Network Analysis and Molecular Mapping for Alzheimer's Disease to Reveal the Drug Targets of Arbutin

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Research Article

Keywords: Alzheimer's Disease, arbutin, network pharmacology and molecular docking

Posted Date: November 3rd, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3474607/v1

Additional Declarations: No competing interests reported.

Abstract

Alzheimer's disease (AD) is a neurodegenerative disease that causes the degradation of brain cells. AD is the most common causative factor of dementia that leads to cognitive decline and loss of independence. Cholinesterase inhibitors and N-methyl-D- aspartate (NMDA) antagonists are currently available drugs to treat AD related symptoms. Several studies have proved that arbutin is found to be beneficial in treating various diseases thereby modulating its brain targets which further helps to reduce AD's side effects. The present research is mainly focused to study the molecular pathways and to determine the mechanism of action of arbutin to mitigate AD using a system pharmacology approach. Bioinformatics tools are explored to identify arbutin's therapeutic targets for AD, including Cytoscape for network analysis, ShinyGo for gene ontology enrichment, and AutoDock for docking molecules. In a Cytoscape network, the Maximal Clique Centrality (MCC) algorithm of the CytoHubba plugin was used to determine the top ten hub genes. Out of 411 targets for arbutin and 395 targets for AD, 37 targets were selected and shared through the data filtering process. The biological activities of these 37 genes include post-translational regulation of the phosphorus metabolic process, response to abiotic stimulus, regulation of cell population proliferation, regulation of programmed cell death and response to oxygen-containing compounds. The top 10 enriched pathways were selected for future study from 284, including AD, cancer pathways, MAPK signaling, Diabetic cardiomyopathy and proteoglycans in cancer. Our results proved that arbutin can reduce the possibility of developing AD by modulating the activity of primary pathways groups, including its pharmacological mechanism of action in AD, revealing its ten therapeutic targets.

1 Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease in the elder persons. In 2019, about 13.14 million people were diagnosed with AD in China, accounting for 20% of the total AD cases worldwide (Ren et al. 2022). Drugs that can either prevent or delay AD progression and subsequently usage of biomarkers for the early detection of disease at the earlier stage are currently unavailable. Moreover the effectiveness of potential treatments has also been questioned in many clinical studies. Therefore, it is a great need to find out effective treatments that tackle the AD related pathogenic pathways. Many therapeutic molecules might activate various targets and systems based on these methods. Since, limited treatments are currently available to mask the AD symptoms at their early stages (Barage and Sonawane. 2015). Alternative agents are needed to enhance the therapeutic efficacy of the drug.

Nature is the best source of therapeutic molecules to be employed for treating AD (Silva et al. 2014). The neuroprotective benefits of these naturally occurring molecules have recently been discovered (Dey et al. 2017). Several illnesses, including neurological disorders like AD, have been characterized. Naturally occurring molecules derived from multiple sources are also emerged recently for the prevention of AD (Rasool et al. 2014). Arbutin (4-hydroxyphenyl-D-glucopyranoside), a naturally occurring hydroquinone glycoside, can be used to treat metabolic problems and diseases related to urinary system. Many plants, like *Bergenia crassifolia* (Saxifragaceae), *Pyrus communis* (Rosaceae), *Origanum majorana* (Lamiaceae)

and *Arctostaphylos uva-ursi* (Ericaceae), contain arbutin. Arbutin has been shown to possess antibacterial (Jurica et al. 2017), gastroprotective (Taha et al. 2012), hepatoprotective (Myagmar et al. 2004), and antihyperlipidemic (Shahaboddin et al. 2011) properties which has been reported in their previous studies. Several enzymes (tyrosinase (Garcia-Jimenez et al. 2017), amylase, glucosidase [11]), free radicals (Shahaboddin et al. 2011) and the production of various pro-inflammatory cytokines (Ahmadian et al. 2019; Kim et al. 2023) were all inhibited by arbutin. Previous research highlights the neuroprotective effect of arbutin by improving the motor functioning and behavioral characteristics (Zoherh et al. 2019, Masoumeh et al. 2018). Arbutin also reduces neurodegeneration by inhibiting excitotoxic and autophagic pathways (Dadgar et al. 2018). Despite these findings, the complete components of arbutin, their various effects, and the underlying mechanisms against AD have not yet been fully understood.

Integrative bioinformatics tools are applied to hasten the finding and development of new therapeutic molecules. Functional annotations were performed to predict the shared genes, to understand the molecular mechanisms and to study their roles and functions. The protein-protein interaction (PPI) network helps to analyze the possible mechanisms of different proteins which work together. Network pharmacology is a relatively much newer approach employed thoroughly and methodically to assess the mechanism of action of drugs that will function in human systems, including arbutin. This approach is more effective than the trial-and-error method for designing the studies to confirm the function of arbutin in various disorders experimentally. By applying integrative bioinformatics tools, the present study was performed to provide an in-depth understanding of the targets and to study the molecular mechanisms by which arbutin protects against AD.

2 Materials and Methods

2.1 Prediction of arbutin targets

The PubChem database (https://pubchem.ncbi.nlm.nih.gov/) (Kim et al. 2023) was used to retrieve the Simplified Molecular-Input Line-Entry System (SMILES) (Dezs et al. 2010) and the 3D structure of arbutin. Potent targets of arbutin were screened using the compound prediction databases such as SwissTarget (http://www.swisstargetprediction.ch/) (Daina, Michielin and Zoete 2019) and PharmMapper (http://lilab-ecust.cn/pharmmapper/) (Liu et al. 2010). To rule out irregular, non-human and repetitive targets, the search for the gene symbols of the active compounds in arbutin was refined by choosing the species "Homo sapiens".

2.2 AD-related targets prediction

GeneCards Database (https://www.genecards.org)(Safran et al. 2021) with a threshold of 10 and DisGeNet (https://www.disgenet.org/)(Piñero et al. 2020) score at 0.11 were set to acquire targets relevant to AD (Stelzer et al. 2016). Terms including Alzheimer’s disease, Alzheimer’s, Dementia, and AD were searched and used to determine the AD targets.

2.3 PPI network construction and hub genes identification

The PPI network of gene lists was predicted using the Search Tool for the Retrieval of Interacting Genes (STRING) database version 11.5 (Li et al. 2020). Using the software Cytoscape networks were constructed for the following: (i) Arbutin and its targets, (ii) AD and its PPI interaction, and (iii) the PPI interaction of common targets that are shared by arbutin and AD (Yang et al. 2021). The top 10 core genes were identified using the Cytoscape plugin CytoHubba utilizing MCC topological analysis and the predicted PPI network (Chin et al. 2014).

2.4 Gene Ontology (GO) and Kyoto Encyclopaedia of Genes and Genomes (KEGG) Pathway Enrichment Analysis

The ShinyGo (http://bioinformatics.sdstate.edu/go/) database was utilized to investigate KEGG pathway enrichment and Gene Ontology of the common targets of arbutin and AD (Xijin et al. 2020). GO (Chord diagram), enrich KEGG (Dot plot & Sankey plot), and pathway class graph plots were created using ggplot2 (https://ggplot2.tidyverse.org). The top targets route class analysis was conducted using the KEGG pathway database (https://www.kegg.jp/) and executed the dot-plot analysis from the KEGG enrichment analysis.

