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Identifying Key Genes and Approved Medications Associated with Major Depressive Disorder Using Network Analysis and Systems Biology

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Abstract

Objective: Major depressive disorder (MDD) stands as one of the serious psychiatric conditions that detrimentally affect patients' quality of life and leads to a significant part of disability worldwide. Due to the limited understanding of the basic molecular mechanisms of depression and antidepressant medications, a clear understanding of the onset and development of MDD is unavailable. This study aims to figure out the pivotal genes and pathways implicated in the MDD development and identify medications that can potentially improve MDD treatment based on their relation with the key genes.

Method: Symbols of human coding genes were retrieved from the HUGO Gene Nomenclature Committee database. These symbols were then queried for MDD-related associations using a Python script in PubMed. Subsequently, genes with two or more related articles to MDD were selected. A union of our search data and MDD-related genes in the DisGeNET database was found. The gene interaction network was generated and analyzed utilizing the STRING and Cytoscape, respectively. Finally, a drug-gene network was constructed and medications that can affect multiple genes were selected.

Results: The union of our search data and DisGeNET data contained 1734 genes. Based on network analysis, TNF, IL1B, IL6, STAT1, and STAT3 were identified as the key genes in the MDD pathogenesis. Eleven drugs that affect more than one gene were detected through a drug-gene network. These medications include Acitretin, Adalimumab, Alteplase, Cisplatin, Digoxin, Etanercept, Infliximab, Insulin, Omeprazole, Pentoxifylline, and Rabeprazole.

Conclusion: In summary, our findings identified five genes as key genes in MDD development, as well as medications related to key genes. This study provides a new vision of the pathogenesis and treatment of MDD. However, further experimental and clinical studies are necessary.

Key words: *Antidepressive Agents; Depressive Disorder; Drug Therapy; Major; Protein Interaction Maps; Systems Biology*

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Major depressive disorder (MDD) is one of the prevalent disorders worldwide, leading to an individual's incapacity in personal, social, and economic domains, significantly affecting the quality of life (1, 2). The World Health Organization (WHO) acknowledges that depression significantly contributes to global disability. Estimates indicate that the annual global cost of lost productivity due to depression and anxiety reaches approximately a trillion dollars. As a result, improving personal, social and occupational functions of patients suffering from depression is crucial for improving global health and economic policies (3).

Existing medications for treating severe depression encompass tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs, dopamine reuptake inhibitors, and medications such as mirtazapine and nefazodone (4). Upon the administration of these medications, serotonin, postulated to contribute to the development of depression, increases in the brains of patients. However, it takes at least two weeks for the medications' early therapeutic effects to become apparent. Only around half of patients benefit from the initial therapy process (5). In addition, primary research on serotonin does not consistently support the idea that depression is due to a reduction in the activity of serotonin or concentration. Only some evidence suggests compatibility between reduced serotonin concentration due to prolonged use of antidepressants (6).

All of these factors have led the way towards new drugs with various mechanisms, and research has been carried out on this topic, highlighting the hypothalamic-pituitary-adrenal axis, inflammation, sex hormones, neuropeptides, and the brain's reward system as other contributing factors or associations with depression (7). Given the significant expenses and extensive time involved in developing and discovering novel medications, repurposing currently approved drugs that have undergone safety tests for other diseases can be a viable approach to addressing depression (8).

Although the genetic basis of depression is not fully understood, researchers have identified numerous genes that are related to depression. The functions of these genes are highly diverse. They could contribute in synaptic plasticity and synapse formation such as NEGR1, or neurodegenerative disorders like TMEM106B (9). Recent studies suggest that the identified genes associated with inflammation may also play a crucial role in causing depression. ESR2, a regulator of estrogen activity, is one such gene (9). Additionally, some genes including AURKA, BTN3A2, CXCL10, ERAP2, MARCO, and PLA2G7 were identified as diagnostic markers to detect Rheumatoid arthritis combined with MDD. Recent studies have demonstrated a correlation between the frequency of unsuccessful treatment trials and the concentrations of plasma TNF and IL-6. Patients with at least three failed trials had more plasma TNF and IL-6 concentrations compared to patients with none or one failed trial (10). These findings highlight the importance of inflammatory pathways in the initiation and treatment response of MDD (11). Despite these and similar studies, the full molecular basis of MDD pathogenesis remains unidentified. Therefore, identifying essential genes involved in depression through bioinformatics along with recommending FDA-approved drugs that can potentially improve depressive symptoms by targeting these genes in addition to their primary indications, can provide valuable insights for developing innovative medications with antidepressant properties.

The limited knowledge about the underlying pathways and mechanisms that lead to depression has posed challenges in identifying efficacious drugs for the treatment of depression. Hence, acquiring a comprehensive understanding of the occurring and development mechanisms of depression will facilitate the availability of more precise treatment options.

This study identifies the most relevant genes associated with MDD through systems biology and bioinformatics. Then, some FDA-approved drugs were recognized that could potentially impact the course and prognosis of MDD.

Materials and Methods

Gene Selection

We retrieved unique symbols of 19200 protein-coding human genes from the HUGO Gene Nomenclature Committee (HGNC) database (http://www.genenames.org) (12). Using a Python 3.9 script and the Selenium library version 4.9, we queried PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) with the following terms: (gene symbol) AND (MDD OR Major depression OR Major depressive disorder OR Depressive disorder, major [MeSH] OR Depressive disorder [MeSH]). (The code for PubMed search is available on GitHub at https://github.com/pporbaha/Genes_PubMed_Scraper.)

Among all genes, those with two or more articles truly related to the role of the gene in MDD were selected based on search results. Then, we rechecked the results to ensure the articles of selected genes were chosen correctly. To enhance the value of the results, we obtained data on genes associated with MDD from the DisGeNET database (https://www.disgenet.org), an advanced platform that boasts an extensive public repository of genes and variants linked to human diseases. The union of search-based data and DisGeNET data was then compiled.

Network Analysis

Networks of gene protein-protein interaction (PPI) have been created using STRING (https://string-db.org), a tool for investigating protein-protein interactions and comprehending the functional connections among proteins. A high confidence (0.700) was set for the minimum interaction score. Networks were analyzed

using four different methods, including Degree (the count of every node connection), Edge Percolated Component (EPC, an approach that aims to pinpoint significant nodes in biological networks by considering their inherent features and thoroughly analyzing their connectivity and relationships), Eccentricity (the maximum distance from one node to another node), and Maximum Neighborhood Component (MNC, the size of the maximum linked component of a node and its neighborhood, the neighborhood being the set of adjacent nodes, excluding the node itself), with the aid of the CytoHubba plugin in Cytoscape 3.10.0. The top 20 genes based on each method were selected and a Venn diagram to identify intersecting genes was created. Additionally, the molecular complex detection (MCODE) plug-in in Cytoscape was utilized to identify modules within the PPI network. The modules were inferred using the default settings, which included a node score cutoff of 0.2, a degree cutoff of 2, a K-core of 2, and a maximum depth of 100.

