Drug Repurposing for Alzheimer's Disease based on Protein-Protein Interaction Network

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Abstract

Background: Alzheimer's disease (AD) is known as a critical neurodegenerative disorder. It worsens as symptoms concerning dementia grow severe over the years. Due to the globalization of Alzheimer's disease, its prevention and treatment is vital. This study proposes a method to extract substantial gene complexes and accomplish an enrichment analysis to introduce the most significant biological procedures. The next step is extracting the drugs related to AD and introduce some new drugs which may be useful for this disease.

Results: To this end, protein-protein interactions (PPI) network was utilized to extract five meaningful gene complexes functionally interconnected. The next step was to construct a five bipartite network representing the genes of each group and their target miRNAs. Finally, a complete network including all the genes related to each gene complex group and genes' target drug was illustrated. medical studies and publications were analyzed thoroughly to introduce AD-related drugs.

Conclusions: This analysis proves the accuracy of the proposed method in this study. Then, new drugs were introduced that can be experimentally examined as future work. RALOXIFENE, GENTIAN VIOLET are two new drugs, which have not been introduced as AD-related drugs in previous scientific and medical studies, recommended by the method of this study. These two drugs.

Background

Alzheimer's disease, as a significant disease, has attracted researchers, especially in recent decades. Our previous study utilized a gene co-expression network to extract the biomarkers, including genes and miRNAs related to Alzheimer's disease(1). This study develops protein-protein interactions (PPI) network and a different methodology to introduce the associated biomarkers and drugs. Interactions between proteins are influential in cellular functions. Functionally related proteins are in the identical complexes and organelles. Thus, uncovering this structure helps us recognize more about the role of genome variation in disease(2). Studying the association of cellular functions and disease has received less attention, while it is as significant as studying the association of cellular functions and protein complexes(3). Studying PPI networks helps us understand the nature of complicated disease as it can highlight significant proteins which can be used in drug designing(4). Many previous studies examined the relationship between disease and protein complexes. For example, in a paper with this context, the writer maintains that patients with some disorders especially concerning the nervous system have mutations in adaptor protein complexes(5). Another paper uses the PPI network of AD and Non-alcoholic fatty liver disease (NAFLD) to discover common pathways in these two diseases (4). Also, analyzing PPI networks in AD and Parkinson's disease illustrates that similar proteins in the identical clusters have analogous ontology and sequence different from other clusters(6). Another related study combines gene network information with brain-tissue proteins interactions and finds effective clusters of genes in AD and expression levels in this disease(7). Many studies in computational biology aim to figure out biomarkers in different diseases, especially in cancer. For instance, there is a study that introduces

biomarkers in breast cancer(8). Reviewing the previous studies indicates that protein complexes are not widely used to find effective genes and related drugs, especially in AD. Therefore, our study concentrates on these gaps and attempts to extract meaningful groups of genes. In the “Results” section, the dataset description, enrichment analysis of these gene groups, and the experiments' outputs are illustrated by relevant charts and tables. The “Discussion” section contains clinical and medical instances supporting the applicability of the proposed method. In the last section, “Method” introduces the proposed method in this study.

Results

In this part, the used dataset is described in detail, and then the adopted methodology and approaches are described.

Dataset

We utilized a dataset provided by J Xin and et al. by retrieving the studies related to the genetic association in Alzheimer’s disease from PubMed. The writers of this paper have extensively reviewed 5298 reports. Then, by omitting the unrelated reports, 823 publications presenting more significant associations were chosen. Finally, there is a list of 431 genes known as Alzheimer-related genes(9).

Extracting protein complexes from Protein-Protein Interaction (PPI) network

First, a STRING database(10), which includes all interactions between proteins, was utilized to construct a PPI network. The network constructed for this study is a collection of genes with experimentally obtained interactions. The constructed PPI network was then clustered by the EAGLE algorithm, which is one of the algorithms in ClusterViz application(11). After examining different values, 3 and 2 values were selected as “CliqueSize Threshold” and “ComplexSize parameters, respectively. These are two parameters associated with the EAGLE algorithm. Among the 9 clusters, constructed by running this algorithm, 5 clusters were selected for the next research step. Four remaining clusters were eliminated because they were meaningless according to their structures and were not able to represent a gene complex. Five selected groups of genes are represented in Table 1.

