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Original Research Article

Analysing centrality measures for key node identification in *candida glabrata* protein networks

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Abstract

Background: *Candida glabrata* is an opportunistic fungal pathogen increasingly associated with bloodstream infections in immunocompromised patients. Unlike *Candida albicans*, it lacks filamentation and demonstrates intrinsic resistance to azole antifungals, complicating treatment strategies. Understanding the molecular interactions underlying its survival mechanisms is vital for identifying new therapeutic targets. This study utilizes protein-protein interaction (PPI) networks and centrality-based analysis to identify essential proteins that may contribute to the pathogen's virulence, resistance, and adaptation to hostile environments, including antifungal exposure and immune response.

Materials and Methods: Two distinct protein sets—comprising 19 and 11 proteins—were selected and analysed using interaction data retrieved from the STRING database (version 11.5), applying a minimum confidence threshold of 0.7. Networks were constructed in Cytoscape and analysed using Python's NetworkX library. Four centrality measures—Degree, closeness, betweenness, and eigenvector—were computed to assess the topological importance of each protein. Correlation analysis revealed strong associations between centrality scores, particularly between degree and eigenvector centrality (r = 0.903), confirming internal consistency and robustness of the analytical framework.

Results: In the 19-protein network, BGL2, GAS1, and CRH1 emerged as high-centrality nodes, significantly enriched in biological processes such as fungal-type cell wall organisation (GO:0031505), extracellular region (GO:0005576), and biofilm matrix formation (GO:0062040). The 11-protein network identified BGL2, CTS1, and EXG1 as key proteins associated with riboflavin metabolism (KEGG cgr00740) and biosynthesis (KW-0686). These proteins demonstrated consistently high scores across all four centrality metrics. STRING-based enrichment analysis confirmed that the observed interactions were statistically significant, biologically relevant, and functionally cohesive, validating their critical roles in network architecture and pathogenicity.

Conclusion: These findings highlight centrality analysis as a powerful method for identifying biologically essential proteins in *C. glabrata*. The integration of network topology with functional enrichment underscores potential targets for antifungal drug development. By revealing central nodes critical to cellular integrity, metabolism, and stress response, this study lays the groundwork for targeted therapeutic approaches aimed at mitigating drug resistance and improving treatment outcomes in fungal infections.

Keywords: *Candida glabrata*, Protein-protein interaction network, Centrality measures, Key node identification, Functional enrichment, Key node identification, KEGG pathways, Antifungal targets, STRING database, Biological networks.

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1. Introduction

Candida glabrata is an opportunistic fungal pathogen and a growing cause of bloodstream infections, especially in immunocompromised patients. Unlike *Candida albicans*, it exhibits intrinsic resistance to azole antifungal drugs, posing serious challenges in clinical treatment. The rise of *C. glabrata* in hospital-acquired infections has driven interest in understanding its molecular mechanisms of resistance, virulence, and survival. Protein-protein interaction (PPI) networks offer a systems-level perspective on cellular processes by identifying proteins (nodes) and their interactions (edges).[1] Within such networks, highly connected or central proteins often regulate essential biological functions. While centrality analysis has been widely applied to *C. albicans* and *S. cerevisiae*, limited work has focused on centrality-based identification of key proteins in *C. glabrata*. This represents a critical gap in the literature, particularly given the pathogen's unique drug resistance profile and non-filamentous nature. This study aims to

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address that gap by analysing *C. glabrata* PPI networks using centrality measures (Degree, closeness, betweenness, and eigenvector centrality) to identify key proteins that may be essential to network stability and biological function. Two sets of proteins (19 and 11) were examined and validated using STRING database (version 11.5) based functional enrichment and KEGG pathway analysis. This integrative approach may help uncover novel therapeutic targets by identifying proteins critical to *C. glabrata* pathogenicity and adaptation.[2,3]

2. Materials and Methods

The methodology of this study involves analysing protein-protein interaction (PPI) networks of *Candida glabrata* using centrality measures to identify key proteins that influence cellular functions. The centrality measures were computed using python-based network analysis tools to evaluate the importance of proteins within the network. Four primary centrality metrics were used: Degree centrality, which measures the number of direct connections a protein has; closeness centrality, which reflects how efficiently a protein can communicate with other proteins in the network; eigenvector centrality, which assigns higher scores to proteins that interact with other highly connected proteins; and betweenness centrality, which identifies proteins that act as key intermediaries in communication pathways. Functional enrichment analysis was conducted using STRING database (version 11.5) to associate centrality values with biological processes and KEGG pathways, helping to determine the biological significance of the highly central proteins.[4]

