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Network Pharmacology and Molecular Docking Perspectives into Lignans for Alzheimer's Disease Treatment

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ABSTRACT

Alzheimer's Disease (AD) is a debilitating neurodegenerative condition with limited treatment options. Lignans, a class of naturally occurring polyphenols found in various plants, have been shown to have the potential to modulate pathways associated with AD pathology. In this study, we used network pharmacology and molecular docking to investigate the therapeutic potential of lignans against AD by targeting specific proteins involved in disease progression. Our established interaction network includes key proteins such as EGFR, HSP90AA1, BCL2, HSP90AB1, IL6, JUN, ESR1, PIK3CA, ERBB2, and PIK3R1. Molecular docking studies have revealed how lignans interact with these proteins and highlighted their potential to influence AD through mechanisms such as inflammation modulation, apoptosis regulation, and signal transduction pathways. The results suggest that lignans have significant binding abilities to these targets, potentially inhibiting their activity and thus alleviating AD symptoms by reducing amyloid-beta accumulation and tau phosphorylation. These findings support the viability of lignans as a basis for the development of new AD therapies and call for further in vivo studies to confirm their efficacy and safety. This integrated approach underscores the value of combining network pharmacology and molecular docking in the search for new therapeutic agents against complex diseases such as AD.

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Alzheimer Hastalığı Tedavisinde Lignanlara Yönelik Ağ Farmakolojisi ve Moleküler Yerleştirme Perspektifleri

ÖZET

Alzheimer hastalığı (AH), sınırlı tedavi seçeneklerine sahip, zayıflatıcı nörodejeneratif bir durumdur. Çeşitli bitkilerde bulunan doğal olarak oluşan bir polifenol sınıfı olan lignanların, AH patolojisiyle ilişkili yolları modüle etme potansiyeline sahip olduğu gösterilmiştir. Bu çalışmada, hastalığın ilerlemesinde rol oynayan spesifik proteinleri hedefleyerek lignanların AH'ye karşı terapötik potansiyelini araştırmak için ağ farmakolojisi ve moleküler yerleştirme kullanılmıştır. Kurulan etkileşim ağımız EGFR, HSP90AA1, BCL2, HSP90AB1, IL6, JUN, ESR1, PIK3CA, ERBB2 ve PIK3R1 gibi önemli proteinleri içermektedir. Moleküler yerleştirme çalışmaları, lignanların bu proteinlerle nasıl etkileşime girdiğini ortaya çıkarmış ve inflamasyon modülasyonu, apoptoz düzenlemesi ve sinyal iletim yolları gibi mekanizmalar yoluyla AH'yi etkileme potansiyellerini vurgulamıştır. Sonuçlar, lignanların bu hedeflere önemli bağlanma yeteneklerine sahip olduğunu, potansiyel olarak aktivitelerini inhibe ettiğini ve dolayısıyla amiloid-beta birikimini ve tau fosforilasyonunu azaltarak AH semptomlarını hafiflettiğini göstermektedir. Bu bulgular, yeni AH tedavilerinin geliştirilmesi için bir temel olarak lignanların yaşayabilirliğini desteklemekte ve bunların etkinliğini ve güvenliğini doğrulamak için daha fazla *in vivo* çalışma yapılması çağrısında bulunmaktadır. Bu entegre yaklaşım,

Moleküler Biyoloji

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Anahtar Kelimeler
Alzheimer hastalığı
Lignan
Moleküler yerleştirme
Ağ farmakolojisi

AH gibi karmaşık hastalıklara karşı yeni terapötik ajanların araştırılmasında ağ farmakolojisini ve moleküler yerleştirmeyi birleştirmenin değerini vurgulamaktadır.

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INTRODUCTION

Alzheimer's disease (AD) is distinguished by several neuropathological changes, primarily extracellular amyloid aggregates (plaques), intraneuronal inclusions of phosphorylated tau (tangles), and neuronal and synaptic degeneration, which are accompanied by tissue reactions to astrocytosis and microglial activation that precede neuronal network disruptions in the symptomatic phase of the AD (Gobom et al., 2024). AD now affects 50 million people, with forecasts increasing to 152 million by 2050 (Dissanayaka et al., 2024; Oliveira Silva et al., 2024).

Currently, drugs licensed for AD therapy mostly provide symptomatic relief, and their effects are frequently poor. The FDA has authorized early-stage Alzheimer's drugs, such as cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists, which only give short-term symptom relief and do not prevent disease progression (Arjmandi-Rad et al., 2024). In recent years, as the research area has expanded, amyloid-related treatment has emerged as a key trend in future clinical trials of novel medications. Aducanumab and lecanemab, amyloid-antibodies that can prevent or reverse AD, have received FDA approval. Nevertheless, this novel therapy against amyloid deposition is flawed by therapy management methods, expensive drug monitoring, and the need for professional tools and imaging studies (Park et al., 2024). Therefore, there is an urgent need to investigate AD pathogenesis and develop novel therapeutic agents to prevent AD's occurrence or delay its course. Hence, exploring the pathophysiological basis of AD and developing novel therapeutics to eradicate or at least slow AD progression is of utmost importance (Qin et al., 2024).

The chemical structure of plants contains secondary metabolites or bioactive compounds including phenols, terpenoids, alkaloids, anthocyanins, chlorogenic acids, flavonoids, tannins, glycosidic replacements, and lignans (Cedillo-Cortezano et al., 2024). Lignans are well-known for their antioxidant, anticarcinogenic, antimutagenic, and anti-estrogenic effects that benefit human health. They are synthesized through the shikimic acid pathway and composed of dimerized phenylpropanoid units. Their structure is characterized by an aromatic moiety carrying different oxidation levels and substitution patterns. The two carbon atoms (8 and 8'), located at the center of the side chain of the phenylpropanoid unit with a C6C3 configuration, are dimerized to form the structure of lignans (Nawfetrias et al., 2024).

Combining mathematics, bioinformatics, and many other fields, network pharmacology assists us in understanding the vast integrative and systematic properties of natural AD drugs obtained as a result of processing relevant plants. Research on molecular processes and the establishment of a drug ingredient target network are key processes of network pharmacology in helping study the AD therapy carried out with natural compounds based on plants through the lens of a systemic and wholesome approach. (Zhi et al., 2024).

Subsequently, lignans' anti-AD characteristics in AD were determined through a network pharmacology technique, which also provided a foundation for future experimental investigations and therapeutic applications. The combination of integrated network pharmacology and bioinformatics research revealed that the anti-AD pharmacological activities of lignans might be mainly attributed to blocking signaling pathways, hence slowing down the course of AD. These findings imply that lignans may be able to target the proposed therapeutic targets for the treatment of AD.

MATERIAL and METHOD

Determination of possible targets of lignans and AD

PubChem provided the canonical SMILES of the 8 lignans (enterodiol, enterolactone, etoposide, lariciresinol, matairesinol, pinoresinol, podophyllotoxin, and secoisolariciresinol) employed in this study. Using the canonical smiles of 8 lignans, their possible targets were obtained from SwissTargetPrediction (Table 1). Possible targets associated with AD were obtained from DisGeNET. Venny was used to link lignans with possible targets associated with AD (Trivedi et al., 2024; Xiaoying et al., 2023).

SwissADME

SwissADME was used to determine the physicochemical properties, lipophilicity, water solubility, pharmacokinetics, drug-likeness, and medicinal chemistry associated with lignans (Daina et al., 2014, 2017; Daina & Michelin, 2016).

Table 1. Canonical SMILES list of the 8 lignans
Çizelge 1. 8 lignanın kanonik SMILES listesi

Lignan name	Canonical SMILES	PubChem compound ID
Enterodiol	C1=CC(=CC(=C1)O)CC(CO)C(CC2=CC(=CC=C2)O)CO	115089
Enterolactone	C1C(C(C(=O)O1)CC2=CC(=CC=C2)O)CC3=CC(=CC=C3)O	10685477
Etoposide	CC1OCC2C(O1)C(C(C(O2)OC3C4COC(=O)C4C(C5=CC6=C(C=C35)OCO6)C7=CC(=C(C(=C7)OC)O)OC)O)O	36462
Lariciresinol	COC1=C(C=CC(=C1)CC2COC(C2CO)C3=CC(=C(C=C3)O)OC)O	332427
Matairesinol	COC1=C(C=CC(=C1)CC2COC(=O)C2CC3=CC(=C(C=C3)O)OC)O	119205
Pinoresinol	COC1=C(C=CC(=C1)C2C3COC(C3CO2)C4=CC(=C(C=C4)O)OC)O	73399
Podophyllotoxin	COC1=CC(=CC(=C1OC)OC)C2C3C(COC3=O)C(C4=CC5=C(C=C24)OCO5)O	10607
Secoisolariciresinol	COC1=C(C=CC(=C1)CC(CO)C(CC2=CC(=C(C=C2)O)OC)CO)O	65373

Protein-Protein Interactions (PPI) Network Analysis

PPI networks are an important tool for understanding the complex interactions of biological processes and cellular functions. In our study, the STRING database was used to determine the interactions of relevant proteins. The STRING database is a large source of biological data integrating known and predicted PPI. The data were analyzed to determine the network structures of the identified proteins and the key nodes (hub proteins) in these networks. Then, the PPI network was visualized using Cytoscape software, and topological features were evaluated. This analysis allows us to better understand the biological functions of proteins and their roles in interaction networks (Szklarczyk et al., 2023, 2019, 2016, 2015, 2010; Franceschini et al., 2016, 2012; Jensen et al., 2009; von Mering et al., 2003, 2005, 2007; Snel et al., 2000).

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

GO enrichment analysis is used to determine whether a particular set of genes is significantly enriched in biological processes, molecular functions, and cellular components. In our study, the ShinyGo tool was used to determine the functional annotations of differentially expressed genes and their roles in biological processes. This tool evaluates the associations of gene sets with GO terms and identifies statistically significant enriched GO terms. The results obtained help us understand the biological functions of genes and their participation in processes (Bindea et al., 2009; Huang et al., 2009).

