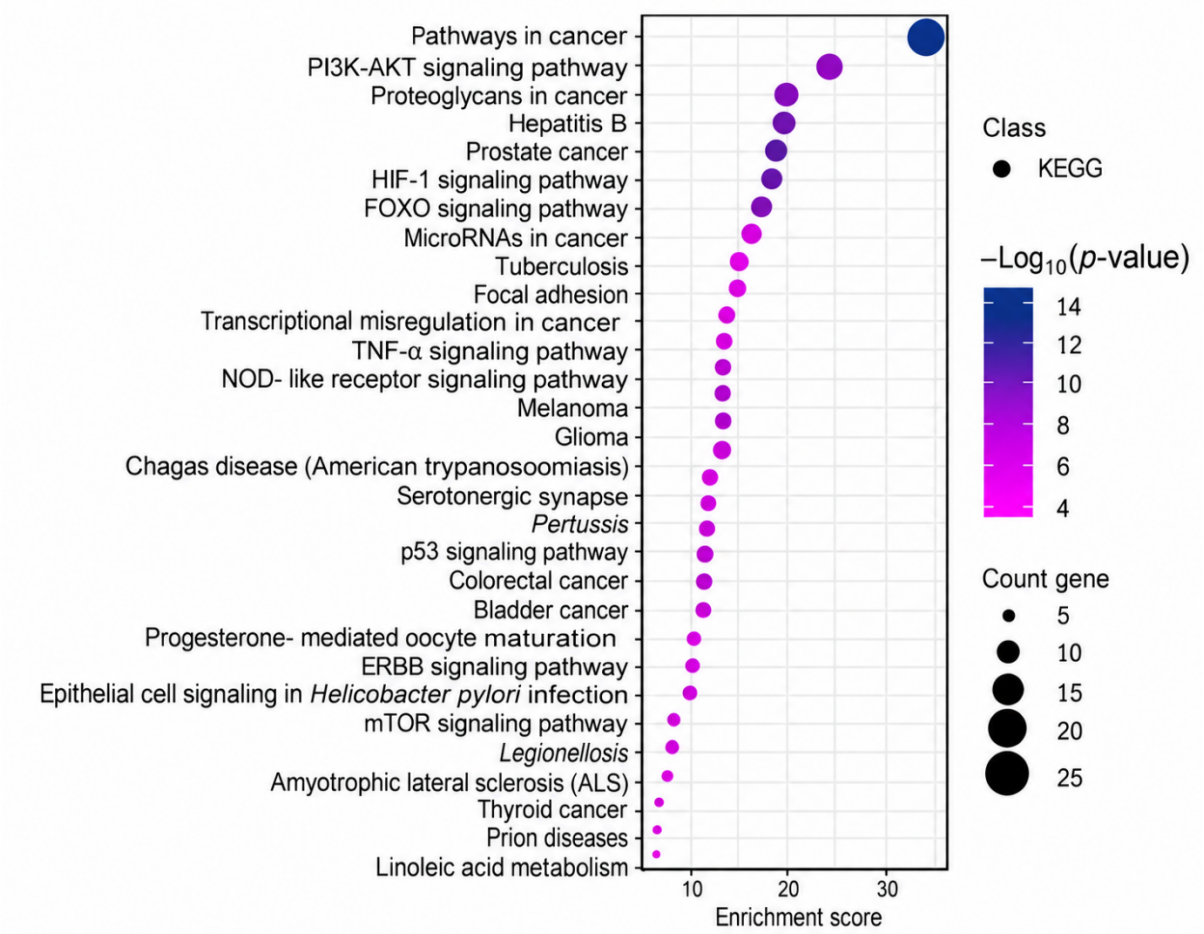


Figure 4. Sesamin targets were identified using a Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis of COVID-19 and malaria. The results of the pathway analysis are sorted using combined scores (based on *p*-value).

interactions (Figure 5).

3.4. Interpretation of protein clusters and hub proteins

Cluster analysis is a widely used technique for determining protein functions, functional modules, and active modules. We identified five important modules in the PPI network. Cluster 1 involved 6 nodes with a cumulative multi-edge connectivity score of 30, and Cluster 2 involved 4 nodes with a cumulative multi-edge connectivity score of 30, reflecting combined STRING evidence channels rather than a simple edge count (Figure 6). Remarkably, all methods commonly identified eight hub proteins (AR, MAPK1, caspase-3, β-catenin, IL-6, albumin, HSP90α, and epidermal growth factor receptor [EGFR]; Figure 7). These proteins may play important roles in host–pathogen interaction and inflammatory signaling pathways associated with malaria and COVID-19. However, these findings are network-based predictions, and the results of albumin may reflect network connectivity bias rather than disease-specific therapeutic relevance. Therefore, the other identified hub proteins should be considered as putative targets for further experimental validation rather than confirmed therapeutic targets of sesamin.

3.5. Correlation between GO terms, KEGG pathways, and hub proteins

Entities were arranged as geometric chords on a traditional chord plot, with arcs linking them indicating their relationships. Several arc colors were used to differentiate between data groupings. The 12 most significant GO keywords (four each of the three BP, CC, and MF categories) related to sesamin's primary targets against COVID-19 and malaria were obtained (Figure 8 and Table A1), including response to the drug, negative apoptotic process, cytosol, extracellular region, enzyme binding, and identical protein binding. According to Figure 9 and Table A2, the top 10 KEGG pathways associated with the main targets involved

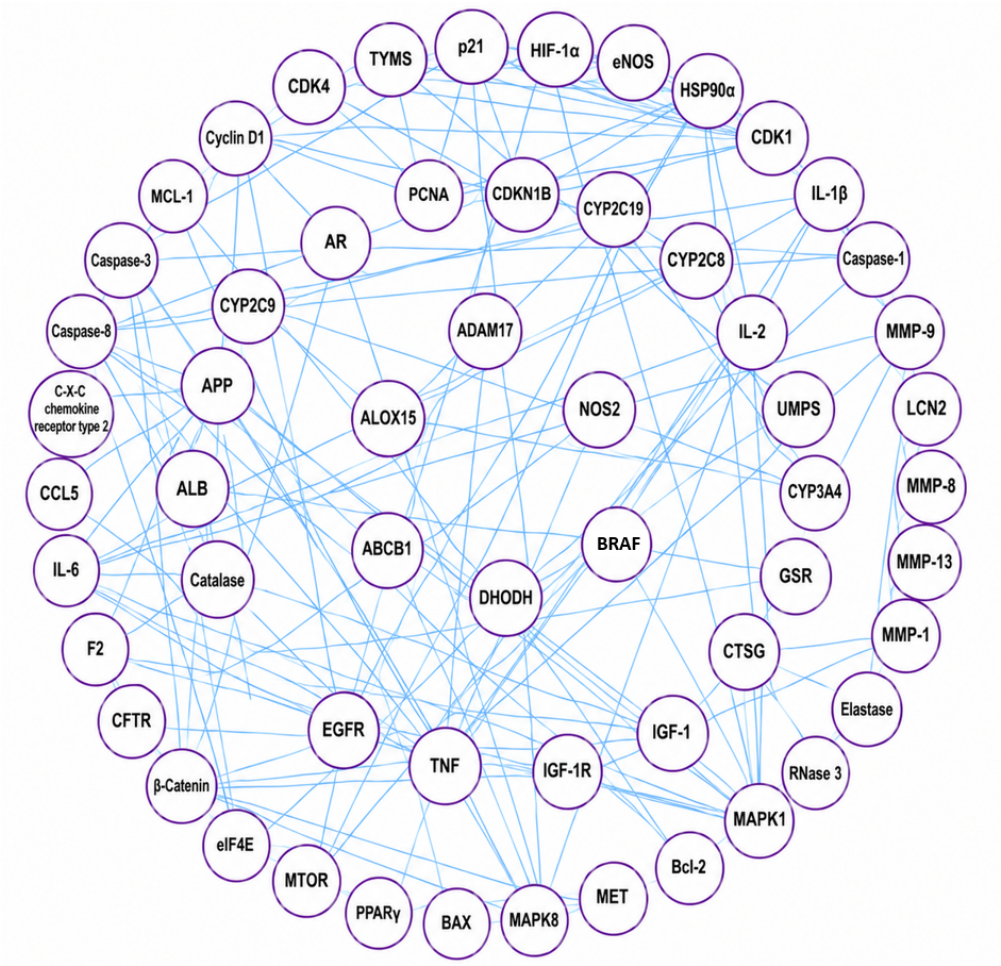


Figure 5. The protein–protein interaction network identifies sesamin as a potential therapeutic target for COVID-19 and malaria. Target proteins are represented as network nodes, and protein–protein interactions are shown by network edges.

in the protective effects of sesamin against COVID-19 and malaria included proteoglycans in cancer, PI3K–AKT signaling, prostate cancer, and hepatitis B.