2.5 Molecular Docking

The target proteins 3D crystal structures in protein databank (PDB) format were retrieved from the RCSB protein Data Bank (https://www.rcsb.org/). Adding charges, removing water and producing .pdbqt format from the protein molecules were done using AutoDock tools (Forli et al. 2016). The 3D structures in the SDF format of arbutin were retrieved from the PubChem database and converted into PDB format (Hummell, Revtovich, and Kirienko 2021). AutoDock tools were used to preprocess the ligands for docking. Using AutoDock (4.2) software, the interaction between the target protein with arbutin and its affinity for binding was estimated. The optimal binding posture for arbutin and rivastigmine with target proteins was visualized using Discovery Studio (DS) visualizer software (https://discover.3ds.com/discovery-studio-visualizer).

3 Results

3.1 Arbutin target network

About 411 arbutin targets were obtained from Swiss Target Prediction and PharmMapper. After eliminating the duplicates, 374 target genes were chosen for the arbutin target network (Fig. 1).

3.2 AD targets and PPI network

From the databases DisGeNet and GeneCards, 395 AD targets are collected for the study which are responsible for AD development. Duplicates were removed, and the AD targets alone were identified using

Cytoscape's Analyze Network method (Fig. 2).

3.3 Common potential targets of Arbutin and AD

Protein-protein interactions were visualized with the help of the STRING database. The Venn Diagram tool (http://www.interactivenn.net/) were used to identify the 37 possible targets shared by arbutin and AD (Fig. 3). The PPI network of common 37 genes are represented in Fig. 4a. The top 10 hub targets (IGF1, IGF1R, EGFR, MAPK1, MAPK14, MMP9, CASP3, GAPDH, ALB and AKT1) were gathered using the CytoHubba plugin and MCC score to build the network for Cytoscape (Fig. 4b).

3.4 GO analysis and KEGG pathway analysis

The common 37 targets were examined using the ShinyGo database. The top 10 GO terms were chosen based on the Fold Enrichment value ((FDR) and the number of gene counts (Fig. 5). ggplot2 depicts the GO results. The top 5 biological processes (BP) were chosen and represented using the Chord Diagram based on the FDR value and the number of gene counts (Fig. 6). In the top 5 BP, nine (out of ten) hub genes were enriched. The effects of post-regulation of the phosphorus metabolic process, response to abiotic stress, regulation of programmed cell death, regulation of cell population proliferation and response to oxygen-containing substances were all directly related to the AD progression.

3.5 KEGG Pathway Enrichment Analysis

A total of 284 paths were retrieved (p-value≤0.05), and out of which top 10 pathways were selected for further analysis (Table 1). The top 10 enriched KEGG pathways were shown in Fig. 7 with their respective genes. Further, the primary 5 KEGG pathway were analyzed with their respective genes (Fig. 8a-8e). The top 2 pathways of common targets were depicted in (Fig. 9a and b) based on the number of genes.

3.6 Molecular Docking

Based on the MCC scores, ten hub genes were selected from the common targets. Further molecular docking studies were carried out with arbutin. From Fig. 10 it is evident that interaction took place between core targets and arbutin. Detailed binding scores of arbutin with the hub genes were shown in the Table. 2. Our results revealed that arbutin significantly interacted with all the potential targets and has significant binding energy. Arbutin had a strong interaction with AKT1, with a binding score of -7.5 for AKT1. A binding score of -4.3 was also observed between arbutin (with IGF1).

Table 1
The KEGG pathway results—pathways common for arbutin and AD based on significance

Pathway	Pathway ID	Total Genes	Gene Count	p-value
Endocrine Resistance	hsa05122	95	9	8.87E-13
Prostate cancer	hsa05215	97	9	8.97E-13
HIF-1 signalling pathway	hsa04066	109	10	9.43E-14
EGFR tyrosine kinase inhibitor resistance	hsa01521	79	7	6.06E-10
FoxO signalling pathway	hsa04068	131	10	4.16E-13
Proteoglycans in cancer	has05205	202	11	5.00E-13
Diabetic cardiomyopathy	hsa05415	203	10	1.31E-11
MAPK signalling pathway	hsa04010	294	11	1.37E-11
Pathways in cancer	hsa05200	530	17	1.51E-16
Alzheimer's disease	hsa05010	383	12	1.07E-11

Table 2
MCC ranking of hub proteins and their corresponding binding affinity

MCC Ranking	Name	PDB ID	Target Name	Docking positions	Affinity of arbutin (kcal/mol)
1	ALB	4L8U	Human Serum Albumin	ARG A:117, LEU A; 182, ARG A:186, ILE A:142	-6.6
2	IGF1R	2OJ9	Insulin like Growth Factor Receptor 1	LEU A:975, GLN A:977, GLY A:978, VAL A:983, ALA A:1001, GLU A:1050, MET A:1052, ASP A:1056, SER A:1059, MET A:1112	-6.9
3	MMP9	1GKC	Matrix Metalloproteinase 9	VAL A: 398, HIS A: 401, GLU A:402, HIS A:411, PRO A:421, TYR A:423	-7.2
4	EGFR	1M17	Epidermal Growth Factor Receptor	VAL A:702, LYS A:721, GLU A:738, THR A:766, THR A:830	-6.2
5	MAPK1	4H3Q	Mitogen Activated Protein Kinase 1	GLY A:34, VAL A:39, ARG A:67, LYS A:114, LYS A:151, SER A:153, CYS A: 166	-6.4
6	MAPK14	2EWA	Mitogen Activated Protein Kinase 14	LYS A:53, LEU A:55, PRO A:58, HIS A:64, ARG A:67, ASP A:168, GLY A:170	-6.2
7	AKT1	3O96	RAC-alpha serine/threonine-protein kinase	GLN A:82, TRP A:83, THR A:84, SER A: 208, LEU A:267, LYS A:271, VAL A:274, TYR A:275	-7.5
8	IGF1	1GZR	Human Insulin like Growth Factor 1	ARG B:21, PHE B:23, ALA B:62, PRO B:63	-4.3
9	CASP3	2XYG	Caspase 3	ARG B:207, ASN B:208, SER B:209, PHE B:250	-5.3
10	GAPDH	1U8F	Glyceraldehyde 3 phosphate dehydrogenase	GLY A:34, VAL A:39, ARG A:67, LYS A:114, LYS A:151, SER A:153, CYS A: 166	-6.3

4 Discussion

Consequences and the medical needs of AD have made the research community learn more about the causes of AD to develop advance treatments. Despite the widespread nature of AD, only five drugs (rivastigmine, galantamine, donepezil, memantine, and memantine in conjunction with donepezil) have been approved by the FDA for AD treatment. Research into the causes of AD and the effort for developing medicines have received much attention recently (Long and Holtzman 2019). Bioactive molecules with unique pharmacological properties are more abundant and can be derived from various natural sources

(Yuan et al. 2016). Natural products and their purified constituents have been widely explored as a potential source of new and more effective medications for treating AD (Kennedy and Wightman 2011). Natural and synthetic cholinesterase inhibitors are currently available for AD treatment (Kumar and Vikas 2006). Recent data suggest that natural sources might improve cognitive function in AD.

