Anti-Cancer Agents in Medicinal Chemistry, 2022, *22*, 1933-1944

RESEARCH ARTICLE

Network Pharmacology-Based and Molecular Docking Analysis of Resveratrol's Pharmacological Effects on Type I Endometrial Cancer

Zixing Zhong[1], Xin Guo[1] and Yanmei Zheng[1,*]

[1]*Department of Obstetrics, People's Hospital of Hangzhou Medical College, Zhejiang Provincial People's Hospital, Hangzhou 310014, China*

ARTICLE HISTORY

Received: March 29, 2021
Revised: July 19, 2021
Accepted: September 02, 2021

DOI: 10.2174/1871520621666211015140455

Abstract: ***Background*:** Resveratrol is a natural polyphenol commonly seen in foods. It has demonstrated an inhibitive effect on endometrial cancer, but the molecular action is still not known.

***Objective*:** We aimed to use network pharmacology to systematically study the possible mechanisms of resveratrol's pharmacological effects on type I endometrial cancer.

***Methods*:** Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) were used to predict resveratrol's possible target genes. They were then converted to UniProt gene symbols. Simultaneously, type I endometrial cancer-related target genes were collected from GeneCards. All data were pooled to identify common target genes. The protein-protein interaction (PPI) network was constructed and further analyzed *via* STRING Online Database. Gene Ontology (GO) functional annotation and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway were also performed afterward. To visualise resveratrol's overall pharmacological effects on type I endometrial cancer, a network of drug components-target gene-disease (CTD) was constructed. Then, we performed in silico molecular docking study to validate the possible binding conformation between resveratrol and candidate targets.

***Results*:** There are 150 target genes of resveratrol retrieved after UniProt conversion; 122 of them shared interaction with type I endometrial cancer. Some important oncogenes and signaling pathways are involved in the process of resveratrol's pharmacological effects on endometrioid cancer. Molecular docking analysis confirmed that hydrogen bonding and hydrophobic interaction are the main interaction between resveratrol and its targets.

***Conclusion*:** We have explored the possible underlying mechanism of resveratrol in antagonising type I endometrial cancer through a network pharmacology-based approach and in-silico verification. However, further experiments are necessary to add to the evidence identifying resveratrol as a promising anti-type I endometrial cancer agent.

Keywords: Endometrial cancer, gynecological cancer, cancer agent, hydrophobic interaction, antagonist, molecular docking.

1. INTRODUCTION

Endometrial cancer is the most common gynecological cancer in the developed world. In China, it also ranks the second most common gynecological cancer, and the number of new cases and deaths due to endometrial cancer has been rising steadily in recent years [1-3]. Type I endometrial cancer is the most prevalent histological subtype. It is associated with obesity, physical inactivity, and sex hormone imbalance, especially the excessive secretion of estrogen. [4]

Pathologically, angiogenesis is a key step in the development of endometrial carcinoma. The vascularization ability of the tumor is of great importance in endometrial cancer progression. Vascular Endothelial Growth Factor (VEGF) is an essential molecule in this part. Its expression can be regulated by estrogen in different ways and tissues [5-7]. Today, treatment of endometrial cancer generally includes (laparoscopic) primary hysterectomy, bilateral salpingo-oophorectomy, and lymphadenectomy if necessary. Chemotherapy or adjuvant treatment is contingent according to specific histology, stage of the tumor, and national/international guidelines per se [4, 8]. Although the comprehensive treatments have worked effectively for years, there should be alternatives if there are unexpected surgical complications or side effects of chemotherapies.

Resveratrol is a natural phytoalexin synthesized by plants. It is widely present in grape skins, wine, berries, nuts, *etc*. [9]. It has shown versatile function in disease intervention [10, 11]. Regarding its anti-carcinogenic activity, it serves as a chemo-preventive agent [12]. Although there have been studies demonstrating the resveratrol's appealing outcomes as a treatment for uterine cancer, the mechanism is not well known yet [13, 14].

Network pharmacology was initially proposed by Prof. Hopkins in 2007 [15]. It first came up with the idea that the medications' pharmacological effects may be exerted not in a point-to-point manner but within network interaction. This newly-developed approach has changed the way researchers used to study the potential mechanism of drugs and their pharmacological effects on certain diseases. Traditional Chinese medicine has benefitted from this new course of research [16, 17]. Our study aims to take advantage of network pharmacology to analyze the possible mechanism of resveratrol in inhibiting type I endometrial cancer. We then performed a molecular docking study to verify the prediction. The whole process of this study can be seen in Fig. (**1**).