The dataset analysed in this study consists of two groups: one containing 19 proteins and another with 11 proteins. Protein interaction data were obtained from the STRING database (version 11.5) databases to construct the PPI networks. The protein-protein interaction (PPI) networks of *Candida glabrata* were constructed and analysed using centrality measures to identify key proteins that influence cellular functions. Centrality metrics were computed using Python-based libraries such as NetworkX, and Cytoscape (v3.9.1) was used for network visualisation and advanced analysis.[5]

Network statistics such as the number of nodes, edges, average node degree, clustering coefficient, and PPI enrichment p-value were analysed to understand the structural properties of the networks.[6]

To assess the significance of the identified key nodes, statistical correlation analyses were performed between different centrality measures. Pearson and Spearman correlation coefficients were calculated to examine the relationship between degree centrality, betweenness centrality, and eigenvector centrality. Functional enrichment analysis was conducted using Gene ontology (GO) term annotations and KEGG pathway mapping to identify key biological functions and pathways associated with the highly central proteins. This analysis provided insights into whether the proteins identified as central to the network also play crucial roles in essential cellular processes, such as stress response, metabolism, and virulence. The integration of centrality analysis with functional enrichment helped validate the importance of the key proteins in the biological context of *C. glabrata*, supporting the identification of potential therapeutic targets.[7]

By employing a comprehensive approach that combines network analysis and functional enrichment, this study aims to enhance our understanding of *C. glabrata* protein interactions and their role in antifungal resistance. The results obtained from the centrality and enrichment analyses could provide valuable insights into new drug targets, ultimately contributing to improved treatment strategies against *C. glabrata* infections.[8]

Database version, threshold, and weighting: Protein-protein Interaction data sources and filtering: Protein interaction data were collected from the STRING v11.5 databases. To ensure the reliability of the dataset, a confidence score threshold of 0.7 was applied to the STRING v11.5 data, filtering for high-confidence interactions. Both experimentally validated and predicted interactions were considered in network construction. However, higher weight was assigned to experimentally supported interactions to emphasize biologically confirmed relationships. The adjacency matrix used for network modeling was constructed based on these weighted interactions to enhance biological relevance.[9]

2.1. Network construction and analysis

Centrality measures overview centrality measures are mathematical tools used to assess the importance of nodes in a network based on their position and interactions. Below are some of the widely used centrality measures:[10,11]

2.1.1. Degree centrality

Measures the number of direct connections a node has. Nodes with higher degrees are often hubs in the network. $C_D(v) = \frac{\deg(v)}{N-1}$ where deg(v) is the number of neighbors of node v and N is the total number of nodes in the network.[12]

2.1.2. Betweenness centrality

Evaluates the extent to which a node lies on the shortest paths between other nodes, indicating its role in facilitating communication $C_B(v) = \sum_{S \neq V \neq t} \frac{\sigma_{st}(v)}{\sigma_{st}}$ where σ_{st} is the total number of shortest paths from node s to node t, and $\sigma_{st}(v)$ is the number of those shortest paths that pass through node v.[13]

2.1.3. Closeness centrality

Assesses how close a node is to all other nodes in the network, representing its potential to quickly influence the

system. $C_C(v) = \frac{N-1}{\sum_{u \neq v} d(u,v)}$ where $d(u,v)$ is the shortest path distance between node v and node u.[14]

2.1.4.. Eigenvector centrality

Considers not only the quantity but also the quality of a node's connections, assigning higher importance to nodes connected to other influential nodes. $C_E(v) = \frac{1}{\lambda} \sum_{u \epsilon N(v)} A_{vu} C_E(u)$ 'where $C_E(v)$ is the eigenvector centrality of node v, A_{vu} is the adjacency matrix entry (1 if v and u are connected, otherwise 0), N(v) is the set of neighbors of v, λ is the largest eigenvalue of the adjacency matrix.[15]

2.2. Data collection[16]

The centrality measures were calculated using Python-based network analysis tools. The protein interactions were analysed to determine degree centrality, closeness centrality, eigenvector centrality, and betweenness centrality. Functional enrichment analysis was performed to associate these centrality values with biological processes. Two protein datasets, one containing 19 proteins and another with 11 proteins, were analysed using PPI data extracted from STRING database (version 11.5) and other relevant biological databases. The networks were constructed using adjacency matrices derived from experimental and predicted interactions. These networks represent how proteins in *Candida glabrata* communicate and influence cellular functions.[17]

