STM JOURNALS

Research & Reviews: Journal of
Computational Biology

https://journals.stmjournals.com/rrjocb/

ISSN: 2319-3433 (Online)
ISSN: 2349-3720 (Print)
Volume 13, Issue 1, 2024
January–April
DOI (Journal): 10.37591/RRJoCB

Research RRJoCB

Unveiling Nature's Potential: In Silico Exploration and Identification of Herbal Remedies for Major Depressive Disorder Through Molecular Interaction Studies

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Abstract

Major depressive disorder (MDD), a globally discussed mental health condition, has drawn significant attention because of its unique and intricate nature. This is marked by the enduring presence of negative emotions stemming from a lack of interest, diminished self-esteem, and excessive rumination. Despite the widespread availability of various antidepressant medications, their effectiveness is hindered by low response rates, prolonged treatment durations, and the prevalence of side effects, such as headaches, dizziness, insomnia, and oversleeping. This underscores the pressing need for alternative therapeutic approaches. In this study, a network biology approach was employed to identify the candidate genes associated with MDD. Among the identified genes, brain-derived neurotrophic factor (BDNF) has emerged as a potential target for further investigation. BDNF was subjected to molecular docking studies that utilized various drugs that are commonly prescribed for MDD treatment. Notably, the drug Paroxetine and Duloxetine demonstrated a superior docking score of -9.3 kcal/mol and -8.7 kcal/mol. To expand our exploration of plant-derived natural compounds (phytochemicals), we investigated substances from Brahmi (Bacopa monnieri), Shatavari (Asparagus racemosus), Ash Gourd (Benincasa hispida), and Marijuana (Cannabis). Phytochemicals such as Quercitin, Kaempferol (from Shatavari), and Dronabinol (from Marijuana) exhibited compelling docking scores of -10.6 kcal/mol, -9.9 kcal/mol and -9.6 kcal/mol respectively. These findings suggest the potential of natural compounds as effective alternatives to synthetic drugs. Furthermore, ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties and 2D structures of these phytochemicals were analyzed to assess their pharmacokinetic profiles and potential toxicity. This comprehensive analysis underscores the potential of phytochemicals as alternative therapeutic agents for MDD, and emphasizes the importance of further research in this area for the development of effective treatments in mental health.

Keywords: Drugs, natural compounds, molecular docking, MDD, marijuana.

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Received Date: April 23, 2024
Accepted Date: May 22, 2024
Published Date: May 28, 2024

Citation: Abhimanyu Chauhan, Chakresh Kumar Jain. Unveiling Nature's Potential: In-Silico Exploration and Identification of Herbal Remedies for Major Depressive Disorder through Molecular Interaction Studies. Research & Reviews: Journal of Computational Biology. 2024; 13(1): 54–62p.

INTRODUCTION

Major Depressive Disorder (MDD) is a common mental illness affecting mood, interest, pleasure, cognitive function, and physical symptoms. Its impact on an individual's life is profound and represents a persistent condition characterized by varying degrees of remission and chronicity [1]. According to the World Health Organization (WHO), depression affects more than 5% of adults globally, with an estimated 280 million affected individuals. Females are more likely to experience depression than male, with a prevalence rate of 2:1

[2]. Based on a report, more than 700,000 cases of suicide are documented annually, attributed to suicide triggered by depression, positioning it as the fourth leading factor contributing to mortality among 15- to 29-year-olds [3]. Epidemiological investigation revealed a notable occurrence of substance abuse among individuals diagnosed with MDD. This includes various forms of intoxication such as alcohol dependence (4.5%), alcohol abuse (4.8%), cannabis abuse (2.5%), dependence (2.9%), abuse (2.3%), and dependence (2.9%) on other substances [4]. Individuals with MDD often struggle with self-harm tendencies and endure persistent feelings of sadness, decision-making difficulties, and reduced concentration, among other symptoms. Although the exact cause of depression remains unclear, factors such as environmental influences, sex differences, genetic predispositions, epigenetic changes, and various biological aspects of the nervous system, as well as the adrenal pituitary axis, immune system, and endocrine system, have been implicated. Many studies have suggested that MDD is a chronic condition that tends to recur at certain intervals throughout an individual's life [5].