Numerous clinical and experimental research has proved that arbutin also possesses antityrosinase (Bhalla et al. 2023) and anti-inflammatory (Jin et al. 2022) properties and it is also much used as an anticancer medication. Arbutin increased the spatial memory and minimized oxidative and nitrosative stress which is noticed by a considerable drop in serum and hippocampal MDA and nitrite (Kumar et al. 2021). As a result, it has been hypothesized in our study that arbutin might also significantly impact AD therapy. The present study uses a network pharmacology approach to demonstrate an interlink between arbutin and AD. Built networks such as the compound and PPI for common targets to thoroughly understand the processes behind arbutin's effectiveness in treating AD are also attempted in our study.

According to conventional wisdom, Arbutin showed better affinity for binding to AD targets. The proteins which are tightly linked to arbutin might lower the symptoms associated with AD. In addition, arbutin can perform various functions and effectively decrease heat and other detoxifying qualities (Bhalla et al. 2023). It has been reported to mitigate the neurotoxicity of monosodium L-glutamate by reducing cognitive dysfunction, inflammatory markers and biochemical disturbances in the brain (Kumar et al. 2021). According to our findings, the study mentioned above is well correlated with our present study. In PPI network analysis, ten essential genes' degrees and betweenness centrality were found to be higher than expected. These ten major target proteins encode crucial proteins for AD progression, specifically in the mitogen-activated protein kinase (MAPK)-associated signaling pathways.

4.1 Details of hub genes of arbutin targets in treating AD

The family of endoproteases, known as matrix metalloproteinases (MMP), might break down the components of the extracellular matrix and need Ca^{2+} and Zn^{2+} as a cofactor. They are released by macrophages, leukocytes, microglia, neurons and astrocytes, and their target substances. Activating preforms of MMPs, and endogenous tissue inhibitors of metalloproteinases (TIMPs) are necessary for their further activation (Brew et al. 2000). From the postmortem of AD brain tissue, it has revealed that expression seems to be increased in neurons. It increases the production of neurofibrillary tangles, senile plaques, and the vascular wall (Asahi et al. 2000). MMP-9 is clinically significant in the pathophysiology of AD. In primary cultured neurons, Tamura et al (1998)., showed that MMP inhibitor II which is highly selective to MMP-9, prevents Aβ induced release of lactate dehydrogenase, thereby stating that MMP-9 is involved in Aβ-induced neuronal cell death (Tamura et al. 1998). A recent study also revealed that active MMP-9 expression levels were significantly higher in the entorhinal cortex at the beginning of AD-related pathology. However, the significance of MMP-9 in the etiology of AD remains debatable. Few studies also have researched on the connection between tau and MMP-9 (Malemud 2019).

Physiologically, insulin binding to the Insulin Receptor (IR) initiates a cascade that regulates essential downstream serine/threonine kinases like protein kinases B (AKT/PKB), mechanistic target of rapamycin (mTOR), and extracellular signal-regulated kinases (ERK), which phosphorylate serine/threonine residues of the insulin receptor substrates (IRS), thereby inhibiting insulin signaling in a negative feedback regulation. It has been postulated that the growth hormone (GH)/ insulin-like growth factor (IGF-1) signaling pathway controls the overall lifespan. Longevity seems to be increased and age-related dysfunction is delayed in worms, rodents and flies when the IGF-1 receptor (IGF-1R) is partially inactivated (Zheng and Flavell 2000). Therefore, blocking the GH/IGF-1 pathway with medication can treat AD (Longo et al. 2015). However, the process of IGF-1 controlling age-related AD is still unclear. A decrease in serum IGF-1 levels has been linked to an increased risk of AD. Ex *vivo* research revealed that there was an increased IGF-1 and insulin resistance which intern regulates the PI3K-AKT pathway in the brain of AD patients (Zheng and Flavell 2000). Finally, therapy with IGF-1 reduced Aβ buildup by increasing its transport out of the brains of AD mouse models, whereas IGF-1R inhibition worsened both behavioral and clinical AD symptoms in mice (Carro et al. 2006). IR activity controls cell survival signaling pathway through phosphoinositide 3-kinase (PI3K), Akt, mTOR, glycogen synthase kinase 3β (GSK3β), Bcl-2 agonist of cell death (BAD), fork-head box (FOX) and MAPK pathways in neurons (Cholerton et al. 2016). MAPK activity is inhibited by the dephosphorylation of MAPK at tyrosine and threonine residues by MAPK phosphatase 1 (MAPK1 or MKP-1) (Groom et al. 1996). MAPK-1 has emerged as a potential key regulator of synaptogenesis in recent research. MKP-1 dysregulation might interfere with neural growth and cognitive function (Jeanneteau et al. 2010). Recent research has demonstrated that MKP-1 protects neurons from oxidative stress, neuroinflammation and apoptosis caused by Aβ (Gu et al. 2018). Mitogen-activated protein kinase 14 (MAPK 14) is an alpha isoform of stress-activated kinase linked to autophagy modulation. In the APP-PSEN1 transgenic mouse model, genetic deletion of MAPK 14 resulted in decreased amyloid pathology and increased autophagy (Schnöder et al. 2016). Regulating the AKT- mTOR signaling pathway results in MAPK 14 and AKT- mTOR crosstalk (Perdiguero et al. 2011).

There are three closely related members of the Akt serine/threonine kinase family; they are Akt1 (PKB, OMIM: 164730), Akt2 (PKB, OMIM: 164731), and Akt3 (PKB, OMIM: 611223). There is a wide range of extracellular signals that could trigger them. In addition to regulating neuronal survival in response to insulin or insulin-like growth factor (IGF), AKT1 protein promotes the survival of various cell types in reaction to other growth factors. Many studies have focused on the insulin PI3K-AKT signaling pathway, which has been shown to reduce GSK3β levels, thereby preventing the accumulation of Aβ protein and abnormal phosphorylation of tau protein which contribute to the formation of senile plaques and neurofibrillary tangles in AD (Hong and M-Y Lee 1997). This significant change in glucose/energy metabolism in Alzheimer's brain is thought to have its patho-biochemical base in the insulin PI3K-AKT signaling pathway. By blocking GSK3β and increasing mTORC1, AKT1 activation is beneficial for AD-related processes such as upstream of Aβ protein and proper phosphorylation of tau protein. Due to its extensive role in neuronal survival, AKT1 protein is naturally under consideration for its protective effects in various disorders, including those affecting the nervous system (Hong and Lee 1997).

Developmental neuronal apoptosis is disrupted in caspase-3-null animals, demonstrating the importance of caspase-3 as an effector caspase in apoptotic cascades leading to neuronal death (Zheng et al. 2000). Caspase-3 has been recently discovered to play a vital role in synaptic plasticity pathways. Aggregation of caspase-cleaved APP might be an early neurological event in AD development, and caspase-3 has been linked to the processing of APP into amyloidogenic fragments. Active caspase-3 is highly correlated with neurofibrillary tangles and plaques in the hippocampus of AD brains, as shown by immunohistochemical studies (Su et al. 2001). Following apoptotic stimuli, caspase-3 has also been distributed in synapses (Mattson and Duan 1999).