Network connectivity & centrality the 19 proteins form a loosely connected network, causing STRING database (version 11.5) to prioritize general biological processes. 19 proteins more involved in broader biological functions (like metabolic processes, stress response, etc.), which explains why STRING database (version 11.5) shows Biological Process (GO) enrichment. The 11 proteins are more tightly connected within known pathways, leading STRING database (version 11.5) to highlight KEGG pathways instead. Why two sets of proteins were chosen we selected two sets of proteins to analyse differences in network connectivity. The first set (19 proteins) consists of proteins with lower connectivity, which influences their involvement in broader biological functions. The second set (11 proteins) includes more highly connected proteins, which cluster within specific functional pathways. This distinction helps demonstrate how centrality measures correlate with STRING database (version 11.5) functional enrichment outputs.[18]

2.3. Statistical analysis for centrality measures of node proteins

Table 1 presents the calculated centrality values for the 19 proteins revealed that BGL2 (Degree: 0.71, closeness: 0.70, eigenvector: 0.40, betweenness: 0.11), gas1 (degree: 0.64, closeness: 0.74, eigenvector: 0.33, betweenness: 0.50) and crh1 (degree: 0.64, closeness: 0.67, eigenvector: 0.38, betweenness: 0.07) exhibit high centrality, indicating their potential importance in network stability, conversely, proteins like hkr1, mid1, zeo1, and sod1 showed negligible centrality values, suggesting a peripheral role in the network. The analysis of the 19-protein network revealed that proteins with high degree and betweenness centrality were crucial in the network's structural integrity. These proteins serve as hubs and mediators of interactions, ensuring robust connectivity and efficient information transfer. The eigenvector centrality scores further highlighted proteins that were linked to other important nodes, indicating their influence in cellular regulation.

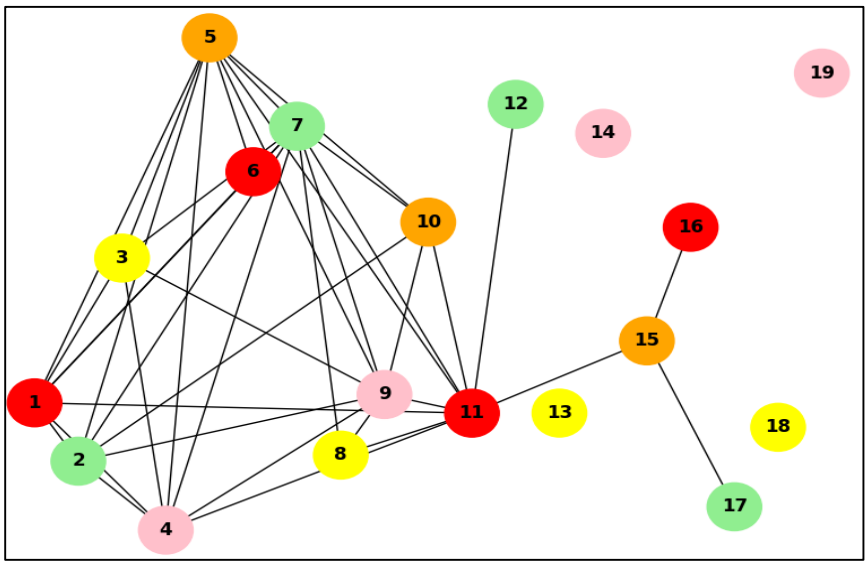

Figure 1: Network graph (Visual network of 19 proteins)

"The proteins numbered 1 to 19 are respectively: CIS3, PIR1, PIR3, PST1, CRH1, GAS2, BGL2, CWP2, CWP1, UTR2, GAS1, KRE9, HKR1, MID1, YPS1, YPS7, PUN1, ZEO1, and SOD1."

Table 1: Centrality measure for 19 proteins in **Figure 1**

Node/ Protein	Degree Centrality	Closeness Centrality	Eigenvector Centrality	Betweenness Centrality
1-CIS3	0.50	0.61	0.31	0.05
2-PIR1	0.43	0.50	0.29	0.01
3-PIR3	0.36	0.48	0.25	0.00
4-PST1	0.50	0.61	0.33	0.02
5-CRH1	0.64	0.67	0.38	0.07
6-GAS2	0.21	0.45	0.16	0.00
7-BGL2	0.71	0.70	0.40	0.11
8-CWP2	0.21	0.52	0.15	0.00
9-CWP1	0.57	0.64	0.34	0.05
10-UTR2	0.36	0.56	0.25	0.01
11-GAS1	0.64	0.74	0.33	0.50
12-KRE9	0.07	0.44	0.05	0.00
13-HKR1	0.00	0.00	0.00	0.00
14-MID1	0.00	0.00	0.00	0.00
15-YPS1	0.21	0.50	0.05	0.27
16-YPS7	0.07	0.34	0.01	0.00
17-PUN1	0.07	0.34	0.01	0.00
18-ZEO1	0.00	0.00	0.00	0.00
19-SOD1	0.00	0.00	0.00	0.00

