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Author (s):	Azmat Aziz[1], Muhammad Shahan[1], Mahfooz Hassan[1,2], Muhammad Ayaz[1,3], Muhammad Awais Ali[1], Mukhtar Alam[4], Murad Ali Rahat[5], and Muhammad Ilyas[1]
Affiliation (s):	[1]Center for Omics Sciences, Islamia College Peshawar, Peshawar, Pakistan [2]University of Lancashire, Preston, United Kingdom [3]Center of Biotechnology and Microbiology, University of Peshawar, Peshawar, Pakistan [4]University of Swabi, Swabi, Pakistan. [5]University of Swat, Swat, Pakistan
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Shared Pathways and Potential Therapeutic Targets in Major Psychiatric Disorders: Integrative Network and Molecular Docking Analysis

Azmat Aziz[1], Muhammad Shahan[1], Mahfooz Hassan[1,2], Muhammad Ayaz[1,3], Muhammad Awais Ali[1], Mukhtar Alam[4*], Murad Ali Rahat[5], and Muhammad Ilyas[1]

[1]Center for Omics Sciences, Islamia College Peshawar, Pakistan
[2]School of Health, Social Work and Sport. University of Lancashire, Preston, England, United Kingdom
[3]Center of Biotechnology and Microbiology, University of Peshawar, Pakistan.
[4]Department of Agriculture, University of Swabi, Pakistan
[5]Department of Biotechnology, Genetics, Forensic and Microbiology, University of Swat, Pakistan