3.6. Identification of the activity of upstream pathways

Transcriptomic analysis identified numerous commonly dysregulated genes, which were then loaded into the SPEED2 online bioinformatic tool to assess signaling activity scores. We tagged the genes to determine the activity of the upstream pathway from the common genes. The implied colors and ranked lists of upstream route activity were determined using adjusted *p*-values and absolute *p*-values, respectively; higher ranks corresponded to more vivid colors. In this signaling pathway, the top-ranked IL-1 played a critical role. IL-1, TNF-α, Toll-like receptor (TLR), Notch, insulin, estrogen, H_2O_2, transforming growth factor beta (TGF-β), and MAPK–PI3K signaling pathways were upregulated. In Figure 10, four signaling pathways were downregulated: Wnt, hypoxia, peroxisome proliferator-activated receptor (PPAR), and Hippo pathways. The target–disease–function–pathway interaction network of sesamin in COVID-19 and malaria is shown in Figure 11.

3.7. Physicochemical properties, pharmacokinetics, and toxicity analysis of sesamin

Sesamin exhibited favorable physicochemical and drug-likeness properties, including a molecular weight of 354.35 g/mol, moderate lipophilicity (XlogP3 = 2.68), compliance with Lipinski's rule of five, and no pan-assay interference compounds (PAINS) alerts. The compound showed acceptable predicted aqueous solubility, high Caco-2 permeability, and 97.81% intestinal absorption, suggesting favorable oral absorption. However, the negligible unbound

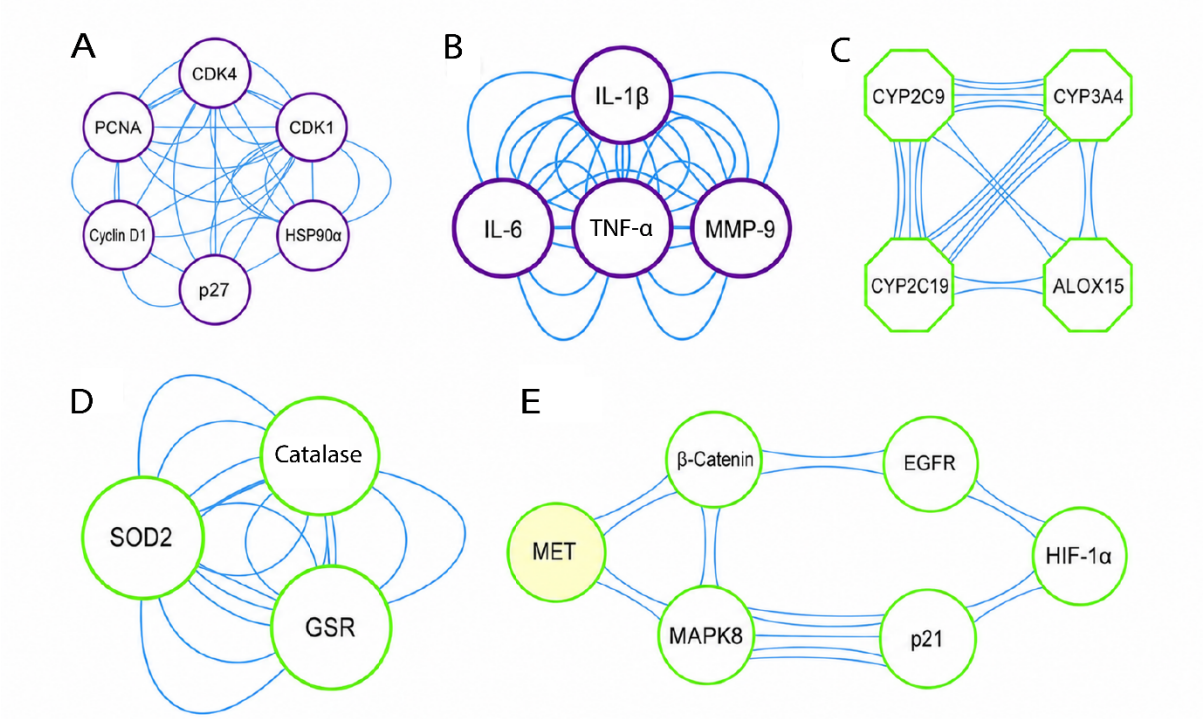


Figure 6. A group of protein property analyses using the ClusterViz plugin of Cytoscape. (A) Cluster 1. (B) Cluster 2. (C) Cluster 3. (D) Cluster 4. (E) Cluster 5.

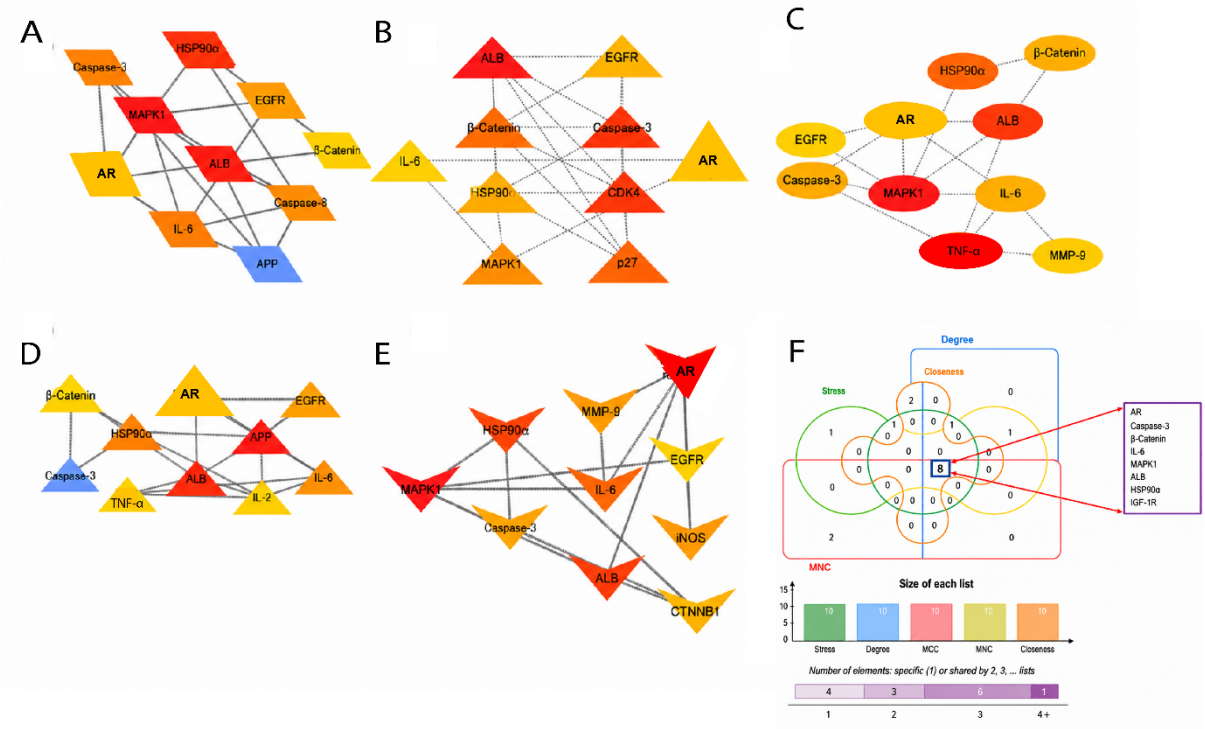


Figure 7. Using five CytoHubba methods, a network map showing sesamin's primary targets for combating COVID-19 and malaria is constructed. (A) Betweenness. (B) Closeness. (C) Degree. (D) Maximum clique centrality. (E) Maximum neighborhood component. (F) A Venn diagram showing eight typical hub proteins.