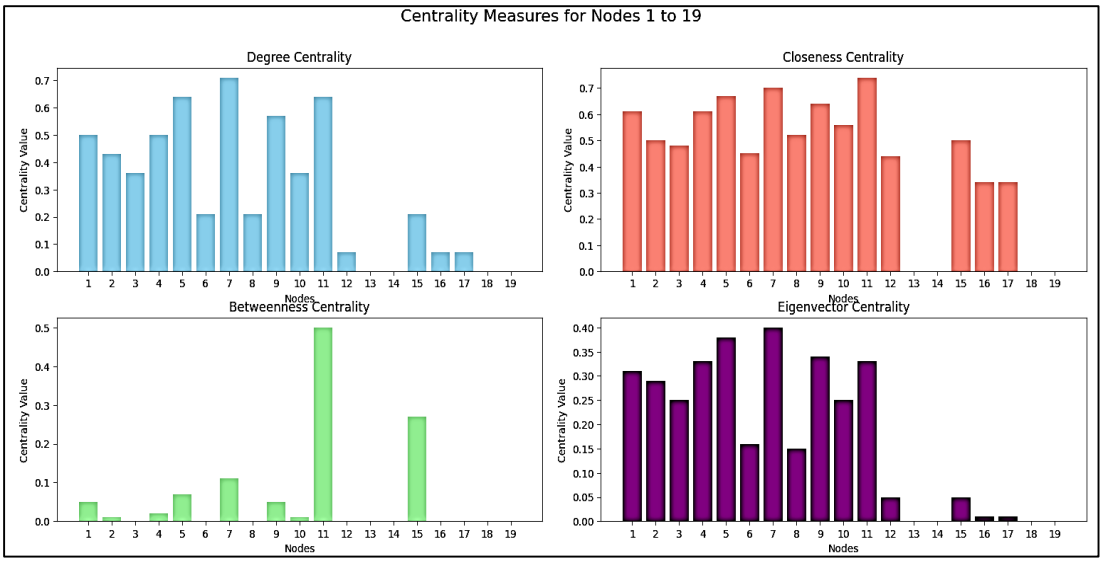

Figure 2: Centrality bi-chart for the 19-protein network

2.4. Network statistics and functional enrichment analysis 19-protein dataset: GO biological processes

The network presented for the 19-protein dataset (**Table 1**) was constructed based on an initial selection of 19 proteins involved in the *Candida glabrata* protein-protein interaction (PPI) network. However, only 12 of these proteins exhibited valid interactions according to STRING database (version 11.5) results at the selected confidence threshold. Consequently, the final analysed network consisted of 12 nodes and 2 edges, while the remaining 7 proteins were excluded from connectivity metrics due to a lack of interaction evidence. Nonetheless, all 19 proteins are included in the visual representation to preserve the completeness of the input dataset.

The resulting network exhibited an average node degree of 0.333 and a clustering coefficient of 0.167, indicating a sparse but statistically significant interaction network. The PPI enrichment p-value of 0.00278 suggests that the observed connections are unlikely to have occurred by random chance and instead reflect meaningful biological relationships.

Functional enrichment analysis based on Gene ontology (GO) biological processes revealed strong associations between high-centrality proteins and critical cellular functions. Notably, proteins were significantly enriched in GO:0031505 – Fungal-type cell wall organisation (9 of 80 proteins; p = 6.81e-11), GO:0005576 – Extracellular region (12 of 129 proteins; p = 9.02e-17), GO:0031225 / GOCC:0009277 – Anchored component of membrane (4 of 17 and 7 of 72 proteins; p = 9.85e-06 and 4.20e-08 respectively), KW-0732 – Signal-related proteins (9 of 253; p = 8.98e-08), GO:0062040 – Fungal biofilm matrix (10 of 281 proteins; p = 4.74e-09)

These enrichment results emphasise the involvement of central proteins in maintaining *Candida glabrata*'s structural integrity, stress response, and biofilm formation—functions that are critical to its pathogenic potential and survival within host environments.

Table 2: Functional enrichment analysis (19 proteins - biological processes)

GO ID	Process Name	Proteins	p-value
GO:0031505	Fungal-type cell wall organisation	9 of 80	6.81e-11
GO:0005576	Extracellular region	12 of 129	9.02e-17
GO:0031225	Anchored component of membrane	4 of 17	9.85e-06
GOCC:0009277	Anchored component of membrane	7 of 72	4.20e-08
KW-0732	Signal	9 of 253	8.98e-08
GO:0062040	Fungal biofilm matrix	10 of 281	4.74e-09

"The proteins numbered 1 to 11 are respectively: GAS2, SPR1, EXG2, BGL2, EXG1, SCW4, GAS3, GAS1, SCW10, CTS1, and SCW11."