According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, MDD is diagnosed when an individual experiences two or more weeks of persistent feelings of sadness or loss of interest and pleasure, accompanied by additional symptoms such as changes in sleep patterns, appetite or weight, and energy levels [6]. Antidepressant therapy is frequently recommended for treating MDD; however, approximately half of patients do not achieve remission with the initial treatment. In the short term, antidepressants work by impeding the breakdown or reuptake of monoamines such as serotonin (5-HT) and norepinephrine. Selective serotonin reuptake inhibitors (SSRIs) are widely utilized in the treatment of depression and related mood disorders, owing to their precise modulation of serotonin (5-HT) reuptake mechanisms [7]. While the monoamine hypothesis of depression initially focused on this acute mechanism of action, the delayed onset of the treatment response indicates that the therapeutic effects of antidepressants may stem from slower modifications of downstream signaling pathways and the regulation of target genes [8].

Protein-protein interactions (PPIs) are fundamental for understanding the cellular activities and biological functions of all organisms. Understanding these interactions can provide insights into infection processes and facilitate the development of various pharmaceutical drugs and therapy optimization strategies. PPI are represented in the form of networks consisting of nodes and edges, which play an important role in understanding biological systems. The PPI Network (PPIN) is a valuable tool for investigating cellular processes, disease mechanisms, and drug development. However, interpreting these networks can be challenging because of their inherent complexities [9].

Ayurveda, a traditional Indian medical system, recommends various compounds and herbs to treat conditions such as MDD. These herbs are commonly employed on their own or in conjunction with other Ayurvedic elements in formulations termed "*rasayanas*," which are aimed at revitalizing both the body and mind. Rasayana drugs function by improving digestion and metabolism, enhancing the nutritional quality of plasma-carrying nutrients (Rasa), and promoting the microcirculation of these nutrients to various fundamental body tissues [10].

MATERIAL AND METHODS

Gene Collection

The extensively recognized and validated genes associated with MDD were downloaded from the NCBI (National Center for Biotechnology Information) database. NCBI serves as an invaluable resource, offering free access to online gene databases for browsing and downloading.

Construction of PPIN

Protein functions encompass a range of characteristics, with PPIs being the most significant. PPIs delineate the connections between two or more proteins facilitated by hydrophobic, biochemical, and electrostatic factors [11]. PPIs can be classified in various ways, based on their structural and functional attributes. One classification method is based on their interaction surfaces, which can be categorized as

homo-or heterooligomeric. Another classification is based on stability, which distinguishes between non-obligate and obligate interactions. Additionally, PPIs can be categorized by their persistence, with some being transient and others permanent [12]. The PPIN of the genes was constructed using the STRING database [13] and visualized using the Cytoscape [14] software. Furthermore, hub genes were identified from multiple genes within the network by assessing their degree and betweenness using the Cytohubba plugin [15]. Genes exhibiting the highest degree and betweenness centralities were chosen for subsequent structural identification and interaction analysis.

Identification of the Known Chemical Drugs

Several FDA-approved drugs of various classes commonly utilized in the treatment of MDD, including Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), Tricyclic Antidepressants (TCAs), and Monoamine Oxidase Inhibitors (MAOIs), were employed for interaction studies. All compounds were downloaded from PubChem in SDF format [16].

Identification of the Known Natural Compounds and Their Phytochemicals

Expanding our investigation to plant-derived natural compounds known as phytochemicals, we explored substances sourced from Brahmi (*Bacopa monnieri*), Shatavari (*Asparagus racemosus*), Ash Gourd (*Benincasa hispida*), and Marijuana (Cannabis). Plant-derived natural compounds have been investigated for their potential as substitutes for known chemical drugs. Bioactive compounds sourced from various plants, compiled from public databases, and published research papers, were retrieved from PubChem in the SDF format [16].