Using a double transgenic mouse model and cell cultures, researchers found that preformed fibrils (PFFs) of misfolded proteins like Aβ activate epidermal growth factor receptors (EGFR) (Wang et al. 2012). Inhibiting EGFR has been shown to have anti-neuroinflammatory, anti-oxidant, and anti-astrogliosis effects (Mansour et al. 2021) and a positive impact on behavior and cognition in various animal models of AD. Treatment with the EGFR inhibitors (gefitinib or erlotinib) reverses the effects of amyloid-beta 42 (Aβ42) driven EGFR activation in transgenic mice and flies mimicking AD.

4.2 The pathways and functional modules of therapeutic targets of arbutin against AD

Our study identified top 37 arbutin and AD targets which are involved in the essential biological processes (cell division, response to oxygen-containing compounds, homeostasis, response to endogenous stimuli and abiotic stress) within cells. The two key pathways underlying AD (hsa05010) and cancer (hsa05200) were enriched with targets, including the top 10 hub genes (Table 1). According to the KEGG pathway enrichment analysis, the highest level of cell cycle activation was discovered to be a common pathogenic characteristic between AD and cancer. Cancer is characterized by unchecked immortal cell cycle repetition. However, the molecular mechanism behind this variation remains unclear (Majd, Power, and Majd 2019).

On the other hand, the neurons in the brain of AD patients exhibit a significant rise in their cell cycle-related kinases despite its gradual neurodegeneration (D'Angelo et al. 2017). Numerous pathogenic pathways connecting AD and cancer exist at their cellular level. PI3K/Akt/mTOR signaling pathway (essential axis in autophagy, growth, metabolism and cell proliferation), is an example which highlights its role in the pathogenesis of AD and cancer (Porta, Paglino, and Mosca 2014). It is clear that this pathway elements either individually or collectively serve as one of the standard links between AD and cancer in a similar pathophysiology path but with distinct outcomes. Finding these connections could help us in future to develop other practical therapeutic approaches.

5 Conclusion

From the present study, it can be concluded that treatment with arbutin might reduce the adverse effects of Alzheimer's disease by controlling the hub genes (IGF1, IGF1R, EGFR, MAPK1, MAPK14, MMP9, CASP3, GAPDH, ALB and AKT1). These hub genes regulate various biological processes involved in AD

progression. Our research also discovered the therapeutic abilities of arbutin in AD through the network analysis. The results clearly indicated that arbutin might prevent and treat AD through various components, targets and pathways. Furthermore, these findings must be confirmed and substantiated through *in vitro* and *in vivo* research.

Declarations

Acknowledgements

The authors greatly acknowledge the Department of Science and Technology (DST)- Fund for Improvement of S&T Infrastructure (FIST), New Delhi, India and The Management of PSG College of Arts & Science, Coimbatore, for this research work.

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Figures

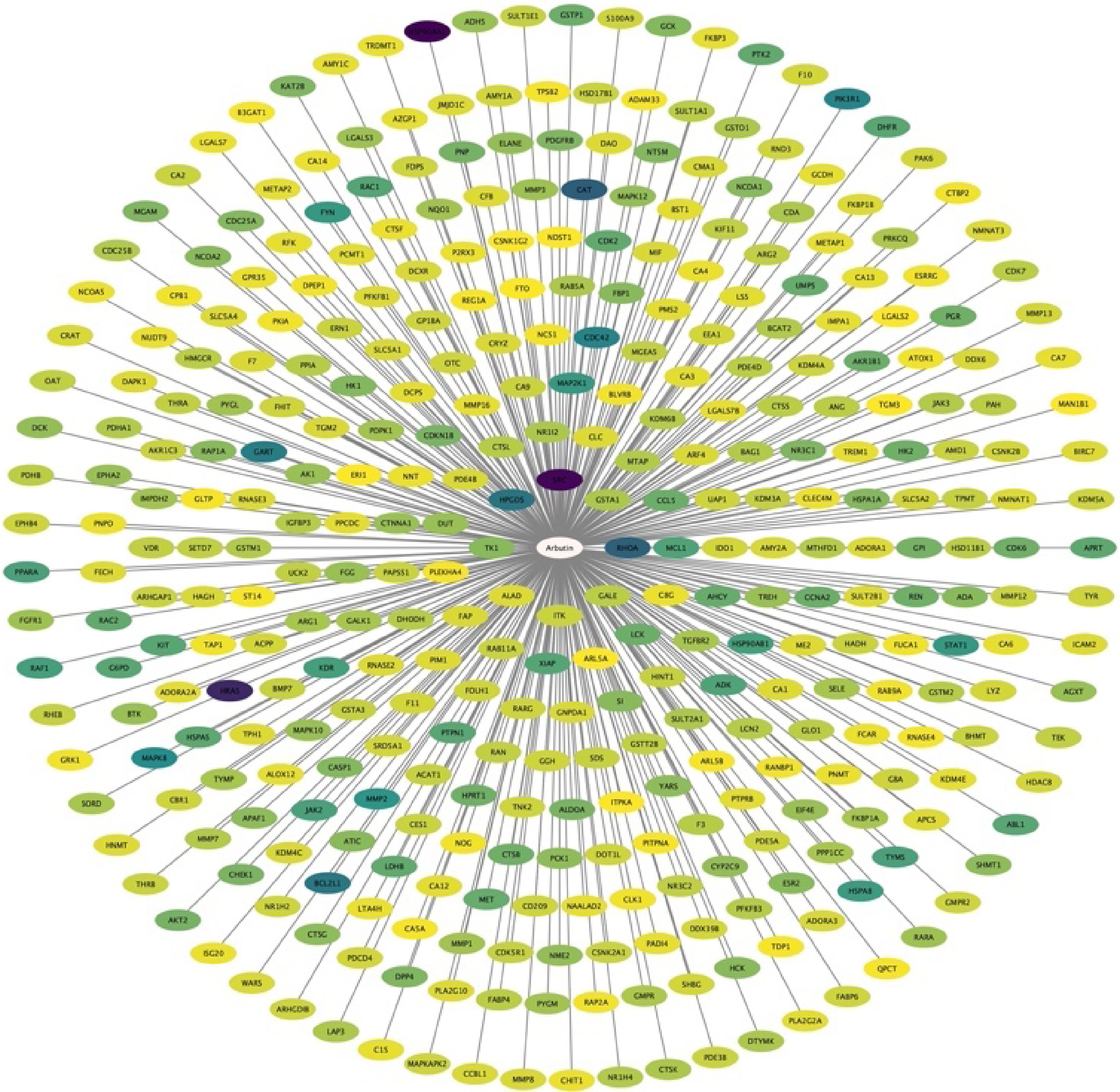

Figure 1

Target genes of arbutin and the node color purple to yellow represents the descending order of degree value