KEGG pathway enrichment analysis is used to determine the relationship of a given gene set to known biological pathways. In this study, the KEGG database was used to determine which biological pathways differentially expressed genes are associated with. Analysis was performed using the ShinyGo tool. These tools map gene sets to KEGG pathways and identify statistically significant enriched pathways. The resulting data enable us to understand which metabolic or signal transduction pathways genes are involved in and how these pathways change in disease (Ge et al., 2020; Huang et al., 2009; Xie et al., 2011).

Molecular Docking CB-Dock2

CB-Dock2 is an improved version of the CB-Dock2 server for protein-ligand blind docking, integrating cavity detection, docking, and homologous template docking. Given the three-dimensional (3D) structure of a ligand and a target protein, it predicts their binding sites and affinities (Liu et al., 2022a; Xiaoying et al., 2023; Yang et al., 2022).

The 3D structure of the target protein was obtained from the Protein Data Bank (PDB) (Table 2). The specific PDB ID for the target protein was identified and downloaded. The protein structure was cleaned by removing any water molecules, ligands, or other heteroatoms that could interfere with the docking process. This was done using molecular visualization software such as PyMOL. Hydrogen atoms were added to the protein structure to ensure proper geometry and charge distribution. This step is crucial for accurate docking predictions.

Table 2. PDB code list of the proteins
Çizelge 2. Proteinlerin PDB kod listesi

Protein name	PDB codes
BCL2	1G5M
EGFR	5WB7
ERBB2	3PP0
ESR1	1XP1
HSP90AA1	81GI
HSP90AB1	1UYM
IL6	1ALU
JUN	1JUN
PIK3CA	7R9V
PIK3R1	5XGI

The 3D structures of the lignans were either obtained from chemical databases like PubChem or ChemSpider or drawn using molecular editing software such as ChemDraw. The structures of the lignans were optimized using quantum chemistry

methods or force field-based energy minimization to achieve a stable conformation. This was done using software such as Gaussian. The optimized lignan structures were converted to the SDF format, which is required for docking studies using CB-Dock2. This conversion was performed using AutoDockTools.

The prepared protein and ligand structures were uploaded to the CB-Dock2 server. CB-Dock2 automatically detected potential binding cavities on the protein surface. This is a crucial step for blind docking, as it identifies the regions where the ligand is most likely to bind. The docking process was initiated, where the ligand was docked into the identified cavities. CB-Dock2 used a combination of docking algorithms and scoring functions to predict the binding affinities and orientations of the ligand within the cavities.

The docking results were scored and ranked based on the predicted binding affinities. The top-ranked poses were selected for further analysis. The binding poses of the ligands were visualized using molecular visualization software to assess the interactions between the ligand and the protein. Key interactions, such as hydrogen bonds, hydrophobic interactions, and pi-pi stacking, were identified and analyzed.

RESULT and DISCUSSION

According to the oral bioavailability radar, the colored zone is the ideal physicochemical space for oral bioavailability when the following characteristics are taken into account: lipophilicity (XLOGP3 between -0.7 and +5.0), size (MW between 150 and 500 g/mol), polarity (TPSA between 20 and 130 $Å_2$), solubility (log S not higher than 6), saturation (the carbon fraction in sp3 hybridization should not be less than 0.25), and flexibility (no more than 9 rotatable bonds) (Ibrahim et al., 2020; Mishra and Dahima, 2019). The lignans (enterodiol, enterolactone, etoposide, lariciresinol, matairesinol, pinoresinol, podophyllotoxin, and secoisolariciresinol) oral bioavailability radar is displayed in Figure 1. All other lignans are within the oral bioavailability radar range, with the exception of etoposide. Abd El-Razek et al. (2024) reported that colchicine and epimagnolin are found in the advised range. Compounds 1-4 were determined to have acceptable values when generated from dibenzylbutyrolactone lignans from *Hydrocotyle bonariensis* parameters related to the oral bioavailability radar, as reported by Souza et al. (2021). Compound 5, on the other hand, violated the saturation criterion and thus was not recommended. Depending on their structural features, lignans may have different acceptance ranges on the oral bioavailability radar.

The BOILED-Egg model was used for simultaneous prediction of blood-brain barrier (BBB) penetration and human gastrointestinal absorption (HIA) of lignans and provides insight into their permeation characteristics (Majahan et al., 2024). The BOILED-Egg graphical interface also visually provides information on polarity (TPSA) and lipophilicity (WLOGP). This graph visually displays PGP (p-glycoprotein) responses and thus more clearly delineates the bioavailability of molecules. Membrane-bound PGP, a transporter that leads to substrate (PGP^+) efflux, reduces intracellular concentrations and lowers molecular bioavailability (Nag et al., 2022). Figure 2 shows lignans' BOILED-Egg plot. Enterolactone (molecule 2) and pinoresinol (molecule 6) are the two molecules with positive BBB penetration and HIA properties as well as positive PGP effects. Enterodiol (molecule 1), lariciresinol (molecule 4), matairesinol (molecule 5), pinoresinol (molecule 6), podophyllotoxin (molecule 7), and secoisolariciresinol (molecule 8) are the molecules with a negative BBB penetration property and a positive HIA property when they are under the effect of the PGP. Etoposide (molecule 3) exerts a positive PGP effect on the molecule and displays a negative HIA property and a negative BBB penetration property. Chopade et al. (2021) reported that phyllanthin and hypophyllanthin originated from *Phyllanthus amarus* and passed through the BBB *in silico* BOILED egg models.

Majahan et al. (2024) reported favorable penetration HIA and BBB penetration properties for enterolactone, favoring the potential of the drug candidate in both bioavailability radar and BOILED Egg model. The lignans' structural characteristics may be influential in their HIA and BBB peneration in the BOILED Egg model.

Using canonical smiles of 8 lignans (enterodiol, enterolactone, etoposide, lariciresinol, matairesinol, pinoresinol, podophyllotoxin, and secoisolariciresinol), 201 possible targets were obtained from SwissTargetPrediction. 3173 possible AD-related targets were obtained from DisGeNET. Venny was used to link lignans to possible targets associated with AD. 224 possible common targets were identified (Figure 3 and Table 3).

Network pharmacology goes beyond the traditional single-drug-single-target paradigm by providing a holistic view of the interactions of ligands, targets, and diseases, enabling the development of multitarget therapies. Integrating systems biology, this approach enables the analysis of biological networks and pathways, thereby helping to elucidate the mechanisms of action of biologically active compounds and their effects on disease pathways (Hopkins, 2007; Li et al., 2011).

The PPI network was created by connecting 224 possible common targets with STRING. The number of nodes was determined as 228, the number of edges was 1165, the average node degree was 10.2 and the average local clustering coefficient was 0.462 (Fi. 4).

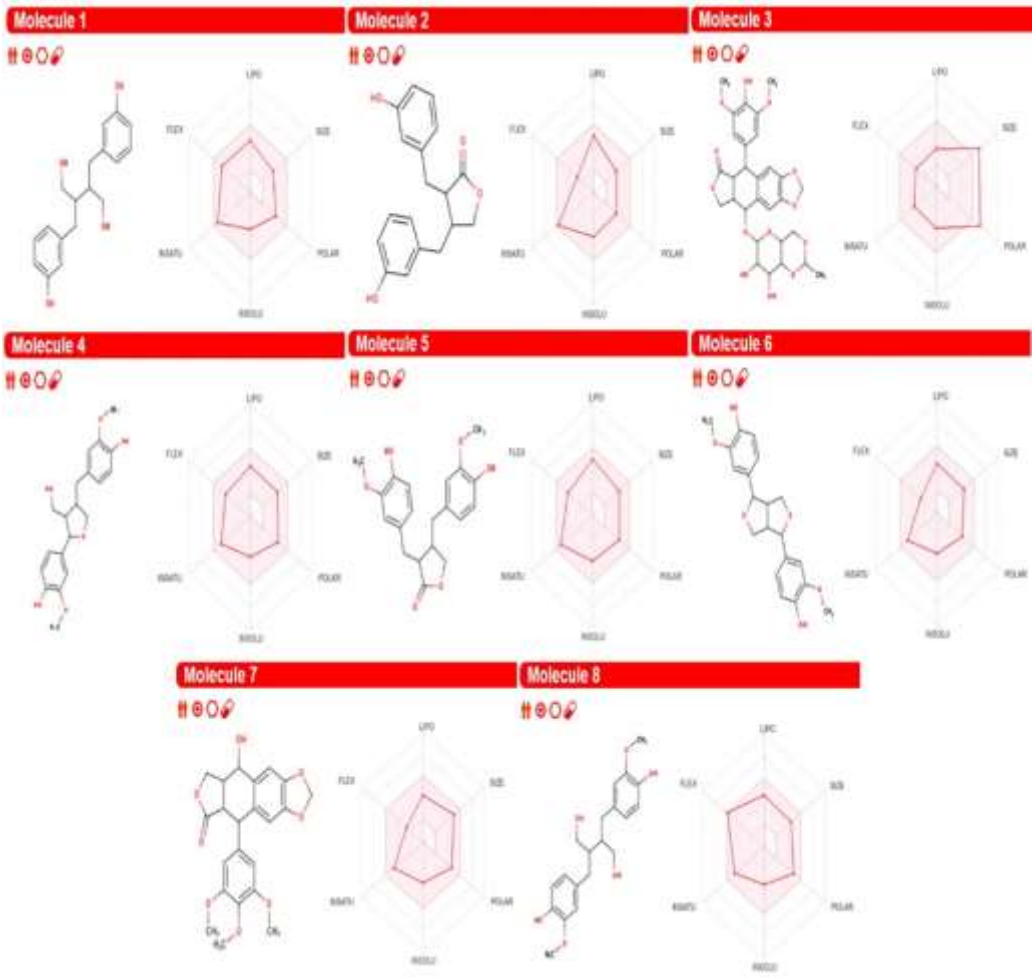

Figure 1. Oral bioavailability radar of lignans (enterodiol (molecule 1), enterolactone (molecule 2), etoposide (molecule 3), lariciresinol (molecule 4), matairesinol (molecule 5), pinoresinol (molecule 6), podophyllotoxin (molecule 7), and secoisolariciresinol (molecule 8)

