Review Paper:

Network Pharmacology Tools used in Identification of Depression Targets

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Abstract

A common and major psychological disorder called depression is characterized by persistent sadness and hopelessness as well as a lack of interest in or enjoyment from routine activities. Millions of people are impacted globally and it interferes with their capacity to go about their daily lives. Depression involves a complicated etiologic that includes genetic, metabolic, environmental and psychological components. Emotional dysregulation, cognitive decline, physical discomfort and behavioural abnormalities are the signs. A combination of medical treatment, psychotherapy and lifestyle changes is usually used in effective treatment. Comprehending the complex nature of depression is vital in order to develop more efficacious therapies and provide comprehensive support to people affected. Depression is difficult to treat since there is a wide range of symptoms, making diagnosis difficult.

Furthermore, depression frequently co-occurs with other health conditions, making treatment more difficult and not everyone has access to mental health services. The branch of network pharmacology is an emerging field which integrates systems biology, bioinformatics and pharmacology to understand the complex interactions existing between targets, medications, protein-protein interactions, biological networks. Rather than focusing on individual drug-target interactions, network pharmacology takes into account several targets and pathways in order to offer a comprehensive understanding of drug action and disease mechanisms. By identifying complex biological networks, this method decreases side effects, estimates synergistic effects and makes it easier to identify possible multi-target medications. It has potential use in medication repurposing, personalized treatment and the creation of more potent therapeutic approaches.

Keywords: Depression, Genetics, Psychotherapy, Network Pharmacology, Bioinformatics, Protein-Protein Interactions, Drug-target interaction.

Introduction

Depression is one of the most common mental disorders. Approximately one in five people at some point in life suffer a depressive episode, making depression one of the most prevalent mental illnesses. The World Health Organization (WHO) estimates that 128 million people globally experienced depression in 2023[18]. The average age at which depression first appears, ranges from 24 to 35 years, with a mean age of 27 years, among population samples drawn from populations aged 18 to 64 years globally. There is presently a trend toward depression onset occurring at younger ages.

Age impacts the symptoms of depression. Children and adolescents with depression are more likely to experience 'atypical' symptoms such as hypersomnia and overeating, while elderly patients with depression are more likely to experience melancholia's depressive features such as loss of interest or pleasure, lack of reactivity and insomnia. Childhood depression is typically characterized by a greater number of somatic complaints along with irritability and social withdrawal[15]. A number of proposals have been made to divide the MD diagnosis into subtypes according to symptom profiles. The most common proposal is to distinguish depression with reverse-vegetative symptoms (weight gain, hypersomnia, increased hunger) and depression with vegetative symptoms (weight loss, sleeplessness, appetite loss etc.)[12].

With a lifetime risk of over 20%, depression is a very common psychiatric illness that is linked to high rates of morbidity and mortality. Patients with depression are more likely to experience major physical health issues such as diabetes and coronary artery disease, as well as a worsening of the prognosis of other illnesses[19]. Medications can be used to treat depression in an effective manner. 65% to 75% of individuals will experience improvement with appropriate antidepressant medication. At the moment, there are three primary groups of antidepressant drugs: tricyclic and similar cyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and other compounds used for treating depression. such as monoamine oxidase inhibitors (MAOIs)[24]. A prevalent and serious psychological condition, depression is marked by a persistently depressed mood, cognitive impairment and decreased social functioning. The pathogenesis of this condition is complicated, but increasing evidence indicates the involvement of neurotrophic factors, inflammatory cytokines, the hypothalamus-pituitary-adrenal axis and glutamate receptors[4].

Pathophysiology of Depression: Depression is linked to an increased risk of premature mortality. The illness is highly

comorbid with medical problems linked to higher mortality including cancer, cardiovascular and autoimmune diseases[14]. Severe depression may be caused by a reduction in dopaminergic neurotransmission. The physiological changes that characterize decreased dopamine (DA) signalling may be caused by either decreased DA release from presynaptic neurons or poor signal transduction as a consequence of changed intracellular signal processing, altered receptor number or function, or both[6]. The ability of the brain to structurally adjust to changes in the internal or external environment is known as neuroplasticity. An essential neuromodulators transmitter with unique neuroplastic properties is serotonin.

Naturally, studies indicate that disruption of synaptic plasticity together with neuronal degeneration and cell death contributes to the pathophysiology of depression, even though synaptic plasticity is a well-known critical mechanism in learning and memory[10].

The development and adaptability of neural networks are crucially regulated by neurotrophic factors. Human serum and plasma both contain high concentrations of brain-derived neurotrophic factor (BDNF), which is widely distributed in the brain and its surrounding tissues. Stress dysregulates the expression of BDNF, according to research on animals. According to the neurotrophic hypothesis about depression, lower brain BDNF levels are linked to depression[13].

Pharmacotherapy of Depression: The first monoamine oxidase inhibitor (MAOI) and monoamine reuptake inhibitor (MAOI) antidepressants were developed in 1957 with the introduction of imipramine and iproniazid[3]. (R, S)-Ketamine, also referred to as ketamine, is an N-methyl-D-aspartate receptor (NMDAR) antagonist which is noncompetitive. Since ketamine binds to NMDAR at low concentrations, NMDAR has been suggested as a potential pharmacological target for the antidepressant effects of ketamine[11].