Enrichment analysis of genes

Functional Enrichment analysis was accomplished for each cluster independently. The results are demonstrated in separate tables. The p-value of the most significant pathway is equal to 4.16E-04 and involved six genes. The related term to this pathway is Transcriptional and is found in cluster 1. In Cluster 3, the substantial pathway is Alzheimer’s disease. Its p-value is equal to 5.13E-11, and it includes ten

genes. In the sixth cluster, the most crucial pathway is Hepatitis c. Its p-value is equal to 0.004662, including four genes. The next cluster, cluster 7, the most significant pathway is the Neuroteoohin signalling pathway with eight genes. Its p-value is 4.74E-11 and it includes eight significant genes. The last cluster, cluster 8, the most crucial pathway is Malaria. Its p-value is 7.32E-04 and includes three genes. These are the most significant pathways for each cluster. More comprehensive information, including all the pathways, is available in Additional File 1 (Supplementary Tables 3-7).

According to the gene ontology analysis, the most important biological processes for cluster 1 were respectively transcription from RNA polymerase II promoter (p-value=4.66E-13), with 21 genes, regulation of transcription from RNA polymerase II promoter (p-value=5.45E-13), with two genes, and positive regulation of cellular metabolic process (p-value=9.75E-13) with 24 genes. For cluster 3, membrane protein proteolysis was the most significant biological process (p-value=1.78E-15) and included nine genes. The next important processes are were notch receptor processing (p-value=7.92E-12) with six genes and membrane protein ectodomain proteolysis (p-value=8.90E-12) with seven genes. In the sixth cluster, the most important biological process with 18 genes (p-value=3.91E-09) was the negative regulation of the biological process. The next three important processes were respectively negative regulation of response to a stimulus with 12 genes (p-value=1.89E-08), regulation of apoptotic process with 12 genes (p-value=2.39E-08), and regulation of programmed cell death with 12 genes (p-value=2.64E-08). In cluster 7, the important processes are respectively, transmembrane receptor protein tyrosine kinase signaling pathway with 11 genes (p-value=4.21E-13), enzyme-linked receptor protein signaling pathway with 11 genes (p-value=1.99E-11), and cell surface receptor signaling pathway with 13 genes (p-value=2.55E-10). In cluster 8, significant processes are respectively vesicle-mediated transport with 10 genes (p-value=5.86E-08), endocytosis with 8 genes (p-value=9.86E-08), transport with 13 genes (p-value=2.08E-07) and establishment of localization with 13 genes (p-value=2.87E-07). The other important biological pathways sorted by their p-value are available in separate tables in the Additional File 1 (Supplementary Tables 8-12).

Bipartite miRNA-gene networks

Bipartite gene-miRNA networks, illustrated by Cytoscape.3.7.0, can examine complexes more in-depth. These bipartite networks are first analyzed by network specifications and then sorted by the degree of the nodes. The miRNAs with a higher degree as well as their associated genes and connections are normally selected. Bipartite gene-miRNA networks for each cluster are shown in Figure 1. The red oval nodes represent the genes, and the blue rectangular ones signify their related miRNAs. There is a representation of the miRNAs concerning each cluster in the Additional File 1 (Supplementary Table 1). After extracting bipartite networks, some of the genes are to be omitted. So, the lists of the genes are changed in the next step. These updated lists of genes are represented in the Additional File 1 (Supplementary Table2).

Table 1

list of the selected clusters along with their genes

Number of Clusters	Number of Nodes	Nodes
1	31	PPARG, CAMK2D, RXRA, SP1, ESR2, GRIN2B, FAS, POU2F1, CDKN2A, NOS3, AR, CCNT1, ABCA1, RUNX1, VDR, NME8, UBE2I, TP63, TP73, PPARA, NR1H2, UBD, PNMT, TBX3, ESR1, CLOCK, SNX3, PIN1, TP53, BCR, CAV1
3	22	PSENEN, APH1A, TARDBP, NCSTN, PSEN1, APP, UBQLN1, APBB1, APBB3, COL25A1, BACE2, BACE1, TRAK2, KLC1, CTSD, MAPK8IP1, APH1B, TGFB1, CD14, APBB2, PSEN2, TLR4
6	19	GSTP1, DAPK1, EIF2AK2, SLC6A3, SNCA, UBE2D1, LRP6, NLRP3, RAB7A, LRRK2, YWHAQ, GSK3B, TRAF2, TNF, SLC6A4, RCAN1, EIF4EBP1, UNC5C, SERPINA1
7	13	NEDD9, NGF, SORCS3, NTRK1, LCK, NTRK2, PTK2B, BDNF, NGFR, NTF3, IRS1, PIK3R1, CD44
8	13	RELN, IL10, IL1B, LDLR, VLDLR, SORL1, LRP8, LRPAP1, LRP2, LRP1, A2M, ATP7B, CLU

drug-gene interaction network

To introduce the potential drugs for Alzheimer's treatment, we used DGIdb 3.0 database to extract drug-gene interactions(12). Utilizing this database, drugs related to each cluster's genes are extracted and visualized in Figure 2.