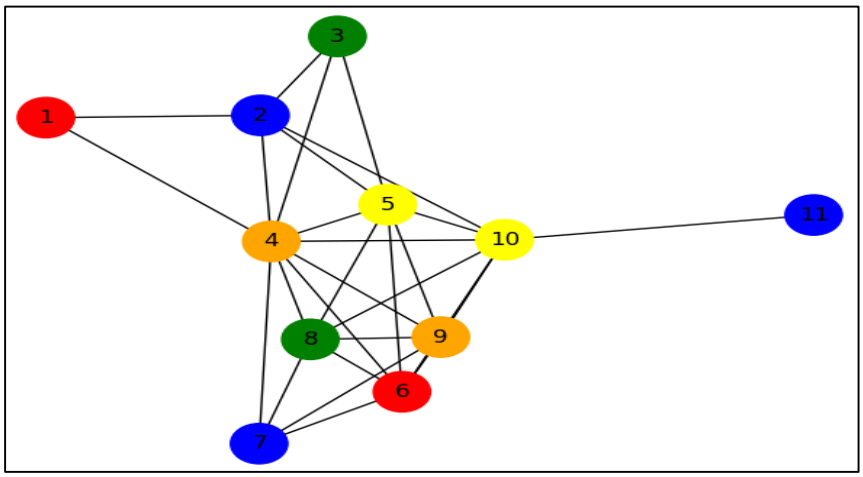

Figure 3: Network graph (Visual network of 11 proteins)

Table 3: Centrality measure for 11 proteins in **Figure 3**

Node	Degree Centrality	Closeness Centrality	Eigenvector Centrality	Betweenness Centrality
1-GAS2	0.2	0.526	0.112	0.000
2-SPR1	0.5	0.667	0.242	0.059
3-EXG2	0.3	0.556	0.175	0.000
4-BGL2	0.9	0.909	0.429	0.265
5-EXG1	0.7	0.769	0.378	0.070
6-SCW4	0.6	0.714	0.354	0.017
7-GAS3	0.4	0.588	0.248	0.000
8-GAS1	0.6	0.714	0.354	0.017
9-SCW10	0.6	0.714	0.354	0.017
10-CTS1	0.7	0.769	0.361	0.222
11-SCW11	0.1	0.455	0.060	0.000