Docking Analysis

The protein structure of 1BND was retrieved from the PDB database. Subsequently, in AutoDock 4.2.6, water molecules were removed and polar hydrogen atoms were added. Kollman charges were assigned to proteins. Finally, the processed proteins were saved in PDBQT format for further analysis. Molecular docking experiments were performed to predict the primary binding positions of the ligands in the three-dimensional protein structure. Docking software such as AutoDock and AutoDock Vina [17] were utilized for this purpose. For molecular docking, the x-, y-, and z-dimensions were set to $62 \times 66 \times 60$, with the maximum number of points in each dimension. The exhaustiveness parameter was configured to 8.0 to ensure a thorough exploration of the conformational space during the docking process.

ADMET Analysis

Absorption, distribution, metabolism, and excretion (ADME) properties are used to assess the drug-like behavior of a chemical agent. ADME properties depict the accessibility of a compound throughout the body in accordance with Lipinski's rule of five [18]. We used admetSAR [19] and SwissADME [20] to identify the ADMET properties.

RESULTS AND DISCUSSION

Gene Collection

All known genes associated with MDD were downloaded from the NCBI for Biotechnology Information Online Gene Database (NCBI). A total of 13 well-identified genes cited in the literature were collected for Homo sapiens genes available in the NCBI database.

Construction of PPIN

The construction of PPIN entailed uploading genes associated with MDD to the STRING database, as shown in Figure 1. Subsequently, protein interactions were extracted from STRING, and the resultant interaction network was visualized using the Cytoscape software. Genes with the highest degree and betweenness were identified using the CytoHubba plugin, which revealed that BDNF exhibited the highest centrality within the network.

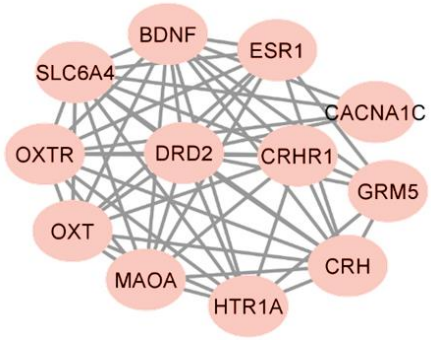


Figure 1. Representation of PPIN of different genes associated with MDD.

Target Protein Identification

The OMIM database (OMIN ID: 113505), UniProt (UniProt ID: P23560), and PubMed databases were used to acquire information regarding BDNF and its naturally occurring variant V66M. The crystallographic structure with the highest level of detail, found in the PDB database under ID 1BND, was chosen as the foundation for the subsequent docking studies (Figure 2).

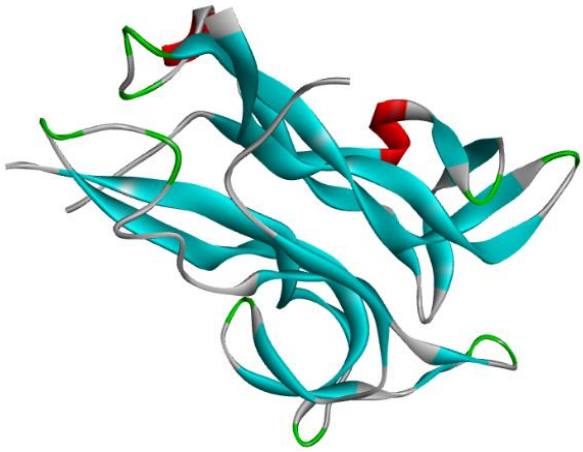


Figure 2. Depicting the target protein structure.

Molecular Docking Between the Target Protein and Ligands

To identify potential phytochemicals against MDD, molecular docking studies were conducted on both the chemical and natural compounds. Molecular docking was performed using the AutoDock and AutoDock Vina software. First, the protein structures were preprocessed and converted into suitable formats using AutoDock. The processed structures were used in AutoDock Vina to identify the best affinity and pose with the ligands. The results of molecular docking experiments are presented in Tables 1 and 2. Paroxetine and Duloxetine exhibited higher affinity scores than other FDA-approved drugs. However, upon docking with multiple natural compounds, quercetin and kaempferol demonstrated even higher affinity scores than drugs commonly used for MDD.