The undirected associations between genes and drugs are illustrated. The relation between each gene group indicates the gene complexes, which are shown by separately drawn clusters. Blue hexagonal nodes and the red oval nodes represent the drugs, represent the genes. Drugs related to each cluster are illustrated in Additional File 1, Table 13.

Discussion

In this article, the genes associated with Alzheimer’s disease were studied. Extracting meaningful gene complexes using PPI networks helps us have enrichment analysis over these gene groups. Significant biological processes and pathways are listed in the related part. In the next step, target miRNAs were extracted, and bipartite subnetworks for each gene group were constructed. In the last step, target drugs of the selected gene groups were introduced and visualized explicitly. In this way, each gene group can be demonstrated by red oval nodes diagnosed as separate groups, and blue hexagonal nodes as the common drugs related to different genes. The drugs are sorted by their degree value to launch a comprehensive inquiry of the obtained results. Since drugs with a higher degree are associated with several genes, fifteen drugs were selected, two of them TAMOXIFEN and VERAPAMIL were with degree value of 5, and the rest with a degree value of 4 which are listed as following: ALTEPLASE, PILOCARPINE,

RALOXIFENE, GENTIAN VIOLET, HEXACHLOROPHENE, NICOTINE, DOXORUBICIN, HALOPERIDOL, DAUNORUBICIN HYDROCHLORIDE, CLOZAPINE, ESTRADIOL, and PROGESTERONE.

These are vital drugs introduced by this study for Alzheimer's disease. All 15 obtained drugs are reviewed in previous experimental and medical studies to acknowledge the accuracy of the present study's results.

Initially, TAMOXIFEN and VERAPAMIL were examined reviewing the previous studies. A case-control study in Taiwan examined the relation between TAMOXIFEN use and AD and concluded that using this drug for a long time, tends to the longer life of Alzheimer's patients(13). Another study indicated the role of TAMOXIFEN in Alzheimer's disease and found that it enhances the ability of memory(14). Another study showed that TAMOXIFEN contributes to the reduction of impairment and improvement of the learning system(15).

According to the literature, a study introduced VERAPAMIL as medication for both male and female samples dealing with Alzheimer's disease(16). According to a review study, VERAPAMIL, previously used for cardiovascular disease, is currently considered as a treatment in neurological disorders(17). In addition to Alzheimer's disease, VERAPAMIL is reported as a treatment in Huntington and Parkinson's disease(18),(19).

The next thirteen drugs were examined as follows. ALTEPLASE, known also as t-PA, contributes to the reduction of AD-related pathology by making progress in the cognitive function of the sample(20). Another study about this treatment method indicated that ALTEPLASE prevents ischemic brain lesions to be progressed while imaging after the stroke(21). Another published paper maintained the role of t-PA in omitting Aβ (deposition of the beta-amyloid peptide which is known as one of the important reasons for Alzheimer's disease). The results of this study also indicated that t-PA reduces the speed of Alzheimer's disease progression(22). The next one is PILOCARPINE which is claimed to be instructive in detecting patients dealt with AD and Dementia(23). But there is no other related study. RALOXIFENE, the next one, which has a neuroprotective role(24), was maintained to help decrease inflammation of the brain. In another study, it was maintained that RALOXIFENE prevents cell death in neurons and meliorate mild cognitive impairment in examined samples. Its useful effects in Parkinson's disease(25) were maintained as well. Another study concluded that 120 mg per day as the dose of RALOXIFENE reduces cognitive impairment risk(26). The next one is GENTIAN VIOLET, yet there is no study on the association of GENTIAN VIOLET and Alzheimer's disease. The next one, HEXACHLOROPHENE, is almost associated with neurodegenerative disease and helps reduction of $A\beta_{42}$ induced toxicity and prevent neural damage(27). Another study indicated HEXACHLOROPHENE as a potential drug in Alzheimer's disease treatment by regulating the levels of tau(28). NICOTINE affects the aetiology of Alzheimer's disease and Parkinson's disease; however, the writers did not recommend it for its other health problems(29). Another paper observed cognitive progress using NICOTINE in Mild Cognitive Impairment (MCI) samples(30). DOXORUBICIN represents a protective effect in the brain over Chemotherapy-induced impairment (CICI) (31). The next study their relationship with cognitive abilities and introduced more evidence about its effect(32). There is no direct relation between AD and this drug, so this study proposes it as an Alzheimer-