Drug-Gene Network

The Drug Gene Interaction Database (DGIdb, https://dgidb.org) was utilized to predict possible approved medications targeting critical genes. Then, Cytoscape was used to create a drug-gene interaction network from DGIdb results. Subsequently, drugs that interacted with more than one gene were found.

Results

Gene Selection

The search carried out through PubMed resulted in the identification of a total of 2,116 genes, out of a total of 19,200 coding genes that were linked to a minimum of two publications based on the query. After conducting an all-encompassing examination of the data, it was determined that a total of 1,060 genes had been validated as the genes selected for the search. This brings the total number of genes that have been validated to 1,060. On the other hand, the DisGeNET dataset included 1,236 genes that have been linked to MDD. A dataset of 1,734 genes was created from our search data and DisGeNET. The gene set listed above was used for additional research and evaluation.

Network Analysis

The protein–protein interaction (PPI) network of final genes that was produced by using the STRING database (threshold = 0.700) had a substantial number of edges, totaling 10,079. It had an excessive number of nodes, 1,370 in total (Figure 1). During the network visualization procedure, genes that had no known interactions or were not recognized by the STRING database or were not recognized by the STRING database were omitted from the analysis.

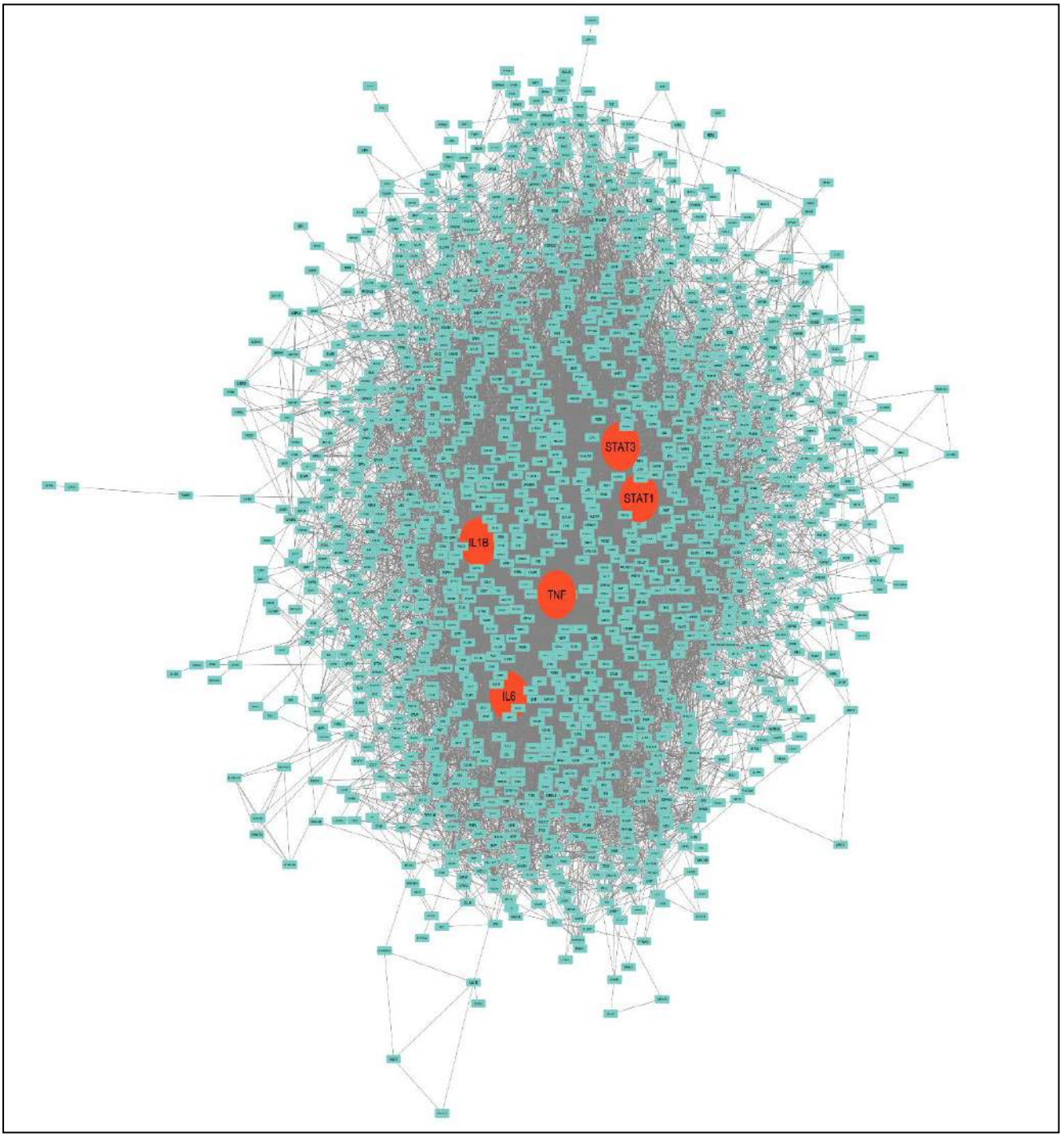
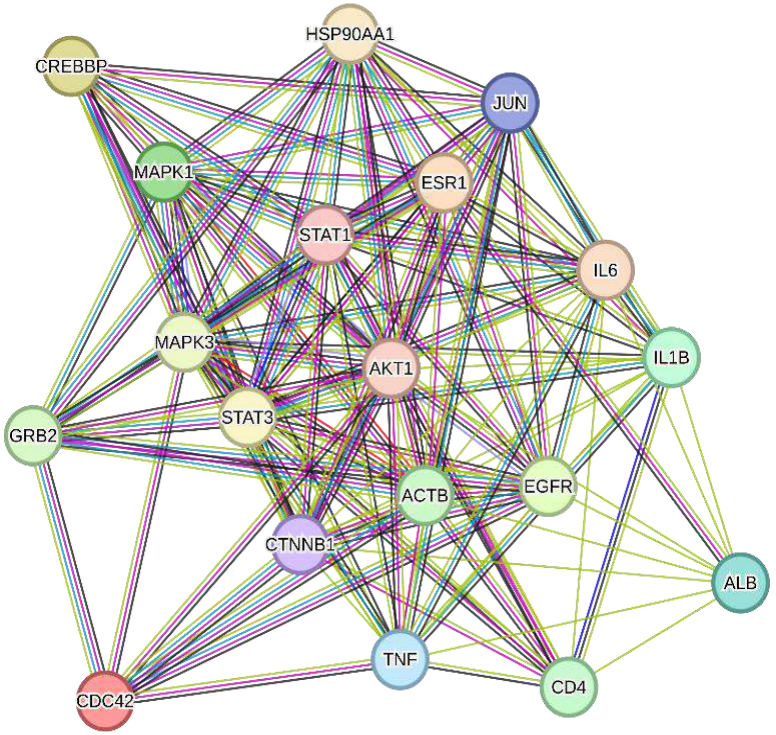
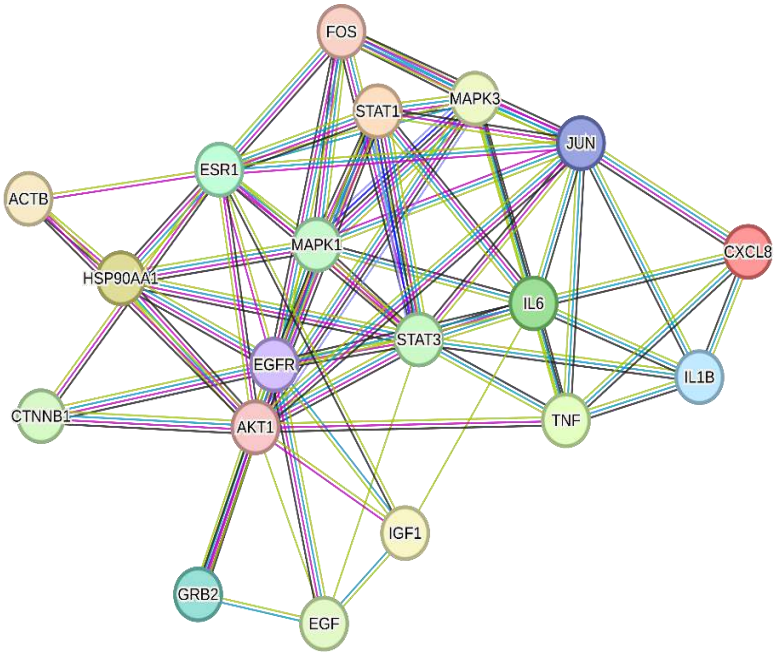