The ultimate goal of patient management is functional recovery which can be attained through the use of therapies that are recovery-oriented, integrated and customized. There are currently a number of advanced pharmacological and other therapies available; interventions should be selected depending on the needs of the patient[23].

Anti-depressant drugs are classified in 3 categories[1].
1) Selective Serotonin Reuptake inhibitor (SSRIs)
2) Monoammino Oxidase Inhibitor (MAOIs)
3) Tricyclic Anti-depressants (TCAS)

Limitation of current anti-depressant: Atypical and typical anti-depressants now on the market function by preventing the synaptic reuptake of biological amines (dopamine, 5-HT and NE) and increasing the availability of monoamine neurotransmitter at post-synaptic receptors.

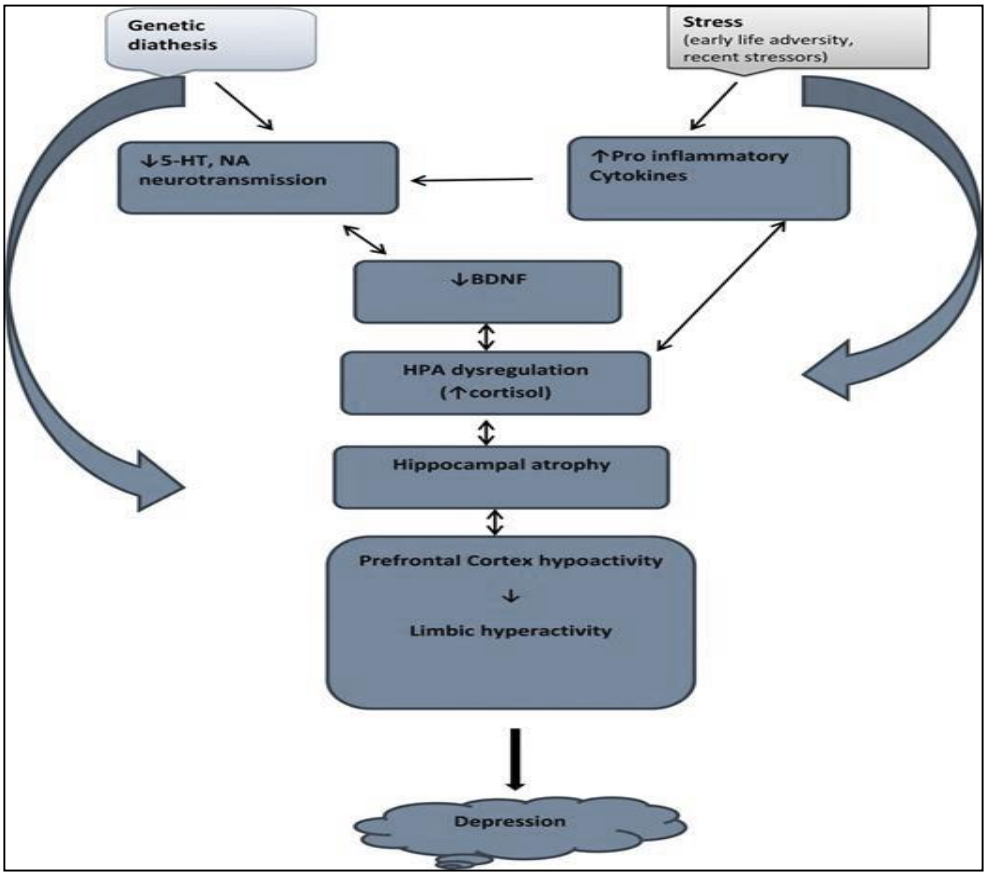

Fig. 1: Pathophysiology of Depression

The primary drawback of modern antidepressants is their slow onset of action, which might increase depression symptoms during the first week of treatment until the 5-HT1A receptor becomes desensitized. Alteration of specific biomarkers is characteristic of mental illness. Depressive patients have been found to have elevated levels of inflammatory cytokines, such as TNF-α, IL-6, IL-1β and C-reactive protein (CRP), in their blood. In addition, the amygdala volume, plasma cortisol level and HPA axis are dysregulated and the prefrontal cortex, hippocampal volume and BDNF level are all decreasing[20].

Network Pharmacology: The term "network pharmacology" was initially introduced in 2007. This approach uses system biology to examine medication intervention and possible therapeutic targets for various diseases. A paradigm change from the existing "one target, one drug" approach to a fresh variation of the "network target, multi-component" technique is highlighted by network pharmacology[8]. Currently, safety, efficacy and sustainability are major obstacles for the one-drug, one-target, one-disease approach to drug discovery.

Approaches based on network biology and polypharmacology have lately acquired popularity as techniques for multitarget drug development and integrating omics data respectively. By combining these two methods, a unique paradigm known as network pharmacology (NP) was developed, which examines how medications affect both the interactome and the diseasome level[5]. Table 2 represents the different network pharmacology tools used in target identification and target validation in drug discovery[25].

We studied depression related targets where we used the different database like UniProtKB, GeneCodis, STRING and Cytoscape.