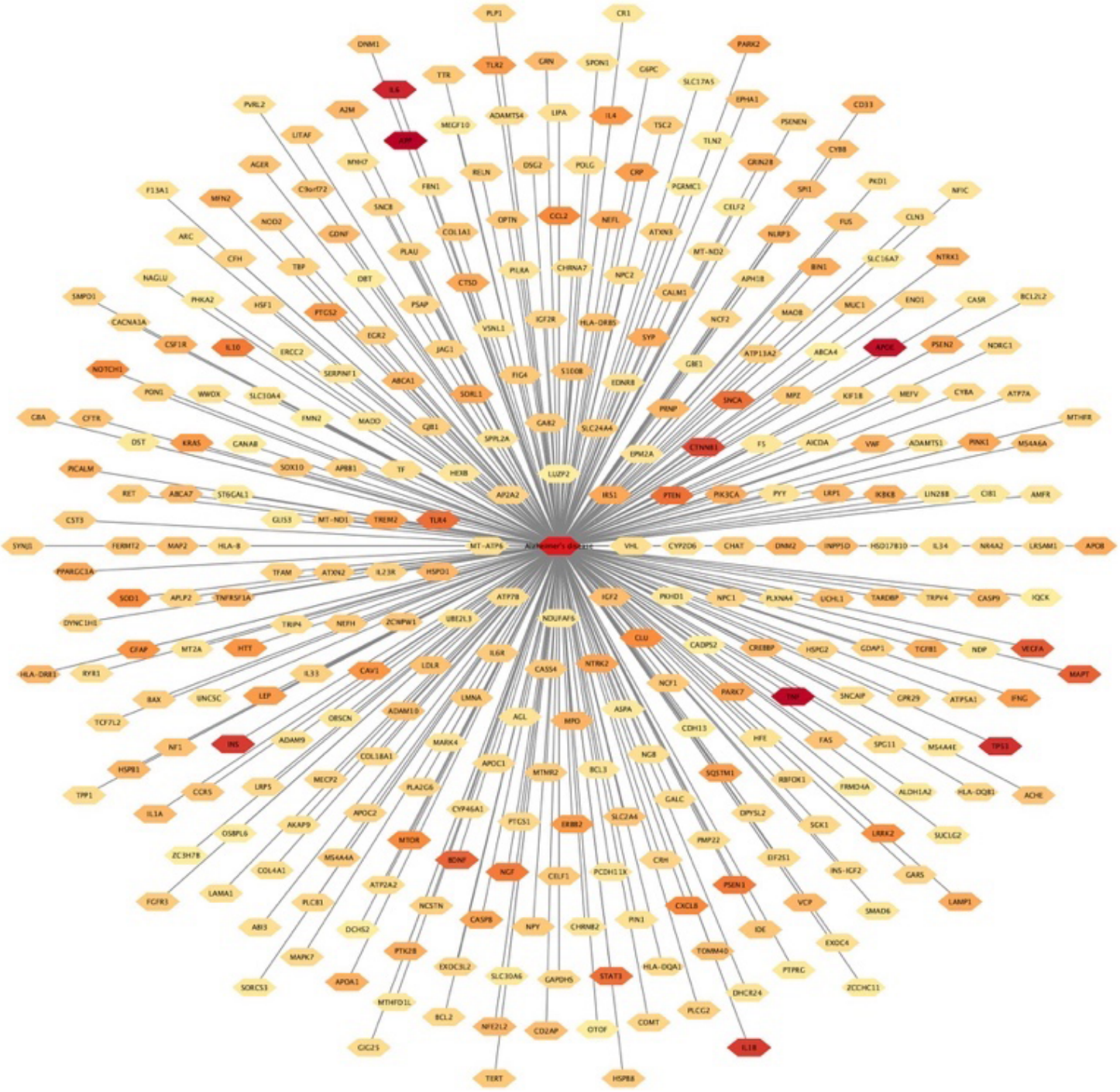

Figure 2

PPI network of AD and the node color red to yellow represents the descending order of degree values