Figure 1. Protein–Protein Interaction (PPI) Network of Final Genes Resulting from the Union of Search-Based Data and DisGeNET Data. Hub Genes Are Shown by Red Color.

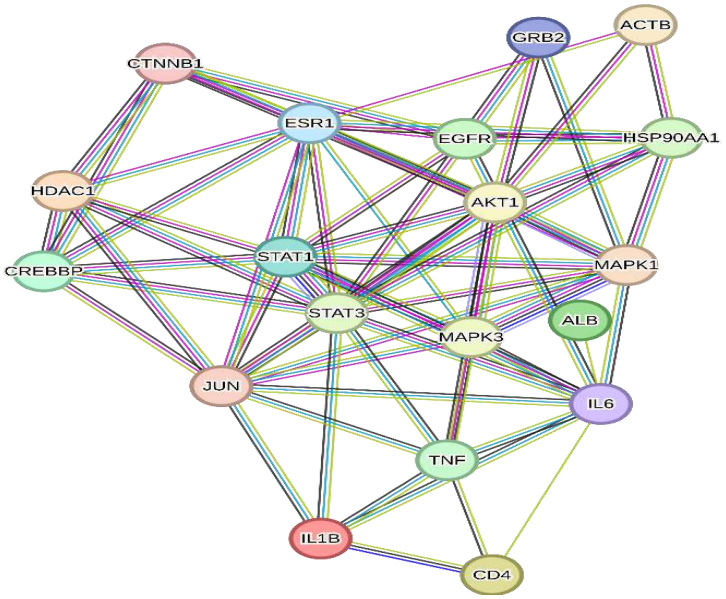
After completing calculations for the top 10, 15, and 20 genes using four different methods (Degree, EPC, MNC, Eccentricity) (Figure 2-A, D), a Venn diagram was constructed to represent the intersection of the top 20 genes identified by each method (Figure 2-E). The earlier described set of four gene clusters exhibited a collective count of five genes that demonstrated overlapping characteristics. These genes were identified explicitly as interleukin-6 (IL6), tumor necrosis factor (TNF), interleukin-1 beta (IL1B), signal transducer and activator of transcription 1 (STAT1), and signal transducer and activator of transcription 3 (STAT3). Each of these genes is indispensable for various pathways and functions that may contribute to developing or ameliorating MDD.