1) UniProtKB (https://www.uniprot.org/): The primary source for comprehensive protein sequence annotations is UniProtKB[16]. The Universal Protein Resource (UniProt) consortium is composed of the Protein Information Resource (PIR), the European Bioinformatics Institute (EBI) and the Swiss Institute of Bioinformatics (SIB). Its principal objective is to give the scientific community a single source for functional data and protein sequences[2]. The homepage of UniProtKB taken from webside is shown in fig. 1.

UniProtKB is functional database for identification of protein targets associated with different diseases. In the homepage search option, we take depression as example for that we identified depression related targets. There are different species option shown in that we choose human in that there are 90 gene associated with depression shown in fig. 2 and all 90 targets protein with name are shown in table 3.

Table 1
Classes antidepressant with brand Names

S.N.	SSRIs	TCAs	MAOIs
1	Fluoxetine (Prozac)	Doxepin(Sinequan)	Phenelzine(Nardil)
2	Fluvoxamine(Luvox,Faverin)	Nortryptyline(Nortrilen)	Isocarboxacid(Marplan)
3	Citalopram (Celexa)	Protryptyline(Vivactil)	Tranylcypromine(Parnate)
4	Escitalopram(Lexapro,Cipralex)	Amytryptylin(Elavil)	Moclobemide(Amira,Depnil)
5	Sertraline (Zoloft, Lustral)	Desipramine(Norpramin)	Salegiline(Emsam)

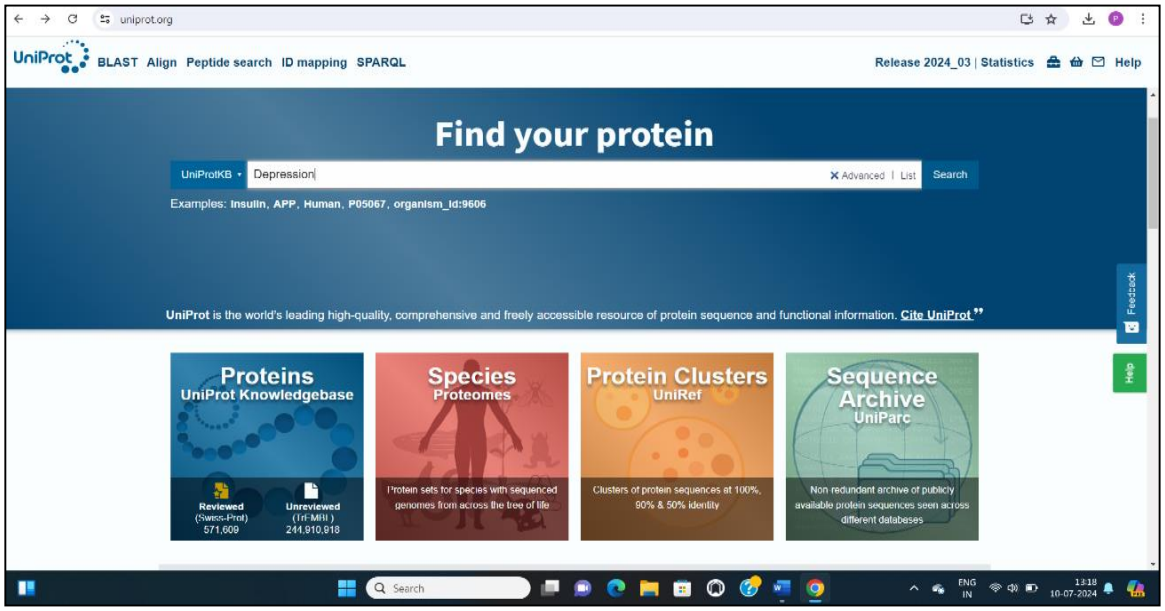

Fig. 2: Homepage of UniProtKB

Table 2
Representative data resources in NP

Data Resources	Logo	Brief Description	Published Year
KEGG		Relationships among genes and genomes	1999
STRING		Relationships among proteins	2003
DrugBank		Relationships between drugs and targets	2008
PubChem		Relationships among small molecules	2009
PDB		3D Structure of protein	1971
DrugCentral		Relationships between drugs and targets	2016
ChEMBL		Relationships among bioactive molecules with drug-like properties	2019
BioGRID		Relationships among proteins	2021
GeneCodis		Relationship among Enrichment analysis-Biological Pathway, Functional Pathway, Cellular Pathway	2016
UniProtKB		Protein Sequence and function information	2002
Cytoscape		Analysing complex Network	2003
AutoDock Vina		For Molecular Docking	2010
Discovery Studio		Molecular modeling, simulation and visualization	2005