*Address correspondence to this author at the Department of Obstetrics, People's Hospital of Hangzhou Medical College, Zhejiang Provincial People's Hospital, Hangzhou 310014, China;
E-mail: 2020020032@hmc.edu.cn

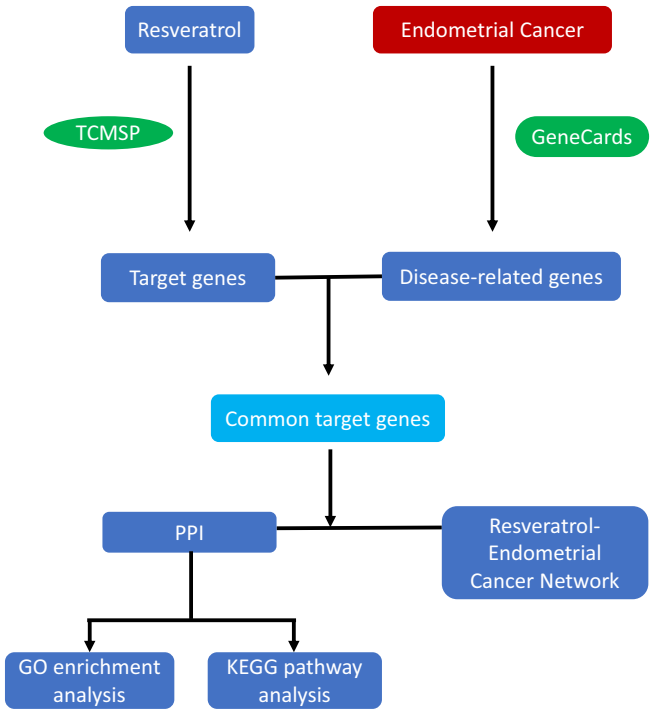


Fig. (1). The flowchart of the whole study design. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

2. MATERIALS AND METHODS

2.1. Acquisition Target Genes of Resveratrol and Endometrial Cancer

We used 'resveratrol' as the keyword to search in Traditional Chinese Medicine Systems Pharmacology (TCMSP) (https://www.tcmspw.com/tcmsp.php, designed by Center for Bioinformatics, Northwest University, Xi'an, Shaanxi, China) and exported the target genes of resveratrol [18]. We then used 'Type I endometrial cancer' as the keyword to explore the associated genes on Human Gene Database (GeneCards, https://www.genecards.org/) and obtained disease-related genes.

2.2. Retrieval of Venn Diagram

We imported target genes of resveratrol and type I endometrial cancer on this website (https://bioinfogp.cnb.csic.es/tools/venny/index.html) and automatically retrieved the overlapping genes and drew the Venn diagram.

2.3. Construction of PPI

A protein-protein interaction diagram was formed after common targets between resveratrol and type I endometrial cancer were uploaded to STRING Database (https://string-db.org/). The selected species were 'Homo Sapiens', and the combined score > 0.4 was the cut-off value for being included in the network. In the PPI diagram, each solid circle represents a target gene, and each line represents the biological process involving regulation of gene expression, signaling pathway, oncogenesis, *etc*.

2.4. GO function and KEGG Pathway Analysis

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG,) enrichment analysis were performed using STRING Database (https://string-db.org/). Before the enrichment, protein names of all targets were converted into corresponding gene names *via* UniProt. Then all the gene names of the targets were imported into the STRING Database to obtain the result. After setting up the criteria of adjusted P-value cut-off at 0.05, we collected and analyzed the data *via* RStudio 3.6.3 (Bioconductor, clusterProfiler).

Kyoto Encyclopedia of Genes and Genomes (KEGG, https://www.kegg.jp/, developed by University of Tokyo and Kyoto University in Japan [19]) Pathway Enrichment Analysis is a database for systematic analysis of gene functions. We typed in all gene names on the website and obtained an analysis of possible biological pathways and the corresponding biological functions.