HSP90AA1
CREBBP
JUN
MAPK1
ESR1
STAT1
IL6
MAPK3
IL1B
AKT1
STAT3
GRB2
ACTB
EGFR
CTNNB1
ALB
TNF
CD4
CDC42

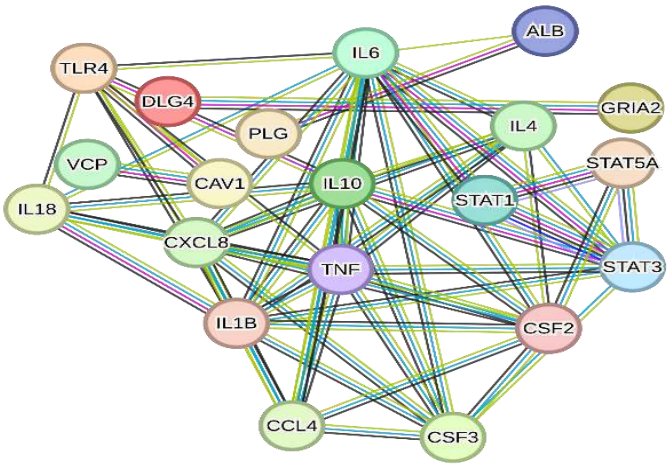
A


FOS
STAT1
MAPK3
JUN
ESR1
ACTB
MAPK1
CXCL8
HSP90AA1
IL6
STAT3
EGFR
IL1B
CTNNB1
AKT1
TNF
IGF1
GRB2
EGF

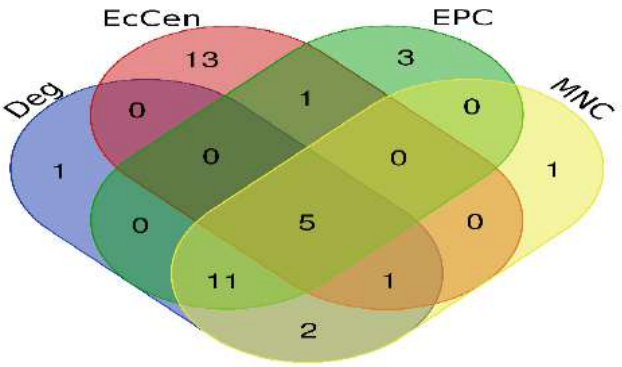
B



C



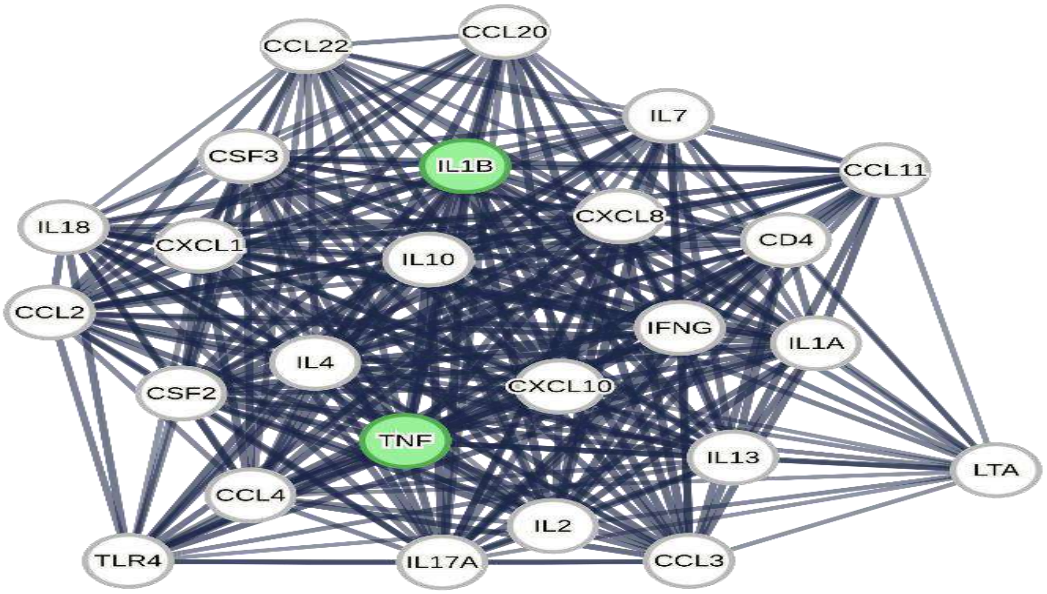
D



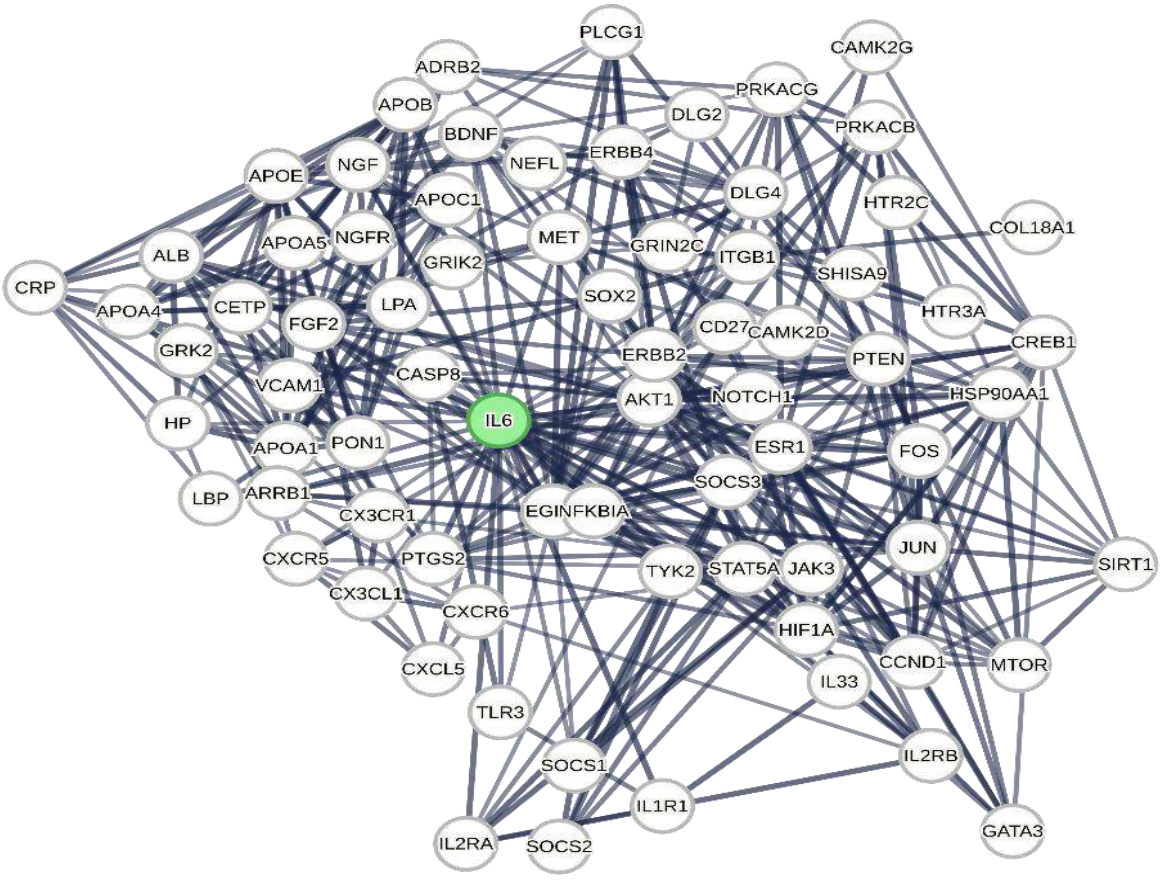
E

Figure 2. Findings from the Protein–Protein Interaction Network Analysis Conducted with the CytoHubba Plugin. (A) Top 20 Genes Based on Degree Scores. (B) Top 20 Genes Based on EPC Scores. (C) Top 20 Genes Based on MNC Scores. (D) Top 20 Genes Based on Eccentricity Scores. (E) Venn Diagram of Top 20 Genes Calculated by Four Methods Including Degree, MNC, EPC, and Eccentricity.

Moreover, the PPI network was analyzed using the MCODE plug-in within Cytoscape, Figure 3 highlights the three most prominent MCODE modules.