Interaction Studies between Protein-ligands

Three-dimensional structures of the docked protein-ligand complexes were employed to understand the binding interactions between the protein target and the ligands, as shown in Figure 3. This information will help in identifying potential drug candidates and understanding their modes of action at the molecular level. Two-dimensional (2D) interaction studies have also been conducted to gain deeper understanding. interactions between protein and ligand complexes, as shown in Figure 4. In 2D interaction studies, specific interactions, such as hydrogen bonding, hydrophobic interactions, electrostatic interactions, and π–π stacking interactions between the protein and ligand complexes, were

Table 1. Molecular docking scores of chemical ligands with protein structures.

S.N.	PubChem CID	Ligands	Docking score (kcal/mol)
1	43815	Paroxetine	-9.3
2	60835	Duloxetine	-8.7
3	3386	Fluoxetine	-8
4	3696	Imipramine	-7.8
5	125017	Desvenlafaxine	-7.5
6	5656	Venlafaxine	-6.9
7	19493	Tranylcypromine	-6.3
8	2160	Amitriptyline	-6.2
9	4543	Nortriptyline	-6.2
10	3675	Phenelzine	-6.1
11	146570	Escitalopram	-6
12	2771	Citalopram	-6
13	68617	Sertraline	-6

Table 2. The results showed the docking score of the natural compounds with the protein structure.

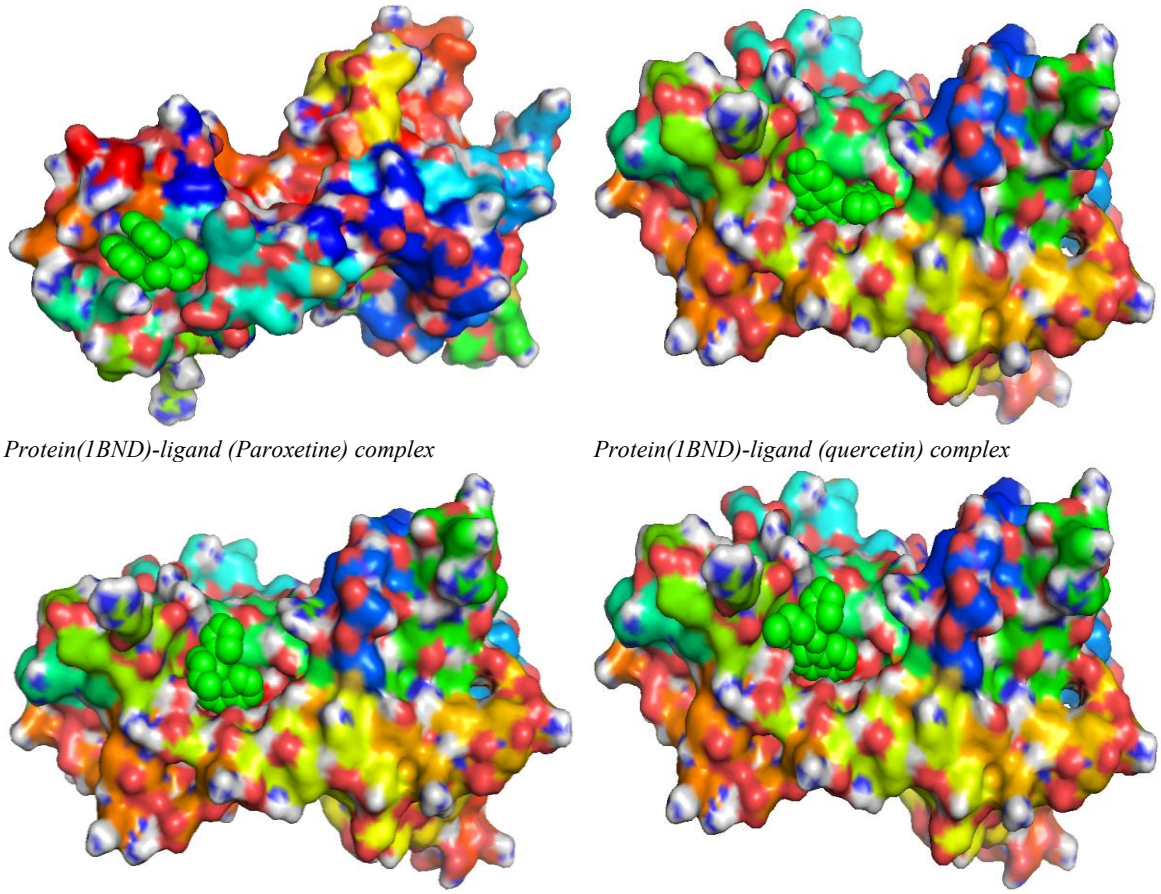
S.N.	PubChem CID	Ligand name (Natural)	Docking score (kcal/mol)
1	5280343	Quercetin	-10.6
2	5280863	Kaempferol	-9.9
3	16078	Dronabinol	-9.6
4	160570	Cannabidiolic acid	-7.7
5	403815	Cannflavin B	-7.7
6	5280450	Linoleic Acid	-7.5
7	445639	Oleic Acid	-7.3
8	624971	Racemosol	-6.5
9	6549	Linalool, (+/-)-	-6.4
10	31253	Myrcene	-6.4
11	10071695	Cannflavin A	-5.9
12	54670067	Ascorbic Acid	-5.8
13	64971	Betulinic Acid	-5.5
14	119287	Cucurbitacin S	-5.3
15	644019	Cannabidiol	-5
16	5281515	Caryophyllene	-4.7
17	119	Gamma-Aminobutyric Acid	-4.2