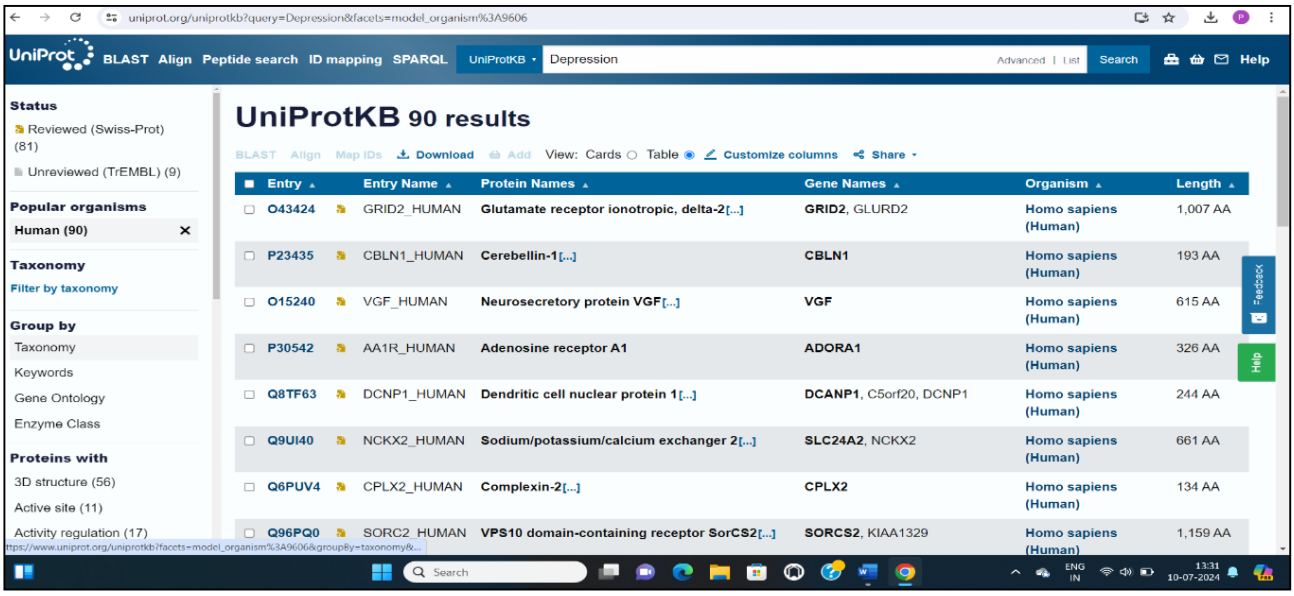

Fig. 3: 90Targets associated with Depression

Table 3
90 gene targets associated with depression

S.N.	Entry	Gene Names	Organism	Length
1	A0A087WV00	DGKI	Homo sapiens (Human)	1057
2	A0A0K0K1K3	HEL-S-172mP ADCY8 hCG_2008967	Homo sapiens (Human)	1251
3	A0A0U1RQS4	SHANK3	Homo sapiens (Human)	1607
4	A6NNN8	SLC38A8	Homo sapiens (Human)	435
5	O14672	ADAM10 KUZ MADM	Homo sapiens (Human)	748
6	O15240	VGF	Homo sapiens (Human)	615
7	O43424	GRID2 GLURD2	Homo sapiens (Human)	1007
8	O60721	SLC24A1 KIAA0702 NCKX1	Homo sapiens (Human)	1099
9	O75912	DGKI	Homo sapiens (Human)	1065
10	O76024	WFS1	Homo sapiens (Human)	890
11	O76090	BEST1 VMD2	Homo sapiens (Human)	585
12	O95264	HTR3B	Homo sapiens (Human)	441
13	P01210	PENK	Homo sapiens (Human)	267
14	P10636	MAPT MAPTL MTBT1 TAU	Homo sapiens (Human)	758
15	P11831	SRF	Homo sapiens (Human)	508
16	P12235	SLC25A4 AAC1 ANT1	Homo sapiens (Human)	298
17	P16615	ATP2A2 ATP2B	Homo sapiens (Human)	1042
18	P17861	XBP1 TREB5 XBP2	Homo sapiens (Human)	261
19	P20813	CYP2B6	Homo sapiens (Human)	491
20	P21728	DRD1	Homo sapiens (Human)	446
21	P21918	DRD5 DRD1B DRD1L2	Homo sapiens (Human)	477
22	P23435	CBLN1	Homo sapiens (Human)	193
23	P23560	BDNF	Homo sapiens (Human)	247
24	P26358	DNMT1 AIM CXXC9 DNMT	Homo sapiens (Human)	1616
25	P26367	PAX6 AN2	Homo sapiens (Human)	422
26	P28907	CD38	Homo sapiens (Human)	300
27	P30542	ADORA1	Homo sapiens (Human)	326
28	P31645	SLC6A4 HTT SERT	Homo sapiens (Human)	630
29	P34972	CNR2 CB2A CB2B	Homo sapiens (Human)	360
30	P40145	ADCY8	Homo sapiens (Human)	1251
31	P42261	GRIA1 GLUA1 GLUH1 GLUR1	Homo sapiens (Human)	906
32	P42262	GRIA2 GluA2 GLUR2	Homo sapiens (Human)	883
33	P46098	HTR3A 5HT3R HTR3	Homo sapiens (Human)	478
34	P49619	DGKG DAGK3	Homo sapiens (Human)	791
35	P53539	FOSB G0S3	Homo sapiens (Human)	338
36	P54098	POLG MDP1 POLG1 POLGA	Homo sapiens (Human)	1239
37	P60484	PTEN MMAC1 TEP1	Homo sapiens (Human)	403
38	P61764	STXBP1 UNC18A	Homo sapiens (Human)	594
39	P78352	DLG4 PSD95	Homo sapiens (Human)	724
40	P84077	ARF1	Homo sapiens (Human)	181
41	Q01814	ATP2B2 PMCA2	Homo sapiens (Human)	1243
42	Q06787	FMR1	Homo sapiens (Human)	632
43	Q12959	DLG1	Homo sapiens (Human)	904
44	Q13224	GRIN2B NMDAR2B	Homo sapiens (Human)	1484
45	Q13255	GRM1 GPRC1A MGLUR1	Homo sapiens (Human)	1194
46	Q14203	DCTN1	Homo sapiens (Human)	1278
47	Q14289	PTK2B FAK2 PYK2 RAFTK	Homo sapiens (Human)	1009
48	Q14416	GRM2 GPRC1B MGLUR2	Homo sapiens (Human)	872
49	Q14721	KCNB1	Homo sapiens (Human)	858
50	Q15109	AGER RAGE	Homo sapiens (Human)	404
51	Q5JU85	IQSEC2 KIAA0522	Homo sapiens (Human)	1488
52	Q6DN90	IQSEC1 ARFGEP100 BRAG2 KIAA0763	Homo sapiens (Human)	963

