RESEARCH ARTICLE

Unveiling the Therapeutic Potential of *Syzygium cumini*: A Network Pharmacology Exploration of Targets and Mechanisms

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ABSTRACT

This study delves into the therapeutic potential of *Syzygium cumini*, a medicinal plant known for its rich bioactive compounds such as quercetin, myricetin, myrcene, and β-sitosterol. By using a network pharmacology approach, we aimed to uncover the mechanisms behind its pharmacological effects, especially concerning breast cancer management and its associated complications. Firstly, we conducted an extensive analysis of the bioactive compounds in *S. cumini*, identifying numerous molecules with potential therapeutic benefits. These compounds, recognized for their varied biological activities, provided a foundation for understanding the plant's medicinal properties. Next, using network pharmacology techniques, we explored the complex interactions between these bioactive compounds and their potential targets within the human body. By mapping out these targets and disease-related genes, we built a network that illuminated the intricate mechanisms through which *S. cumini* exerts its effects. Particularly intriguing were the high-affinity interactions found, such as those between prostaglandin-endoperoxide synthase 2 and Cytochrome P450 Family 19 Subfamily A Member 1. These interactions are promising for targeted therapeutic interventions and warrant further investigation to fully understand their roles in disease modulation. Additionally, pathway analysis highlighted several key biological processes and signaling pathways involved in breast cancer pathogenesis. Metabolic pathways, estrogen signaling, and proteoglycans in cancer emerged as crucial pathways influenced by the bioactive compounds in *S. cumini*. Understanding how these pathways are modulated provides valuable insights into the plant's potential effectiveness in breast cancer management. In summary, our study offers a deeper insight into the pharmacological properties of *S. cumini* and its potential application in breast cancer therapy. By elucidating the molecular mechanisms behind its therapeutic effects, we pave the way for further exploration and clinical development of this herbal remedy for breast cancer and its related complications.

Keywords: Network pharmacology, *Syzygium cumini*, Bioactive compounds, Pathway analysis, Target prediction, Disease-related genes, Breast cancer.

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INTRODUCTION

Syzygium cumini, commonly recognized as Jamun, is a medicinal plant renowned for its diverse therapeutic properties.[1] Traditionally utilized in various forms of herbal medicine, this plant has gained significant attention for its potential health benefits, which are attributed to its rich composition of bioactive compounds.[2] Notable among these compounds are quercetin, myricetin, kaempferol, and eugenin,[3] which are known for their antioxidant, anti-inflammatory,[4] and antimicrobial activities.[5]

In recent years, the rising incidence of breast cancer has spurred the search for novel therapeutic agents capable of addressing the complexities of this disease. Breast cancer remains one of the most prevalent cancers worldwide, posing

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substantial challenges due to its heterogeneous nature and the intricate molecular mechanisms underlying its progression.[6] Traditional treatments, while effective, often come with significant side effects and limitations, necessitating the exploration of alternative and complementary therapies.

This study aims to investigate the therapeutic potential of *S. cumini* in the context of breast cancer management and its associated complications. By leveraging a network pharmacology approach,[7] we seek to unravel the intricate interactions between the bioactive compounds of *S. cumini* and their molecular targets within the human body. This methodology allows for a comprehensive understanding of the plant's pharmacological effects, providing insights into the underlying mechanisms that contribute to its therapeutic efficacy.

Our research involves a systematic analysis of bioactive compounds present in *S. cumini*, identification of potential molecular targets, and mapping of disease-related genes. By integrating data from various bioinformatics databases and employing sophisticated network construction techniques, we aim to construct a detailed network that elucidates the connections between bioactive compounds, their targets, and relevant disease pathways.

The findings of this study hold promise for advancing the clinical development of *S. cumini* as a complementary therapy for breast cancer. By shedding light on the molecular interactions and pathways influenced by this medicinal plant, we hope to pave the way for novel therapeutic strategies that enhance the efficacy and safety of breast cancer treatment..

MATERIALS AND METHODS

Collection of Bioactive Compounds

To comprehensively gather information on the bioactive constituents of *S. cumini*, extensive investigations were conducted in the PubMed database by means of both the botanical name *S. cumini* and associated substance terms. This method ensured a thorough collection of relevant scientific literature. Additionally, data on bioactive compounds were sourced from specialized phytochemistry databases, namely the IMPPAT database[8] and the KnapSack database.[9] These databases provided a wealth of information on the variety of bioactive compounds present in *S. cumini*, which are essential for understanding its medicinal properties.