related drug to be studied extensively. The next drug is HALOPERIDOL that has a relation with patients with Alzheimer's disease who have behaviour problems and represents relatively good changes in patients' behavior(33). The next study indicated that using a special dose of HALOPERIDOL decreases behavioral problems (Psychosis and destructive behaviors) in above-mentioned patients (34). Another study showed a decrement in delays for finding new objects through the examinations (35). Almost all the studies related to this drug, reviewed in this part, are not directly related to AD, but they are indirectly associated with changes in behaviors of patients with Alzheimer's disease or dementia. The next drug is DAUNORUBICIN HYDROCHLORIDE which is known as DAUNOMYCIN with trade names ADRIAMYCIN, CERUBIDINE, and BLENOXANE(36). A study stated that the compounds containing DAUNOMYCIN prevent Abeta fibril formation and so slow down the progression of Alzheimer's disease(37). This is the only study that stated the relation between Alzheimer's disease and DAUNOMYCIN. Another study proposed it for the long-term treatment of patients with Alzheimer's disease. Its results also maintained its effect in the reduction of amyloid-beta (Aβ) deposition(38). Another study also introduced CLOZAPINE for psychosis treatment in patients affected by Alzheimer's dementia or Parkinson's disease(39). The next paper introduced CLOZAPINE as the related drug for Alzheimer's treatment that improves short-term memory(40). The next drug is ESTRADIOL which is stated as a useful drug for enhancement of cognitive functions(41). The other study maintained that ESTRADIOL in higher levels provides a higher covariance in-memory network and a better cognitive health specially for women(42). There are two other studies that suggested using ESTRADIOL as a therapy in Alzheimer's disease(43, 44). The last one is PROGESTERONE which contributes to progression in learning and memory abilities by improving glucose metabolism in neurons(45). Another article maintained that PROGESTERONE increased increases cognitive abilities, prevents Aβ inflammation and is a therapy method in Alzheimer's disease(46). The next study asserted about some behavioral problems like depression cause by Alzheimer's disease and claimed that PROGESTERONE decreases these behavioral problems(47).

According to the extensive and detailed review, the drugs extracted by this article can be divided into three groups. The first group is about AD-related drugs introduced by previously published researches. The second group is the drugs that are not directly related to AD, or there has not been enough study about them so far. The third group is about the drugs that have not been mentioned concerning AD in previous studies. This categorization is presented in Table3.

Table 3

A categorization of the extracted drugs

Number of drugs	Drug names
9	TAMOXIFEN, VERAPAMIL, ALTEPLASE, RALOXIFENE, HEXACHLOROPHENE, NICOTINE, CLOZAPINE , ESTRADIOL, PROGESTERONE
4	PILOCARPINE, DOXORUBICIN, HALOPERIDOL, DAUNOMYCIN
2	RALOXIFENE, GENTIAN VIOLET

The first group's drugs prove the accuracy of the proposed method in this study because the obtained results are consistent with previous medical publications. The second list of drugs is proposed in previous research, but they can be studied more in detail as future works. The two drugs in the third group are proposed by this study as Alzheimer-related drugs which can be examined experimentally.

Conclusions

The presented study aimed to suggest Alzheimer' disease-related drugs and introduce significant processes and pathways by extracting important gene complexes. The proposed method utilized PPI networks to extract these gene complexes. Then for each gene complex, a bipartite subnetwork was drawn using their most important target miRNAs. In the next phase of the study, Drug-gene networks were extracted and illustrated, along with related gene groups. By detailed investigation over the selected drugs, RALOXIFENE and GENTIAN VIOLET were proposed as Alzheimer-related drugs by this study.

Methods

This part describes a step-by-step method used in this study.

Gene complex extraction

We used the STRING database to construct a PPI network. This database provides a comprehensive global network that integrates all the available PPI information(10). We just considered, in the process of constructing this network, the interactions that are obtained experimentally. ClusterViz is an application to analyze and visualize the clusters in biological networks and is supported by the Cytoscape platform. Cytoscape is a versatile platform and popularly used to visualize biological researches (11). We used Cytoscape.3.7.0. in this study. There are also two other clustering algorithms named MCODE and FAG-EC. Testing these three algorithms with different parameters led to choose EAGLE to construct the gene complexes.