analyzed, and visualized using the Biovia Discovery Studio visualizer (Table 3). These investigations yield invaluable insights into the binding patterns and pivotal residues that contribute to stabilizing the interactions between proteins and ligands. This knowledge is indispensable for enhancing the design and optimization of prospective therapeutic agents.

ADMET Analysis of Natural Compounds

These properties were used to determine whether our natural compound could serve as a suitable alternative to conventional drugs. The pharmacokinetic profiles of quercetin and kaempferol are shown in Table 4, demonstrating that they do not contravene any Lipinski rule criteria and do not exhibit mutagenic properties.

Protein-ligand complex (Chemical) ***Protein-ligand complex (Natural)***

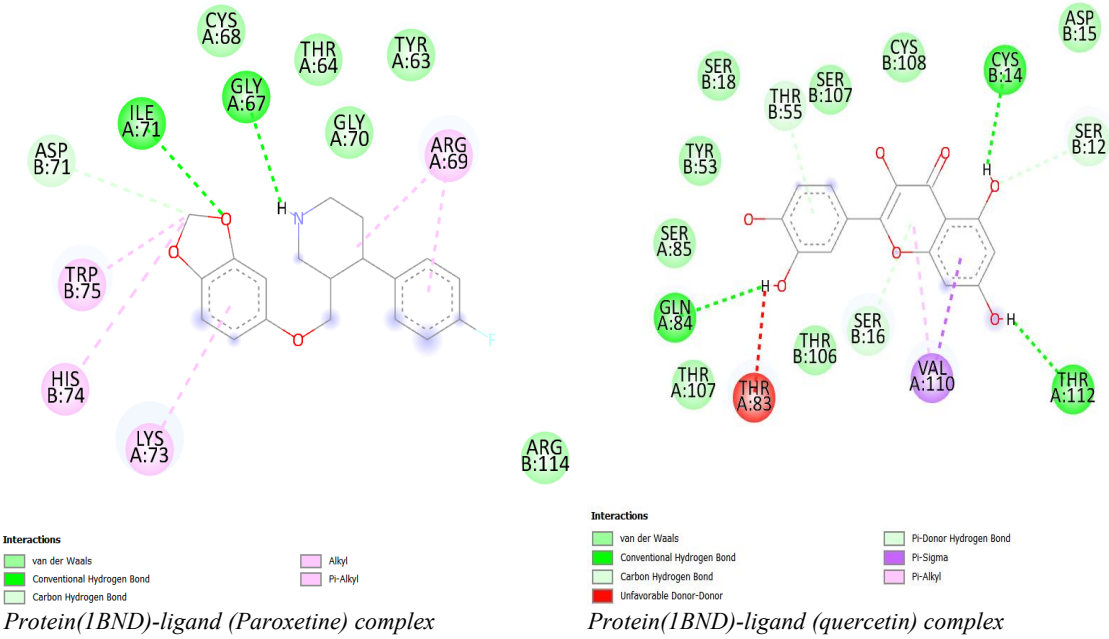