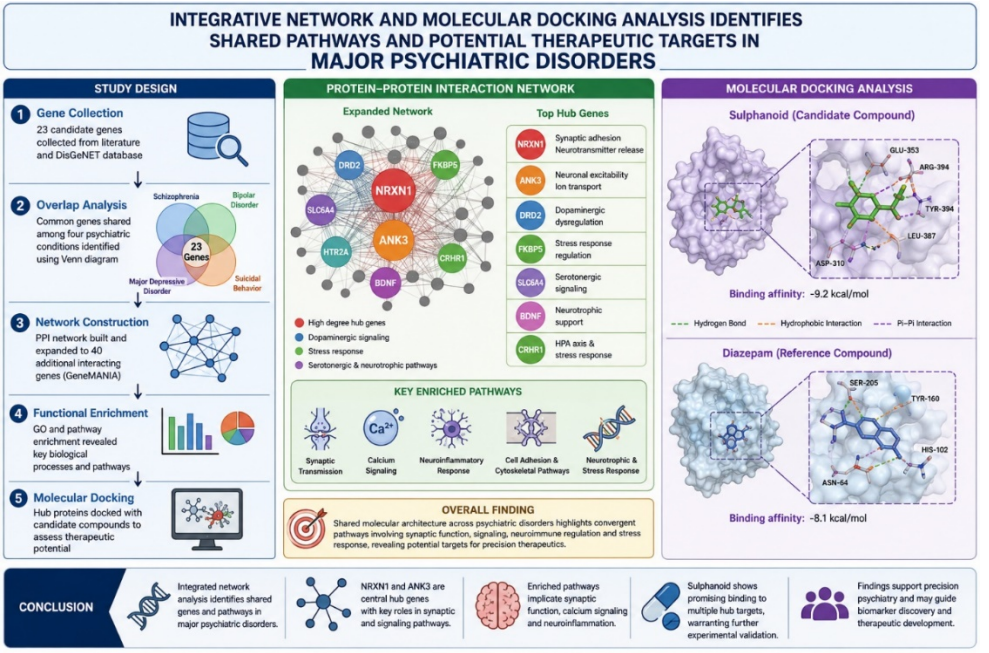
ABSTRACT

There is significant clinical and genetic similarity between mental health disorders, such as schizophrenia, bipolar disorder (BD), major depressive disorder (MDD), and suicidal behavior. This indicates that there are shared molecular mechanisms in the pathogenesis of these disorders. Understanding these shared biological pathways is crucial to finding strong biomarkers and targeted therapies. The current study focused on the detailed network biology with an aim to uncover the genes that play a major role in neuropsychiatric disorders. The study used different diseases, specific databases, and literature search to identify twenty-three diseases, associated genes, and developed a Protein-Protein Interaction (PPI) network. Forty genes that were functionally interacting and enriched in biologically relevant processes were added to the network to provide a broader picture of the molecular landscape. NRXN1 is the most important molecule in all four disorders, according to an analysis of network topology. This suggests that NRXN1 plays a crucial role in synaptic architecture and neural transmission, which is consistent with its function in the brain. Other hub genes that have been found to be essential to interconnected regulatory networks implicated in neuropsychiatric pathophysiology include ANK3, DRD2, BDNF, FKBP5, SLC6A4, HTR2A, and CACNA1C. The results revealed converging molecular pathways and identified important regulatory hubs that could be of interest in diagnostics and therapy. Based on the prioritized hub proteins, selected candidate compounds were used for structure-based molecular docking to explore the therapeutic potential. The

*Corresponding Author: muk2000pk@yahoo.com

docking analysis showed that the identified molecular targets had favorable protein-ligand binding interactions, indicating their potential for therapeutic applications. While experimental validation is needed, the combination of network biology and molecular docking offers important clues to the common molecular environment of complex psychiatric disorders and can be used to identify potential targets for precision medicine. In conclusion, this study contributed to the understanding of the common molecular architecture of the major neuropsychiatric disorders and offered a systems biology approach to biomarker discovery and targeted therapeutic strategies.

GRAPHICAL ABSTRACT



***Keywords*:** docking, network, neurology, Protein-Protein Interaction (PPI), psychology

Highlights

- NRXN1 and ANK3 emerged as central hubs across major psychiatric disorders.
- Synaptic, calcium-signaling, and neuroinflammatory pathways were enriched.

- Sulphanoids showed favorable docking interactions with prioritized targets.

1. INTRODUCTION

Neuropsychiatric and mental health conditions are a significant burden of disease in the world. These conditions account for a substantial proportion of Disability Adjusted Life Years (DALYs), decreased quality of life, and premature deaths [1]. While they are considered separate clinical conditions, there is increasing epidemiological, clinical, and genetic evidence of significant overlap in their heritability, symptomatology, and response to treatment patterns [2,3]. These observations suggest that there are no clear diagnostic boundaries. Furthermore, these observations reinforce the notion that there are common molecular and neurobiological mechanisms underlying major psychiatric disorders.

The genetic basis of psychiatric disorders has been greatly elucidated by the use of advances in genotyping technologies and high-throughput sequencing. These conditions are now known to be highly polygenetic, with many genetic variants having a small individual effect that together add up to disease susceptibility [4,5]. Notably, many susceptibility genes have been identified that are linked to basic biological processes that are shared across several psychiatric disorders, such as synaptic transmission, neuronal development, calcium signaling, neuroinflammation, and cell adhesion [6–8]. Genetic variation, however, only explains a part of the pathogenesis of disease. This is because proteins do not generally work alone but are part of highly interconnected and dynamic molecular networks.

Protein-Protein Interaction (PPI) networks offer a systems-level approach to understand the relationship between disease-associated proteins. PPI networks help identify biologically relevant regulatory modules and critical hub proteins that coordinate cellular signaling and preserve network integrity by incorporating molecular interactions. Highly connected hub proteins tend to have a disproportionate influence on network stability, signal transduction, and biological regulation, and are therefore promising candidates for the discovery of biomarkers and therapeutic targets [9,10]. Therefore, the discovery of common hub genes and interaction modules for several psychiatric diseases could help to gain insights into common pathophysiological mechanisms.

In addition to direct protein interactions, complex gene regulatory

networks also play a role in disease susceptibility, phenotypic heterogeneity, and clinical outcomes. Integrative network biology approaches that integrate PPI analysis with functional enrichment and pathway annotation have therefore become powerful strategies for prioritizing high-confidence disease genes. These are helpful in uncovering biologically coherent modules and for elucidating the signaling pathways underlying complex neuropsychiatric disorders. These methods provide a systems-level view that can be used in conjunction with traditional genetics. Moreover, these may help identify common molecular mechanisms that might be important for diagnosis and therapy [11]. Such methods are particularly valuable in cross-disorder investigations, where studying overlapping molecular signatures can explore possible pathogenic pathways and shared therapeutic targets. The shared hub genes and signaling pathways have important clinical implications. Common molecular biomarkers may improve early diagnosis, disease classification, and patient stratification. Network-based therapeutic strategies could facilitate drug repurposing by targeting multiple interconnected pathways instead of individual proteins. Such an approach may improve treatment outcomes for patients presenting overlapping psychiatric symptoms and reduce the trial-and-error approach commonly associated with psychiatric medication selection.