Şekil 1. Lignanların (enterodiol (molekül 1), enterolakton (molekül 2), etoposid (molekül 3), larisiresinol (molekül 4), matairesinol (molekül 5), pinoresinol (molekül 6), podofillotoksin (molekül 7) ve sekoizolarisiresinol (molekül 8) oral biyoyararlanım radarı

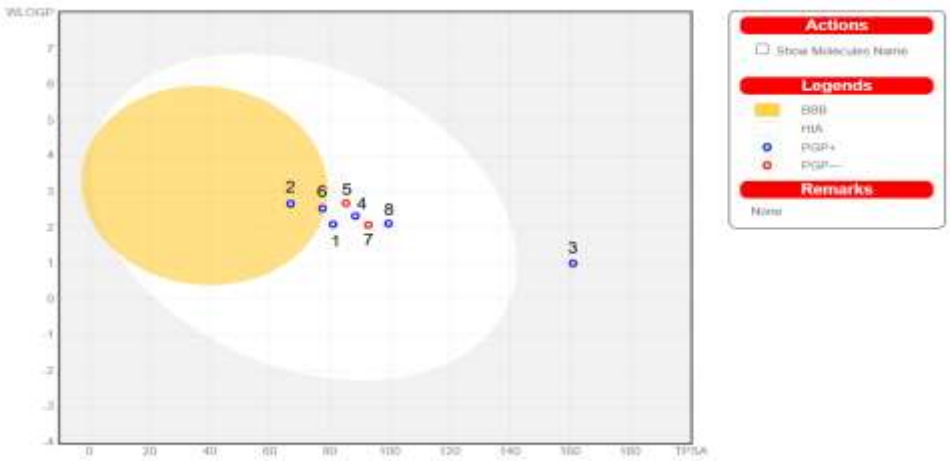

Figure 2. BOILED-Egg plot of lignans (enterodiol (molecule 1), enterolactone (molecule 2), etoposide (molecule 3), lariciresinol (molecule 4), matairesinol (molecule 5), pinoresinol (molecule 6), podophyllotoxin (molecule 7), and secoisolariciresinol (molecule 8)

Şekil 2. Lignanların (enterodiol (molekül 1), enterolakton (molekül 2), etoposid (molekül 3), larisiresinol (molekül 4), matairesinol (molekül 5), pinoresinol (molekül 6), podofilotoksin (molekül 7) ve sekoizolarisiresinol (molekül 8) haşlanmış yumurta grafiği

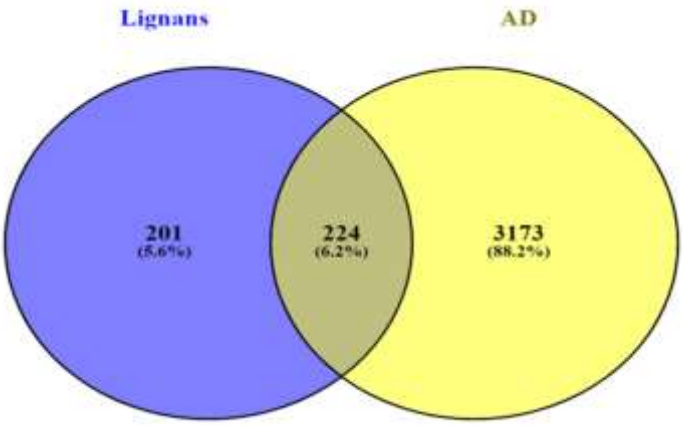

Figure 3. Venn diagram of lignans and possible targets of AD
Şekil 3. Lignanların ve AH'nin olası hedeflerinin Venn diyagramı

Table 3. 224 common targets in "Lignans" and "AD"
Çizelge 3. "Lignanlar" ve "AH"nin 224 ortak hedefi

KDR	MMP9	NOX4	MTOR	CDC25B	ALOX5AP
ESR2	MMP1	JUN	PIK3CA	ACE	QPCT
POLB	TYK2	FLT4	HCAR2	PIK3CB	GSK3A
ESR1	MAPK1	PITRM1	GBA	HCK	ABCC9
ALOX5	MMP8	ABL1	PIK3CD	PIK3CG	MTNR1A
NR3C1	PTGS2	MAP2	PNP	MAPK3	EDNRA
AR	ROCK2	MTNR1B	BCHE	EIF2AK3	GRM5
STS	TYR	DRD1	P2RX7	AKT2	PDE2A
TTR	SLC22A2	BCL2	EGFR	CDK4	PDE10A
ESRRA	NR1I3	ALB	LCK	SERPINE1	TAOK2
GPER1	SYK	FTO	PTGER3	CLK1	FLT1
SHBG	MAP3K7	SGK1	CASP3	DNM1	PDGFRB
WEE1	CAPN1	RAF1	GAPDH	HTR7	INSR
ADCY10	BACE1	MAPK8	MMP14	PNMT	IKBKB
ALOX15	HTR2C	PLK1	OGA	PRKACA	MAP2K3
ALOX12	RET	NOS1	SIRT2	MET	PRKAA2
CYP19A1	CHRM1	FGFR1	MME	PDK1	CAMK4
IGF1R	CHRM3	NOS2	TACR2	ABCG2	CHEK2
HSD17B1	ROCK1	ERBB2	NUDT1	PPARG	DAPK1
SLC6A4	RELA	ANPEP	MCL1	YES1	CAMKK2
CDK5	MAPK14	DYRK1A	MAPK9	EPHB2	INSRR
ADRA2A	HSP90AA1	PLA2G7	HIF1A	LYN	HMGCR
HTR1A	HSP90AB1	CYP2C9	CFTR	EPHA4	ACVRL1
CHEK1	CHRM2	CYP2C19	DPP4	BTK	XIAP
PGR	PARP1	SLC5A2	LNPEP	TYRO3	
IL6	BRD4	CYP3A4	ERN1	EPHA1	
ADAM17	NTRK1	ADORA1	FFAR1	OPRK1	
GLUL	MMP3	MMP13	HDAC6	BMP1	
GPBAR1	CREBBP	MMP2	HDAC2	PCNA	
SLC6A2	ADA	SLC29A1	PRSS3	KMO	
SLC6A3	OPRM1	IRAK4	CSF1R	TDP1	
JAK2	MAP2K1	ST6GAL1	F9	ABCB1	
LRRK2	NR1H3	PDE5A	TLR4	NR1H2	
GSK3B	PPARD	AGTR1	CXCR2	HDAC4	
CNR1	F2	HK1	CXCR1	MAP3K12	
CNR2	TGFBR1	P2RX3	PAK3	PIK3C3	
HDAC1	NQO2	CA2	PAK1	TDP2	
CDK1	ADORA2A	HSPA5	DHFR	MAPKAPK2	
MAP2K2	MMP7	F3	SLC2A1	NR3C2	
MAPKAPK5	HSD11B1	HSPA8	SOAT1	CTSD	

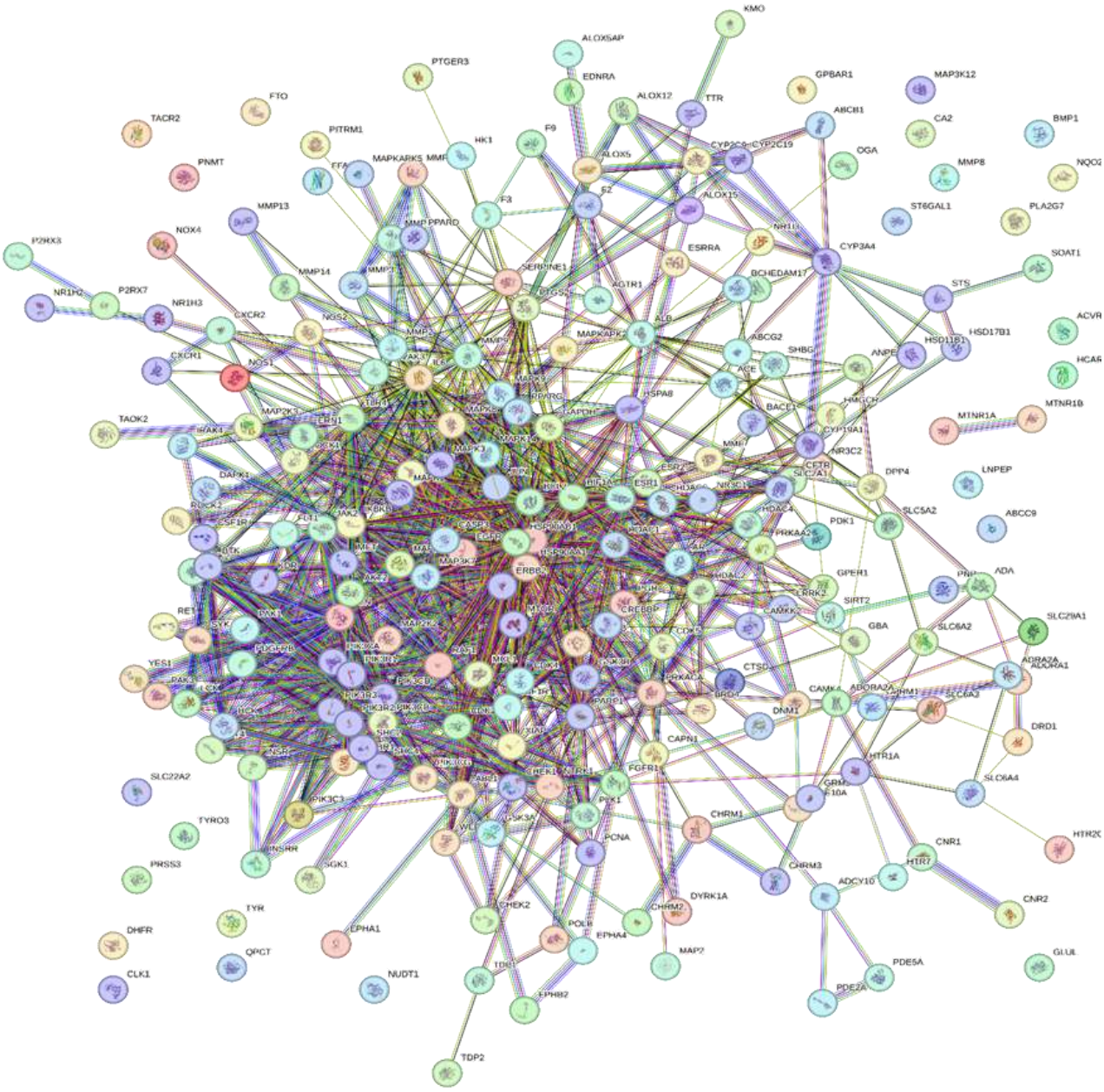

Figure 4. The PPI network

The different node colors show the different levels of interactions whereas the edge colors show their known, predicted, and other interactions. Color code for edges interpretation: neighborhood (green), gene fusion (red), cooccurrence (blue), coexpression (dark), experiments (pink), databases (sky blue), textming (kelly), and homology (purple).