Functional enrichment analysis

Gene ontology analysis and biological pathway analysis have been developed to accomplish enrichment analysis using The Annotation Visualization and Integrated Discovery (DAVID) database(48) that helped us extract biological mechanism and gene ontology information. Kyoto Encyclopedia Gene and Genomes (KEEG) database(49) was utilized to study the pathways that they involve.

Bipartite Gene-miRNA networks

In this step, target miRNAs of the genes in each group were extracted separately using the miRWalk2.0. So five bipartite gene-miRNA networks were constructed and illustrated by Cytoscape.3.7.0. The miRNAs, which have a more considerable degree, achieve a more regulatory role. So subnetworks are constructed by selecting miRNAs with a more considerable degree and their related genes.

Drug-gene networks

In the next step, Drug-gene networks were constructed using DGIdb, which represents drug-gene interactions from different resources. Its user-friendly interface facilitates searching and filtering for easy access. We used DGIdb 3.0(12) that indicates a significant update in the database by updating resources and adding new resources.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The utilized dataset is obtained from the following paper and is available to download.

https://alzres.biomedcentral.com/articles/10.1186/s13195-017-0252-z#MOESM2

Competing interests

Not applicable

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Authors' contributions

Negar.S created PPI networks and performed network analysis over the dataset. Saeid.P and Habib.M performed enrichment analysis over the obtained results. Writing the manuscript was performed by the contribution of all authors. All authors read and approved the final manuscript.