This study built and analyzed PPI networks of 23 candidate genes previously associated with schizophrenia, BD, MDD, and suicidal behavior. The interaction network was extended to include functionally associated genes to gain a general picture of the common molecular space. Thus, this allowed the identification of common regulatory modules shared by these neuropsychiatric disorders. Network topology analysis was then used to detect highly connected hub genes and Gene Ontology (GO). Additionally, pathway enrichment analyses were used to characterize the key biological processes, molecular functions, cellular components, and signaling pathways associated with the identified gene networks.

To gain deeper insights into the translational relevance of these findings, structure-based molecular docking was conducted with prioritized hub proteins and selected candidate compounds. The docking analysis aimed to assess the binding affinity and interaction pattern of the proteins with the ligand, which gave the preliminary idea about the therapeutic potential of the identified molecular targets. This approach combines systems biology

and computational drug discovery to take genetic association studies one step further in order to identify candidate therapeutic targets and potential lead compounds.

Overall, this study provided a comprehensive network biology framework to identify the shared molecular mechanisms between the major neuropsychiatric disorders. The results shed light on the common molecular architecture of these disorders and identified enriched biological pathways. Moreover, the results also identified promising targets for therapeutic intervention as well as for the discovery of new biomarkers and therapeutic target prioritization. The results provided a foundation for precision medicine strategies in psychiatry.

2. MATERIALS AND METHODS

2.1. Data Curation and Retrieval

A thorough literature search was performed to determine genes related to schizophrenia, BD, MDD, and suicidal behavior. The disease-specific keywords were used to search relevant publications from publicly available scientific databases, such as PubMed, Google Scholar, and other scientific repositories. The DisGeNET database [12] was used to collect additional disease-associated genes to ensure a comprehensive gene collection. The common genes shared among the four psychiatric disorders were identified and visualized with Venny 2.1.0 [13], an online tool for comparing multiple gene sets. This method allowed the discovery of common and disorder-specific genetic factors.

2.2. Functional Annotation

The identified candidate genes were functionally characterized using Web Gestalt [14]. Significant enrichment in GO biological processes (BP), molecular functions (MF), and cellular components (CC) was performed. Furthermore, pathway enrichment analysis was carried out to determine the biological pathways that were significantly enriched with the candidate genes. This could provide clues to the molecular mechanisms of the neuropsychiatric disorders studied.

2.3. Biological Network Analysis

To explore the functional relationships among the disease-associated genes identified, PPI networks were built using Gene MANIA [15]. Gene MANIA combines several types of biological evidences, such as physical

interactions, co-expression, genetic interactions, co-localization, shared pathways, and protein domain similarity, to create comprehensive networks of interactions. The networks were visualized and analyzed in terms of topology in Cytoscape [16]. To identify highly connected nodes (hub genes), network centrality metrics were computed, with the degree centrality being the most relevant measure. These hub genes were thought to be potential key regulators of the shared molecular architecture of the neuropsychiatric disorders investigated.

2.4. Molecular Docking Analysis

The prioritized hub proteins were assessed for therapeutic potential by structure-based molecular docking. The crystal structure of the selected target proteins was downloaded from the Protein Data Bank (PDB) [17] in three dimensions. To predict the binding affinity and the best binding conformation of the selected candidate ligands towards the target proteins, molecular docking simulation was carried out using the AutoDock Vina [18] software. The protein-ligand complexes thus generated were then analyzed and visualized using UCSF Chimera [19] to assess the binding orientation, hydrogen-bonding interactions, hydrophobic contacts, and overall stability of the predicted complexes.

3. RESULTS

3.1. Identification and Collection of Candidate Genes

A systematic literature search, combined with database mining with DisGeNET [12], identified several candidate genes. Meanwhile, Gene MANIA [15] was used for the validation of network-based functional association analysis. The foremost search dug out 23 genes, already been listed for downstream analysis as candidates for psychiatric disorders (Figure 1). These genes were chosen for downstream network construction and functional analyses due to their known role in neuronal signaling, synaptic organization, stress responses, and neurodevelopment. Comparative analysis suggested the genetic overlap of MDD, BP, schizophrenia, and suicidal thoughts. This further indicates shared genetic risk factors for these separate psychiatric conditions.