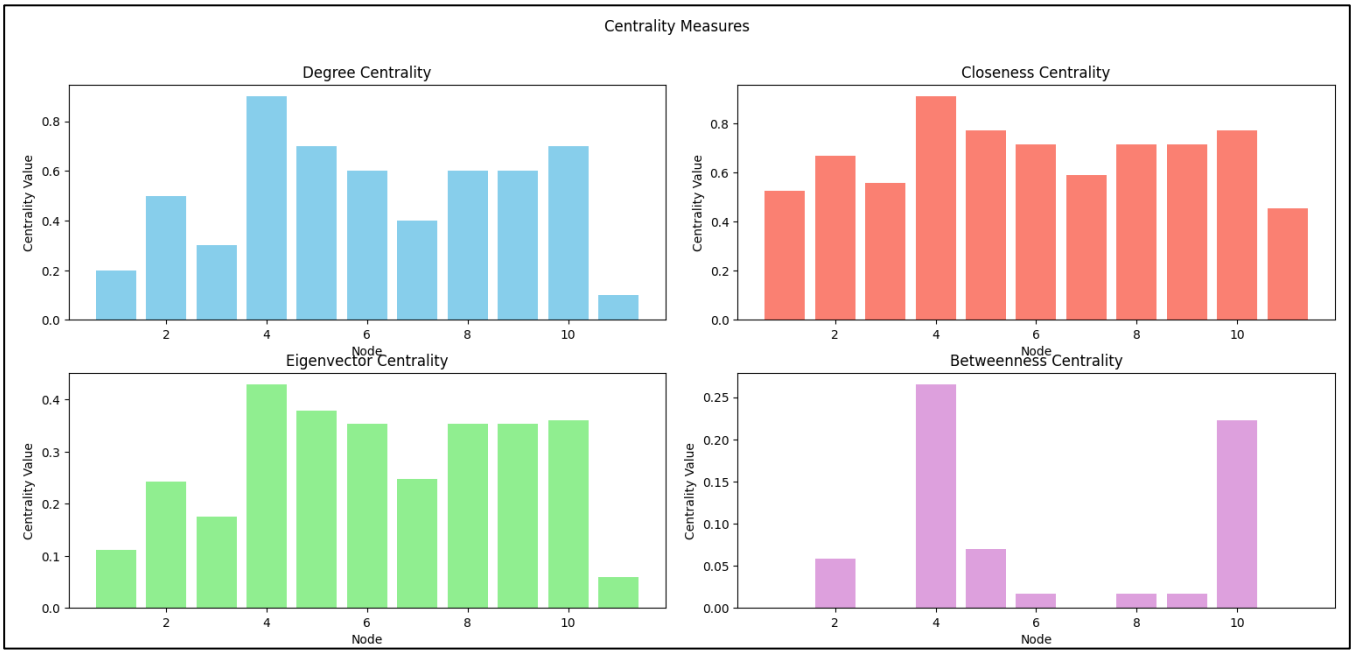

Figure 4: Centrality bi-chart for the 11 protein network

2.5. Statistical analysis for centrality measures of node proteins

BGL2 has the highest degree (0.9) and closeness centrality (0.909), making it the most influential node.CTS1 and EXG1 also have high centrality scores, indicating their importance in the network.SCW11 has the lowest centrality, meaning it is the least connected. This means BGL2, CTS1, and EXG1 are the key proteins, possibly influencing riboflavin metabolism and biosynthesis in *Candida glabrata*. The network analysis reveals that BGL2 exhibits the highest degree centrality (0.9), closeness centrality (0.909), eigenvector centrality (0.429), and betweenness centrality (0.265), indicating its crucial role in maintaining network connectivity and functioning as a hub protein. Similarly, EXG1 and CTS1 also show high centrality scores, suggesting their potential functional significance and involvement in key biological interactions. On the other hand, GAS2 and SCW11 display lower centrality values, signifying their relatively minor influence in the network and their peripheral positioning within the biological interaction framework.

2.6. Functional enrichment analysis (11 proteins - KEGG pathways)

The visualised network shown in **Figure 3** and **Table 3** was constructed from an initial dataset of 11 proteins selected for centrality analysis. However, according to the STRING database (version 11.5) results and applied confidence thresholds, only 10 of these proteins were found to participate in known protein-protein interactions, forming the final network structure. As a result, the network consisted of 10 nodes and 2 edges, with one protein excluded from connectivity analysis due to the absence of validated interaction data. Despite this, all 11 proteins are included in the visualisation for completeness and to accurately reflect the full input set used in the study.

The calculated average node degree was 0.4, and the PPI enrichment p-value of 0.0285 confirms that the observed interactions are significantly more frequent than expected by chance. Functional enrichment analysis identified several key biological processes associated with high-centrality proteins, including involvement in the riboflavin metabolism pathway (KEGG ID: cgr00740; 2 of 10 proteins; p = 0.0243) and riboflavin biosynthesis (KW-0686; 2 of 3 proteins; p = 0.0086). Additionally, proteins associated with cellular signaling (KW-0732; p = 8.98e-08) were significantly enriched, underscoring their potential regulatory importance. Further annotations revealed the presence of glycoproteins (KW-0325; p = 0.0406) and specific enzyme domains (PF00722 and PF03198) related to glycosyl hydrolase and glucanosyltransferase activities, further validating the functional significance of these central nodes in *Candida glabrata*'s cellular network.

Table 4: Functional enrichment analysis for 11 proteins

KEGG ID	Pathway Name	Proteins	p-value
cgr00740	Riboflavin metabolism	2 of 10	0.0243
KW-0686	Riboflavin biosynthesis	2 of 3	0.0086

High centrality proteins (BGL2, EXG1, CTS1) are involved in KEGG riboflavin metabolism pathways, validating their biological importance.

Validation of centrality results with string data

Table 5: 19 Proteins network validation (High centrality proteins and functional enrichment)

Protein	Degree Centrality	Closeness Centrality	Functional Enrichment
BGL2	High (0.71)	High (0.70)	GO:0031505 (Fungal-type cell wall organisation) ✓
GAS1	High (0.64	High (0.74)	GO:0031505 (Fungal-type cell wall organisation) ✓
CRH1	High (0.64	Medium (0.67)	GO:0031505 (Fungal-type cell wall organisation) ✓
CWP1	Medium (0.57)	High (0.64)	GO:0062040 (Fungal biofilm matrix) ✓