A



B

C

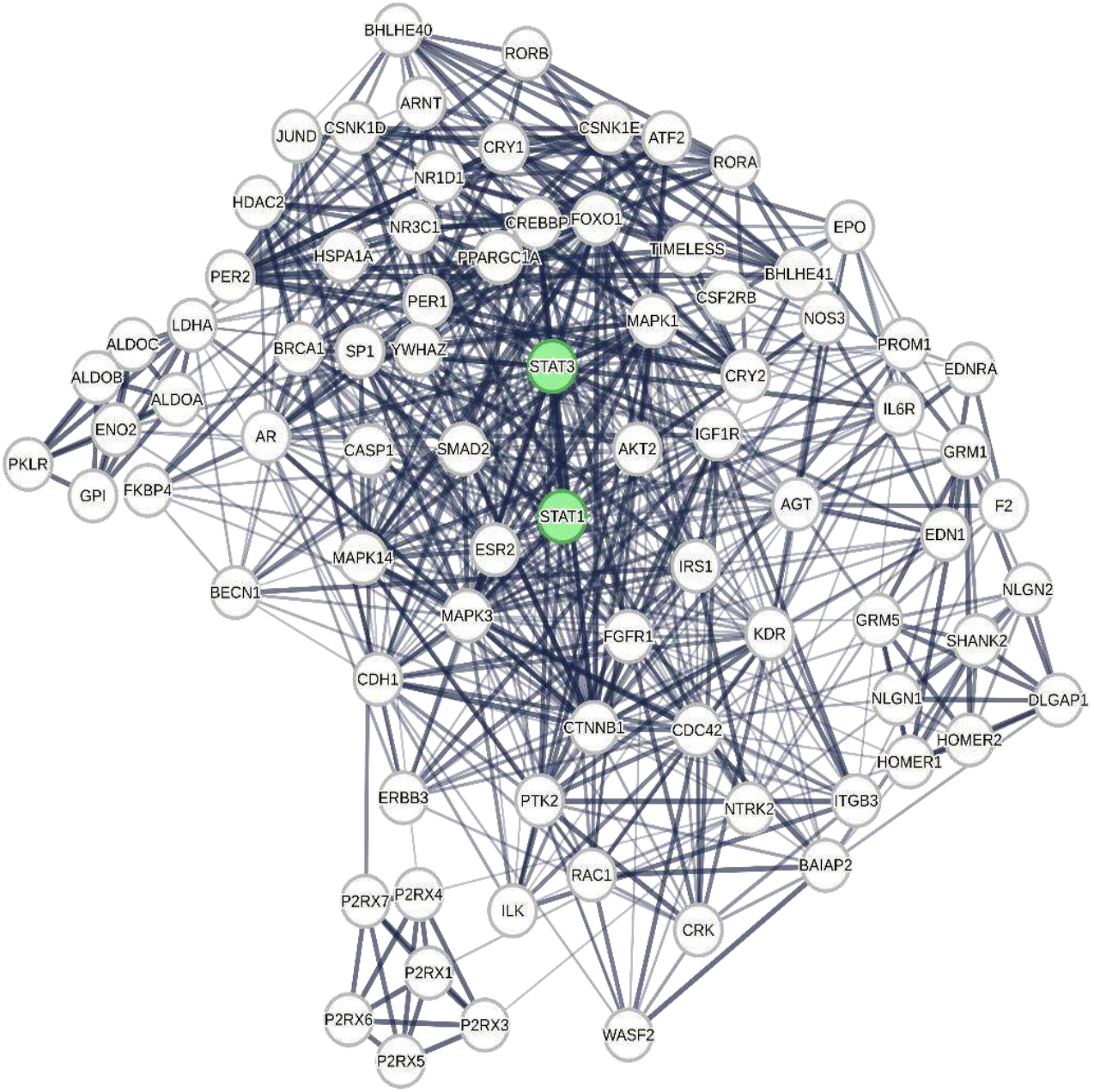


Figure 3. Top Three Most Significant Modules Form the Genes Protein–Protein Interaction Network by MCODE. Key Genes Are Displayed in Green Color. (A) Module 1, (B) Module 2, and (C) Module 3.

Drug-Gene Interaction

The identification of drugs that specifically target crucial genes was facilitated through the utilization of DGIdb. Additionally, a drug-gene network was constructed utilizing the Cytoscape. TNF exhibited the highest number of associated drugs, totaling 41. IL1B ranked second with 28 drugs, while IL6 occupied the third position with 14 drugs. In Figure 4, it can be observed that STAT3 was related to six medications as the fourth-rank. On the other hand, only one drug was found to be associated with STAT1, implying the smallest number of related drugs among all the genes.