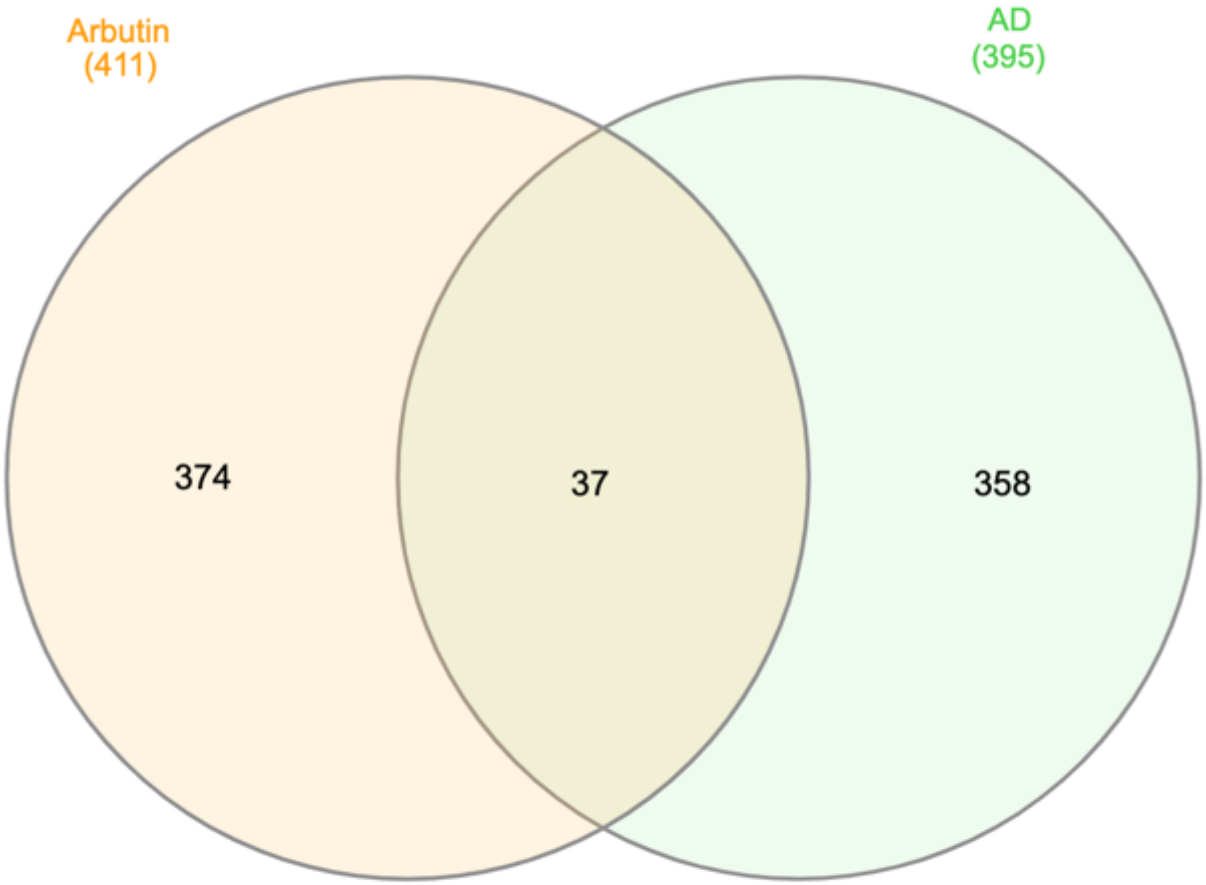

Figure 3

The common Targets of arbutin and AD are shown in the Venn diagram intersection

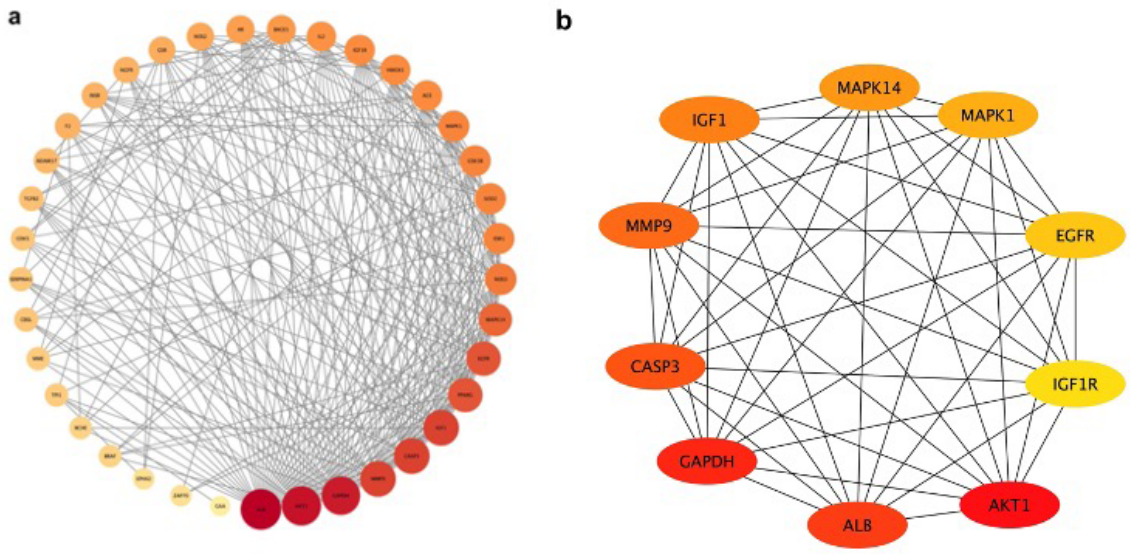

Figure 4

a Network of 37 shared targets of arbutin and AD **b** Diagram of top 10 hub genes ranked by MCC and their degree values displayed in descending order from red to yellow