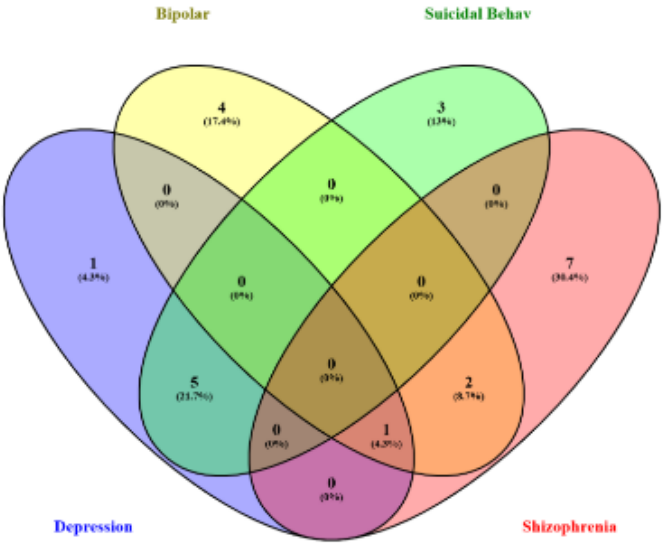


Figure 1. Venn Diagram Showing Different Diseases Sharing Associated Genes

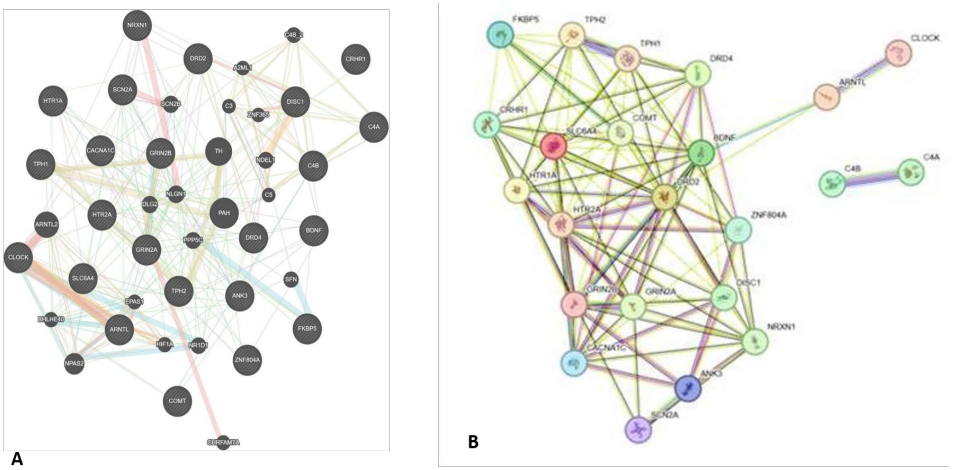


Figure 2. (A) General Protein-Protein Network Showing Different Interactions of Candidate Genes (B) General Protein-Protein Network Showing Different Interactions of Candidate Genes

3.1.1. Protein–Protein Interaction (PPI) Network Analysis. The Molecular model exposed through PPI network analysis revealed efficient union between the candidate genes**.** Network expansion included some 40

additional related genes for the complete topological evaluation of the molecular network.

NRXN and ANK3 were identified as high-degree hub genes through topological analysis. These play a directing role in signal propagation and sustaining integrity. Furthermore, FKBP5, SLC6A4, HTR2A, BDNF, and CRHR1 genes are shared among major depressive conditions, involving paths related to serotonergic signaling, neurotrophic support, stress response regulation, and suicidal thoughts (Figure 2A-2B). While, the overlap of multiple conditions, that is, schizophrenia, MDD, and, was found to be associated with DRD2. This highlights dopaminergic dysregulation as a cross-investigative molecular report.

3.2. Functional Enrichment Analysis

Some biological processes associated with synaptic transmission, neuroinflammatory responses, cell adhesive pathways, and calcium signaling were substantially overrepresented by GO and pathway enrichment analysis. This highlights the pathophysiology of psychiatric disorders along with key roles of neuronal excitability, synaptic flexibility, and neuroimmune regulation.