Şekil 4. PPI ağı

Farklı düğüm renkleri farklı etkileşim seviyelerini gösterirken kenar renkleri bilinen, tahmin edilen ve diğer etkileşimleri göstermektedir. Kenarların yorumlanması için renk kodu: komşuluk (yeşil), gen füzyonu (kırmızı), birlikte oluşum (mavi), birlikte ifade (koyu), deneyler (pembe), veritabanları (gök mavisi), metin madenciliği (kelly) ve homoloji (mor).

These data show that the network is highly dense and tightly connected, indicating that interactions between proteins are strong and reflect potentially important biological functions. The average node degree of 10.2 indicates that each protein interacts with approximately 10 other proteins on average, increasing the complexity and biological significance of the network. The average local clustering coefficient is 0.462, indicating that there is a high level of interaction in subsets of the network and these interactions may play critical roles in biological processes. Such dense interaction networks mean that certain proteins play central roles and that these proteins may be potential therapeutic targets.

The top 10 targets (EGFR, HSP90AA1, BCL2, HSP90AB1, IL6, JUN, ESR1, PIK3CA, ERBB2, and PIK3R1), ranked according to their node degrees, have been determined (Table 4). PPI networks of the first 10

targets ranked according to their node degrees are drawn. It was determined that there were 43 interactions between 10 targets (Figure 5). These interactions help us understand the effects of these proteins on biological processes and disease mechanisms. Growth factor receptors such as EGFR and ERBB2 promote neuronal development and survival, whereas chaperone proteins like HSP90AA1 and HSP90AB1 can minimize the toxicity of amyloid beta and tau proteins by controlling protein folding (Ahsan et al., 2012; Dent et al., 2021). BCL2, an apoptosis regulator, and signal transduction modulators JUN, PIK3CA, and PIK3R1 play critical roles in nerve cell survival and death, providing neuroprotection (Behl et al., 1993; Jimenez et al., 2011). On the other hand, molecules like IL6 and ESR1 may contribute to AD through inflammatory responses and hormonal interactions (Boada et al., 2012; Liu et al., 2022b; Miron et al., 2018). While each of these genes contributes to the complicated etiology of AD in various ways, a thorough knowledge of these relationships may pave the way for the creation of new disease management and treatment options.

Table 4. Node and node degree of targets
Çizelge 4. Hedeflerin düğüm ve düğüm derecesi

#Node	Node_degree
EGFR	58
HSP90AA1	58
BCL2	45
HSP90AB1	44
IL6	41
JUN	41
ESR1	39
PIK3CA	39
ERBB2	38
PIK3R1	38

Although it is well known that the protein known as the epidermal development factor receptor (EGFR) is involved in cell development, differentiation, and survival, recent studies have indicated that EGFR may also have a role in AD. By stimulating tyrosine kinase signalling pathways that support brain cell growth and survival, EGFR may contribute to cellular dysfunction and neuronal death in AD (Jayaswamy et al., 2023). Moreover, it is postulated that EGFR signalling triggers neuroinflammatory processes by stimulating brain-resident immune cells called microglia and astrocytes (Qu et al., 2025). The production of amyloid beta peptides and aberrant tau protein phosphorylation, which are the main pathogenic features of AD, may also be impacted by these activities (Rajmoran and Reddy, 2017). Neuronal loss can result from either excessive or insufficient EGFR activation (Tavassoly et al., 2020).

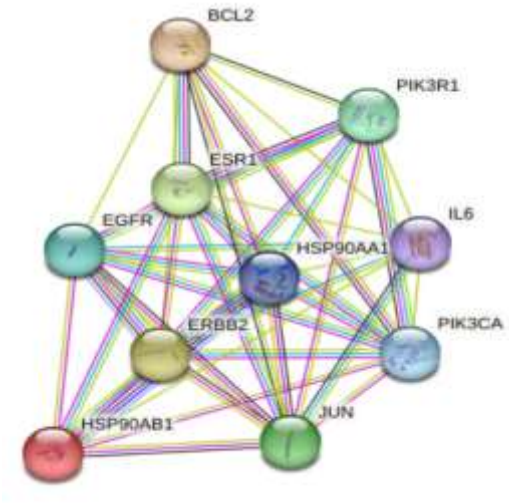

Figure 5. PPI network of top 10 targets
The different node colors show the different levels of interactions whereas the edge colors show their known, predicted, and other interactions. Color code for edges interpretation: neighborhood (green), gene fusion (red), cooccurrence (blue), coexpression (dark), experiments (pink), databases (sky blue), textming (kelly), and homology (purple).
Şekil 5. İlk 10 hedefin PPI ağı
Farklı düğüm renkleri farklı etkileşim seviyelerini gösterirken kenar renkleri bilinen, tahmin edilen ve diğer etkileşimleri göstermektedir. Kenarların yorumlanması için renk kodu: komşuluk (yeşil), gen füzyonu (kırmızı), birlikte oluşum (mavi), birlikte ifade (koyu), deneyler (pembe), veritabanları (gök mavisi), metin madenciliği (kelly) ve homoloji (mor).

Intracellular heat shock protein 90 (HSP90) is involved in the folding, defense, and operation of proteins (Hoter et al., 2018). Heat shock protein 90 alpha family class A member 1 (HSP90AA1) and heat shock protein 90 alpha family class B member 1 (HSP90AB1) are its two isoforms. According to reports, HSP90AA1 and HSP90AB1 may have a significant impact on the accumulation of proteins and neuroprotective processes, which may influence the aetiology of AD (Gonzalez-Rodriguez et al., 2021). Heat shock protein 90 is significant because it inhibits the improper folding of tau and amyloid beta and their accumulation in the central nervous system, which lessens the harmful intracellular consequences of these proteins in neurodegenerative diseases (Bohush et al., 2019). By reducing the development of amyloid plaque and hyperphosphorylating tau, HSP90AA1 inhibition may be able to prevent neural damage and cell death. Additionally, this chaperone protein may benefit AD by promoting stress resistance of neuronal cells (Astillero-Lopez et al., 2024).

B-cell lymphoma 2 (BCL2), a protein that provides protection against cellular death and increases cell longevity, mainly functions by inhibition of apoptosis (Alam et al., 2021). It exerts cellular protective effects against neurodegeneration and thus has a central role

in AD (Shacka & Roth, 2005). AD is essentially characterized by apoptotic neuronal cell death through oxidative stress and mitochondrial malfunction (Eckert et al., 2003). Signals for cellular death can be effectively inhibited by BCL2 through the preservation of an intact mitochondrial membrane and the prevention of cytochrome c release (Scorrano & Korsmeyer, 2003). Hence, BCL2 can halt neuron loss in AD (Zhu et al., 2004).

Interleukin 6 (IL6) is a cytokine with pro-inflammatory properties and takes part in the regulation of immune response. It has been suggested that IL6 plays a role in the neuroinflammatory aspect of AD (Lyra e Silva, 2021). Accumulation of amyloid beta peptides and neurofibrillary tangles are responsible for the activation of immune cells, namely astrocytes, and microglia, in AD (Webers et al., 2020). According to Weisman et al. (2006), these deposits cause an increase in IL6 release, which fortifies the immunological response. According to Rubio-Perez et al. (2012), increased IL6 can cause neuronal injury and dysfunction, which would hasten the onset and course of the disease. On the other hand, IL6 may also have neuroprotective properties, such as promoting the survival and repair of neurons (Kummer et al., 2021).

The AP-1 transcription factor complex, which regulates cell growth and differentiation, is primarily composed of Jun proteins (Liebermann et al., 1998). The pathophysiological connection between the Jun proteins and AD is believed to be represented by neuroinflammation and neuronal responses to stress (Salminen et al., 2009). In reacting to oxidative stress or various undesirable stimuli, neurons produce proteins called jun proteins, which control the expression of genes that aid cells in adapting and surviving (Maise and Chong, 2004). According to Yarza et al. (2016), there is evidence that Jun proteins contribute to AD-related neuronal damage and cell death. According to Wu et al. (2020), the neuroinflammatory response is defined by Jun activation, which leads to an increase in the generation of inflammatory cytokines as well as other mediators. This, in turn, damages neurons and speeds up the onset of disease.

Estrogen receptor 1 (ESR1), an important protein that is responsible for estrogen's cellular effects (Sundermann et al., 2010), has a pivotal role in AD, due to its and estrogen's neuroprotective properties (Lan et al., 2015). Estrogen favorably improves brain function and cognitive health by upregulating the expression of proteins that support neuronal development and survival (Russell et al., 2019). Decreased estrogen levels during the postmenopausal stage may be associated with AD in women (Pike, 2017). Facilitating ESR1-mediated estrogen signaling may improve neuronal endurance and synaptic plasticity in addition to avoiding amyloid-beta damage (Sato et al., 2023).