Protein(1BND)-ligand (Paroxetine) complex *Protein(1BND)-ligand (quercetin) complex*

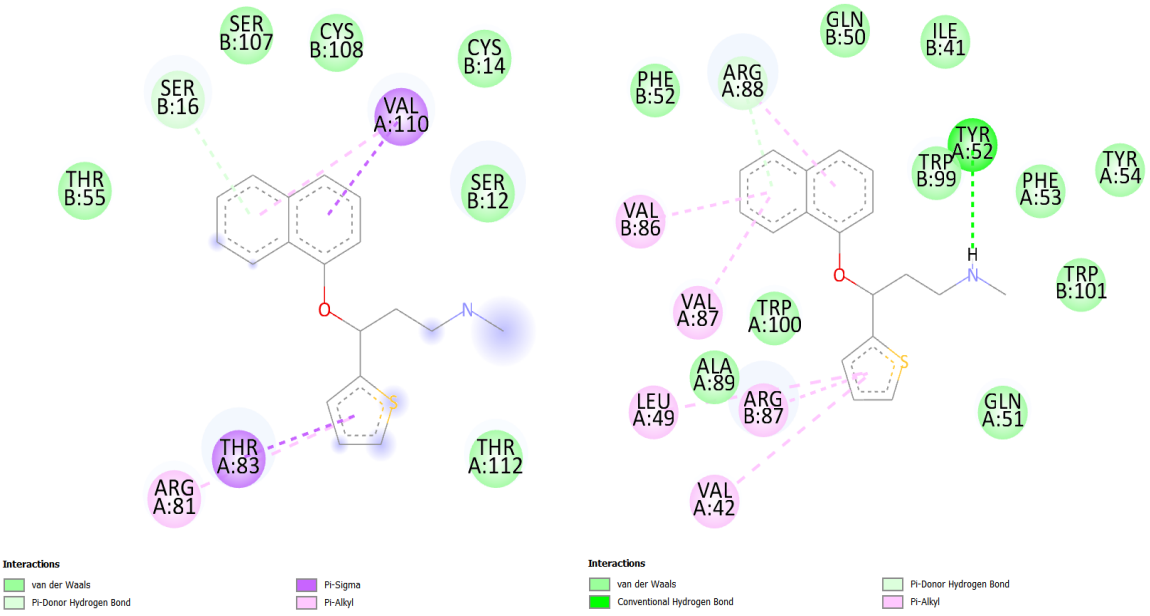
Protein(1BND)-ligand (Duloxetine) complex *Protein(1BND)-ligand(kaempferol) complex*

Figure 3. Depicting the complex 3D structure of receptor protein-multicolored structure and ligand (chemical, natural) green-colored structure).

2D interaction between Protein-ligand complex (Chemical) ***2D interaction between Protein-ligand complex (Natural)***



Protein(1BND)-ligand (Paroxetine) complex *Protein(1BND)-ligand (quercetin) complex*



Protein(1BND)-ligand (Duloxetine) complex *Protein(1BND)-ligand (kaempferol) complex*

Figure 4. Various 2D interactions between proteins and ligands (chemical and natural).

Table 3. Specific interactions were observed between the protein residues/atoms and ligands.