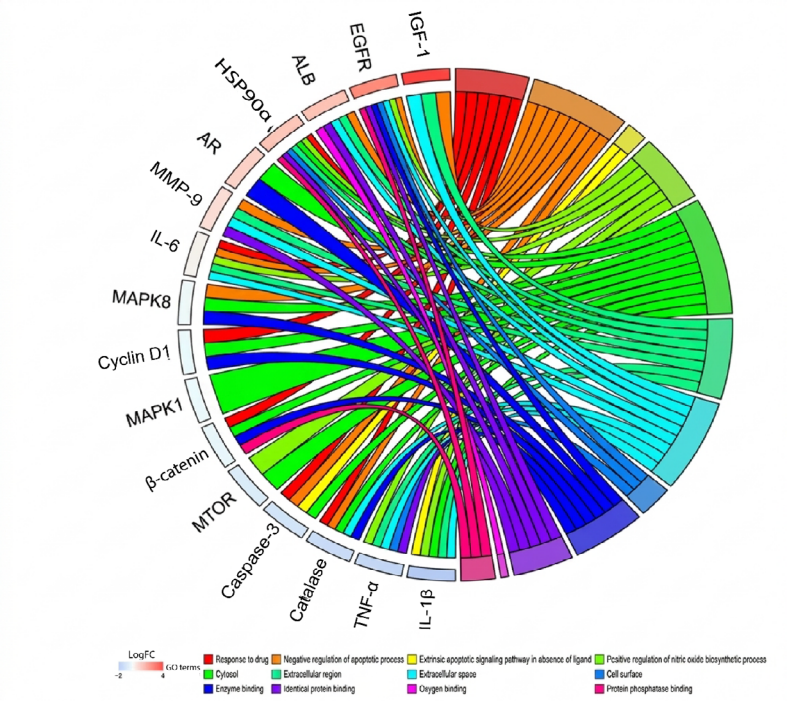


Figure 8. Chord plot representing the correlation between Gene Ontology (GO) and potential hub proteins of sesamin, malaria, and COVID-19
Abbreviation: FC: Fold change.

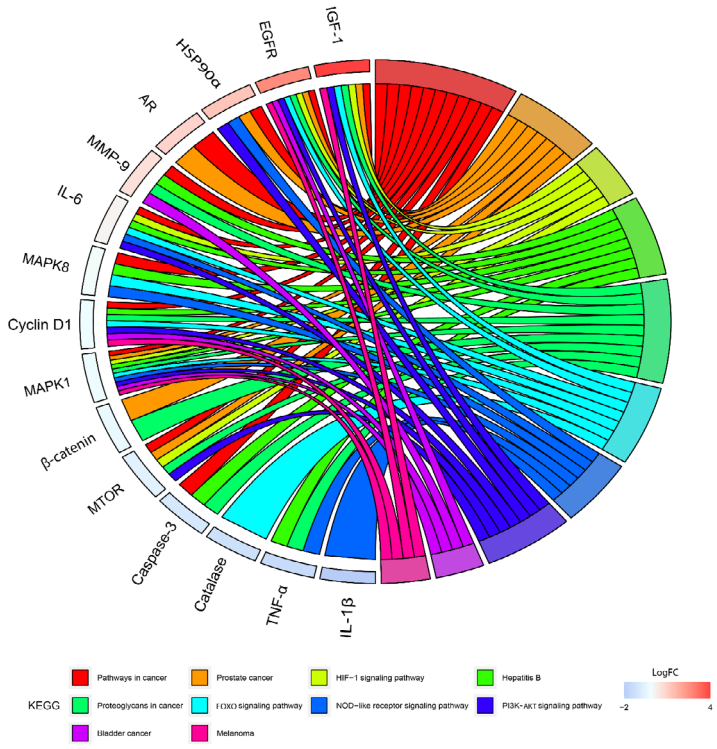


Figure 9. Chord plot representing the correlation between Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways and potential hub proteins of sesamin, malaria, and COVID-19
Abbreviation: FC: Fold change.

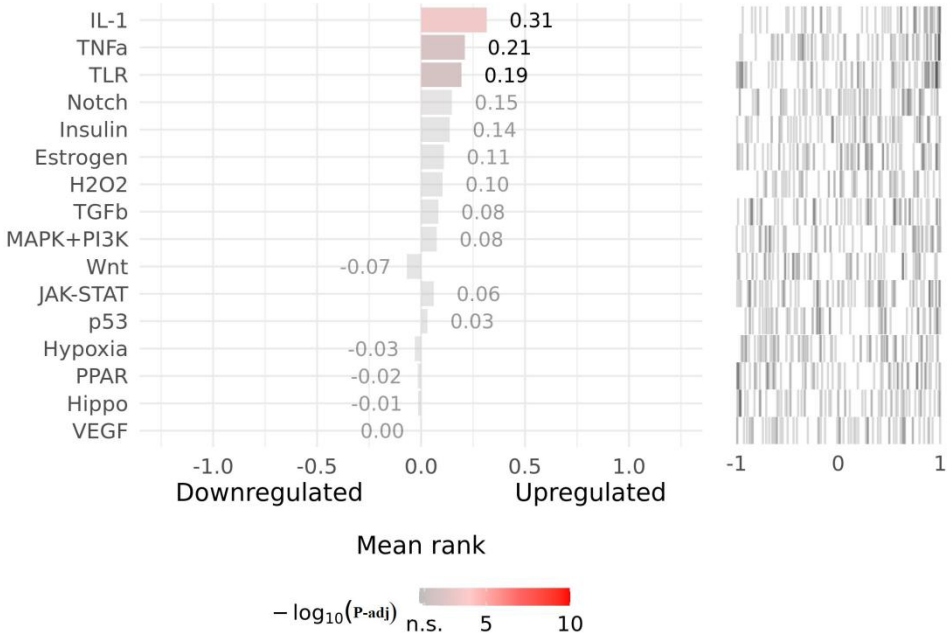


Figure 10. Inferring upstream pathway activity of sesamin-mediated malaria and COVID-19 co-infection