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Figures

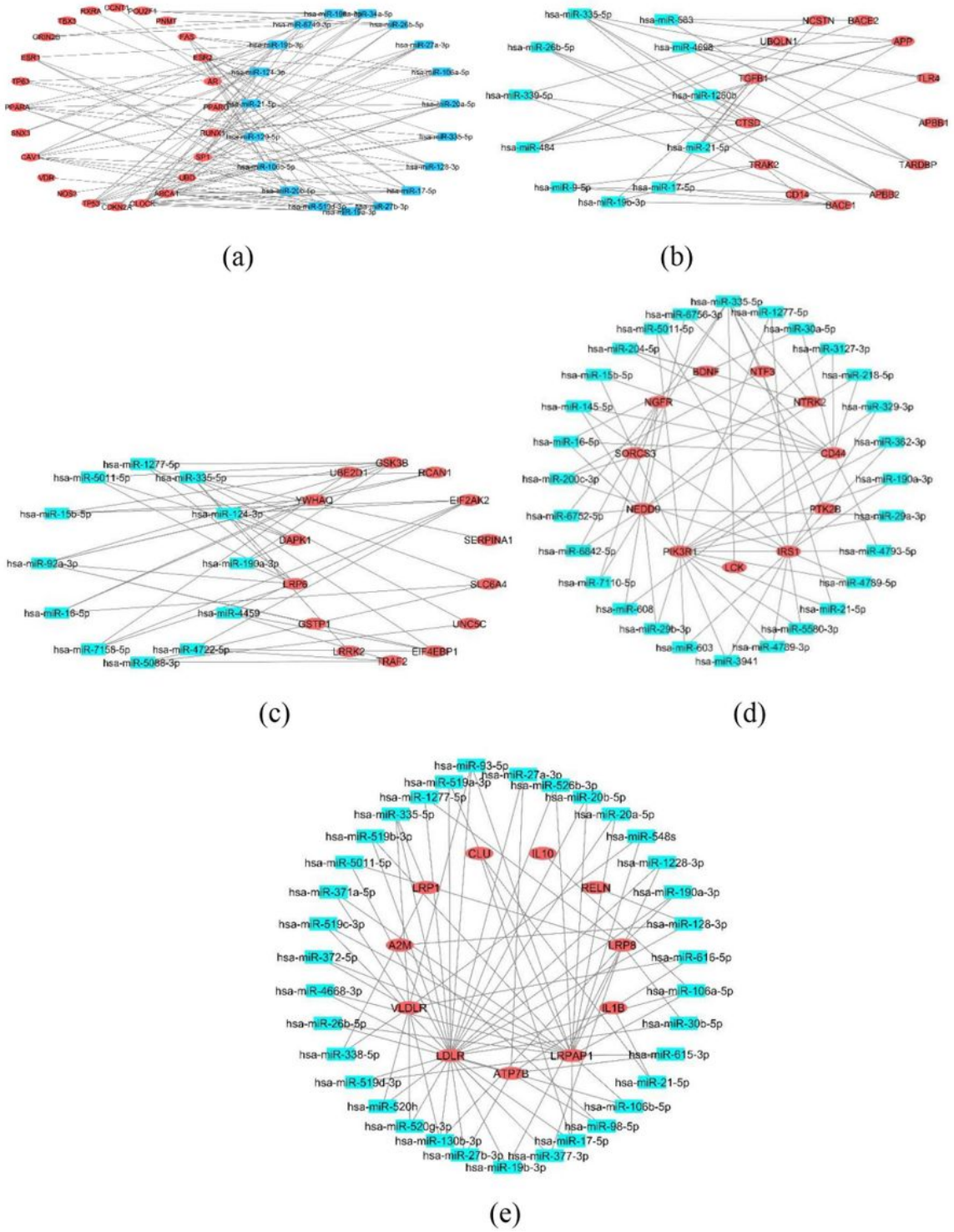

Figure 1

Bipartite gene-miRNA subnetworks for all of the clusters. (a) Cluster1. (b) Cluster3. (c) Cluster6. (d) cluster7. (e) Cluster8.

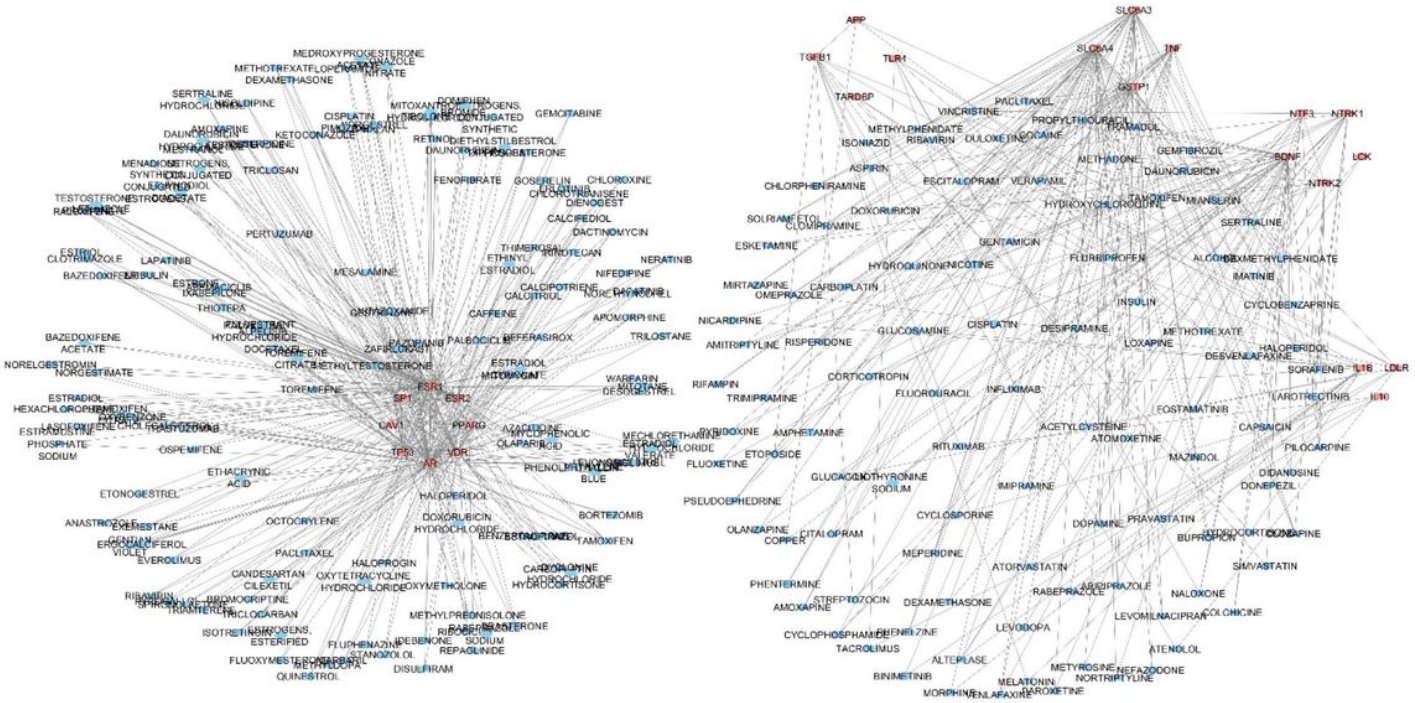

Figure 2

drug-gene interaction network along with related protein complexes

Supplementary Files

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- Supplementaryfile.docx