S.N.	Ligands	Interaction bonds		
		No. of Hydrogen bonds	*Hydrogen binding interaction*	*Hydrophobic interaction*
1.	Paroxetine	2	ILE A:71, GLY A:67	THR A:64, GLY A:70, TYR A:63 ARG B:114, CYS A:68
2.	Duloxetine	-	-	SER B:107, CYS B:108, CYS B:14, SER B:12, THR A:112, THR B:55
3.	Quercetin	3	GLN A:84, THR A:112, CYS B:14	SER B:18, SER B:107, CYS B:108, ASP B:15, THR B:106, THR A:107, SER A:85, TYR B:53
4.	Kaempferol	1	TYR A:52	PHE B:52, TRP A:100, ALA :89, GLN B:50, ILE B:41, TRP B:99, PHE A:53, TYR A:54, TRP B:101, GLN A:51

Table 4. Specific ADMET properties of natural compounds.

S.N.	Ligands	Carcinogenicity	Hydrogen bond donor	Hydrogen bond acceptor	Acute toxicity rule	BBB penetration	Lipinski
1	Quercetin	Non-carcinogenic	5	7	II	No	Yes
2	Kaempferol	Non-carcinogenic	4	6	II	No	Yes

DISCUSSION

Natural compounds, such as quercetin and kaempferol, can be used as alternative treatments for MDD compared to conventional drugs. These compounds, which are abundant in various plant sources, have gained attention owing to their diverse pharmacological activities and favorable safety profiles. Quercetin and kaempferol exhibit multiple biological effects, including antioxidant, anti-inflammatory, neuroprotective, and antidepressant. These effects are attributed to their ability to modulate various molecular targets involved in the pathophysiology of depression, such as the neurotransmitter systems, neurotrophic factors, and inflammatory pathways. Moreover, both compounds have shown promising results in interaction studies and have different properties, thereby demonstrating their potential as antidepressants. One significant advantage of natural compounds, such as quercetin and kaempferol, is their relatively low toxicity and minimal side effects compared to synthetic drugs commonly used for

MDD treatment. This makes them appealing candidates for long-term therapy, as they may offer a safer alternative for patients who experience adverse reactions or poor tolerance to conventional antidepressants. Furthermore, the availability of quercetin and kaempferol from dietary sources makes them easily accessible and cost-effective compared to pharmaceutical drugs, which may be particularly beneficial for individuals seeking complementary or alternative treatments for depression. However, despite promising preclinical evidence and favorable safety profiles, further clinical studies are warranted to evaluate the efficacy, safety, and optimal dosing regimens of quercetin and kaempferol in patients with MDD. Additionally, it is essential to consider factors such as bioavailability, pharmacokinetics, and potential drug interactions when translating preclinical findings into clinical practice.

CONCLUSION

This study highlights the potential of plant-derived phytochemicals as alternative therapeutic agents for Major Depressive Disorder (MDD). Using a comprehensive network biology approach, brain-derived neurotrophic factor (BDNF) has been identified as a critical target for the treatment of MDD. Molecular docking studies have revealed that traditional antidepressants, such as Paroxetine and Duloxetine, have strong binding affinities with BDNF. However, several natural compounds demonstrated higher docking scores, suggesting superior or comparable efficacies.

Specifically, phytochemicals such as Quercetin, Kaempferol, and Dronabinol exhibit notable binding affinities with BDNF, coupled with favorable ADMET profiles, indicating good pharmacokinetic properties and minimal toxicity. These findings highlight the potential of these compounds as effective and safe alternatives to conventional synthetic drugs for MDD treatment. The promising results of this study require further investigation, including in vivo and clinical trials, to validate the therapeutic efficacy and safety of phytochemicals. Additionally, elucidating the precise mechanisms underlying their antidepressant effects will provide deeper insights into their potential applications in mental health treatment.

Acknowledgment

We are thankful to the Department of Biotechnology, Jaypee Institute of Information Technology, NOIDA, for providing the necessary support for this study.

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