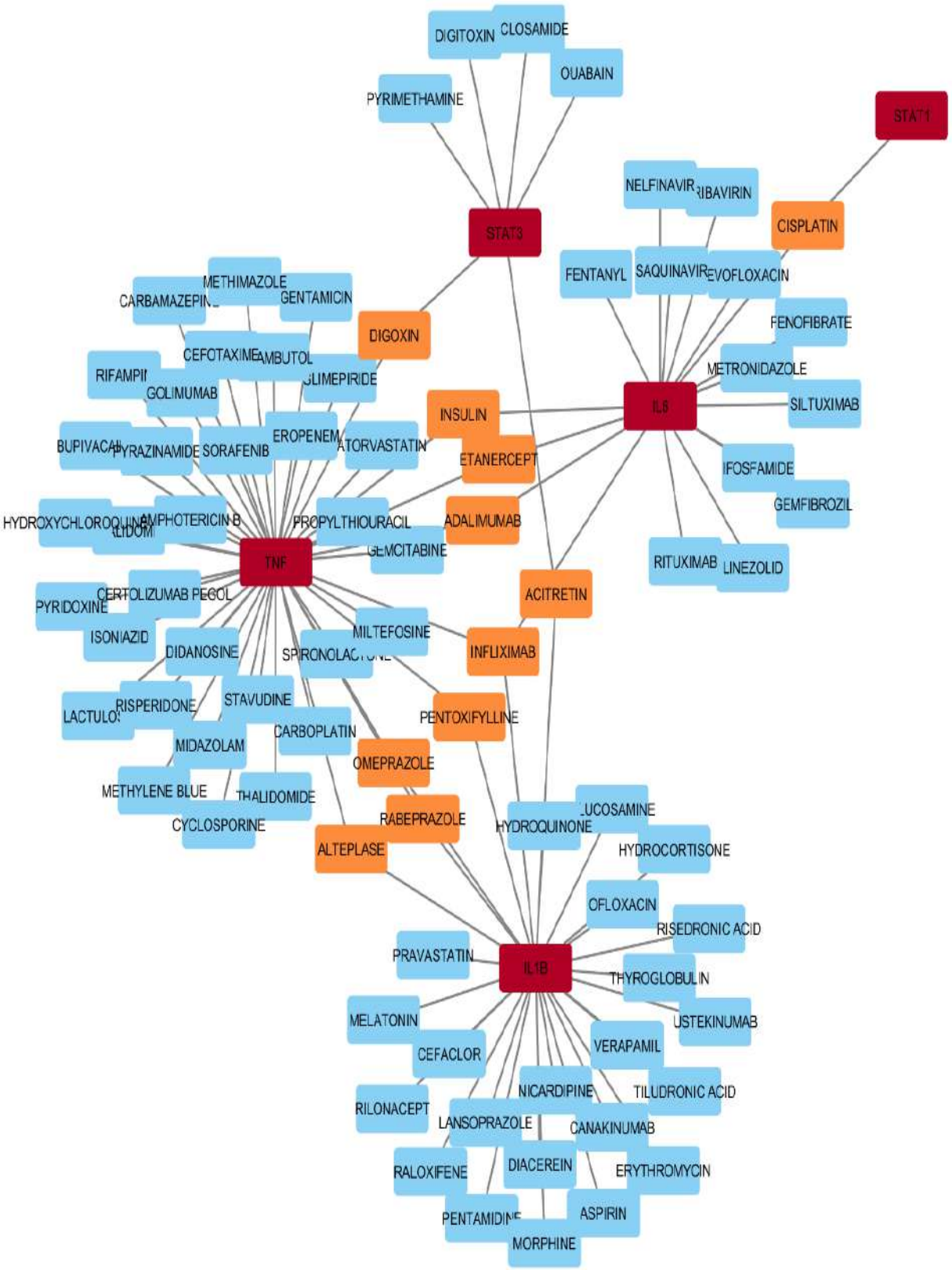
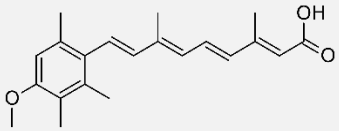
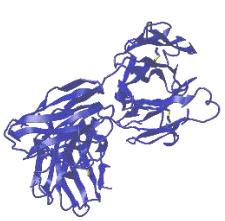
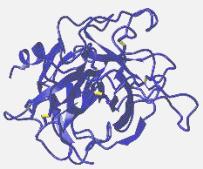
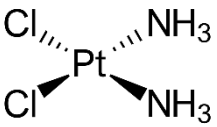
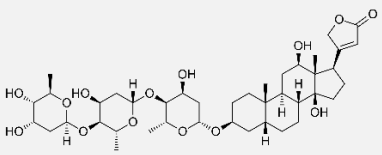
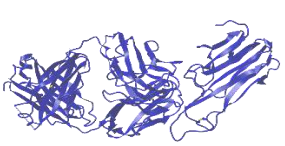
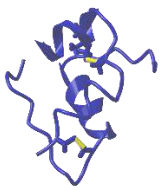
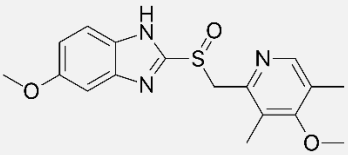
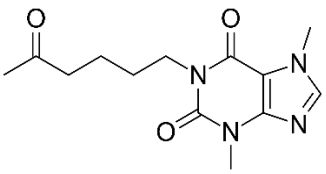
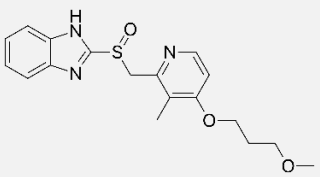


Figure 4. The Drug-Gene Network Which Was Created Using DGIdb. The Red Color Represents Key Genes, Blue Color Corresponds to Drugs, and Drugs That Affect more than One Gene Are Indicated in Orange.

A total of 11 drugs were identified as having multiple interactions with genes. These medications include Adalimumab, Insulin, Etanercept, Rabeprazole, Pentoxifylline, Alteplase, Infliximab, Acitretin, Digoxin, Omeprazole, and Cisplatin. Among the drugs under consideration, only Infliximab is linked with three specific genes, including TNF, IL1B, and IL6. Regarding the remaining medications, it has been established that Acitretin exhibits an association with IL1B and STAT3, Adalimumab is linked to TNF and IL6, Alteplase is associated with TNF and IL1B, and Cisplatin is related to IL6 and STAT1. Moreover, Digoxin exhibits a connection with TNF and STAT3. Furthermore, the drugs Etanercept and Insulin have been associated with the pro-inflammatory cytokines TNF and IL6. Also, it is worth noting that Omeprazole, Pentoxifylline, and Rabeprazole exhibit a relationship with TNF and IL1B (Table 1).

Table 1. Drugs That Associated with Major Depressive Disorder (MDD) Key Genes, Their Structure and Summary of Function

Drug	Structure	Associated Genes	Function on MDD	Summary of Function and Application
Acitretin		IL1B, STAT3	Protective	A retinoid, which is a derivative of vitamin A, is now being used to treat psoriasis. Acitretin, like other retinoids, can cause an increase in serum aminotransferase levels.
Adalimumab		TNF, IL6	Protective	Adalimumab, a monoclonal antibody and TNF inhibitor, eliminates inflammation. Adalimumab, which inhibits the activation of TNF receptors, is used for treating several autoimmune diseases.
Alteplase		TNF, IL1B	Protective	Alteplase is a thrombolytic agent derived from recombinant DNA technology. The FDA approved the use of this medicine in cases of thrombosis.
Cisplatin		IL6, STAT1	Detrimental	Cisplatin is an antineoplastic and chemotherapeutic medication employed in the treatment of several types of cancers. Cisplatin interferes with DNA replication, leading to the death of cells that have a high rate of reproduction.
Digoxin		TNF, STAT3	Detrimental	Digoxin is a medication employed for the treatment of cardiac failure, certain irregular heart rhythms, and induces abortion. This medicine is classified as a cardiac glycoside.

Etanercept	 *	TNF, IL6	Protective	Etanercept is a biopharmaceutical that is employed for the treatment of immune-mediated diseases. This chemical works by inhibiting TNF.
Infliximab	 *	TNF, IL1B, IL6	Protective	The chimeric monoclonal antibody infliximab is effective in treating autoimmune disorders. This encompasses Crohn's disease, ulcerative colitis, and other related medical diseases.
Insulin	 *	TNF, IL6	Detrimental	Pharmaceutical insulin refers to any version of the protein hormone insulin that is utilized to manage elevated levels of glucose in the bloodstream.
Omeprazole		TNF, IL1B	Protective	Omeprazole is a drug that falls under the category of proton-pump inhibitors (PPIs).
Pentoxifylline		TNF, IL1B	Protective	Pentoxifylline, a vasoactive agent and xanthine derivative is used as a pharmacological intervention to relieve muscular discomfort in persons diagnosed with peripheral artery disease. The method of action includes decreasing the thickness of blood, hence improving blood circulation.
Rabeprazole		TNF, IL1B	Protective	Rabeprazole is classified as an antiacid medication and plays a role in the treatment of conditions like gastroesophageal reflux disease.