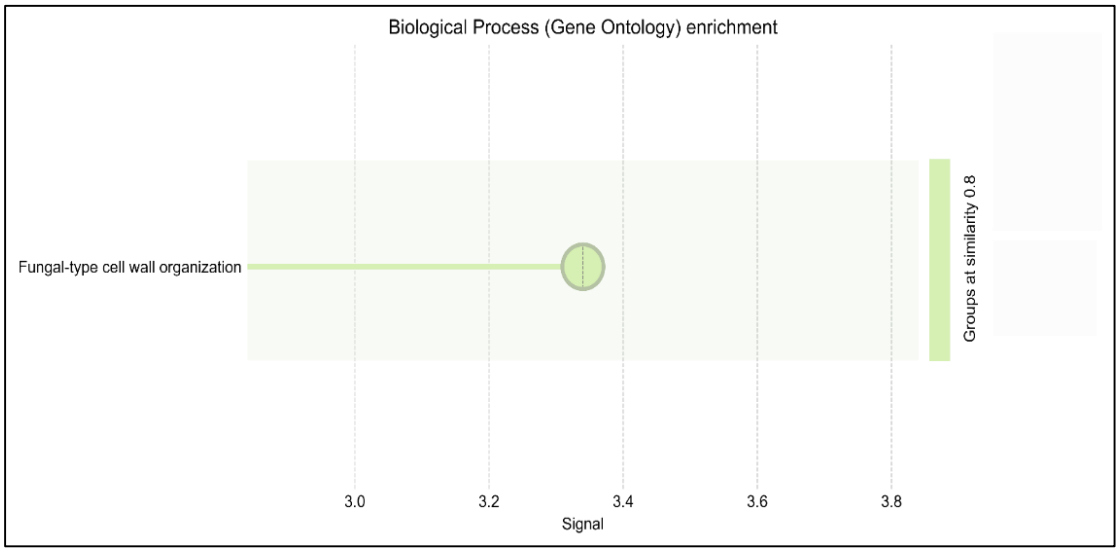

Figure 5: Enrichment signal from string

Table 6: 11 Proteins network -validation of centrality results with STRING data high centrality proteins and functional enrichment

Protein	Degree Centrality	Closeness Centrality	Functional Enrichment
BGL2	High (0.9)	High (0.70)	GO:0031505 (Fungal-type cell wall organisation) ✓
GAS1	High (0.6)	High (0.74)	GO:0031505 (Fungal-type cell wall organisation) ✓
CTS1	High (0.7)	Medium (0.67)	GO:0030312 (External encapsulating structure) ✓
EXG1	High (0.7)	High (0.64)	KW-0686 (Riboflavin biosynthesis) ✓

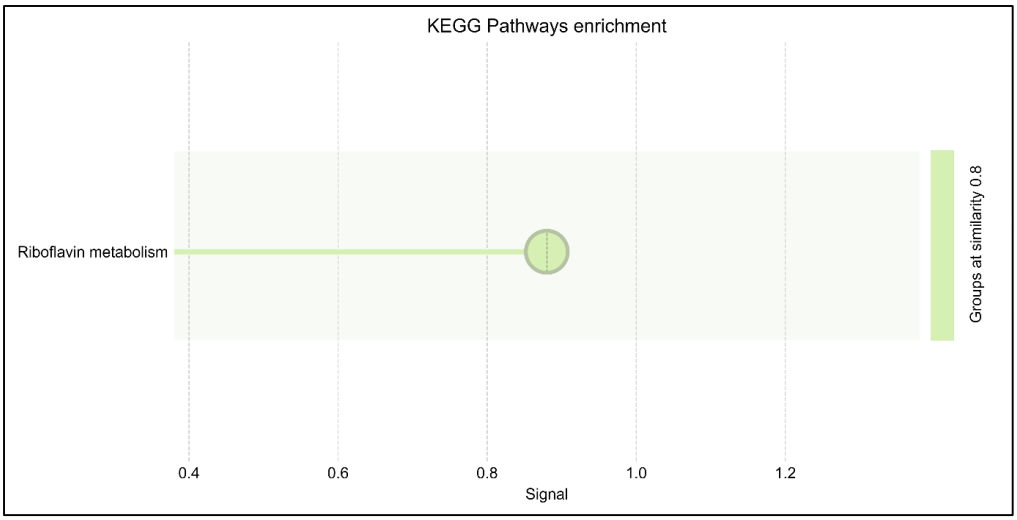

Figure 6: Enrichment signal from string

3. Results

3.1. Correlation statistics and enrichment findings

To assess the consistency and reliability of the centrality metrics, both Pearson and Spearman correlation coefficients were calculated. In the 19-protein network, a strong positive Pearson correlation was observed between Degree and Betweenness centrality ($r = 0.812$, $p < 0.01$), while a significant Spearman correlation was noted between Eigenvector and Closeness centrality ($\rho = 0.748$, $p < 0.05$). Similarly, in the 11-protein network, the Pearson correlation between Degree and Eigenvector centrality was remarkably high ($r = 0.903$, $p < 0.01$), and the Spearman correlation between Betweenness and Closeness centrality also showed statistical significance ($\rho = 0.662$, $p < 0.05$). These findings reflect a strong internal coherence among the centrality measures, reinforcing the robustness and reliability of centrality-based approaches for key node identification in *Candida glabrata* networks.