Phosphoinositide-3-kinase regulatory subunit 1 (PIK3R1) and phosphoinositide-3-kinase catalytic subunit alpha (PIK3CA) are the two primary genes involved in the phosphatidylinositol 3-kinase (PI3K) pathway (Zhou et al. 2012). Essential biological processes like growth, proliferation, survival, and metabolism are carried out by this pathway (Martini et al. 2014). The PI3K/Akt signalling pathway is essential for brain cell survival and functioning during Alzheimer's disease (Razani et al., 2021). According to Munkley et al. (2015), PIK3R1 serves as the regulatory subunit and PIK3CA as the catalytic subunit. For the signalling pathway to be activated and controlled, they must work in concert. AD-related neuronal loss and damage may be caused by an impaired PI3K/Akt pathway (Hoxhaj and Mannig, 2020). A compromised PI3K/Akt pathway may have a negative impact on energy expenditure, synaptic plasticity, and cellular stress responses (Parihar and Brewer, 2010). These factors are closely linked to nerve cell loss and dysfunction in the aetiology of AD (Kumar and Bansal, 2022). Additionally, the route might trigger neuroprotective chemicals to shield cells from the damaging impacts of tau and amyloid-beta proteins (Fakhri et al., 2021).

The epidermal growth factor receptor ERB-B2 receptor tyrosine kinase 2 (ERBB2), commonly referred to as HER2, controls cell survival, proliferation, and differentiation (Eccles, 2011). There is debate regarding its involvement in AD, and studies are being conducted to clarify its function in neurodegenerative illnesses (Ou et al., 2021). The effects of ERBB2 on the cell life cycle and neuronal signalling may be the cause of AD (Wang et al., 2017). According to Ledonne et al. (2018), ERBB2's action on synaptic plasticity and neuronal transmission is directly associated with both memory and learning impairments that are hallmarks of AD. Furthermore, it has been proposed that ERBB2 signalling influences neuroprotective processes, making neurons more vulnerable to the harmful effects of neurotoxic peptides, such as amyloid-beta. Nevertheless, overactivation of ERBB2 can cause dysfunction and set off detrimental processes in brain cells, as several cancer types show (Atoki et al., 2023).

Gene and protein functions are examined in detail using advanced bioinformatics techniques such as GO analysis and KEGG pathway. GO analysis makes it easy to fully characterize the roles of target genes and proteins in biological processes, their molecular functions, and their location in cellular components. In this way, it is understood how the relevant biological processes are affected and which molecular functions come into play. KEGG pathway analysis shows the connections between various proteins in metabolic or signal transduction pathways and how these activities change in disease state. This method provides detailed information about complex biological networks and interactions so that the molecular mechanisms of

diseases can be better understood.

These analyses are critical for understanding how targeted molecules affect disease processes and discovering potential therapeutic targets. Consequently, GO and KEGG analyses contribute to the creation of more effective and focused therapeutic strategies, thus playing an important role in combating diseases (Chen et al., 2017; Gene Ontology Consortium, 2017; Xing et al., 2016).

The GO biological processes of the top 10 targets were identified (Figure 6). There are numerous distinct biochemical pathways that play a major role in the etiopathogenesis of AD. According to Lee et al. (2017), the ability of positive regulation of peptidyl-serine phosphorylation to hyperphosphorylate tau protein indicates that it is the most dominant activity in AD. Furthermore, changes in global protein phosphorylation may impact neuronal function and cellular signalling networks, which may accelerate the course of the illness (Oliveira et al., 2017). Since neuronal loss is one of the main characteristics of AD, apoptotic process regulation and controlled death of cells are strongly related to the illness (Gong and Iqbal, 2008). Furthermore, as noted by Hernandez et al. (2009), intracellular signaling and its regulation play a critical role in neurodegenerative illnesses like AD. It will be crucial to carefully look at the roles that each of these processes plays in AD to develop successful treatment strategies and a deeper understanding of the disease.

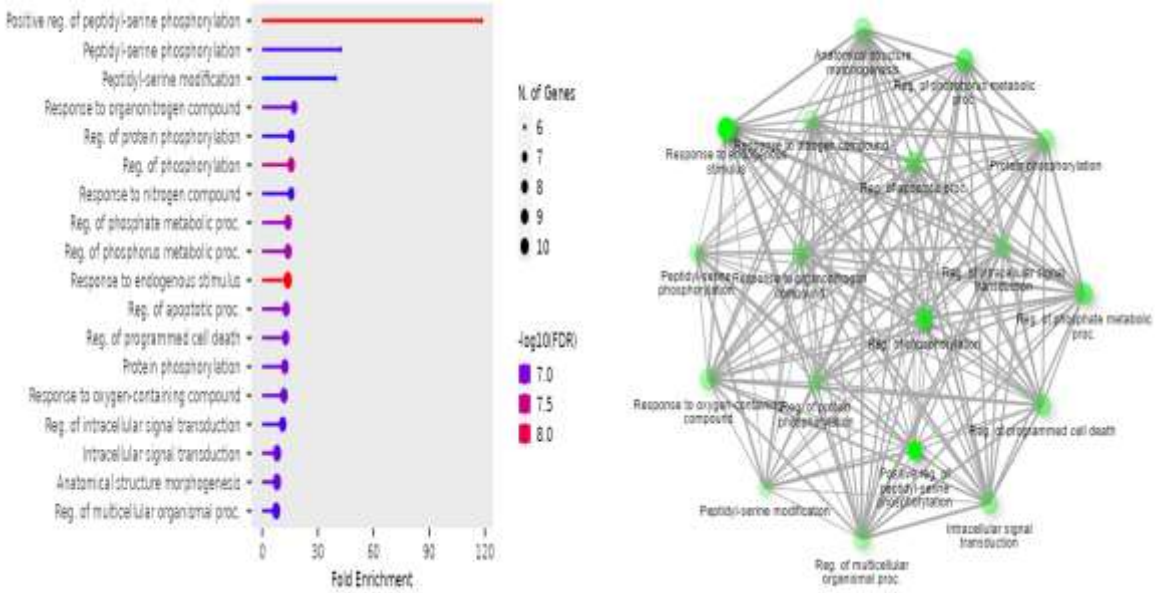

Figure 6. GO biological processes of top 10 targets
Şekil 6. İlk 10 hedefin GO biyolojik süreçleri

GO cellular components of the top 10 targets were identified (Figure 7). Cellular components related to AD can be identified by considering the illness's fundamental features and the cellular processes it impacts. The modulation of neuronal signaling pathways and cell development is very critical in AD. In this setting, the phosphatidylinositol 3-kinase complex (particularly class 1 and class 1A) performs key roles in neural signaling and cell survival processes, making it intimately associated with AD (Fraser et al., 2008). Furthermore, because dendritic growth cones and axonal growth cones play critical roles in controlling neuronal development and connections, this condition may be linked to neuronal network disturbance (Weinkove et al., 2008). The myelin sheath is another critical cellular component that influences the speed and efficiency of neuronal transmission and can be impaired in AD (Fraser et al., 2008). To have a grip on AD and develop treatment alternatives, every one of these elements might be a key focus.

The top 10 targets' GO molecular functions were determined (Figure 8). The effect of AD on neuronal function and the roles of protein changes can be used to determine molecular activities associated with AD. In this regard, the regulation of nitric oxide synthase is essential for both inflammatory and neural processes, and it may also help prevent neurodegeneration in AD patients (Bredt et al., 1992). Reversal of protein phosphorylation and regulation of cellular signalling processes need two essential chemical reactions, namely protein phosphatase binding and phosphatase binding, which may be operational in the development of AD (Sontag & Sontag, 2014). Kinase and enzyme regulatory activities mediate signal transduction processes and preserve cellular homeostasis, the two processes that may potentially alter AD course (Austin and Katusic, 2016). Additionally, protein breakdown and cell longevity are related to ubiquitin-protein ligase and ubiquitin-like protein ligase binding, which may be involved in the regulation of protein aggregation and

cellular stress in AD (Prete et al., 2016). The pathophysiology of AD can be better explained and potential new targets for treatment can be identified if these molecular effects are more deeply scrutinized.

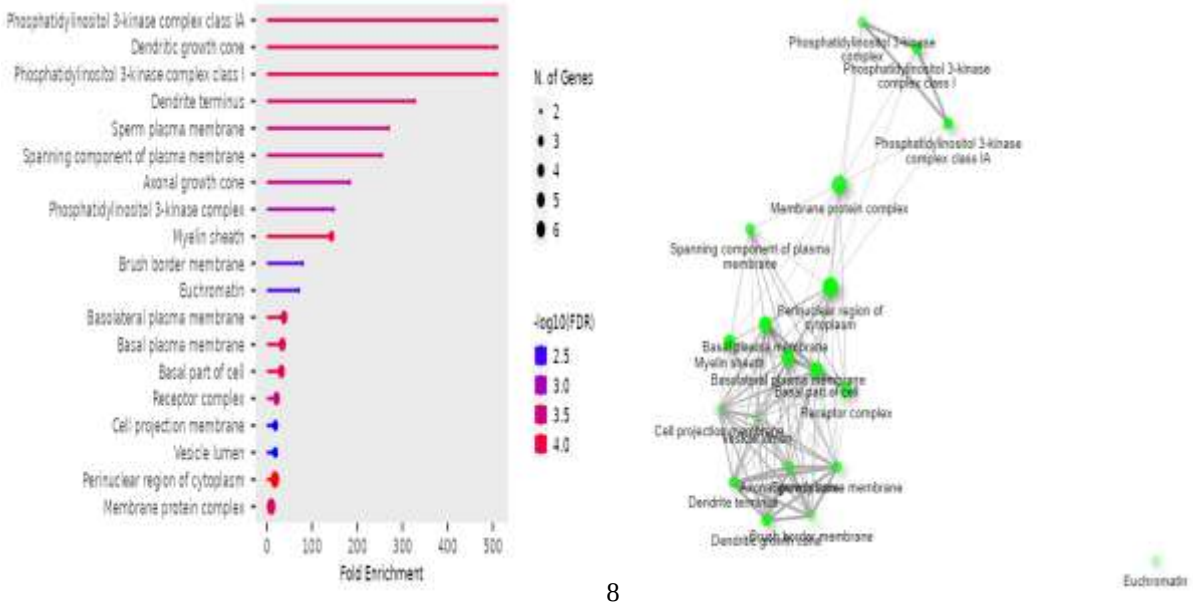

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Figure 7. GO cellular components of top 10 targets
Şekil 7. İlk 10 hedefin GO hücresel bileşenleri