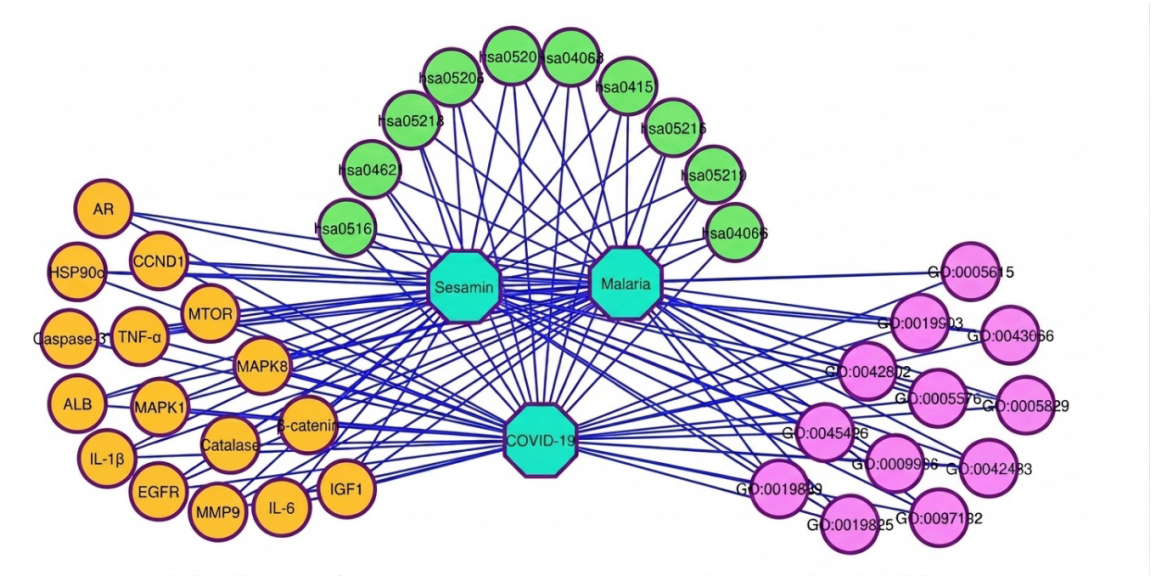


Figure 11. Combined network of COVID-19, malaria, and sesamin to visualize potential targets and therapeutic agents

fraction, limited penetration into the central nervous system and across the blood–brain barrier, and predicted inhibition of CYP1A2, CYP2C19, CYP2C9, and CYP3A4 may influence systemic exposure and increase the potential for metabolic drug–drug interactions. Toxicity predictions indicated no hepatotoxicity, neurotoxicity, Ames mutagenicity, respiratory toxicity, or skin sensitization. Nevertheless, potential immunotoxicity and cardiotoxicity signals were identified, highlighting the need for further experimental safety evaluation (Table A3).

3.8. Validation of hub proteins

3.8.1. Binding interaction analysis

Molecular docking showed that sesamin had more

favorable predicted binding scores than artemisinin and nirmatrelvir for all seven selected proteins (Table 1). MAPK1 exhibited the strongest interaction with sesamin (−10.0 kcal/mol), followed by AR (−9.4 kcal/mol) and EGFR (−9.2 kcal/mol).

The three-dimensional binding poses and corresponding two-dimensional interaction maps are presented in Figure 12. Sesamin interacted with HSP90α through hydrogen bonds with GLY135 and GLY137 and hydrophobic contacts with MET98 and LEU107 (Figure 12A). In AR, one hydrogen bond with LYS808 and five hydrophobic interactions involving ARG752, GLU681, PRO682, VAL715, and ALA748 were observed (Figure 12B). Sesamin formed two hydrogen bonds and three hydrophobic contacts with β-catenin (Figure 12C), whereas its interaction with caspase-3 was predominantly stabilized by six hydrophobic contacts without conventional hydrogen bonding (Figure 12D).

For EGFR (Figure 12E) and IL6 (Figure 12F), sesamin formed three and two hydrogen bonds, respectively, along with several hydrophobic interactions. The MAPK1–sesamin interaction involved three hydrogen bonds with GLY34, ASP106, and MET108 and six hydrophobic contacts with ILE31, TYR36, VAL39, ALA52, LYS54, and LEU156 (**Figure 12G**). Overall, the docking results identified MAPK1 and AR as the most promising targets for subsequent MDS and MM-GBSA analysis.

3.8.2. Molecular dynamics simulation analysis

The 200-ns MDSs were performed to evaluate the stability and dynamic behavior of sesamin bound to AR and MAPK1 compared with the reference ligands artemisinin and nirmatrelvir. The AR–sesamin and MAPK1–sesamin complexes maintained relatively stable protein conformations (Figure 13A), with mean protein RMSD values of 1.20 ± 0.10 Å and 1.80 ± 0.25 Å, respectively. The protein RMSD of AR–sesamin was lower than those

Table 1. Binding interaction analysis of eight reported target proteins with sesamin and control ligand

Protein (PDB)	Docking score (kcal/mol)			Hydrogen bond interaction		Hydrophobic bond interaction	
	CID: 68827 _Artemisinin (Control of malaria)	CID: 155903259 _Nirmatrelvir (Control of CoVID-19)	Sesamin	No. of bonds	Residues involved	No. of bonds	Residues involved
HSP90α (1BYQ)	−7.8	−7.2	−7.9	2	GLY135 and GLY137	2	LEU107 and MET98
AR (1E3G)	−7.2	−6.7	−9.4	1	LYS808	5	ARG752, GLU681, PRO682, VAL715, and ALA748
β-catenin (1G3J)	−7.3	−6.0	−8.6	2	A:ARG486 and C:LYS354	3	C:PRO355, C:VAL358, and C:GLU359
Caspase-3 (1I3O)	−6.6	−7.3	−8.6	0		6	A:LYS259, B:TYR329, B:TYR331, B:PRO335, C:LYS259, and D:PRO335
EGFR (1IVO)	−7.5	−6.8	−9.2	3	B:GLY9, B:THR10, and D:LYS48	3	B:MET30, B:PHE380, and D:TRP49
IL-6 (1P9M)	−7.8	−7.1	−8.4	2	C:MET250 and C:LYS252	2	C:ARG233 and C:PHE279
MAPK1(6SLG)	−7.4	−8.2	−10.0	3	A:GLY34, A:ASP106, and A:MET108	6	A:ILE31, A:TYR36, A:VAL39, A:ALA52, A:LYS54, and A:LEU156

Abbreviations: AR: Androgen receptor; EGFR: Epidermal growth factor receptor; HSP90α: Heat shock protein 90 alpha; IL-6: Interleukin 6; MAPK1: Mitogen-activated protein kinase 1; PDB: Protein Data Bank.