3.3. Molecular Docking and Therapeutic Target Assessment

The hub proteins were targeted through structure-based molecular docking to explore likely therapeutic implications. AutoDock Vina [18] was used for Docking simulations and AutoDock Tools for structure preparation. Hydrogen bonding and hydrophobic contacts were found in tested compounds, including sulphanoids, demonstrating binding interactions in the functional domains of targeted proteins. Similarly, Diazepam showed receptor-specific interaction in GABAergic modulation with its recognized role (Figure 3). Surprisingly, sulphanoids showed transparent interaction with network-central proteins, indicating regulatory impacts through multiple pathways. These impacts are certainly identified in the psychiatric molecular network (Figure 4). The findings obtained in silico still need experimental validation. The results showed that for further therapeutic investigations of complex psychiatric disorders, sulphanoids are a hopeful candidate.

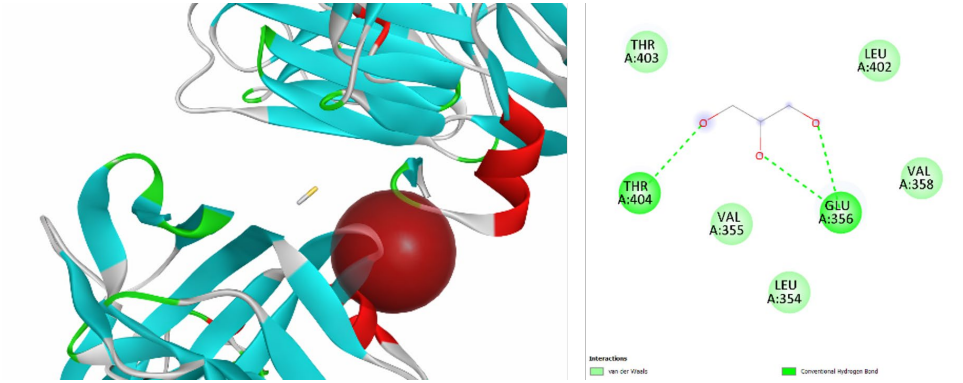


Figure 3. Docking of Sulphanoids with the Targeted Site

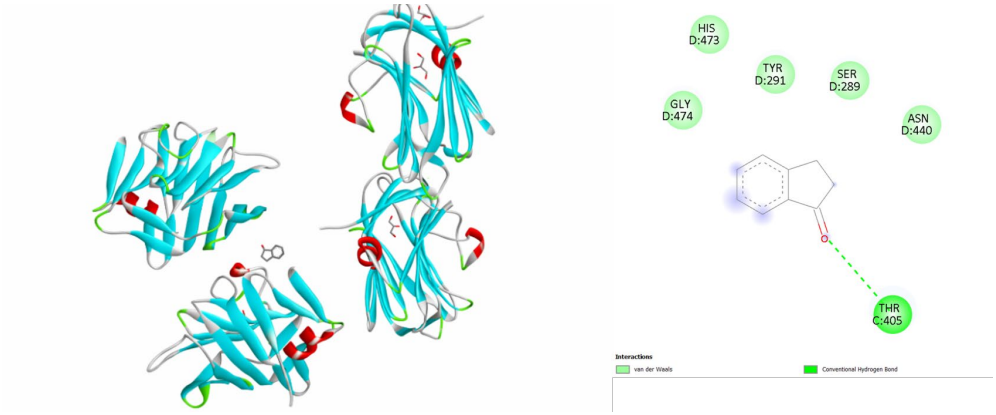


Figure 4. Docking of Diazepam with the Targeted Site

4. DISCUSSION

Psychiatric illnesses are characterized by clinically significant instabilities in emotional control, cognition, and actions that arise due to psychological dysfunctions, developmental, and biological processes that trigger mental inabilities. These circumstances are coupled with significant individual stress, reduced public and professional activities, as well as bigger risk of disability and early death [20,21]. Even though this has been classified as different analytical objects in old traditions, the increasing genetic and neurobiological evidence supports dimensional models. Notably, BD, MDD, schizophrenia, and suicidal behavior partially overlap and share etiological mechanisms.

This study revealed the PPI of 23 candidate genes in a concurrent parallel molecular network, showing usable meeting within psychiatric

disorders. To identify central regulatory components in polygenic conditions and disease modules, powerful tools are network-based approaches [22, 23]. The two high-degree hub genes NRXN1 and ANK3 were identified in an expanded interaction network through topological analysis. These genes emphasize their potential impact throughout connected molecular pathways.