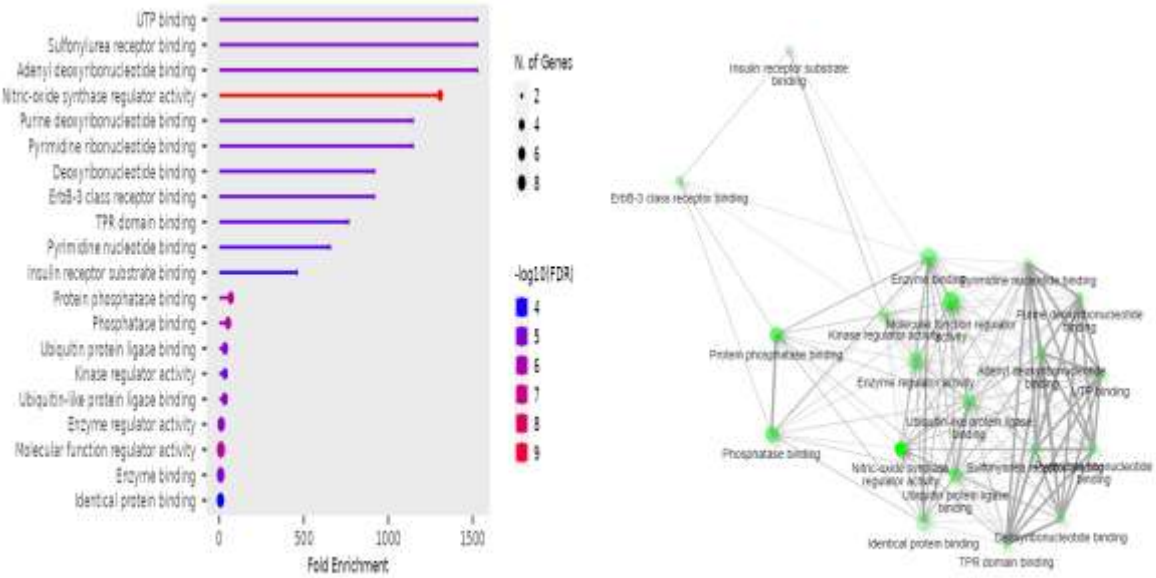


Figure 8. GO molecular functions of top 10 targets
Şekil 8. İlk 10 hedefin GO moleküler fonksiyonları

KEGG pathways of the top 10 targets were determined (Figure 9). KEGG pathways related to AD are expected to reveal the basic characteristics of AD and the molecular interactions involved. According to Li et al. (2003), the ErbB signalling pathway is associated with the growth and survivability of neurons and may help to maintain the connections and functioning of neurons in AD. When activated in the event of neuronal stress and damage, the HIF-1 signalling pathway governs hypoxia-related cellular responses and may be crucial in AD (Abdul and Butterfield, 2007). According to Jimenez et al. (2011), the PI3K-Akt signalling system regulates cell survival, proliferation, and metabolism, making it a potential target for halting the progression of AD. A thorough examination of these pathways may lead to novel therapy approaches as they are crucial for understanding how AD governs damage to neurons and how that damage influences the course of the disease.

The CB-Dock2 server provides the AutoDock vina-based molecular docking technique and the curvature-based cavity identification approach to CB-Dock2, an enhanced version of the protein-ligand blind docking programme (URL1). Binding positions are evaluated

using the binding energies expressed in kcal/mol when using the CBDOCK2 vina technique (Thangavel et al., 2021). Vina's empirical scoring method is based on a scoring function (Ugurlu et al., 2024). Greater affinity for binding is shown by a higher negative vina score (Quiroga and Villarreal, 2016). Table 5 displays the molecular docking data for the target proteins (EGFR, HSP90AA1, BL2, HSP90AB1, IL6, JUN, ESR1, PIK3CA, ERBB2, and PIK3R1) and lignans (enterodiol, enterolactone, etoposide, lariciresinol, matairesinol, pinoresinol, podophyllotoxin, and secoisolariciresinol). The target proteins have the following order of binding affinity for lignans: ERBB2 > PIK3CA > HSP90AB1 > PIK3R1 > EGFR > JUN > ESR1 > IL6 > HSP90AA1 > BCL2, in that order. Etoposide > enterolactone > pinoresinol> matairesinol > enterodiol > podophyllotoxin > lariciresinol > secoisolariciresinol is the order from highest to lowest in which the lignans attach to their particular target proteins. The molecular docking experiments revealed a considerable binding affinity between the target proteins (EGFR, HSP90AA1, BL2, HSP90AB1, IL6, JUN, ESR1, PIK3CA, ERBB2, and PIK3R1) and the lignans, which indicated the potential of the proteins to function.

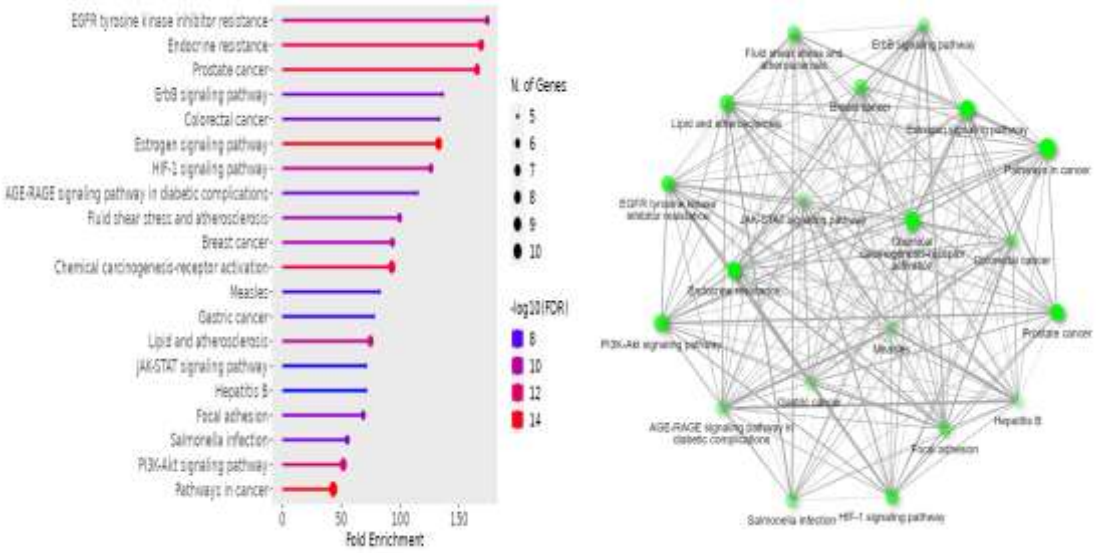


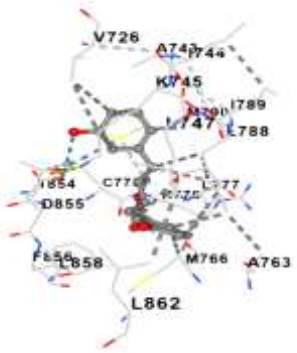
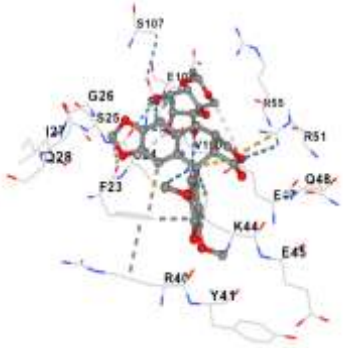
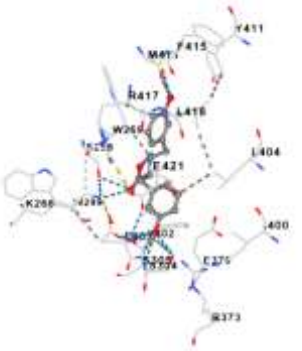
Figure 9. KEGG pathways of targets
Şekil 9. Hedeflerin KEGG yolakları

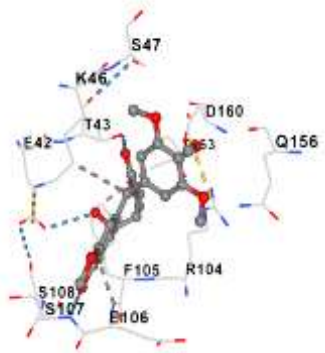
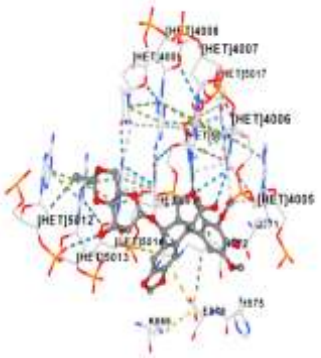
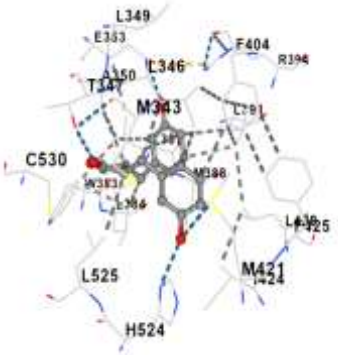
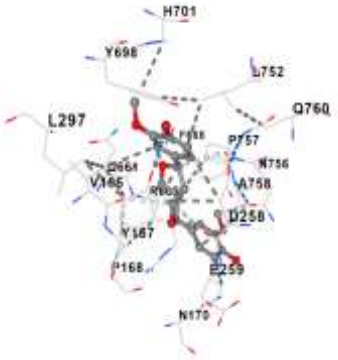
The contact residues of the main lignans (enterolactone, etoposide, podophyllotoxin, and pinoresitol) to the target proteins (EGFR, HSP90AA1, BL2, HSP90AB1, IL6, JUN, ESR1, PIK3CA, ERBB2, and PIK3R1) by the respective vina scores are shown on Table 6. The contact residues and bindings between the ligands and target proteins were found to have contact amino acids and bond structures. The teal dotted lines show the reactions between hydrogen bonds. Aguilar-Carrillo et al. (2024) state that electrostatic interactions are displayed as yellow dotted lines, whereas hydrophobic interactions are depicted by grey dotted links.