53	Q6IB77	GLYAT ACGNAT CAT GAT	Homo sapiens (Human)	296
54	Q6P1N0	CC2D1A AKI1 LGD2	Homo sapiens (Human)	951
55	Q6PUV4	CPLX2	Homo sapiens (Human)	134
56	Q6ZSJ9	SHISA6	Homo sapiens (Human)	500
57	Q7LC44	ARC KIAA0278	Homo sapiens (Human)	396
58	Q7LG56	RRM2B P53R2	Homo sapiens (Human)	351
59	Q8IWU9	TPH2 NTPH	Homo sapiens (Human)	490
60	Q8N423	LILRB2 ILT4 LIR2 MIR10	Homo sapiens (Human)	597
61	Q8N5K1	CISD2 CDGSH2 ERIS ZCD2	Homo sapiens (Human)	135
62	Q8NER1	TRPV1 VR1	Homo sapiens (Human)	839
63	Q8TF63	DCANP1 C5orf20 DCNP1	Homo sapiens (Human)	244
64	Q8WU03	GLYATL2	Homo sapiens (Human)	294
65	Q96HC4	PDLIM5 ENH L9	Homo sapiens (Human)	596
66	Q96NW7	LRRC7 KIAA1365 LAP1	Homo sapiens (Human)	1537
67	Q96PQ0	SORCS2 KIAA1329	Homo sapiens (Human)	1159
68	Q96RR1	TWNK C10orf2 PEO1	Homo sapiens (Human)	684
69	Q99946	PRRT1 C6orf31 NG5	Homo sapiens (Human)	306
70	Q9BV23	ABHD6	Homo sapiens (Human)	337
71	Q9BYB0	SHANK3 KIAA1650 PROSAP2 PSAP2	Homo sapiens (Human)	1731
72	Q9HBJ8	CLTRN TMEM27 UNQ679/PRO1312	Homo sapiens (Human)	222
73	Q9NRD5	PICK1 PRKCABP	Homo sapiens (Human)	415
74	Q9NUL3	STAU2	Homo sapiens (Human)	570
75	Q9NYY3	PLK2 SNK	Homo sapiens (Human)	685
76	Q9UHN1	POLG2 MTPOLB	Homo sapiens (Human)	485
77	Q9UI40	SLC24A2 NCKX2	Homo sapiens (Human)	661
78	Q9UPX8	SHANK2 CORTBP1 KIAA1022 PROSAP1	Homo sapiens (Human)	1849
79	Q9Y232	CDYL CDYL1	Homo sapiens (Human)	598
80	A4D2P6	GRID2IP	Homo sapiens (Human)	1211
81	Q969I3	GLYATL1 GNAT	Homo sapiens (Human)	302
82	Q96CW6	SLC7A6OS	Homo sapiens (Human)	309
83	Q9UPU3	SORCS3 KIAA1059	Homo sapiens (Human)	1222
84	B3KM22		Homo sapiens (Human)	415
85	D6RCF4	CISD2	Homo sapiens (Human)	145
86	F6V107	PICK1	Homo sapiens (Human)	229
87	Q53HE0		Homo sapiens (Human)	415
88	A0A1U9X8D6		Homo sapiens (Human)	306
89	A9ZM15	GATF-C GLYATL1 hCG_1729956	Homo sapiens (Human)	302
90	Q8IZM0		Homo sapiens (Human)	81