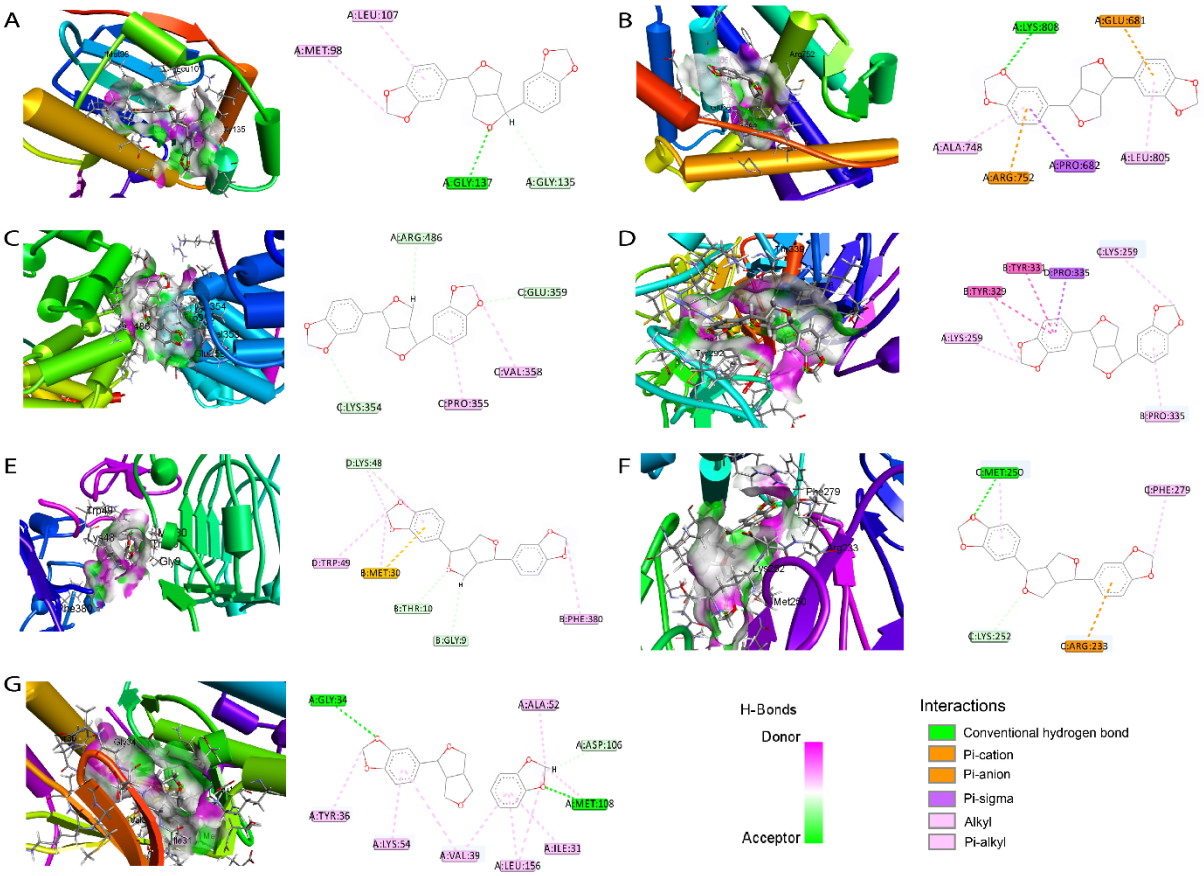


Figure 12. Binding interaction analyses represented using 3D and 2D diagrams. (A) HSP90α (Protein Data Bank ID: 1BYQ). (B) Androgen receptor (1E3G). (C) β-catenin (1G3J). (D) Caspase-3 (1I3O). (E) Epidermal growth factor receptor (1IVO). (F) Interleukin-6 (1P9M). (G) Mitogen-activated protein kinase 1 (6SLG).

of AR–artemisinin (1.50 ± 0.15 Å) and AR–nirmatrelvir (1.30 ± 0.14 Å). For MAPK1, the sesamin complex showed lower RMSD than MAPK1–artemisinin (2.30 ± 0.31 Å) but slightly higher than MAPK1–nirmatrelvir (1.60 ± 0.19 Å), indicating acceptable conformational stability. The mean ligand RMSD (Figure 13B) of sesamin was 2.80 ± 1.30 Å in the AR complex and 5.00 ± 2.30 Å in the MAPK1 complex. Sesamin therefore displayed greater positional stability within the AR-binding pocket. In comparison, substantial ligand displacement was observed for AR–nirmatrelvir (17.0 ± 15.0 Å) and MAPK1–artemisinin (34.0 ± 17.0 Å), whereas MAPK1–nirmatrelvir remained highly stable (2.60 ± 0.41 Å). Residue-level fluctuations were also limited, with mean RMSF values of 0.92 ± 0.32 Å for AR–sesamin and 0.98 ± 0.42 Å for MAPK1–sesamin, suggesting that sesamin binding did not induce extensive local structural flexibility (Figure 13C).

In addition, the Rg (Figure 13D) remained relatively stable for the AR–sesamin and MAPK1–sesamin complexes, with mean values of 4.60 ± 0.14 Å and 4.50 ± 0.25 Å, respectively. No progressive increase or decrease was observed, indicating preservation of the overall ligand conformational compactness. The mean SASA values (Figure 13E) were 94 ± 29 Å^2 for AR–sesamin and 176 ± 65 Å^2 for MAPK1–sesamin. Although transient fluctuations occurred, particularly in the MAPK1 complex, neither system exhibited sustained solvent exposure or continuous structural expansion, supporting maintenance of conformational integrity of each ligand during the simulation. Hydrogen-bond analysis (Figure 13F) further showed that sesamin formed an average of 2.80 ± 1.10 hydrogen bonds with AR and 3.70 ± 1.30 hydrogen bonds with MAPK1. These persistent interactions potentially contributed to the stabilization of sesamin within the respective binding sites. Overall, the RMSD, RMSF, Rg, SASA, and hydrogen-bond profiles support stable interactions of sesamin with both AR and MAPK1, with the AR–sesamin complex showing greater ligand and conformational stability.

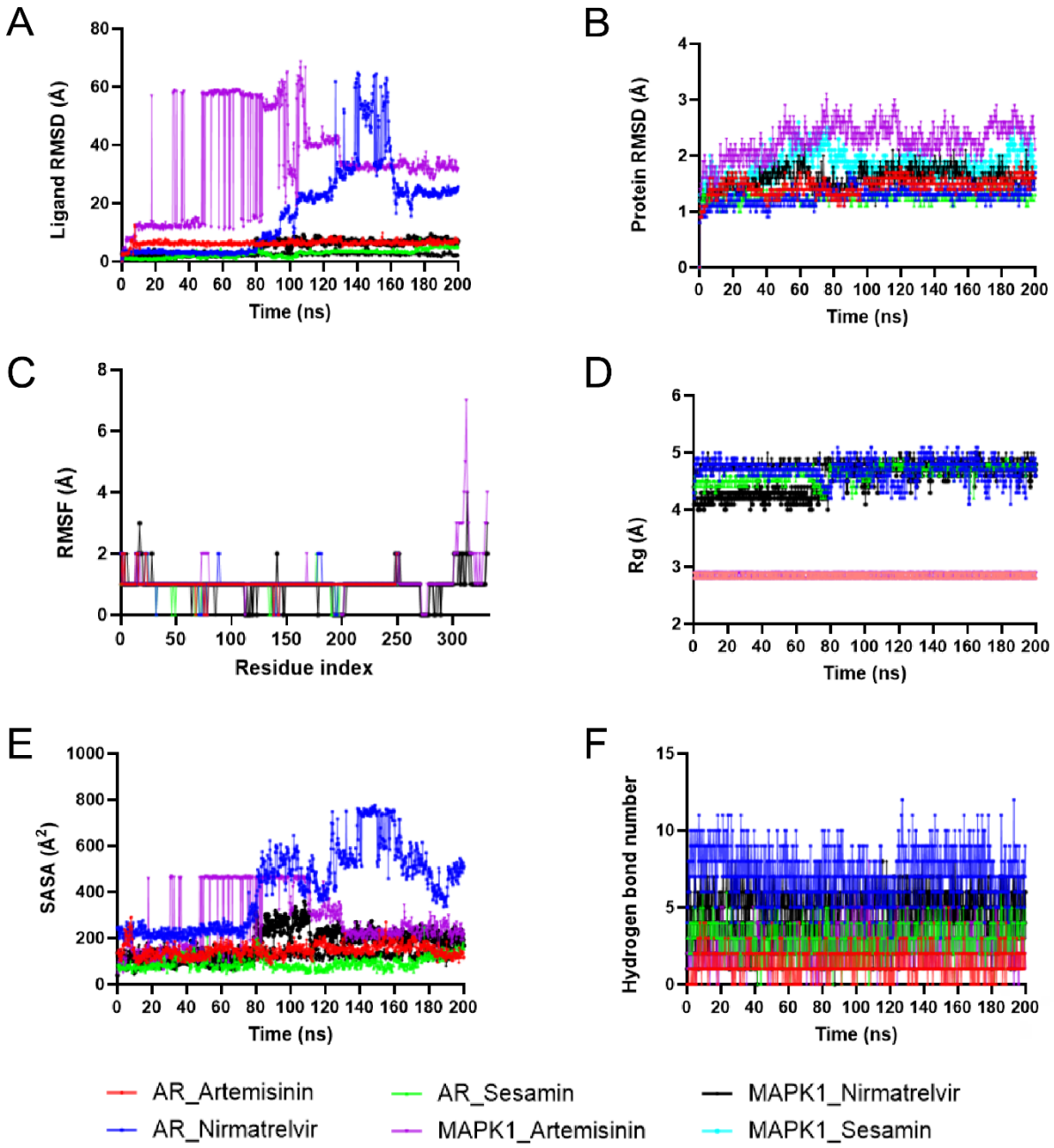


Figure 13. Molecular dynamics simulation analysis of androgen receptor (AR) and mitogen-activated protein kinase 1 (MAPK1) bound to sesamin, artemisinin, and nirmatrelvir over 200 ns. (A) Ligand root mean square deviation (RMSD). (B) Protein RMSD. (C) Residue-level root mean square fluctuation (RMSF). (D) Radius of gyration (Rg). (E) Solvent-accessible surface area (SASA). (F) Number of hydrogen bonds formed during the simulations.