* 3D structures were retrieved from NCBI structure (https://www.ncbi.nlm.nih.gov/structure).

Discussion

In light of our findings, five genes including TNF, IL1B, IL6, STAT1, and STAT3 can be identified as key genes in depression development. We hypothesize that these genes participate in both the development and progression of MDD's behavioral symptoms. They regulate the fundamental molecular processes that contribute to the initiation and progression of depression. Multiple medications have an impact on the genes. Eleven drugs that affect more than one gene were identified. These drugs consist of Adalimumab, Insulin, Etanercept, Rabeprazole, Pentoxifylline, Alteplase, Infliximab,

Acitretin, Digoxin, Omeprazole, and Cisplatin. We hypothesize some components provide protective functions, whereas others have deleterious consequences. TNF, known as a pre-inflammatory cytokine, has multiple effects on innate and adaptive immunological functions (13). TNF is ubiquitously distributed in the human body and plays a pivotal role in the pathogenesis of various disorders as well as the physiology of the immune system. This cytokine is released by phagocytes, CD4+ T cells, and natural killer cells. More TNF or an unusual quantity of it can cause or make worse the inflammation and cancer diseases (14). In addition, an increase in intracerebral expression of TNF during brain injuries has been shown in several studies (15, 16). Depression has been demonstrated to be related to TNF increase. Preclinically, if animals have intracerebroventricular micro infusion near the hippocampus, they show signs of depression (17). Moreover, many studies have reported increasing TNF levels in human patients with depression (18-25).

It has been demonstrated that increased TNF-α levels are strongly linked to higher availability of the serotonin transporter (5-HTT). Additionally, administering a TNF inhibitor is connected to reduced 5-HTT availability (26). Furthermore, TNF can change the brain neuroplasticity and reduce neurogenesis (17).

The cytokine TNF-α significantly impacts various cell types. The molecule controls inflammatory reactions and contributes to autoimmune and inflammatory diseases (27). In a study, MDD patients were proven to have higher serum TNF-α levels than the control group. Patients reported significant symptom improvements and reduced TNF-α levels after using antidepressants. Recent research links depression to TNF-α activation, which can predict antidepressant response in persons with MDD (28).

Adalimumab is an anti-inflammatory drug which decreases the release of TNF-α (12, 13). Etanercept, a TNF-α inhibitor, reduces depressive-like symptoms without impacting locomotor activity, suggesting a function for TNF-α in emotional regulation (29). In a study, Rabeprazole was found to dramatically lower TNF-α levels; however, Rabeprazole-induced hypergastrinemia could result in neuropsychiatric side effects and regulate behaviors altered in depression, anxiety, and dementia (30). Pentoxifylline (POF) inhibits lipopolysaccharide (LPS)-stimulated human monocytes' TNF-alpha production (31). Pentoxifylline may reduce depression through multiple pathways, according to the idea. These include neuroinflammation inhibition, oxidative stress reduction, cerebral blood flow augmentation, and neurotrophic factor synthesis (32, 33). A study by Wang *et al*. found that alteplase-based intravenous thrombolysis for acute cerebral infarction enhanced therapeutic effectiveness, inflammatory responses, brain damage, and depression symptoms (34). Infliximab, a chimeric monoclonal antibody medication, targets TNF-α. Infliximab reduced HAM-D depressed symptoms, especially in patients with increased inflammatory genes like TNF and CRP 32 (35). Digoxin has been shown in an in-vivo study to suppress proinflammatory cytokines like IL-17, IL-1β, IL-6, TNF-α, and IL-21, suggesting that it may also improve MDD (36). Co-administrated of capecitabine and omeprazole significantly reduces TNF-α induction, suggesting a relationship with reduced symptoms of MDD (37). In contrast, some medications might trigger inflammation and elevate levels of inflammatory markers. For instance, Cisplatin, when administered in large doses, might cause nephro-inflammation, and therefore, its use should be restricted in patients with MDD (38).

IL1B has a major impact in immune induction and the inflammatory process (39). It regulates the body's reaction to infections, injuries, and immune challenges, both on a systemic and local level. IL1B provides this by activating lymphocytes, causing a fever, and assisting in migrating white blood cells to the injured or infected sites (40). Notably, IL1B has been widely studied in mental studies, such as the association between depression and genetic polymorphisms (41). Increasing intracerebral amounts of IL1B have been detected as a crucial mediator in the inflammation process of brain injuries (15). Among the cytokines, IL1B plays an important role in MDD. Exogenous administration of IL1B causes some depression symptoms, such as changes in sleep patterns or anorexia (42). These behavioral changes are related to activating the hypothalamic-pituitary-adrenal axis seen in MDD patients (43, 44).

The Nod-like receptors family pyrin domain containing 3 (NLRP3) inflammasome, a key regulator of IL1B maturation, has been implicated in MDD pathophysiology. Autophagy, a cellular degradation pathway, plays a crucial role in preventing increased activation of the NLRP3 inflammasome and subsequent neuroinflammation. This regulation of NLRP3 may be associated with the pathogenesis of MDD (45).

We found that Omeprazole, Rabeprazole, Acitretin, Infliximab, Pentoxifylline, and Alteplase can be effective in treating MDD due to their impact on ILIB. Omeprazole decreases oxidative stress, thereby releasing IL1B (46). Rabeprazole prevents cell pyroptosis caused by an infection or other cell-damaging factors by inhibiting the release of IL1B. This medication accomplishes this purpose by suppressing the GSDMD-induced pyroptosis. (47). Acitretin inhibits both proliferation and inflammation, so it can reduce IL1B secretion (48). Infliximab is a fully-humanized monoclonal antibody that functions by suppressing the activity of TNF-α and IL1B (49). Pentoxifylline also inhibits IL1B (50). Furthermore, in a study, researchers showed that the use of Alteplase can prevent depression after a stroke (51). Overall, these medications have the potential to prevent the progression of MDD due to their ability to reduce IL1B and act as a protective factor.

IL-6 family cytokines have been related to a wide range of roles, such as activation of B-cell activity and the acute phase protein creation induction in the liver. They are also

involved in metabolic and neurological activities (52). Research in clinical and animal contexts has shown that higher levels of IL-6, whether in the peripheral or central nervous systems, are linked to the development of MDD (53). For example, three meta-analyses have indicated that patients with MDD exhibit distinctly different levels of IL-6 compared to those without MDD (54-56). This could be related to stimulation of the hypothalamic-pituitary-adrenal axis or changes in neurotransmitter metabolism (53). Also, studies indicate that IL-6 levels lower than normal at admission are correlated with more favorable treatment outcomes, whereas higher baseline IL-6 is associated with less favorable outcomes. This indicates that managing IL-6 levels might improve overall treatment outcomes (57).