NRXN1 is the gene for neurexin-1, a presynaptic cell adhesion protein essential for synapse formation, maintenance, and neurotransmitter release. The gene NRXN1 has been found to be consistently associated with schizophrenia and other neurodevelopmental and psychiatric disorders, and is known to be essential for synaptic connectivity and neuronal communication [24,25]. Evidence suggests that loss of synaptic adhesion and defects in neuronal connectivity are common pathological hallmarks in the major psychiatric disorders, further supporting the central role of NRXN1 in their shared molecular pathogenesis.

Likewise, ANK3 is responsible for the coding of ankyrin-G, a scaffolding protein that organizes voltage-gated sodium channels at the axon initial segment and nodes of Ranvier. This is helpful in regulating neuronal excitability and action potential initiation. Variations in ANK3 have been found many times to be associated with BD and other mood disorders. This indicates that the dysregulation of neuronal excitability is involved in the pathophysiology of affective instability and susceptibility to BD [26].

These hub genes indicate that the molecular networks that are disrupted in the pathophysiology of multiple neuropsychiatric disorders are interconnected. Moreover, disturbances in synaptic organization, ion channel regulation, and neuronal signaling spread through these networks. A systems-level paradigm is further supported by the co-occurring disease-related genes across diagnostic categories. Significantly, the genes FKBP5, BDNF, and SLC6A4, which are known to be crucial for stress-response regulation, neuroplasticity, serotonergic neurotransmission, and susceptibility to suicidal conduct, were shared by MDD and suicidal behaviors. The discovery that the DRD2 gene is shared by major depression, bipolar illness, and schizophrenia implies that dopaminergic signaling is essential for mood, cognition, and psychosis. These shared genetic characteristics suggest that the clinically different main mental diseases may share cellular and molecular causes.

Additionally, the functional enrichment analysis revealed a high enrichment in biological pathways associated with cell adhesion, neuroinflammatory response, calcium signaling, and synaptic transmission. These findings are in line with earlier genomic research which indicates that areas linked to genes involved in neurotransmission, synaptic plasticity, and neuronal communication are enriched in psychiatric risk variants [27]. These pathways come together and suggest that disturbance of fundamental neuronal signaling networks is a common mechanism for the pathophysiology of a number of neuropsychiatric diseases.

Synaptic interference may disrupt the balance between excitation and inhibition and the movement of impulses between the nervous system. It may lead towards cognitive and affective dysfunction. Calcium leakage across the cell membrane is one of the most prominent cellular processes. Research indicates associations between the exposure of psychiatric conditions and the calcium regulatory voltage-gated gene and its family members, CACNA [28].

The calcium gates regulate the release of neurotransmitters, synaptic plasticity, and formation of mRNA. This consequently induces both quick neural response and long-term nerve adaptations. Moreover, the over-representation of neuroinflammatory routes supports the association of psychiatric illness to cytokine imbalance, microbial activation, and immune dysregulation [29]. Metabolic rate of neurotransmitters, synaptic pruning, and stress sensitivity might be influenced due to long-term low-grade neuroinflammation. Likewise, the importance of primary neurexin-neuroligin complexes in synaptic structural stability and supplementary fixing proteins needs to be emphasized by cytoskeletal pathways and cell adhesion enrichment for the maintenance of active neural circuitry [30]. According to the results, the PPI network in the molecular system directs neuroimmune regulations, intercellular signaling, and synaptic configurations. This is seen repeatedly across multiple psychiatric phenotypes. These biological domains strengthen the perception of shared pathophysiological substrates and exceed the old traditional beliefs.

The therapeutic potential of the hub proteins, that were selected, was assessed using structure-based molecular docking. After that, the selected candidate ligand "sulphanoid" was screened for structural compatibility and binding affinity to the molecular targets that were discovered. In the anticipated binding pockets, the docking simulations showed favorable

interactions between proteins and ligands, such as hydrogen bonding, hydrophobic, and electrostatic interactions, which suggested stable binding conformations. The findings imply that important proteins implicated in shared biological pathways of neuropsychiatric disorders may be able to interact with sulphanoids. Structure-based molecular docking is a crucial computational technique for finding possible lead compounds and logically developing focused treatment methods for the regulation of disease-associated proteins, even though experimental validation is still required [31].