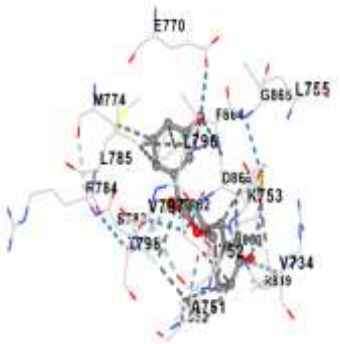
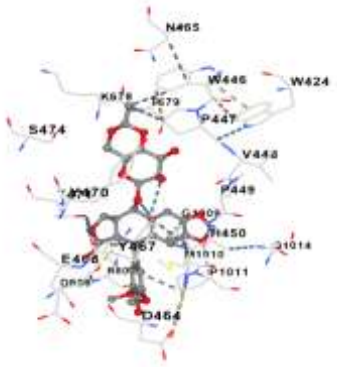
Table 5. Molecular docking results (vina score) of lignans and target proteins
Çizelge 5. Lignanların ve hedef proteinlerin moleküler kenetlenme sonuçları (vina skoru)

Lignan	**Target Protein**									
	EGFR	HSP90 AA1	BCL2	HSP90 AB1	IL6	JUN	ESR1	PIK3CA	ERBB2	PIK3R1
Enterodiol	-8.1	-6.1	-6.2	-8.4	-7.0	-8.9	-8.0	-7.9	-8.7	-8.0
Enterolactone	**-9.5**	-6.9	-7.1	**-9.4**	-6.9	-7.8	**-10.0**	-8.5	**-9.8**	-7.8
Etoposide	-8.2	**-7.7**	**-7.8**	-8.7	-7.1	**-9.8**	-7.8	-9.5	-9.0	**-10.8**
Lariciresinol	-8.1	-6.3	-6.1	-8.4	-6.8	-7.2	-6.8	-8.5	-8.8	-7.8
Matairesinol	-8.3	-6.9	-6.0	-8.6	-6.8	-7.2	-8.7	-9.5	-9.0	-7.8
Pinoresinol	-8.5	-6.6	-6.8	-8.1	-6.1	-8.1	-7.8	**-9.6**	-9.5	-8.1
Podophyllotoxin	-7.7	-6.6	-6.4	-8.2	**-7.3**	-7.4	-6.7	-8.6	-8.1	-8.8
Secoisolariciresinol	-7.6	-6.4	-6.1	-7.8	-6.3	-7.0	-7.5	-7.2	-8.8	-7.4

Table 6. Molecular docking results (contact residues) of lignans and target proteins
Çizelge 6. Lignanların ve hedef proteinlerin moleküler kenetlenme sonuçları (temas kalıntıları)

Lignan	Target Protein	Contact Residues	
Enterolactone	EGFR	Chain A: PHE723 VAL726 ALA743 ILE744 LYS745 LEU747 ARG748 GLU749 ALA750 THR751 SER752 PRO753 LYS754 ALA755 ASN756 GLU758 ILE759 LEU760 GLU762 ALA763 MET766 VAL769 CYS775 ARG776 LEU777 ILE780 LEU782 THR783 SER784 THR785 VAL786 LEU788 ILE789 MET790 THR854 ASP855 PHE856 GLY857 LEU858 LEU861 LEU862	
Etoposide	HSP90AA1	Chain A: ASN161 PRO162 ASN163 GLU164 GLY165 ALA166 THR167 THR189 GLU192 ASP195 LYS204 GLU207 GLU251 LYS252 ALA253 LYS254 GLU255 SER256 TRP257 MET259 LYS262 GLU263 GLU266 GLN267 ILE270 VAL271 LYS274 MET285 VAL288 ILE289 GLN290 TYR291 GLY292 LYS293 VAL295 SER296 TRP297 GLU299 MET300 GLU301 PHE320 LEU323 TYR327 LYS335 GLU338 CYS339 LYS342	
Etoposide	BCL2	Chain A: PHE23 CYS24 SER25 GLY26 ILE27 GLN28 ARG40 TYR41 LYS44 GLU45 GLU47 GLN48 ARG51 ARG55 SER58 GLN59 VAL100 SER103 GLU104 LEU106 SER107 ARG108 GLY109	
Enterolactone	HSP90AB1	Chain A: ASN413 MET414 PHE415 ARG417 LEU418 GLU421 Chain B: GLU370 ARG373 ILE400 GLN403 LEU404 GLU407 TYR411 Chain C: SER258 TRP259 MET261 ASN262 SER263 LYS266 SER298 TRP299 LEU300 GLU301 TYR302 GLU303 SER304 SER305 PHE306	

Podophyllotoxin	IL6	Chain A: GLU42 THR43 LYS46 SER47 ARG104 PHE105 GLU106 SER107 SER108 GLN156 ASP160 THR163	
Etoposide	JUN	Chain N: ILE535 ARG537 LYS538 ASN539 ARG541 GLN571 ARG572 HIS575 GLU576 LEU577 LYS664 ARG665 LYS666 ARG667 GLN669 Chain J: LYS268 ARG269 ARG271 ASN272 LYS283	
Enterolactone	ESR1	Chain A: MET343 LEU346 THR347 ASN348 LEU349 ALA350 ASP351 GLU353 TRP383 LEU384 LEU387 MET388 LEU391 ARG394 PHE404 MET421 ILE424 PHE425 LEU428 LYS520 GLY521 MET522 HIS524 LEU525 CYS530	
Pinoresitol	PIK3CA	Chain A: ARG154 ARG162 TYR165 VAL166 TYR167 PRO168 PRO169 ASN170 LYS253 ASP258 GLU259 TYR260 MET288 SER292 LEU293 GLN296 LEU297 PRO298 ASP300 GLN661 ARG662 PHE666 CYS695 GLY696 MET697 TYR698 HIS701 GLN749 GLY750 PHE751 LEU752 ASN756 PRO757 ALA758 GLN760 LEU761 GLY762 ASN763 PRO786	

Enterolactone	ERBB2	Chain B: LEU726 GLY727 SER728 VAL734 ALA751 ILE752 LYS753 LEU755 GLU770 MET774 SER783 ARG784 LEU785 LEU796 VAL797 THR798 GLN799 LEU800 MET801 PRO802 TYR803 GLY804 CYS805 ASP808 ARG849 ASN850 LEU852 THR862 ASP863 PHE864 GLY865 PHE1004	
Etoposide	PIK3R1	Chain A: GLY364 TRP424 TRP446 PRO447 VAL448 PRO449 HIS450 LEU452 ASP454 LEU455 LEU456 ASN457 PRO458 ILE459 ASN465 CYS604 ASN605 LYS678 THR679 ASP806 ARG808 LEU1006 GLY1009 MET1010 PRO1011 GLN1014 SER1015 PHE1016 ASP1017 Chain B: ASP464 TYR467 GLU468 TYR470 THR471 SER474	

It has been observed that gefitinib ligand, while binding to the EGFR protein, interacts with residues ASP800, VAL726, LYS745, MET790, LEU788, ILE744, LEU844, ALA743, GLN791, LEU792, MET793, LEU718, PRO794, GLY796, SER719 (URL2; Yoskikawa et al., 2013). Erlotinib has been observed to interact with residues ASP831, VAL702, LYS721, THR830, LEU764, ILE720, ILE765, ALA719, THR766, GLN767, LEU820, LEU694, LEU768, MET769, PHE771, PRO770, GLY772, CYS773, ASP776 (URL3; Park et al., 2012). Lapatinib has been observed to interact with residues LEU792, MET1002, GLY796, CYS797, GLY719, ASP800, LEU799, ARG803, ARG841, PO481, LEU718, VAL726, LEU858, THR854, MET766, PHE856, ASP855, LEU777, ARG776, THR790, CYS775, LYS745, LEU788, ILE744, ALA743, GLN791, ILE789, MET793, LEU844 (URL4; Wood et al., 2004). Bilobol has been observed to interact with residues ASN86, ARG84, GLU60, ALA62, VAL36, VAL37, LEU38, GLY39, TYR251, GLY264, ALA265, THR249, THR266, PRO248, GLU221, SER222, ASP223, CYS236, CYS224, THR235, ALA234, LEU225, VAL226, CYS227, ARG231 (Adabi et al., 2023). 2,9-disubstituted 8-phenylthio/phenylsulfinyl-9h-purine derivatives have been observed to interact with residues MET793, THR854, LEU718, LEU844, MET766, VAL726, ALA743, LYS745, MET790 (İbrahim et al., 2020). In our study, enterolactone and gefitinib, erlotinib, lapatinib, bilobol, and 2,9-disubstituted 8-phenylthio/phenylsulfinyl-9h-purine derivatives were found to interact with similar residues. Enterolactone was found to be more similar in interaction with gefitib and lapatinib.