Process of Identification of Potential Targets and Genes Associated with Disease

To identify potential targets for the bioactive compounds found in *S. cumini*, we employed the Swiss target prediction[10] and STITCH databases.[11] These resources are instrumental in predicting the connections among bioactive compounds and their potential protein targets in the human body. Concurrently, disease-connected genes were acquired from the OMIM[12] and gene cards databases.[13] OMIM provides comprehensive information on genetic disorders and the genes involved, while gene cards offers a detailed compilation of human genes and their functions. To determine the intersection between potential targets of the bioactive compounds and disease-related genes, venn diagram analysis was used.[14] This approach helped identify common targets that could be crucial for therapeutic interventions.

Pathway Analysis using DAVID Database

A pathway analysis was conducted to determine the biological processes affected by the discovered genes. The evaluation was conducted utilizing the DAVID archive, which consolidates many bioinformatics tools for the functional study of extensive gene lists.[15] The pathways linked to the discovered genes were retrieved from various databases, such as KEGG, biological processes, molecular functions and cellular components. The importance of these pathways was evaluated utilizing adjusted *p-values*, which offered a statistical indication of the pathways that are most likely affected by the bioactive components of *S. cumini*. The study identified crucial biological processes and signaling pathways that have a role in the development of breast cancer.

Network Construction using Cytoscape

A network was created employing Cytoscape version 3.10.1, a robust bioinformatics software platform designed for visualizing intricate networks, in order to depict the connections between genes and their corresponding pathways. Within this network, the source nodes were designated to represent bioactive substances, whereas the target nodes were designated to represent genes and proteins. Hub genes, characterized by their extensive interconnectedness, were found through the STRING database. STRING offers both documented and hypothesized protein-protein interactions that are essential for comprehending the molecular pathways that underlie the effects of *S. cumini*. The created network not only yielded valuable insights into the complex gene relationships, but also enabled future investigation of possibilities for molecular pathways and biological targets for the treatment of breast cancer.[16]

RESULT AND DISCUSSION

Results of Collection of Bioactive Compounds in *S. cumini*

A thorough examination of the PubMed library revealed a compilation of biologically active substances found in the key components of *S. cumini*.[17] We have found a range of bioactive compounds with promising medicinal potential in this plant by using chemical terms and botanical nomenclature. *S. cumini*, commonly referred to as jamun, is rich in many bioactive components such as quercetin, myricetin, kaempferol, and eugenin. These chemicals possess potential health advantages, including antioxidant, anti-inflammatory, and antibacterial characteristics. Table 1 provides a comprehensive overview of the botanical species *S. cumini*, including its bioactive constituents and their corresponding PubChem IDs.[18]

Results of Identification of Potential Targets and Disease-Related Genes

The active chemicals found in *S. cumini* were analyzed using bioinformatics databases such as Swiss target prediction and

Table 1: Botanical – Bioactive

Botanicals	*PubChem ID*	*Bioactives*
S. cumini	5280343	Quercetin
S. cumini	5281672	Myricetin
S. cumini	31253	Myrcene
S. cumini	222284	b-sitosterol
S. cumini	5280863	Kaempferol
S. cumini	10189	Eugenin
S. cumini	326186	1-(2-Hydroxy-4,6-dimethoxy-3-methylphenyl)etan-1-one
S. cumini	24135	2',6'-Dihydroxy-4'methoxyacetophenone
S. cumini	66065	Bergenin
S. cumini	91472	Friedelin
S. cumini	348029	Friedelanol
S. cumini	5282102	Astragalin
S. cumini	64971	betulinic acid
S. cumini	5481663	isorhamnetin 3O-rutinoside
S. cumini	44256919	delphinidin-3-gentiobioside
S. cumini	44256979	malvidin-3-laminaribioside
S. cumini	44256956	petunidin-3-gentiobioside
S. cumini	5281520	alpha-humulene
S. cumini	73568	Corilagin
S. cumini	6616	Camphene

STITCH to identify possible targets. There were a total of 57 targets obtained from these databases, as specified in Table 2. A total of 24,964 disease-related genes were obtained from the GeneCards and OMIM databases. The Venn diagram analysis, shown in Figure 1, helped identify the common genes shared by potential targets and disease-related genes. This provided valuable insights into the molecular pathways that underlie the therapeutic actions of *S. cumini*. After conducting an investigation, a total of 40 genes that are commonly found were identified. This discovery provides valuable insights into important connections within the molecular structure. CD38 SQLE F10 NMUR2 AKR1B10 ABCB1 CA7 ERN1 PTGS2 MAPT NOX4 CA2 CYP51A1 CYP19A1 VCP PNP