In contrast, Diazepam has a well-established clinical use and continues to be a reference medication for the treatment of mental symptoms. Diazepam mainly functions as a positive allosteric modulator of the GABA receptor, induces tranquillization and anxiolysis, and increases inhibitory neurotransmission [32].

The molecular docking results showed that the binding interaction remained consistent with its known receptor-based mechanism. Yet, the sulphanoid interaction network demonstrated a wider engagement towards regulatory proteins. This interaction pattern enhanced the possibility of network-level therapeutic modulation rather than targeting typical neurotransmitter receptors.

Though these findings were obtained in silico, they still need experimental validation through *in vivo* functional studies, chemical analyses, and cellular representations. However, sulphanoid serves as a leading compound for therapeutic optimization, due to its docking stability and binding compatibility.

Consequently, this study supported the understanding of the shared molecular architecture of psychiatric illnesses through a network-driven pattern. PPI topology, pathway enrichment analysis, computational drug discovery, and cross-disorder gene overlapping techniques were integrated. Overall, these findings suggested neuroimmune responses, signaling, and convergent synapses. These suggestions would help in pharmaceutical expansion and future biomarker discovery in developing psychiatric models.

The candidate genes were obtained from publicly available databases and published literature, which may introduce selection bias. PPI networks depend on currently available biological knowledge and may change as new

interactions are discovered. Functional enrichment analysis identifies statistically significant pathways but does not establish causal biological relationships. Furthermore, molecular docking predicts binding affinity rather than therapeutic efficacy, pharmacokinetic behavior, toxicity, or clinical safety. Additional validation using cell-based assays, animal models, transcriptomic analysis, proteomics, and clinical investigations is essential before translating these findings into clinical practice.

4.1. Conclusion

This study focused on structural molecular designs that share common features triggering major psychiatric disorders, including depressive disorders, BD, schizophrenia, and suicidal thoughts. NRXN1 and ANK3 were identified as central hub genes, using a PPI network, implying main roles in neural signaling and synaptic configuration. Moreover, functional enrichment of genes determined overlapping pathways associated with neuroinflammatory responses, calcium signaling, and synaptic transmission.

The binding exchanges of sulphanoids to prioritized targets, uncovered through structure-based molecular docking, further revealed potential therapeutic interactions that warrant experimental investigation. Although additional laboratory and clinical validation is required, the present findings support the application of network medicine as an effective strategy for biomarker discovery, psychiatric approaches, shared disease mechanisms, potential targets, therapeutic target identification, and future precision psychiatry.

4.2. Future Research Directions

Future research should integrate multi-omics datasets, including genomics, transcriptomics, proteomics, metabolomics, epigenomics, and single-cell sequencing, to provide a more complete understanding of psychiatric disease biology. Machine Learning (ML) and Artificial Intelligence (AI) may further improve biomarker discovery by integrating heterogeneous biological datasets. Functional validation of hub genes through CRISPR-Cas9 gene editing, RNA interference, induced pluripotent stem cell-derived neurons, and animal models would strengthen computational predictions. Molecular dynamics simulations and free-energy calculations should complement docking studies to improve prediction accuracy. These approaches may accelerate precision psychiatry,

personalized medicine, and the identification of novel therapeutic targets.

Author Contribution

Azmat Aziz: conceptualization, methodology, data Curation, formal analysis, writing-orignal draft. **Muhammad Shahan:** conceptualization, methodology, data Curation, formal analysis, writing-original draft. **Mahfooz Hassan:** data Curation, writing-review & editing. **Muhammad Ayaz:** data Curation, writing-review & editing. **Muhammad Awais Ali:** data Curation, writing-review & editing. **Mukhtar Alam:** data Curation, writing-review & editing. **Murad Ali Rahat:** data Curation, writing-review & editing. **Muhammad Ilyas:** supervision, writing – review & editing. **Mukhtar Alam:** supervision, writing – review & editing.

Conflict of Interest

The authors of the manuscript declare that they have no financial or non-financial conflict of interest in the subject matter or materials discussed in this manuscript.

Data Availability

Data availability is not applicable as this study was based on publicly available databases and computational analyses and did not generate new experimental datasets.

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Generative AI Disclosure Statement

The authors did not use any type of generative artificial intelligence software for this research except for the graphical abstract.

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