2.5. Chemical-Target-Disease Network (CTD Network) Construction

We used resveratrol, type I endometrial cancer, and their common targets to build the multi-level network *via* Cytoscape 3.8.0, a software environment for integrated models of biomolecular interaction networks [20]. The nodes represent the chemical (*i.e.*, resveratrol), shared target genes, and the disease (*i.e.*, type I endometrial cancer), while the edges represent the interactions.

2.6. Molecular Docking Between Resveratrol and Its Key Targets

The structure of resveratrol (MOL012744) was downloaded in mol2 format from TCMSP (https://www.tcmspw.com/tcmsp.php). Then it was imported into the software of ChemBio3D Ultra 14.0 to minimise its energy and saved in mol2 format. It was then modified using AutodockTools-1.5.6 for hydrogen addition, charge calculation, and distribution, and the torsional bonds were retained. Results were saved in pdbqt format.

The crystal structures of candidate protein targets of resveratrol were downloaded from RCSB Protein Data Bank (http://www.rcsb.org/) and modified with ligand and water removal. They were then imported into AutodockTools-1.5.6 for hydrogen addition, charge calculation and distribution, determination of types of atoms to construct the docking grid box. Results were saved in pdbqt format.

The docking simulation was conducted *via* Autodock vina 1.1.2 with selected target proteins according to degree value obtained from PPI and the grid coordinates used are as follows: AKT1 (x = 14.780, y = 25.232, z = 17.669), IL6 (x = -5.730, y = -13.432, z = -0.288), TNF (x = 12.744, y = 5.715, z = 13.745), TP53 (x = 97.959, y = 82.651, z = -29.952), MAPK3 (x = 37.095, y = 54.481, z = 50.058), MAPK8 (x = 11.483, y = 6.109, z = 21.523), MYC (x = 3.398, y = 1.752, z = 45.532), CASP3 (x = 34.866, y = 8.204, z = 64.633), STAT3 (x = 12.486, y = 55.921, z = -1.328), JUN (x = -16.120, y = 23.426, z = 26.623), VEGFA (x = 10.485, y = -4.128, z = 22.379). The binding site was defined using a grid of 50 × 50 × 50 points each with a grid spacing of 0.375 Å and the default value were used for other parameters. The values of affinity and scores were used to predict best ranked docking pose. Lower score indicates higher affinity. The lowest 3 docking scores were selected and the corresponding conformation were visualised *via* Pymol 2.3.0.

3. RESULTS

3.1. Identification of Target Genes of Resveratrol and Type I Endometrial Cancer-Related Genes

There were 151 target genes extracted from TCMSP. After modification of names and species in UniProt, 150 genes remain in Table **1** [21]. Concurrently, 3255 disease-related genes were obtained from GeneCards (S2, Supplementary **2**).

The two data sets were pooled for co-analysis, and 122 common genes (3.7% of the total) were retrieved and showed in Fig. (**2**).

Table 1. Information of resveratrol's target genes.

Target Genes	Gene Symbol (From UniProt)
Cell division protein kinase 4	CDK4
Cell division protein kinase 6	CDK6
Heparin-binding growth factor 2	FGF2
Cell division protein kinase 7	CDK7
X-ray repair cross-complementing protein 6	XRCC6
Xanthine dehydrogenase/oxidase	XDH
Vascular endothelial growth factor A	VEGFA
Vascular cell adhesion protein 1	VCAM1
TNF receptor-associated factor 2	TRAF2
Cellular tumor antigen p53	TP53
Tumor necrosis factor ligand superfamily member 10	TNFSF10
Tumor necrosis factor receptor superfamily member 10B	TNFRSF10B
Tumor necrosis factor receptor superfamily member 10A	TNFRSF10A
Tumor necrosis factor	TNF
Transforming growth factor beta-2	TGFB2
Transforming growth factor beta-1	TGFB1
Protransforming growth factor alpha	TGFA
Telomerase protein component 1	TEP1
Estrogen sulfotransferase	SULT1E1
Signal transducer and activator of transcription 3	STAT3
Signal transducer and activator of transcription 1-alpha/beta	STAT1
Sterol regulatory element-binding protein 1	SREBF1
SPARC	SPARC
Superoxide dismutase [Mn], mitochondrial	SOD2
Superoxide dismutase [Cu-Zn]	SOD1
Solute carrier family 2, facilitated glucose transporter member 4	SLC2A4
NAD-dependent deacetylase sirtuin-2	SIRT2
NAD-dependent deacetylase sirtuin-1	SIRT1
E-selectin	SELE
Protein CBFA2T1	RUNX1T1
40S ribosomal protein S6	RPS6
Transcription factor p65	RELA
Pygopus homolog 1	PYGO1
Tyrosine-protein phosphatase non-receptor type 1	PTPN1
Prostaglandin G/H synthase 2	PTGS2
Prostaglandin G/H synthase 1	PTGS1
Prostaglandin E synthase	PTGES
Phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN	PTEN
Serine/threonine-protein kinase D1	PRKD1
Protein kinase C delta type	PRKCD
Protein kinase C beta type	PRKCB
Protein kinase C alpha type	PRKCA
5'-AMP-activated protein kinase subunit gamma-2	PRKAG2
Peroxisome proliferator-activated receptor gamma	PPARG
Peroxisome proliferator-activated receptor alpha	PPARA
Serum paraoxonase/arylesterase 1	PON1
Phorbol-12-myristate-13-acetate-induced protein 1	PMAIP1
Urokinase-type plasminogen activator	PLAU