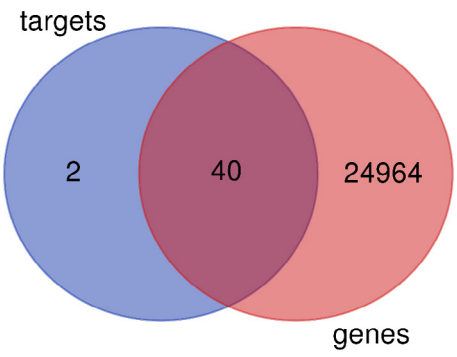

Figure 1: Venn diagram

Table 2: Bioactives and identified targets

S. No.	*Bioactives*	*Targets*
1	Quercetin	Insulin-like growth factor I receptor
2	Quercetin	Hepatocyte growth factor receptor
3	Quercetin	Serine/threonine-protein kinase AKT
4	Myricetin	Xanthine dehydrogenase
5	Myricetin	Microtubule-associated protein tau
6	Myricetin	G-protein coupled receptor 35
7	Myricetin	Aldose reductase
8	Myricetin	Carbonic anhydrase I
9	Myrcene	Peroxisome proliferator-activated receptor alpha
10	Myrcene	Cannabinoid receptor 2
11	b-sitosterol	Testis-specific androgen-binding protein
12	Kaempferol	Epidermal growth factor receptor erbB1
13	Eugenin	Serine/threonine-protein kinase PIM1
14	Eugenin	Cyclooxygenase-2
15	Eugenin	P-glycoprotein 1
16	Eugenin	ATP-binding cassette sub-family G member 2
17	1-(2-Hydroxy-4,6-dimethoxy-3-methylphenyl) ethan-1-one	Beta-secretase 1
18	2',6'-Dihydroxy-4'-methoxyacetophenone	Cannabinoid receptor 1
19	2',6'-Dihydroxy-4'-methoxyacetophenone	Cannabinoid receptor 2
20	2',6'-Dihydroxy-4'-methoxyacetophenone	Monoamine oxidase B
21	2',6'-Dihydroxy-4'-methoxyacetophenone	HMG-CoA reductase
22	Bergenin	Adenosine deaminase
23	Bergenin	Purine nucleoside phosphorylase
24	Friedelin	Cytochrome P450 19A1
25	Friedelin	Carbonic anhydrase II
26	Friedelin	Androgen receptor (by homology)
27	Friedelin	Cyclooxygenase-1
28	Friedelanol	UDP glucuronosyltransferase 2B7
29	Friedelanol	Dual specificity phosphatase Cdc25B
30	Friedelanol	Cytochrome P450 19A1

31	Friedelanol	Transient receptor potential cation channel subfamily M member 8
32	Friedelanol	11-beta-hydroxysteroid dehydrogenase 1
33	Friedelanol	Nitric oxide synthase, inducible(by homology)
34	Astragalin	Aldose reductase (by homology)
35	Astragalin	Carbonic anhydrase XII
36	Astragalin	Adrenergic receptor alpha-2
37	Betulinic acid	DNA polymerase beta(by homology)
38	Betulinic acid	Aldo-keto reductase family 1 member B10
39	Betulinic acid	Peroxisome proliferator-activated receptor gamma
40	Isorhamnetin 3-O-rutinoside	Cyclooxygenase-2
41	Isorhamnetin 3-O-rutinoside	NADPH oxidase 4
42	Isorhamnetin 3-O-rutinoside	Alpha-2a adrenergic receptor
43	Isorhamnetin 3-O-rutinoside	Neuromedin-U receptor 2
44	Delphinidin-3-gentiobioside	Lymphocyte differentiation antigen CD38
45	Delphinidin-3-gentiobioside	NADPH oxidase 4
46	Delphinidin-3-gentiobioside	TNF-alpha
47	Alpha-humulene	Zinc finger protein GLI2
48	Corilagin	Squalene monooxygenase (by homology)
49	Corilagin	Transitional endoplasmic reticulum ATPase
50	Corilagin	Thrombin and coagulation factor X
51	Camphene	High-affinity choline transporter (by homology)
52	Camphene	Estrogen receptor beta
53	Camphene	Cyclooxygenase-1
54	Camphene	Cytochrome P450 2C19