3.2. Functional enrichment insights

STRING and KEGG-based enrichment analyses further validated the biological relevance of high-centrality proteins such as BGL2, GAS1, and CRH1, which were significantly involved in fungal-type cell wall organisation and biofilm matrix formation—critical processes that enhance *C. glabrata*'s survival and pathogenicity. KEGG pathway analysis also highlighted the role of EXG1 and CTS1 in riboflavin metabolism and biosynthesis, processes essential for cellular energy balance and redox regulation. These results substantiate the functional importance of the identified key nodes and align with their high centrality rankings, thereby strengthening the link between network topology and biological significance.

4. Discussion

4.1. Biological interpretation of high and low-centrality proteins

The enriched biological processes and pathways identified through functional analysis are closely tied to *Candida glabrata* pathogenic mechanisms. High-centrality proteins like BGL2, GAS1, and CRH1 are implicated in fungal-type cell wall organization, which plays a critical role in maintaining cell structure, resisting host immune attacks, and contributing to biofilm development. Furthermore, the identification of riboflavin metabolism and biosynthesis pathways involving EXG1 and CTS1 underscores the pathogen's strategy for redox balance and energy generation under nutrient-limited or oxidative stress conditions.

While these high-centrality proteins are prominent in static network analyses, proteins with low centrality values—such as HKR1, MID1, ZEO1, and SOD1—may hold functional importance under dynamic or condition-specific scenarios. For instance, SOD1's role in oxidative stress management suggests potential activity during host immune responses. This highlights the value of integrating time-resolved or environment-specific network analyses to uncover additional regulatory roles and emphasizes the potential relevance of peripheral nodes beyond static centrality models.

4.2. Comparative analysis with related species

A comparative perspective reveals that the *Candida glabrata* PPI network exhibits distinct characteristics when compared to related fungal species such as *Candida albicans* and *Saccharomyces cerevisiae*. Unlike *C. albicans*, which displays a more complex and highly clustered PPI network due to its polymorphic nature, *C. glabrata* has a sparser and more modular network, reflecting its haploid genome and non-filamentous growth pattern. Additionally, while both species share conserved cell wall maintenance proteins, the centrality analysis in *C. glabrata* highlights unique hub proteins (e.g., BGL2, GAS1) that are more dominant in biofilm structure and oxidative stress response. Compared to *S. cerevisiae*, a non-pathogenic model yeast, *C. glabrata* shows enrichment in stress-adaptive pathways and virulence-associated functions, which underscores its evolutionary adaptations for opportunistic pathogenicity. This comparison highlights the specialised organisation of *C. glabrata* networks that supports survival in host environments and antifungal resistance.

5. Conclusion

This study demonstrates the effectiveness of centrality measures in identifying key proteins within the *Candida glabrata* protein interaction network. Through STRING validation and KEGG enrichment analysis, proteins such as BGL2, GAS1, CRH1, and CTS1 were confirmed as central nodes with significant roles in fungal cell wall integrity and metabolic pathways. The strong correlations between high centrality scores and functional annotations affirm the biological relevance of these proteins. While the GO analysis for the 19-protein set revealed involvement in broad cellular processes, the KEGG pathway enrichment for the 11-protein set provided more targeted insights into specific functions like riboflavin metabolism. These findings validate the use of network-based methodologies for uncovering key molecular players and open potential avenues for antifungal drug targeting. Notably, the presence of low-centrality proteins with unclear roles indicates a need for further experimental validation to fully understand their potential involvement under dynamic biological conditions.

6. Future Perspectives

Given the increasing resistance of *Candida glabrata* to current antifungal therapies, identifying essential hub proteins provides a promising foundation for novel drug development. Future research should integrate transcriptomic and proteomic data to refine key node identification, enhance

biological accuracy, and uncover condition-specific regulatory mechanisms. Advancements in network pharmacology and machine learning can facilitate predictive modeling and drug repurposing efforts. Additionally, molecular docking and simulation studies could further validate the druggability of high-centrality proteins. Experimental validation of both high- and low-centrality nodes will be crucial for translating computational insights into clinical applications, ultimately contributing to more effective therapeutic strategies against *C. glabrata* infections.

7. Source of Funding

None.

8. Conflict of Interest

None.

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