3.8.3. MM-GBSA-based binding free-energy analysis

MM-GBSA analysis (Table 2) identified sesamin as the most favorable ligand for both targets. For AR (PDB ID: 1E3G), sesamin showed a binding free energy of −55.77 kcal/mol, compared with −34.05 kcal/mol for nirmatrelvir and −33.30 kcal/mol for artemisinin. This favorable binding was mainly driven by van der Waals, lipophilic, Coulombic, and hydrogen-bonding interactions. For MAPK1 (PDB ID: 6SLG), sesamin also exhibited the most negative binding energy (−122.17 kcal/mol), followed by nirmatrelvir (−114.20 kcal/mol) and artemisinin (−109.80 kcal/mol). In a nutshell, sesamin demonstrated the strongest predicted binding affinity for both AR and

MAPK1.

4. Discussion

Since the emergence of COVID-19, increasing attention has been given to its potential interactions with malaria, particularly in endemic regions where both diseases may coexist. Sesamin has been proposed as a potential therapeutic candidate against COVID-19,[53] although its effectiveness against COVID-19 and malaria remains unconfirmed. In this study, network pharmacology and bioinformatics approaches were used to identify shared molecular targets and pathways associated with sesamin, COVID-19, and malaria. The predicted mechanisms were further explored through GO enrichment, pathway analysis, upstream regulator analysis, molecular docking, MDS, and MM-GBSA binding free-energy calculation. These findings provide computational evidence for the potential multitarget activity of sesamin but require experimental validation.

The top 10 pathways identified in each database are largely involved in drug response, identical protein binding, viral infection, inflammation, immunological responses, cancer, metabolic reactions, and respiratory illnesses. The pathway with the lowest *p*-value and the highest number of identified hub genes was analyzed. Therefore, we hypothesize that sesamin may be helpful in COVID-19 treatment by affecting the GO and signaling pathways linked to viral infection, immune responses, and inflammation.[54] This hypothesis is supported by experimental evidence that sesamin suppresses IL-6 and TNF-α production through inhibition of p38 MAPK and nuclear factor kappa B (NF-κB) signalling.[23]

The GO enrichment analysis identified various pathways associated with cancer, inflammatory, and metabolic responses, including the negative regulation of the apoptotic process, the G1/S transition of the mitotic cell cycle, the extrinsic apoptotic signaling pathway in the absence of ligand, and the perinuclear region of the cytoplasm. The apoptotic mechanism is negatively regulated, thereby affecting lung tissue peroxidation and the progression of COVID-19 in patients with ARDS/septic shock.[23] People with malaria who have an extrinsic apoptotic signaling pathway may induce apoptosis of $CD4^+$ T-cells by activating the tumor necrosis factor receptor 1 (TNFR1) in the absence of a ligand (extrinsic pathway).[55] Sesamin can induce rapid cell death by activating the apoptotic signaling pathway, triggering caspase activation and inducing cell death.[56]

Our KEGG pathway analysis identified connections among metabolic and immunological responses, cancer, viral infection, and inflammatory responses. The treatment of COVID-19 with sesamin altered signaling pathways, including those associated with cancer, HIF-1 signaling, hepatitis B, FOXO signaling, NOD-like receptor (NLR)

Table 2. MM-GBSA binding free-energy and energy-component analysis of sesamin, artemisinin, and nirmatrelvir with AR (PDB ID: 1E3G) and MAPK1 (PDB ID: 6SLG)

Components	r_psp_ MMGBSA_ dG_Bind_ vdW	r_psp_ MMGBSA_dG_ Bind_Solv_GB	r_psp_ MMGBSA_ dG_Bind_ Lipo	r_psp_ MMGBSA_ dG_Bind_ Hbond	r_psp_ MMGBSA_dG_ Bind_Covalent	r_psp_ MMGBSA_dG_ Bind_Coulomb	r_psp_ MMGBSA_ dG_Bind
1E3G_Artemisinin	−29.78409	14.17747	−8.52782	−0.64416	0.84538	−9.36920	−33.30242
1E3G_Nirma	−30.52172	17.84106	−9.41788	−0.72924	2.29528	−13.52222	−34.05472
1E3G_Sesamin	−40.91329	18.01177	−21.11565	−0.99005	0.93544	−10.06531	−55.76898
6SLG_Artemisinin	−101.02593	−16.12497	−29.20440	−2.81309	3.97928	37.27163	−109.80006
6SLG_Nirma	−105.76386	−7.97410	−31.58535	−2.66042	3.54657	31.90181	−114.19844
6SLG_Sesamin	−106.12525	−26.23724	−32.51758	−3.81944	0.99988	47.98341	−122.16814

Abbreviations: AR: Androgen receptor; MAPK1: Mitogen-activated protein kinase 1; MM-GBSA: Molecular mechanics/generalized Born surface area; PDB: Protein Data Bank.

signaling, and PI3K–AKT signaling, according to KEGG pathway analysis.

Hypoxia is common in inflammatory areas and involves specific factors, such as HIF-1, which has a range of consequences in COVID-19 patients.[57] HIF-1 activates both PI3K and MAPK signaling pathways.[58] Inhibition of the MAPK signaling pathway may help mitigate COVID-19-associated inflammation by modulating pro-inflammatory cytokines, particularly IL-6, which plays an important role in inflammatory responses and acute lung injury during COVID-19.[59] In addition, the MAPK signaling pathway is important for malaria parasites.[60] Sesamin reduces colon damage and the generation of TNF, IL-1, and IL-6 via MAPK signaling pathways.[61] Recent research has revealed that pregnant women in Ghana have a high prevalence of malaria and hepatitis B virus infection.[62] By modulating survival, oxidative stress, and T and B lymphocyte development and maturation, the transcription factor FOXO is thought to contribute to maintaining normal cell physiology. It is considered a significant anti-inflammatory approach, depending on FOXO activation as an appealing strategy against the novel coronavirus.[63] FOXO may also be regulated by microRNAs implicated in cerebral malaria.[64] Sesamin may activate sirtuin 3 (SIRT3) to reduce reactive oxygen species (ROS) levels by activating FOXO3a-dependent antioxidants. Sesamin also inhibits FOXO3a phosphorylation in response to pressure overload.[65] In response to parasites, NOD proteins (e.g., NLRs) are activated and regulate host inflammatory responses during malaria infection.[66] By producing pro-inflammatory cytokines, NLRs are implicated in acute lung injury/ARDS, chronic obstructive pulmonary disease, pneumoconiosis, and asthma.[67] The PI3K–AKT signaling pathway, which activates dendritic cells, releases certain cytokines implicated in malaria development.[68] Additionally, it is critical to the immunological response in COVID-19 patients.[69] Sesamin, which inhibits PI3K–AKT signaling, may lower cyclooxygenase-2 (COX-2) expression in lung cancer by inducing apoptosis and G1 phase arrest.[70]