TRPM8 CNR1 AR HMGCR GLI2 ADRA2C CA1 XDH SLC5A7 POLB CNR2 HSD11B1 GPR35 AKR1B1 AVPR2 ADA UGT2B7 SHBG KDM4E ABCG2 MAOB ADRA2A CA4 PPARA.[19]

Results of GO Enrichment and Pathway Analysis

The paths with the highest statistical significance, as determined by corrected *p-values*, were chosen and are displayed in Table 3. This excerpt provides a thorough understanding of the molecular mechanisms that are responsible for the pharmacological actions of *S. cumini*.

Table 4 presents a list of pathways influenced by compounds from *S. cumini*, including responses to xenobiotic stimuli, one-carbon metabolic processes, electron transport chain, ethanol response, lipopolysaccharide response, utero embryonic development, cell-cell signaling, deoxyadenosine catabolic process, regulation of chloride transport, and dAMP catabolic process. These pathways provide insights into the biological processes influenced by compounds from *S. cumini*. The low *p-value* indicates the importance of these pathways in biological processes. The response to xenobiotic stimuli involves an organism's response to foreign substances, while the one-carbon metabolic process involves the transfer of one-carbon units in metabolic reactions. The electron transport chain generates ATP through protein complexes, while the response to ethanol involves the organism's reaction to alcohol. The dAMP catabolic process refers to the catabolism of deoxyadenosine monophosphate.

Table 3: The findings of the investigation into the biological process pathways

Rank	*Term*	*p-value*
1	Response to xenobiotic stimulus	0.001447393
2	One-carbon metabolic process	0.0000444
3	Electron transport chain	0.000193
4	Response to ethanol	0.001094362
5	Response to lipopolysaccharide	0.002581167
6	In-utero embryo growth	0.009361194
7	Cell with cell signalling	0.010553436
8	Deoxyadenosine catabolic process	0.0000114
9	Regulation of chloride transport	0.0000227
10	Damp catabolic process	0.0000227

Table 4: Results of cellular component (CC) pathways analysis

Rank	*Term*	*p-value*
1.	Membrane	0.001229
2.	Plasma membrane	0.005883
3.	Endoplasmic reticulum membrane	0.0000384
4.	Endoplasmic reticulum	0.000238
5.	Side of the plasma membrane that is external	0.041825
6.	The side of the apical plasma membrane that is exposed	0.01135

A number of essential words that are related with cell membranes can be identified through the investigation of cellular component (CC) pathways, for example. The membrane that surrounds the ER is extremely significant since it is involved in the process of protein synthesis as well as the metabolism of lipids. A substantial amount of significance is attached to the plasma membrane's exterior surface, which is also commonly referred to as the external side. It is possible that certain regions of the cell membrane correlate to the outer surface of the apical plasma membrane, which is exposed to a body cavity or lumen.

The MF pathways analysis in Table 5 reveals several key pathways involved in proteins. These pathways are crucial for

Table 5: Results of molecular function (MF) pathways analysis

Rank	*Terms*	*P-value*
1.	Identical protein binding	0.023282
2.	Zinc ion fastening	0.002057
3.	Protein homo dimer formation	0.00394
4.	Oxidoreductase activity	0.0000751
5.	Enzyme binding	0.00721
6.	Carbonate dehydrase	0.00000543
7.	Electron carrier activity	0.000257
8.	Flavin adenine dinucleotide binding	0.000372
9.	Heme binding	0.003992
10.	Sequence-precise DNA fastening	0.031358

Table 6: Pathway analysis results obtained from the KEGG database

Rank	*Term*	*p-value*
1.	Metabolism pathways	0.000074
2.	Neuroactive ligand-receptor interaction	0.004236019
3.	Bile secretion	0.000531
4.	Nitrogen metabolism	0.0000468
5.	Pentose and glucuronate interconversions	0.010209092
6.	Steroid hormone biosynthesis	0.028591668
7.	Chemical carcinogenesis - DNA adducts	0.03574758