IL-6 signaling occurs via two pathways: the membrane-bound IL-6 receptor (IL-6R) and the soluble IL-6 receptor (sIL-6R) trans-signaling (58). While IL-6R signaling has anti-inflammatory effects, sIL-6R trans-signaling primarily mediates pro-inflammatory functions (59). Elevated levels of IL-6 and sIL-6R have been observed in depressed patients, suggesting their involvement in MDD pathogenesis (60). IL-6 affects multiple systems, including the hypothalamic-pituitary-adrenal axis, tryptophan metabolism, and oxidative stress, contributing to depression symptomatology (59).

We found that Cisplatin, Infliximab, Adalimumab, Etanercept, and Insulin can be effective in the treatment of MDD due to their effect on IL-6. Cisplatin has been observed to elevate the IL-6 level (61). Infliximab has been demonstrated to have a decreasing effect on IL-6 in Human Osteoblastic Cells (62). Similarly, Adalimumab and Etanercept have shown the ability to reduce IL-6 levels (63, 64). Additionally, a study found that 100 ng Insulin can stimulate a 2.3-fold increase in IL-6 mRNA expression (65).

STAT3 is a critical signaling molecule that responds to a diversity of cytokines and growth factors, resulting in a range of biological outcomes including cellular growth, differentiation, and survival (66). There is in-vivo evidence indicating that STAT3 may be involved in the appearance of depressive-like behaviors. Moreover, there is a correlation between genetic variations in the human STAT3 gene and an individual's responsiveness to antidepressant medications (67-69). In addition, the STAT3 protein plays a significant role in determining whether T-cells develop into regulatory T-cells (Treg) or inflammatory T-cells (Th17). The formation of Th17 cells has been associated with the development of neurodegenerative diseases (NDDs). Furthermore, the Janus Kinase2 (JAK2)/STAT3 pathway, activated by pro-inflammatory cytokines, contributes to neuroinflammation and neuronal apoptosis in neurodegenerative diseases (70).

Acitretin modulates the proliferation of keratinocytes by regulating the STAT3 signaling pathways (71). It is critical to note that there are no clinical trials that have conclusively shown a causal relation between Acitretin use and the development of depression or suicidal ideation. Hence, it can be inferred that the correlation between acitretin and affective disorders is more accurately characterized as a classification based on shared characteristics rather than a scientifically substantiated causal relationship (72). The phosphorylation of Src and the associated EGFR/STAT3 pathway are suppressed by Digoxin in diverse lung cancer cell types (73). Although cardiac glycosides, including digoxin, have been implicated in the development of various psychiatric disorders, the evidence is largely anecdotal, and there is a lack of high-quality prospective trials. It is important to consider that patients receiving either β-blockers or digoxin frequently have comorbid heart failure, which can cause mood disorder (74). Depression associated with the use of digoxin, similar to other mood syndromes linked to cardiovascular medications, is characterized by prominent fatigue, reduced appetite, and impaired sleep (75).Results of a recent study showed that in a group of depressed patients, there was an observed upregulation of JAK3 and a decrease in the expression of STAT1 (76). Furthermore, compared to the control group, the expression of some immune-related genes, such as STAT1 and CCL2, were dramatically increased in MDD patients (77).

Cisplatin, a chemotherapy agent with cytotoxic properties, is frequently used in the treatment of different solid tumors. It has been observed that the administration of cisplatin leads to the phosphorylation of STAT1, thereby inducing tumor cell death (78). The results of Abdelkader *et al*. indicated that nebivolol could be a promising method for reducing the depressed symptoms associated with cisplatin use (38). In rats treated with cisplatin and exhibiting symptoms of sadness, elevated depressive-like behaviors were reported (79).

Some studies explored genetic factors associated with MDD, including many meta-analyses and genome-wide association studies (GWAS). The studies explored genetic factors associated with MDD through meta-analyses and genome-wide association studies (GWAS). Lopez-León *et al*. identified six MDD susceptibility genes (APOE, DRD4, GNB3, MTHFR, SLC6A3, and SLC6A4) through meta-analyses of candidate gene studies (80). However, Bosker *et al*. found poor replication of these candidate genes using GWAS data, with only four genes (C5orf20, NPY, TNF, and SLC6A2) showing significant associations (81). The results reported by Chang *et al*. include protein coding genes involved in neuronal signaling and structure, such as glutamate receptors (GRM1, GRM7), GABA receptors (GABRA2, GABRA4), and neurotrophic factors (BDNF, RELN), providing insights into potential molecular mechanisms of MDD (82). As it is clear, there are both differences and similarities between these studies' results and also findings of the current study, which can be explained by the extent of genes and factors that have a place in the pathogenesis of depression.

Based on our findings, inflammatory genes and pathways play an undeniable role in the pathogenesis and development of MDD. It may guide us to the relationship between depression and diseases that these pathways are highly activated such as cancers, autoimmune, and chronic diseases. MDD is remarkably more prevalent and related to reduced survival in these patients (83, 84). The findings of this study may offer new insights into the mental health care of the mentioned patients and also all people who suffer from MDD. On the other hand, these genes and their related pathways can play a role as new targets for designing medications against depression.

Limitation

In this computational study, the absence of clinical and experimental data underscores the need for additional research. Specifically, further investigations are warranted to fully explore the therapeutic efficacy of these drugs in treating MDD.

Conclusion

MDD is known as one of the most prevalent and disabling psychiatric disorders. Our findings suggest five hub genes that play a critical role in depression pathogenesis: TNF, IL1B, IL6, STAT1, and STAT3. These genes could be ideal targets for innovative therapeutic strategies, including drug development. In conclusion, Acitretin, Adalimumab, Alteplase, Etanercept, Infliximab, Omeprazole, Pentoxifylline, and Rabeprazole can potentially improve MDD. In clinical settings they may be drugs of choice over similar drugs in patients with comorbid MDD due to their dual efficacy in addressing both the primary condition and depressive symptoms. However, Cisplatin, Digoxin, and Insulin may play a detrimental and harmful role in depression. Our study provides promising results and pave the path for future researchers to find more efficient and novel treatments for depression, which will enhance the living quality of MDD patients. Additionally, further studies are necessary to explore the therapeutic potential of these drugs for the treatment of MDD.

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Conflict of Interest

None.

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