It has been observed that 17-AAG ligand, while binding to the HSP90AA1 protein, interacts with residues ASN161, PRO162, ASN163, GLU164, GLY165, ALA166, THR167, GLU192, ASP195, LYS204, GLU207, TRP257, MET259, LYS262, GLU263, GLN267, ILE270, VAL271, LYS274, MET285, VAL288, ILE289, GLN290, TYR291, GLY292, LYS293, VAL295, SER296, TRP297, GLU299, MET300, GLU301, PHE320, LEU323, TYR327, LYS335, GLU338, CYS339, LYS342 (URL5; Stebbins et al., 1997). Geldamycin has been observed to interact with residues ASN161, PRO162, ASN163, GLU164, GLY165, ALA166, THR167, GLU192, ASP195, LYS204, GLU207, TRP257, MET259, LYS262, GLU263, GLN267, ILE270, VAL271, LYS274, MET285, VAL288, ILE289, GLN290, TYR291, GLY292, LYS293, VAL295, SER296, TRP297, GLU299, MET300, GLU301, PHE320, LEU323, TYR327, LYS335, GLU338, CYS339, LYS342 (URL6; Stebbins et al., 1997). Radicicol has been observed to interact with residues ASN161, PRO162, ASN163, GLU164, GLY165, ALA166, THR167, GLU192, ASP195, LYS204, GLU207, TRP257, MET259, LYS262, GLU263, GLN267, ILE270, VAL271, LYS274, MET285, VAL288, ILE289, GLN290, TYR291, GLY292, LYS293, VAL295, SER296, TRP297, GLU299, MET300, GLU301, PHE320, LEU323, TYR327, LYS335, GLU338, CYS339, LYS342 (URL7; Roe et al., 1999). In our study, etoposide and 17-AAG, geldamycin, and radicicol were found to interact with similar residues.

It has been observed that ABT-737 ligand, while binding to BCL-2 protein, interacts with residues PHE23, ARG55, TYR41, ARG108 (URL8; Murray et al., 2019). Venetoclax (ABT-199) has been observed to interact with residues PHE23, TYR41, ARG55, GLU45, CYS24 (URL9; Birkinshaw et al., 2019). S55746 has been observed to interact with residues PHE23, ARG55, TYR41, GLU47 (URL10; Casara et al., 2018). Novel 9-(alkylthio)-Acenaphtho[1,2-e]-1,2,4-triazine derivatives has been observed to interact with residues GLU13, MET16, LYS17, HIS20, ALA32, ASP35, VAL36, GLU38, ASN39, THR41, ASP10, GLY46, GLU50, ASP35 (Mohammadi et al., 2014). In our study, etoposide and ABT-737, venetoclax (ABT-199), S55746, and novel 9-(alkylthio)-Acenaphtho[1,2-e]-1,2,4-triazine derivatives were found to interact with similar residues.

It has been observed that the 17-AAG ligand, while binding to the HSP90AB1 protein, interacts with residues GLU370, ARG373, ILE400, GLN403, LEU404, GLU407, TYR411 (URL5; Stebbins et al., 1997). Geldamycin has been observed to interact with residues ASN413, MET414, PHE415, ARG417, LEU418, GLU421 (URL6; Stebbins et al., 1997). Radicicol has been observed to interact with residues SER258, TRP259, MET261, ASN262, SER263, LYS266, SER298, TRP299, LEU300, GLU301, TYR302, GLU303, SER304, SER305, PHE306 (URL7; Roe et al., 1999). Chelerythrine has been observed to interact with residues TRP162, VAL150, ASP93, TYR139, PHE138, LEU107, MET98 (Sharma and Kumar, 2023). In our study, enterolactone and 17-AAG, geldamycin, radicicol, and chelerythrine were found to interact with similar residues.

It has been observed that the olokizumab ligand, while binding to the IL6 protein, interacts with residues GLU42, THR43, LYS46, ARG104, PHE105, GLU106, SER107, ASP160 (URL11; Shaw et al., 2014). Procyanidin has been observed to interact with residues GLU42, THR43, LYS46, SER47, ARG104, PHE105, GLU106, SER107, ASP160 (Zeng et al., 2023). In our study, podophyllotoxin, olokizumab, and procyanidin were found to interact with similar residues.

It has been observed that the 4-OHT ligand binds to the ESR1 protein and interacts with the MET343, LEU346, THR347, LEU349, ALA350, ASP351, GLU353, TRP383, LEU384, LEU387, MET388, LEU391, ARG394, PHE404, MET421, ILE424, PHE425, LEU428, LYS520, GLY521, MET522, HIS524, LEU525, CYS530 (URL12; Maximov et al., 2018). Chalcone derivatives (HNS10) have been observed to interact with residue LEU346, THR347, LEU349, ALA350, GLU353, LEU387, MET388, LEU391, ARG394, MET421, LEU525 (Muctaridi et al., 2017). Benzophenone imine inhibitors have been observed to interact with residues LEU346, THR347, LEU349, ALA350, GLU353, TRP383, LEU384, LEU387, MET388, LEU391, ARG394, PHE404, MET421, ILE424, GLY521, HIS524, LEU525 (Shtaiwi et al., 2019). In our study, it was determined that enterolactone and 4-OHT, chalcone derivatives, and benzophenone imine inhibitors interact with similar residues.

It has been observed that the covalent inhibitor 19 ligand binds to the PIK3CA protein and interacts with the CYS862 residue (URL13; Borsari et al., 2022). Fragments 12 and 15 were observed to interact with residue GLU542 (URL14; Miller et al., 2017). Alpelisib (BYL719) has been observed to interact with residues ARG154, TYR165, TYR167, PRO169, ASP300, GLU542, ASP544 (Pattar et al., 2020). In our study, it was determined that pinoresitol and covalent inhibitor 19, fragments 12 and 15, and alpelisib (BYL719) interact with similar residues.

It has been observed that doxazosin ligand, while binding to the ERBB2 protein, interacts with residues LEU726, GLY727, SER728, VAL734, ASP863, PHE864, MET774, SER783, LEU785, LEU796, THR798, MET801, TYR803, GLY804, CYS805, LEU852, THR862 (URL15). Gefitinib has been observed to interact with residues LEU726, VAL734, CYS805, LEU852, THR862, ASP863, and PHE864 (URL15). Lapatinib has been observed to interact with residues LEU726, ALA751, LYS753, GLU770, MET774, SER783, LEU785, LEU796, THR798, GLN799, LEU800, MET801, TYR803, GLY804, CYS805, LEU852, THR862, ASP863, PHE864, GLY865 (URL15). Tyrosine kinase inhibitors from *Panax biinnatifidus* and *Panax psudoginseng* have been observed to interact with residues LYS753, ALA751, MET774, LEU852, THR798, LEU800, MET801, GLY804, CYS805, ASP808, LYS724, LEU726, VAL734, GLY729, ALA730, ASP863 (Paul et al., 2021). In our study, enterolactone and doxazosin, gefitinib, lapatinib, and tyrosine kinase inhibitors from *Panax biinnatifidus* and *Panax psudoginseng* were found to interact with similar residues.

It has been observed that PI-103 ligand interacts with HIS450, LEU455, and ASP454 residues while binding to the PIK3R1 protein (URL16). Alpelisib has been observed to interact with residues GLY364, TRP424, and ASP806 (URL17). Wortmannin has been observed to interact with residues ASN605, CYS604, and GLY1009 (URL18). In our study, etoposide and P-103, alpelisib, and wortmannin were found to interact with similar residues.

The interaction residues between ligands and their target proteins were observed to significantly overlap with those detected for enterolactone, etoposide, podophyllotoxin, and pinoresitol.

These consistent interactions suggest that the binding affinities and mechanisms of action of these ligands

may be comparable, thus common pathways or mechanisms can be investigated for therapeutic purposes.

Studies in the literature showing the relationship of enterolactone with EGFR, HSP90AB1, ESR1, and ERB2 are associated with cancer and hepatic fibrosis. There is no study showing its relationship with AD. However, Reddy et al. (2020), enterolactone is an inhibitor of acetylcholinesterase and butyrylcholinesterase and therefore provides neuroprotection against AD. Hoang et al. (2024) suggested that diets rich in matairesinol could inhibit the effect of $A\beta_{1-42}$, since enterolactone is a matairesinol-derived metabolite produced through intestinal microbiota activity.

Studies in the literature showing the relationship of etoposide with HSP90AA1, BCL2, JUN, and PIK3R1 are associated with cancer. There is no study showing its relationship with AD. However, Lu et al. (2002) showed that although etoposide is neurotoxic, it also activates a cell survival pathway involving AMPA receptor-mediated activation of p42/p44 MAP kinases. They stated that agents that selectively inhibit cell survival or death pathways triggered by DNA damage may be useful in cancer and neurodegenerative diseases.

Studies in the literature show the relationship between podophyllotoxin and IL6 is associated with cancer. There is no study showing its relationship with AD. However, Xu et al. (2022), the extract from the Juniperus plant exhibited significant anti-butyrylcholinesterase activity, which was positively correlated with high levels of podophyllotoxin and deoxypodophyllotoxin.

Studies in the literature showing the relationship of pinoresitol with PIK3CA are associated with cancer. There is no study showing its relationship with AD. However, Lei et al. (2021) found that pinoresitol could alleviate neuroinflammation, neuronal apoptosis, and oxidative stress through the TLR4/NF-κB and Nrf2/HO-1 pathways and ameliorate $A\beta_{1-42}$-induced memory dysfunction in mice.

CONCLUSION

Our study explores the potential of lignans, natural polyphenols, that can be used in the treatment of AD. Using network pharmacology and molecular docking techniques, we examined how lignans interact with various key proteins associated with AD pathology. These proteins include EGFR, HSP90AA1, BCL2, HSP90AB1, IL6, JUN, ESR1, PIK3CA, ERBB2, and PIK3R1. Our findings suggest that interactions of lignans with these proteins may alleviate AD symptoms by modulating inflammation, regulating apoptosis, and affecting signal transduction pathways. Additionally, these interactions may reduce amyloid-beta accumulation and tau phosphorylation, thus slowing disease progression. These results support the use of lignans as potential therapeutic agents in the treatment of AD and highlight the need for further *in vivo* studies. This integrated approach highlights the importance of developing new strategies in the treatment of complex diseases such as AD.

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Contribution of Authors

SŞ and SND: Designed, performed, analyzed, writing, review and editing.

Conflict of Interest

The authors declare no conflict of interest.

Ethics Committee Permission

An ethics committee permission is not required for the article.

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