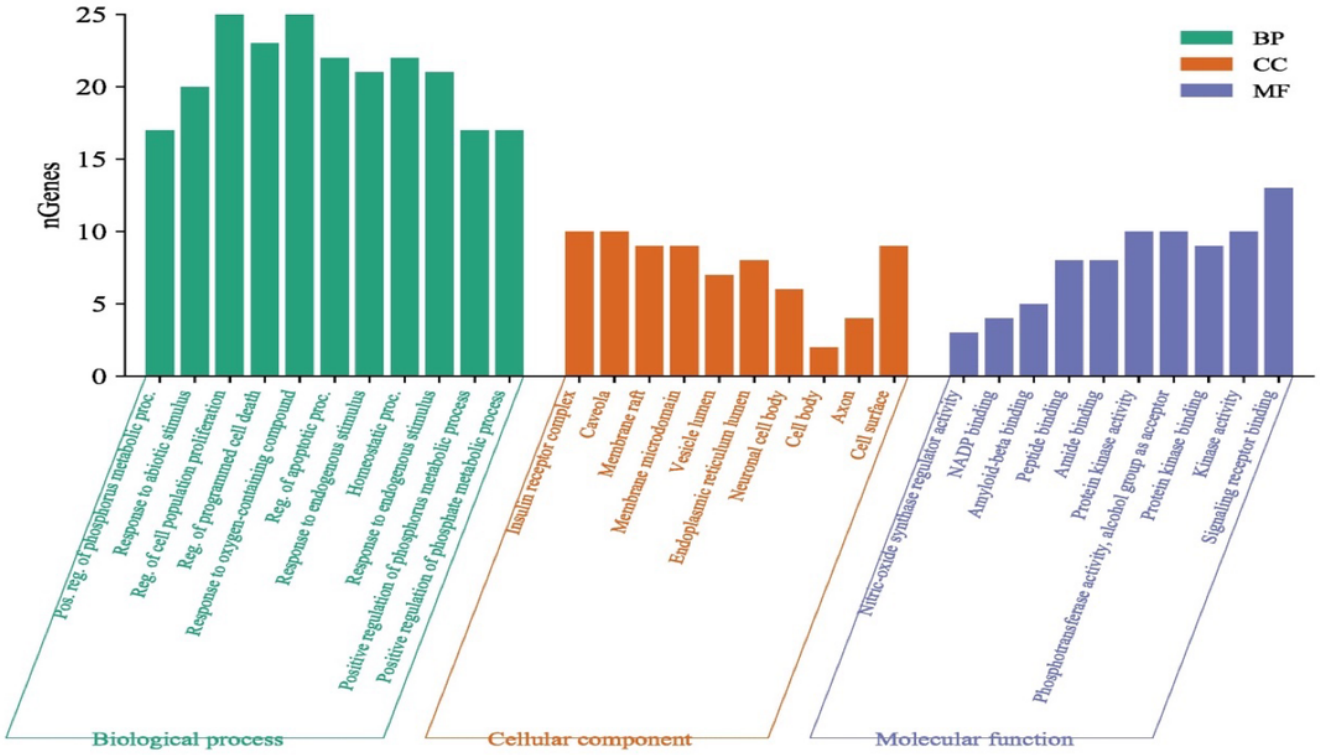

Figure 5

GO enrichment analysis

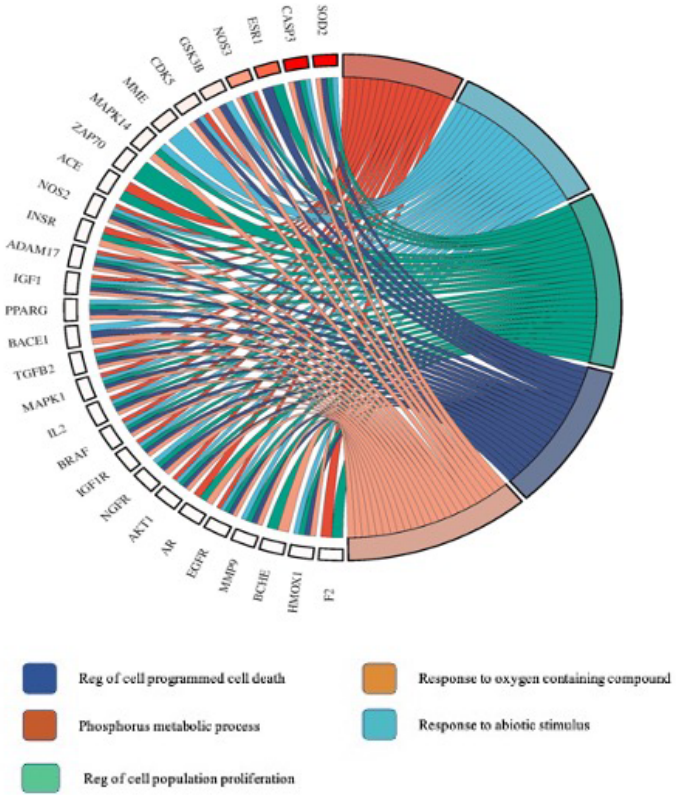

Figure 6

The top 5 out of 10 enriched biological processes with their respective genes

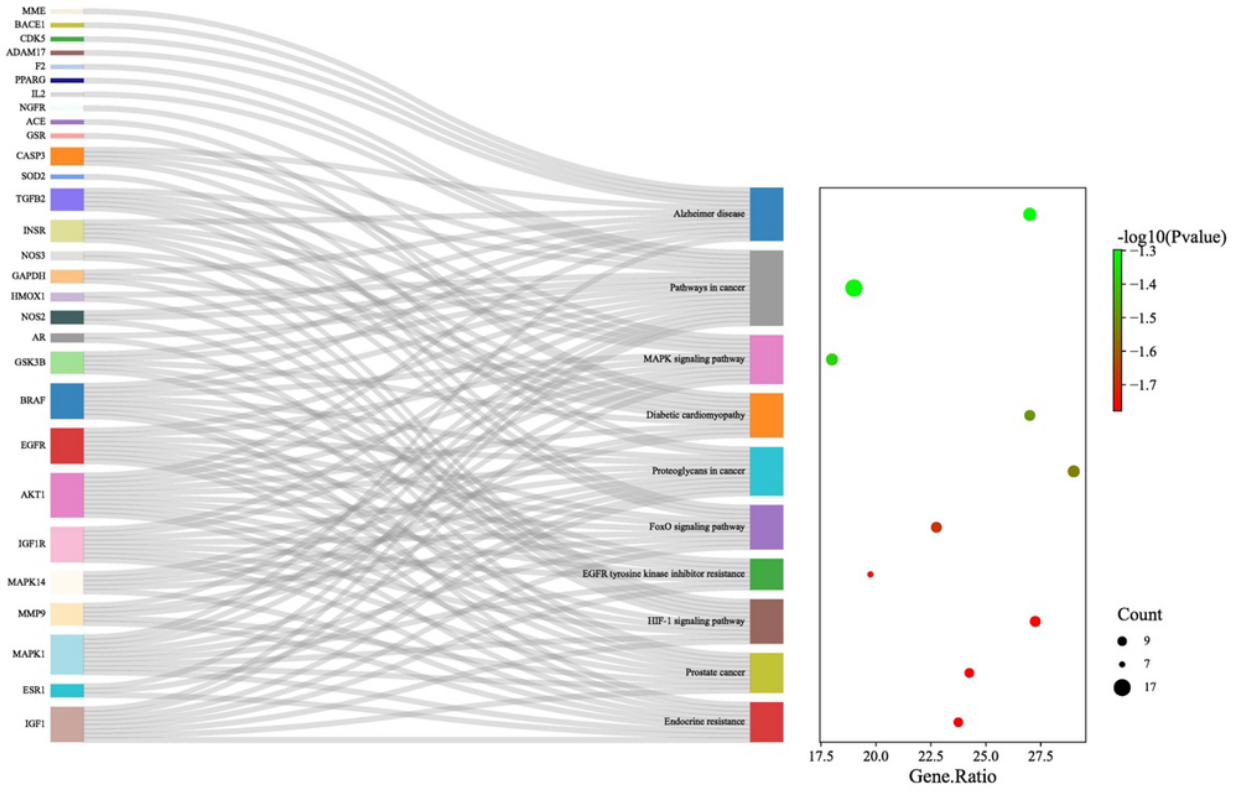

Figure 7

The KEGG pathway enrichment analysis of the common 37 therapeutic targets with the top 10 significantly enriched pathways with respective genes

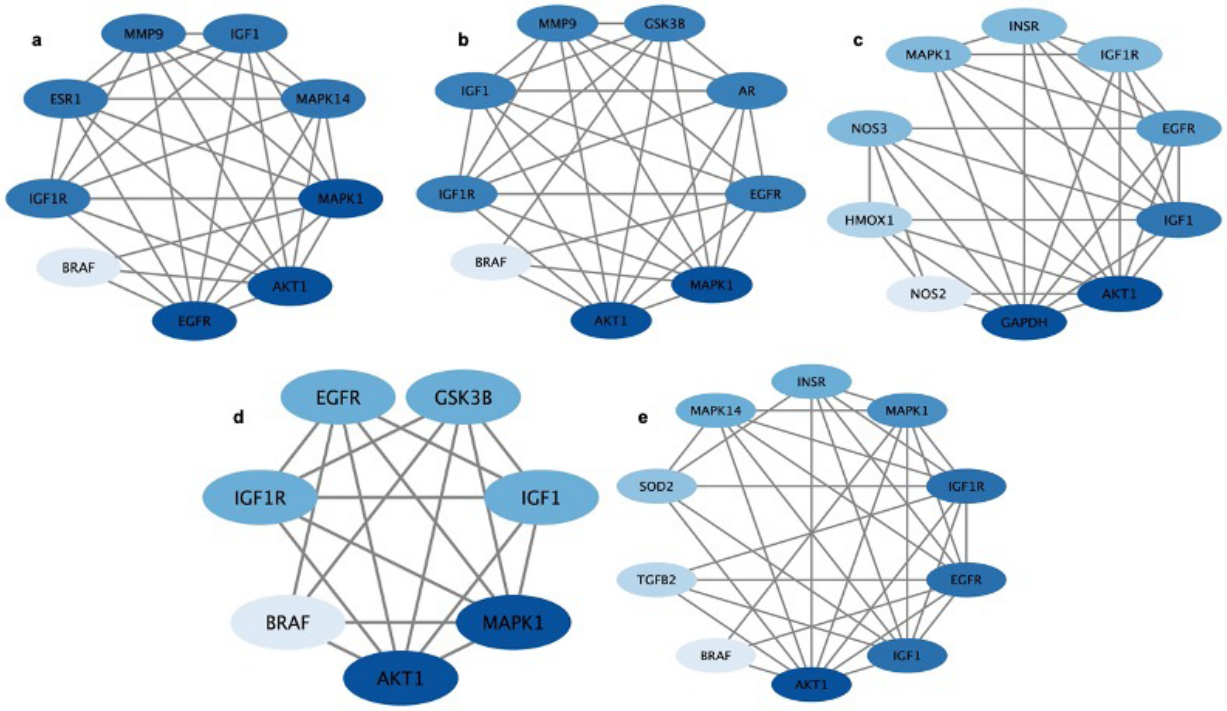

Figure 8

Top 5 KEGG enriched pathways with their top 10 genes identified through degree ranking **a** endocrine resistance **b** prostate cancer **c** HIF-1 signaling d EGFR tyrosine kinase signaling e FOX- O signaling