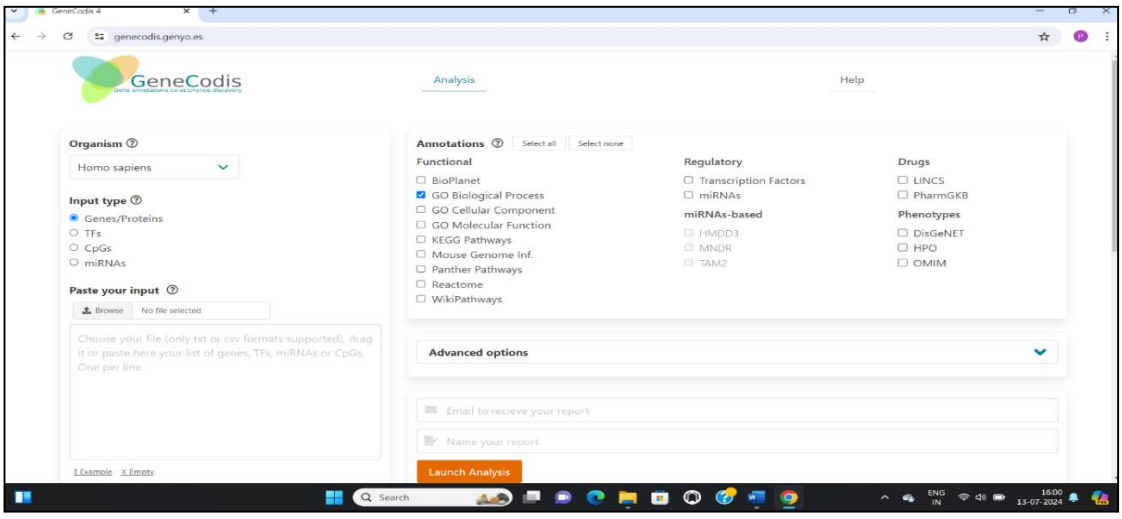

Fig. 4: Homepage of GeneCodis

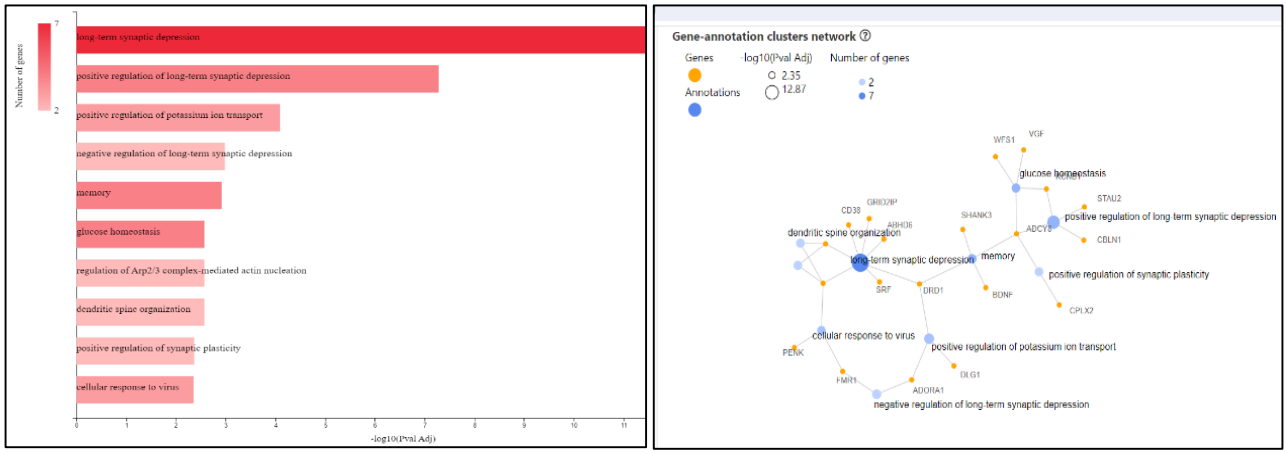

Fig. 5: Bar chart and Network Obtained from GeneCodis

Table 4
Depression Targets Biological Process Pathways obtained from GeneCodis

Description	Genes Count	Pval adj	Relative enrichment	Genes
long-term synaptic depression	Jul-17	1.35E-13	255.62	CD38,GRID2IP,ABHD6,DRD1,SRF,PI...
positive regulation of long-term synaptic depression	04-Jul	5.17E-08	354.74	ADCY8,KCNB1,STAU2,CBLN1...
positive regulation of potassium ion transport	03-Oct	8.15E-05	186.24	DRD1,DLG1,ADORA1
negative regulation of long-term synaptic depression	02-Mar	1.02E-03	413.86	FMR1,ADORA1
memory	Apr-87	1.20E-03	28.54	DRD1,ADCY8,BDNF,SHANK3...
glucose homeostasis	4/120	2.68E-03	20.69	ADCY8,KCNB1,WFS1,VGF...
regulation of Arp2/3 complex-mediated actin nucleation	02-Jun	2.68E-03	206.93	PICK1,ARF1
dendritic spine organization	02-Jun	2.68E-03	206.93	PICK1,ARF1

2) GeneCodis (https://genecodis.genyo.es): GeneCodis, a modular enrichment analysis program was designed to combine data from many sources and to identify enriched annotation combinations in big gene or protein lists[17]. Biological annotations that are overrepresented in a gene list relative to a reference list can be found using a commonly used technique called functional enrichment analysis. These significant annotations are then used to interpret the molecular pathways and biological mechanisms underlying the phenotype under study[9]. Gene Codis is for analysis of the biological process, cellular components, molecular functions, KEGG Pathway. Paste the input of protein or gene collected from UniProtKB. We take biological process for example of depression targets. The homepage of genecodis taken from webside is shown in fig. 3 and bar chart, network of protein is shown in fig. 4.