In the upstream pathway activity, top-ranked IL-1 played a critical role in COVID-19-associated effects in malaria patients. Scientists have revealed that the IL-1 signaling pathway is a key mediator in COVID-19-induced lung inflammation and fibrosis, and that it also causes severe malaria.[71] IL-1 blockade with anakinra has been shown to improve clinical outcomes and reduce mortality in selected patients with COVID-19.[72] According to an *in vitro* investigation, sesamin has the potential to inhibit pro-inflammatory cytokine levels.[73] In patients admitted with imported falciparum malaria, C-reactive protein (CRP) and albumin levels are associated with illness severity and respiratory complications.[74] The CRP/albumin ratio may be a useful predictive marker of disease severity in COVID-19.[75]

Furthermore, using cytoHubba algorithms, we constructed a PPI network and identified seven of the eight hub proteins identified in Section 3.4 (excluding albumin, which may reflect network connectivity bias rather than a disease-specific target): AR, MAPK1, caspase-3, β-catenin, IL-6, HSP90α, and EGFR. These hub proteins were abundant in each signaling and GO network. Deng *et al.*[76] suggested that AR may play a role in regulating the SARS-CoV-2 receptor and co-receptor in prostate and lung cells. Androgen signaling may modulate host immune responses during malaria infection. Notably, Duncombe *et al.*[77] reported, using an *in vivo* mouse model, that androgen signaling suppresses $CD8^+$ T-cell–mediated immune protection during the pre-erythrocytic stage of malaria infection. MAPK mediates some cytokines that play a vital role in controlling TGF-β1 activity in *P. falciparum*.[78] The involvement of MAPK1 in COVID-19 is not fully understood; however, the MAPK pathway regulates the rate of COVID-19 incidents.[79] IL-6 promotes acute-phase responses to infection and tissue injury, thereby contributing to host defense.[80] In COVID-19 patients and during malaria infections,[81] like other viral infections, IL-6 is associated with adverse lung damage and pulmonary inflammation.[82,83] EGFR inhibitors are used to manage the increasing prevalence of COVID-19 patients and may be significantly influenced by SARS-CoV-2 and epidermal growth factor (EGF),[84] and are also used to treat chronic pulmonary diseases.[85] The *EGFR* gene encodes EGFR, which may be involved in malaria.[86] *CASP3* is a key apoptosis-related gene that contributes to the regulation of programmed cell death and may help limit malaria-associated liver tissue damage,[87] and patients with COVID-19 have higher *CASP3* levels than healthy individuals.[88] Lung adenocarcinoma with a *CTNNB1* mutation is uncommon, and nothing is known about its clinicopathologic features, disease progression, or prognosis.[89] The involvement of β-catenin in malaria is not well understood. The SARS-CoV-2 envelope protein targets HSP90α and activates the PI3K–AKT signaling pathway, suggesting that this interaction may influence host-cell survival and inflammatory responses during COVID-19.[90] HSP90α was significantly upregulated in patients with *P. falciparum* infection, supporting its potential association with host stress and immune responses in malaria; however, its precise mechanistic role remains unclear.[91]

Molecular docking helps identify novel treatments or enhance existing ones, and seven crucial targets were identified as binding partners for sesamin using docking.

Sesamin has strong binding affinity for receptor proteins, including EGFR (−9.2 kcal/mol), AR (−9.4 kcal/mol), and MAPK1 (−10 kcal/mol). Sesamin is a lignan extracted from *S. indicum* seeds that exhibits potent pharmacological activity. Experimental evidence partially supports the predicted interactions of sesamin with EGFR, AR, and MAPK1. Sesamin has been reported to reduce EGFR and phosphorylated MAPK expression in MCF-7 tumor-bearing mice,[92] modulate AR expression and MAPK signaling in dihydrotestosterone-stimulated HaCaT cells,[93] and alter extracellular signal-regulated kinase 1/2 (ERK1/2) phosphorylation in human osteoblasts.[94] Sesamin is also thought to alleviate COVID-19 symptoms by restoring T-helper cell 1 (Th1)/Th2 balance and preventing inflammation and cytokine storms.[23] Sesamin may dramatically reduce the expression of *IL6* and *IL1* mRNA in human primary synovial fibroblasts, suggesting that sesamin might suppress the TNF-induced expression of pro-inflammatory cytokines.[23] Gomes *et al.*[95] found that sesamin has larvicidal activity against *Aedes aegypti*. Recently, the stem bark of *Zanthoxylum heitzii* was discovered to have larvicidal activity against *Anopheles gambiae* and was used to isolate sesamin.[96] Sesamin also showed favorable drug-likeness, membrane permeability, and predicted intestinal absorption; however, its low aqueous solubility and negligible unbound fraction may limit systemic bioavailability. Poor water solubility has previously been identified as a major limitation of oral sesamin delivery.[97] Predicted inhibition of cytochrome P450 (CYP450) enzymes indicates potential metabolic drug–drug interactions, consistent with experimental evidence showing that sesamin inhibits several CYP450 isoenzymes.[98] Although most toxicity endpoints were favorable, the predicted immunotoxicity and cardiotoxicity signals warrant further investigation. As these findings were generated using computational tools, experimental pharmacokinetic and toxicological studies are required to confirm them.[22] MDS is a computational technique used to evaluate the time-dependent stability, flexibility, and interactions of protein–ligand systems under simulated physiological conditions.[99] In our study, the low RMSD and RMSF values indicated that sesamin did not induce substantial global or residue-level destabilization of AR and MAPK1. The AR-bound system showed lower ligand RMSD and SASA, suggesting greater positional stability and reduced solvent exposure, whereas the higher ligand RMSD of MAPK1 indicated greater reorientation within the binding site. Stable Rg profiles further supported maintenance of molecular compactness.[100] Although MAPK1 formed more hydrogen bonds, hydrogen-bond number alone does not establish stronger binding and should be interpreted alongside ligand mobility, solvent exposure, and contact persistence.[101] Sesamin showed more favorable MM-GBSA binding energies than both reference ligands, supporting its predicted interactions with AR and MAPK1; however, these values are approximate and require experimental validation.[102]

Our findings suggest that sesamin may modulate multiple molecular targets and signaling pathways associated with antiviral defense, oxidative stress, inflammation, and immune regulation in COVID-19 and malaria. Its predicted physicochemical and pharmacokinetic properties support further investigation, although potential CYP-mediated interactions and selected toxicity signals require experimental confirmation. The integrated network pharmacology, transcriptomic, molecular docking, molecular dynamics, and MM-GBSA analyses provide convergent computational evidence for the potential multitarget activity of sesamin. However, these findings remain hypothesis-generating and do not establish clinical efficacy. Further biochemical, cellular, antiplasmodial, pharmacokinetic, toxicological, animal, and clinical studies are required to determine whether sesamin could be developed as an adjunct therapeutic candidate for COVID-19 and malaria.

5. Conclusion

Malaria and COVID-19 remain major public-health concerns, particularly in regions where both diseases coexist. This study integrated transcriptomic analysis, network pharmacology, molecular docking, MDS, MM-GBSA binding free-energy analysis, and ADMET prediction to investigate the potential multitarget activity of sesamin against molecular processes relevant to both diseases. The findings identified AR, MAPK1, caspase-3, β-catenin, IL-6, HSP90α, and EGFR as potential targets and highlighted the PI3K–AKT, FOXO, MAPK, and HIF-1 signaling pathways, as well as apoptosis- and immune-related biological processes. The 200-ns MDS demonstrated that sesamin maintained stable interactions with both AR and MAPK1. The AR-bound system showed greater ligand positional stability and lower solvent exposure, whereas the MAPK1-bound system exhibited more persistent hydrogen-bond interactions despite greater ligand mobility. MM-GBSA analysis further supports the potential interaction of sesamin with AR and MAPK1, yielding more favorable binding energies than those of the reference ligands for both targets. However, these results remain computational and do not establish biological activity. Further clinical studies are required to validate the proposed mechanisms and determine the translational potential of sesamin as an adjunct therapeutic candidate for COVID-19 and malaria.