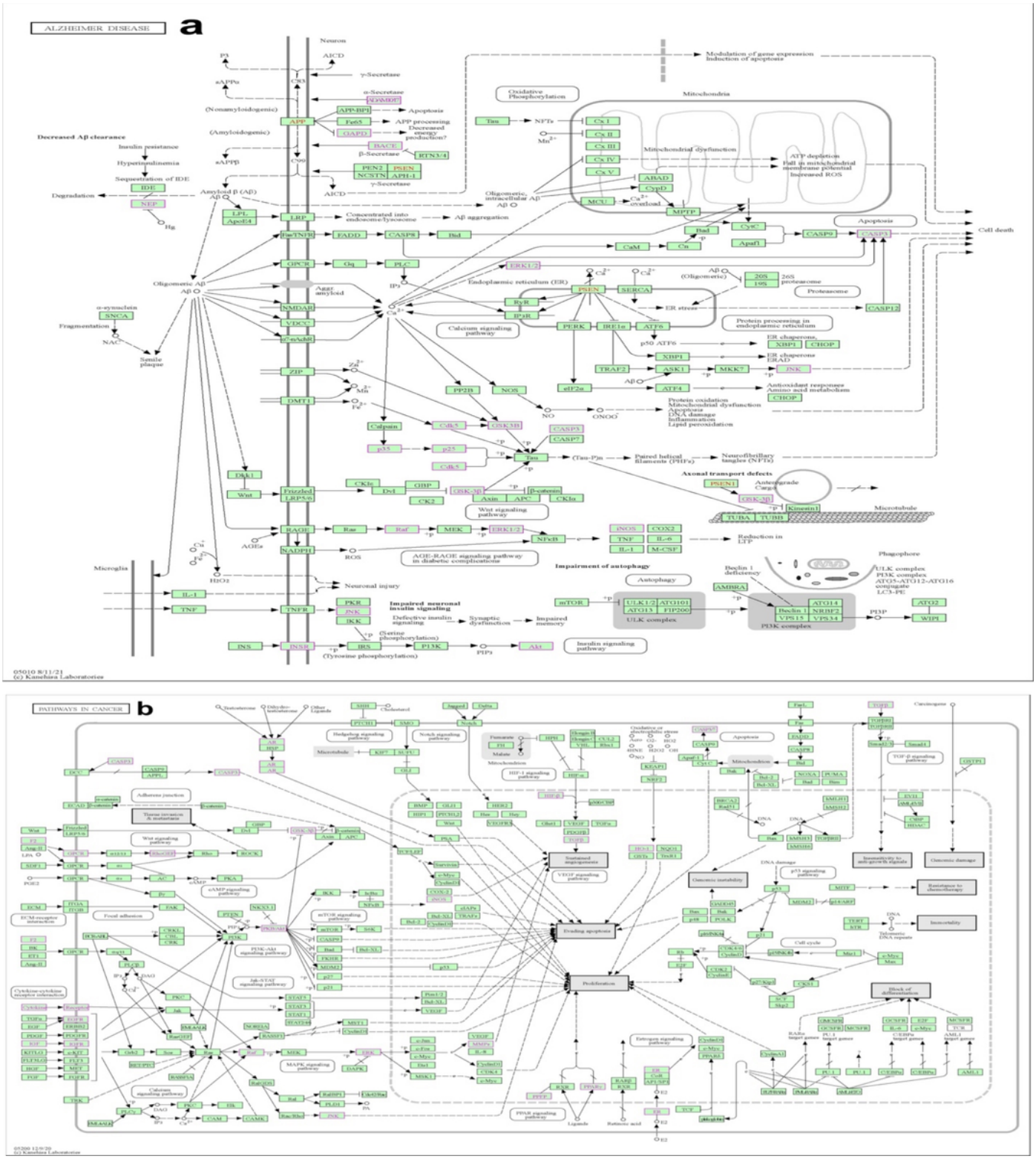

Figure 9

Distribution of potent targets on selected pathways and the nodes in purple represent the common target genes **a** Alzheimer's disease **b** Pathways in cancer

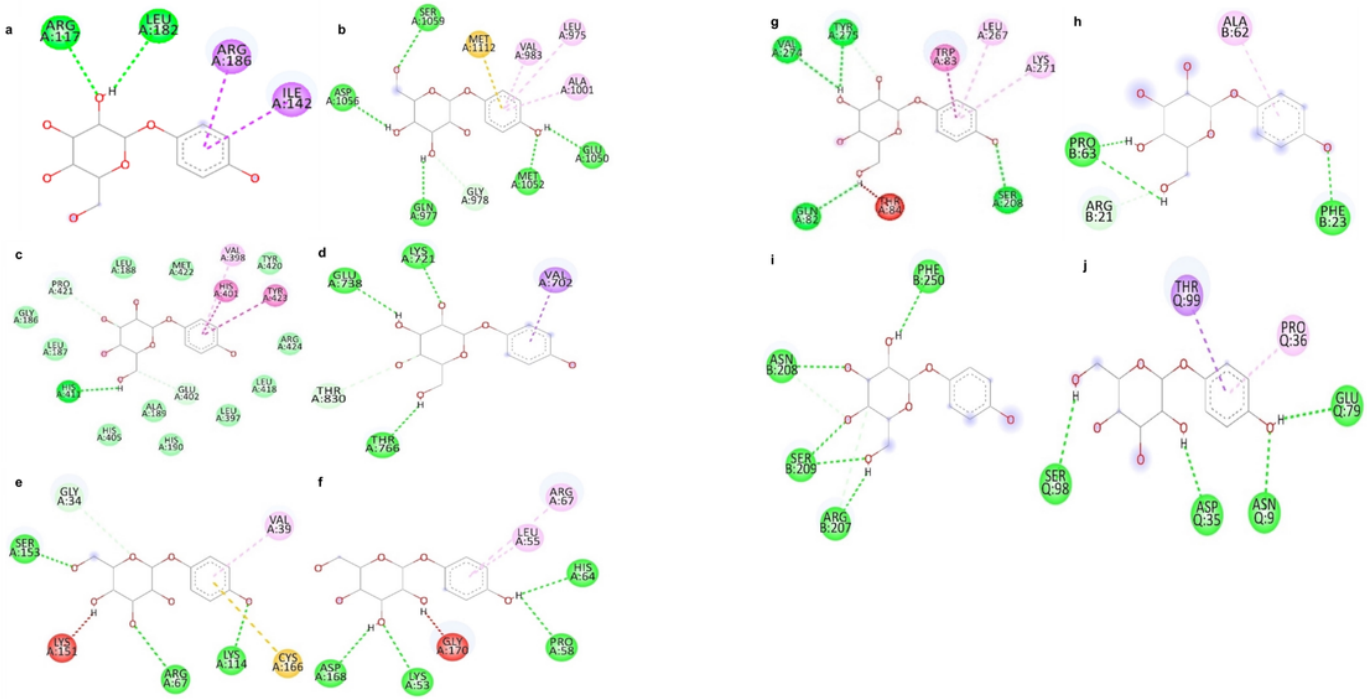

Figure 10

Molecular docking results of arbutin with hub genes **a** ALB **b**IGF1R **c**MMP9 **d**EGFR **e**MAPK1 **f**MAPK14 **g**AKT **h**IGF1 **i**CASP3 **j**GAPDH