3) STRING (http://string-db.org): Several web resources are available for studying organism-wide protein association networks including the STRING database[22]. The goal of the STRING database is to offer an integrated and comprehensive evaluation of protein-protein interactions, encompassing both direct (physical) and indirect (functional) relationships[21]. In string database for identification of protein-protein interaction, paste the gene obtained from biological process in GeneCodis.

4) Cytoscape (https://cytoscape.org/): On the other hand, the Cytoscape program gives more versatility when it comes to network analysis, importing and visualizing more data, making it far more appropriate for handling big networks[7]. In Cytoscape, all network obtained from string was inserted into cytoscape software which gives information of all protein degree.

Conclusion

Bioinformatics is highly effective less time-consuming tool for target identification. By using the computational tools, targets are identified related to the different diseases. We have studied about different network pharmacology tools like string genecodis, cytoscape etc.

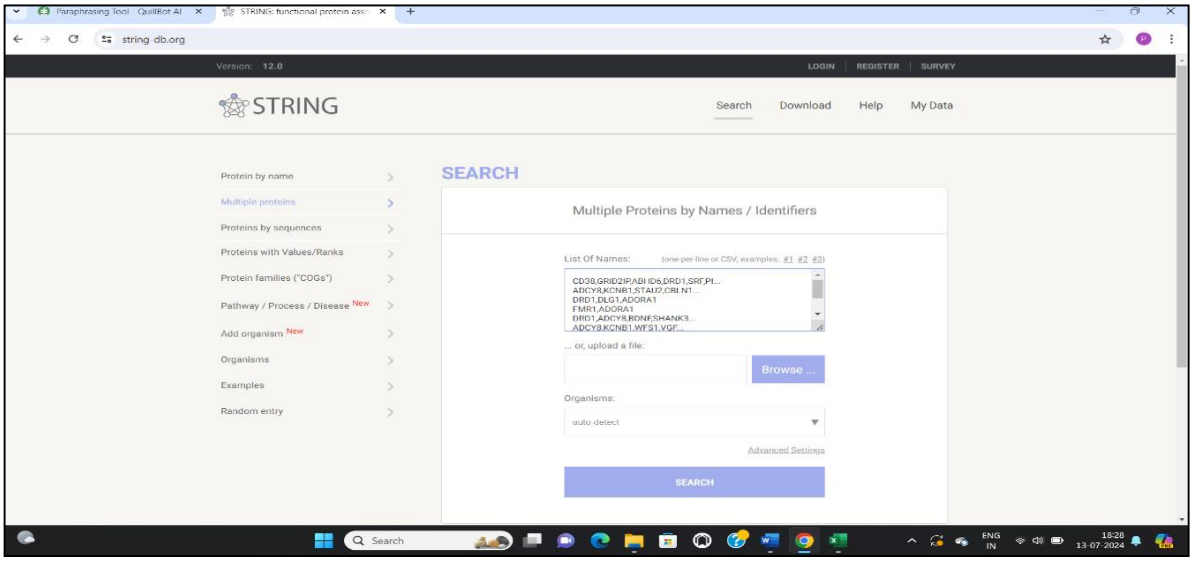

Fig. 6: Homepage of STRING

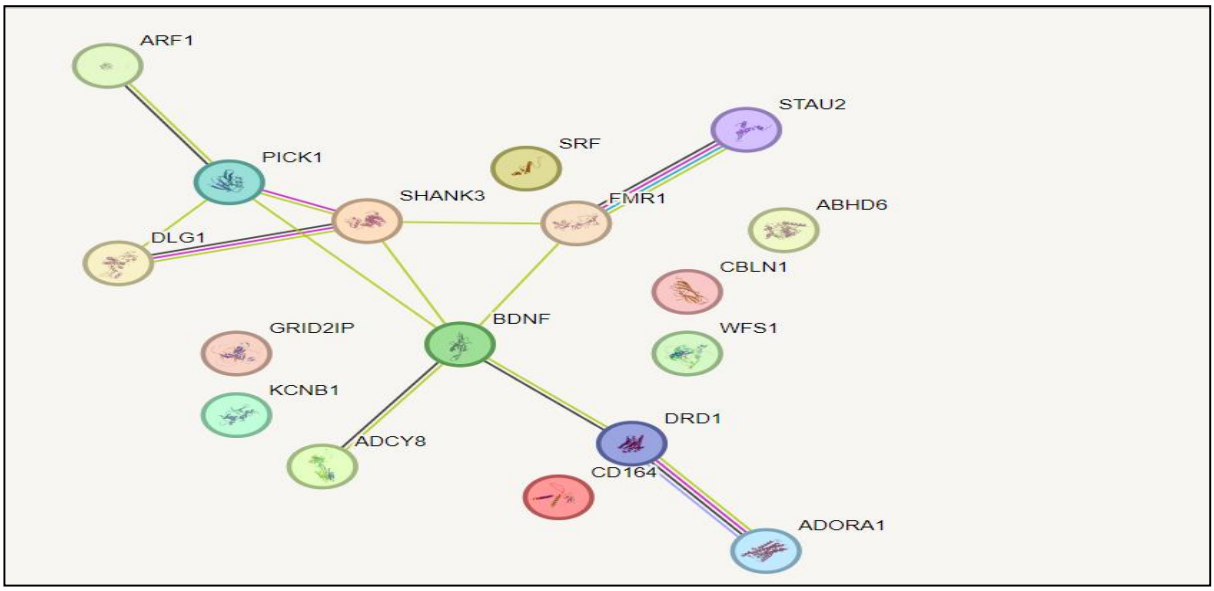

Fig. 7: Protein-Protein Network in STRING

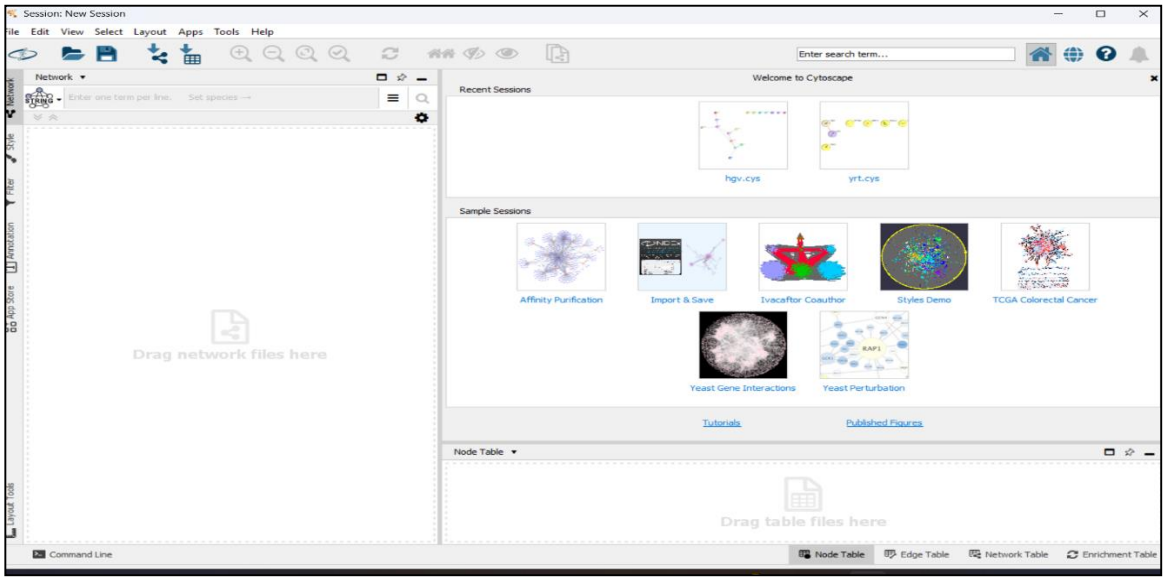

Fig. 8: Homepage of Cytoscape

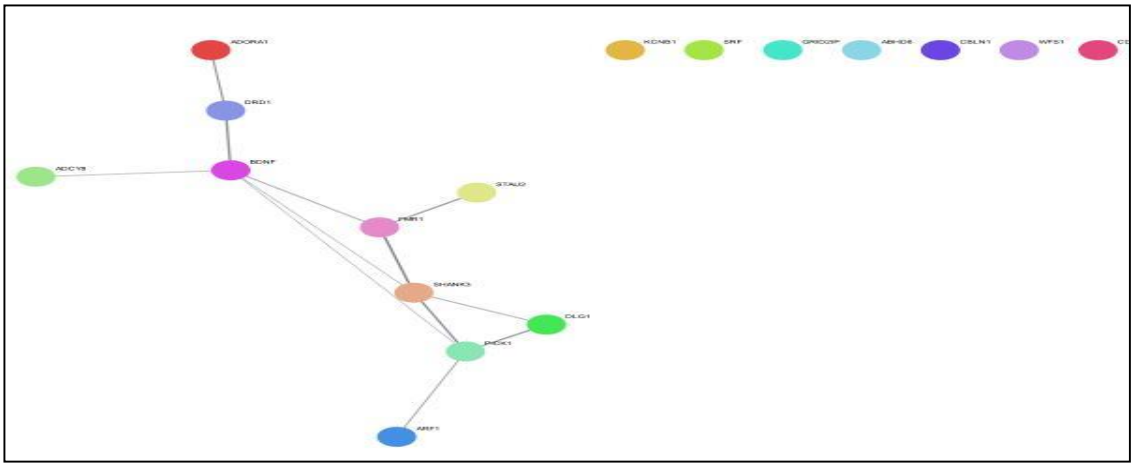

Fig. 9: Protein-Protein Network in Cytoscape

We identified depression related 90 target genes and all 90 targets paste in GeneCodis give the information about biological process, cellular components, molecular functions and their bar chart shows the major pathways involved in depression related targets. In biological process, different pathways were analysed and take nine targets from pathways for protein-protein interaction determination into the string. The network string shows the interaction between the ARF1, PICK1, DLG1, SHANK3, FMR1, STAU2, BDNF, DRD1, ADCY8, ADORA1 proteins. All protein network is exported to the cytoscape software and shows the cytoscape network of depression related targets and degree.

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