proteins to function properly and efficiently. The *p-value* of 0.023282 indicates statistical significance, while a low *p-value* of 0.002057 suggests strong evidence for their significance. Proteins with these functions also form homodimers, which are interactions between identical protein subunits. The *p-value* of 0.0000751 indicates high significance, while a very low *p-value* of 0.0000751 indicates high significance. The *p-value* of 0.00721 represents interactions between proteins and enzymes. The KEGG examination table reveals seven top-ranked pathways in the human body (Table 6). These include metabolic pathways, neuroactive ligand-receptor interactions, bile secretion, nitrogen metabolism and chemical carcinogenesis - DNA adducts. Metabolic pathways involve biochemical reactions within cells, such as glycolysis and amino acid metabolism. Neuroactive ligand-receptor interactions involve the interaction between neurotransmitters and their receptors in the nervous system. Bile secretion aids digestion and fat absorption. Nitrogen metabolism is essential for protein and nucleic acid building. Pentose and glucuronate interconversions involve the interconversion of sugars for nucleotide synthesis and detoxification. Steroid hormone biosynthesis outlines the production of hormones.

Network Construction using Cytoscape

Cytoscape version 3.10.1 was utilized for the building of the network shown, followed by the installation of any essential applications and plugins. The STRING database was utilized in order to determine hub genes, as well as to establish source nodes and target nodes. The network that was formed highlighted interactions between the genes that were found, which provided insights into the intricate biochemical pathways that *S. cumini* altered.

The protein-protein interaction (PPI) analysis using the STRING database revealed significant interactions among the target proteins of *S. cumini*'s bioactive compounds. Key hub proteins identified included prostaglandin-endoperoxide synthase 2 (PTGS2) and cytochrome P450 family 19 subfamily A member 1 (CYP19A1), which exhibited high connectivity within the network. These hub proteins are critically involved in pathways related to inflammation and hormone regulation, respectively, suggesting their pivotal roles in the pharmacological effects of *S. cumini*. The interaction network constructed highlighted the complex interplay between these proteins, providing insights into the molecular mechanisms through which *S. cumini* may exert its therapeutic effects, particularly in the context of breast cancer management.

The network analysis constructed using cytoscape revealed intricate interactions between *S. cumini*'s bioactive compounds, their molecular targets, and associated diseases. Key bioactive compounds such as quercetin, myricetin, kaempferol, and eugenin were mapped to their respective targets, including prostaglandin-endoperoxide synthase 2 (PTGS2) and cytochrome P450 family 19 subfamily A member 1 (CYP19A1). These targets are significantly associated with breast cancer and related pathways, such as inflammation and hormone regulation.

The analysis identified several hub genes that play central roles in the network, highlighting their importance in disease modulation. The interconnected nature of these nodes suggests potential synergistic effects of the bioactive compounds, enhancing their therapeutic efficacy. This network provides a comprehensive overview of how *S. cumini*'s bioactive constituents interact with specific targets to influence breast cancer pathways, paving the way for targeted therapeutic strategies.[20]

CONCLUSION

The systematic investigation of bioactive compounds within *S. cumini* unveiled a rich reservoir of potential therapeutic agents. Through meticulous analysis, notable compounds such as quercetin, myricetin, kaempferol, and eugenin were identified, showcasing significant health-promoting attributes, including antioxidative, anti-inflammatory, and antimicrobial properties. This discovery underscores the botanical's potential as a source of natural remedies for various ailments.

Moreover, the exploration of potential targets and disease-related genes, coupled with pathway analysis, revealed intricate molecular mechanisms underlying *S. cumini*'s pharmacological effects. Venn diagram analysis demonstrated the convergence of 40 common genes between potential targets and disease-associated genes, indicating pivotal intersections within the molecular landscape.

Pathway analysis using the DAVID database unveiled enriched pathways influenced by the identified genes. Noteworthy pathways such as responses to xenobiotic stimuli, one-carbon metabolic processes, and neuroactive ligand-receptor interactions emerged as significantly impacted by *S. cumini* constituents. These findings provide quantitative insights into the biological processes modulated by the botanical's bioactive compounds.

Furthermore, network construction using Cytoscape facilitated the visualization of molecular interactions, highlighting key hub genes and their interconnectedness. This comprehensive network analysis offers a holistic view of the molecular pathways modulated by *S. cumini*, laying the groundwork for further mechanistic studies and therapeutic applications.

In conclusion, the documented findings underscore the therapeutic potential of *S. cumini* and provide a scientific basis for its utilization in healthcare. The identified bioactive compounds, targets, and pathways offer valuable insights into the botanical's pharmacological effects, driving future research toward the development of novel therapeutic interventions. Harnessing the natural resources of *S. cumini* holds promise for addressing various health challenges and improving human well-being.

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