This study is based entirely on computational predictions, which may not fully reflect the complex biological responses occurring in living systems. The identified targets, pathways, docking interactions, and molecular dynamics results therefore require experimental confirmation. In addition, differences in database coverage, target-prediction algorithms, protein structures, and simulation conditions may influence the findings. Further *in vitro, in vivo*, and clinical studies are needed to validate the therapeutic efficacy, safety, bioavailability, and molecular mechanisms of sesamin against COVID-19 and malaria.

Acknowledgments

We would like to express our gratitude to the members of the Center for Advanced Bioinformatics and Artificial Intelligence Research Lab staff, led by Dr. Md. Habibur Rahman, for their assistance and insightful contributions to this study.

Funding

The authors extend their appreciation to Ongoing Research Funding project number ORF-2026-17, King Saud University, Riyadh, Saudi Arabia.

Conflict of interest

The authors declare no conflicts of interest.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

The data that support the findings of this study are available in the Appendix and are available from the corresponding author upon reasonable request.

Further disclosure

The authors used AI-assisted tools only for language editing and proofreading. All scientific content, analysis, and conclusions were developed and verified by the authors.

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Appendix

Table A1. Correlation between Gene Ontology pathways and potential hub proteins of sesamin, malaria, and COVID-19

Proteins	Positive regulation of protein phosphorylation	Negative regulation of apoptotic process	Protein autophosphorylation	Nucleus	Apical plasma membrane	Nucleoplasm	Perinuclear region of cytoplasm	Protein phosphatase binding	Protein tyrosine kinase activity	ATP binding	logFC
EGFR	1	1	1	0	0	0	0	1	1	1	−0.69979
HER2	1	0	1	0	1	0	1	1	1	1	−0.39517
ATM	0	0	1	0	0	0	0	0	0	1	−0.45182
MCL-1	0	1	0	0	0	0	0	0	0	0	−0.18485
VEGF-A	1	1	0	0	0	0	0	0	0	0	1.23546
AKT1	1	1	1	0	0	0	0	0	0	1	0.07934
HSP90α	0	0	0	1	1	1	1	1	1	1	1.28119
Caspase-3	0	1	0	1	0	1	0	0	0	0	−0.62946

Abbreviations: AKT1: RAC-alpha serine/threonine-protein kinase; ATM: ATM serine/threonine kinase; EGFR: Epidermal growth factor receptor; FC: Fold change; HER2: Human epidermal growth factor receptor 2; HSP90α: Heat shock protein 90 alpha; MCL-1: Myeloid cell leukemia 1; VEGF-A: Vascular endothelial growth factor A.

Table A2. Correlation between metabolic pathways and potential hub proteins of sesamin, malaria, and COVID-19

Proteins	PI3K-AKT signaling pathway	Pathways in cancer	Proteoglycans in cancer	Pancreatic cancer	Prostate cancer	HIF-1 signaling pathway	Estrogen signaling pathway	FOXO signaling pathway	Focal adhesion	Rap1 signaling pathway	logFC
EGFR	1	1	1	1	1	1	1	1	1	1	−0.69979
HER2	0	0	0	0	0	0	0	0	0	0	−0.39517
ATM	0	0	0	0	0	0	0	1	0	0	−0.45182
MCL-1	1	0	0	0	0	0	0	0	0	0	−0.18485
VEGF-A	0	1	1	1	0	1	0	0	1	1	1.23546
AKT1	1	1	1	1	1	1	1	1	1	1	0.079337
HSP90α	1	1	0	0	1	0	1	0	0	0	1.281194
Caspase-3	0	1	1	0	0	0	0	0	0	0	−0.62946

Abbreviations: AKT: Protein kinase B; AKT1: RAC-alpha serine/threonine-protein kinase; ATM: ATM serine/threonine kinase; EGFR: Epidermal growth factor receptor; FC: Fold change; FOXO: Forkhead box O; HER2: Human epidermal growth factor receptor 2; HIF-1: Hypoxia-inducible factor 1; HSP90α: Heat shock protein 90 alpha; MCL-1: Myeloid cell leukemia 1; PI3K: Phosphoinositide 3-kinase; Rap1: Ras-related protein 1; VEGF-A: Vascular endothelial growth factor A.

Table A3. Detailed predicted physicochemical properties, drug-likeness, pharmacokinetics, and toxicity profile of sesamin

Category	Parameter	Predicted value	Interpretation
Physicochemical	Molecular formula	$C_{20}H_{18}O_6$	Chemical formula of sesamin
	Molecular weight	354.35 g/mol	Within the preferred range for small-molecule drugs
	Log $P_{o/w}$ (XlogP3)	2.68	Moderate lipophilicity
	Hydrogen-bond acceptors	6	Within the Lipinski limit
	Hydrogen-bond donors	0	Within the Lipinski limit
Drug-likeness	Lipinski rule	Accepted	No Lipinski violation
	PAINS alerts	0	No pan-assay interference alert
Water Solubility	Log *S* (ESOL)	−3.93	Predicted to have acceptable aqueous solubility
	Solubility class	Soluble	
Absorption	Caco-2 permeability	1.339 log cm/s	Acceptable intestinal permeability
	Intestinal absorption	97.81 %	High
	Skin permeability	−2.772 log kp	Moderate skin permeability, suggesting limited transdermal absorption
	P-glycoprotein I inhibitor	No	Suggesting a low risk of related transporter-mediated interactions
	P-glycoprotein II inhibitor	Yes	Indicating a potential risk of altered drug transport and drug–drug interactions.
Distribution	VDss	−0.17 log L/Kg	Moderate predicted tissue distribution
	Fraction unbound	0 Fu	Low free fraction in plasma
	CNS permeability	−2.939 log PS	Low predicted penetration into the central nervous system
	Blood–brain barrier probability	−0.862 log BB	Low probability of BBB penetration
Metabolism	CYP1A2 inhibitor probability	Yes	Indicating a possible risk of CYP1A2-mediated drug–drug interactions.
	CYP2C19 inhibitor probability	Yes	Suggesting possible interference with the metabolism of CYP2C19 substrates.
	CYP2C9 inhibitor probability	Yes	Indicating a possible risk of altered metabolism of CYP2C9 substrates.
	CYP2D6 inhibitor probability	No	Unlikely to inhibit CYP2D6-mediated drug metabolism
	CYP3A4 inhibitor probability	Yes	Suggesting a possible risk of clinically relevant metabolic drug–drug interactions.
Excretion	Total clearance	−0.126 log mL/min/kg	Suggesting relatively slow elimination
	Renal OCT2 substrate	No	Unlikely to be eliminated through renal OCT2
Toxicity	LD50 (Class)	1,500 mg/kg (Class 3)	Indicates moderate predicted acute oral toxicity
	Hepatoxicity	0.81	Inactive
	Neurotoxicity	0.79	Inactive
	Immunotoxicity	0.84	Active
	Respiratory	0.54	Inactive
	Cardiotoxicity	0.55	Active
	Ames mutagenicity probability	0.60	Inactive
	Skin-sensitization probability	No	No sensitization signal
	Respiratory-toxicity probability	0.436	Indicates a low-to-moderate probability of respiratory toxicity