(Table 1) Contd….

Target Genes	Gene Symbol (From UniProt)
Tissue-type plasminogen activator	PLAT
Platelet endothelial cell adhesion molecule	PECAM1
Pappalysin-1	PAPPA
Ornithine decarboxylase	ODC1
High affinity nerve growth factor receptor	NTRK1
Oxysterols receptor LXR-alpha	NR1H3
NAD(P)H dehydrogenase [21] 1	NQO1
Nitric oxide synthase, endothelial	NOS3
NF-kappa-B inhibitor alpha	NFKBIA
Nuclear factor erythroid 2-related factor 2	NFE2L2
Nuclear receptor coactivator 2	NCOA2
Myc proto-oncogene protein	MYC
Serine/threonine-protein kinase mTOR	MTOR
Multidrug resistance protein 1	MRP
Myeloperoxidase	MPO
Matrix metalloproteinase-9	MMP9
72 kDa type IV collagenase	MMP2
Maltase-glucoamylase, intestinal	MGAM
Induced myeloid leukemia cell differentiation protein Mcl-1	MCL1
Mitogen-activated protein kinase 8	MAPK8
Mitogen-activated protein kinase 3	MAPK3
Mitogen-activated protein kinase 1	MAPK1
Amine oxidase [flavin-containing] B	MAOB
Lengsin	LGSN
Krueppel-like factor 10	KLF10
Transcription factor AP-1	JUN
Tyrosine-protein kinase JAK1	JAK1
Integrin beta-1	ITGB1
Insulin receptor substrate 1	IRS1
Interleukin-6	IL6
Interleukin-1 beta	IL1B
Interleukin-1 alpha	IL1A
Interleukin-17B	IL17B
Interleukin-10	IL10
Insulin-like growth factor 1 receptor	IGF1R
Intercellular adhesion molecule 1	ICAM1
Heat shock protein HSP 90 Hypoxia-inducible factor 1-alpha	HSP HIF1A
Hepatocyte growth factor	HGF
Probable E3 ubiquitin-protein ligase HERC5	HERC4
78 kDa glucose-regulated protein	HEL-S-89n
Gap junction alpha-1 protein	GJA1
GTP cyclohydrolase 1	GCH1
Forkhead box protein O1	FOXO1
Proto-oncogene c-Fos	FOS
Tissue factor	F3
Eukaryotic translation initiation factor 6	EIF6
Eukaryotic translation initiation factor 2 subunit 1	EIF2S1
Endothelin-1	EDN1
Dual oxidase 2	DUOX2

(Table 1) Contd….

Target Genes	Gene Symbol (From UniProt)
DNA damage-inducible transcript 3 protein	DDIT3
Cytochrome P450 1B1	CYP1B1
Cytochrome P450 1A1	CYP1A1
Cytochrome P450 19A1	CYP19A1
Interleukin-8	CXCL8
Catenin beta-1	CTNNB1
C-reactive protein	CRP
CREB/ATF bZIP transcription factor	CREBZF
Collagen alpha-1(II) chain	COL2A1
CASP8 and FADD-like apoptosis regulator	CFLAR
Cyclin-dependent kinase inhibitor 1	CDKN1A
Cell division control protein 42 homolog	CDC42
Cell division control protein 2 homolog	CDC2
T-lymphocyte activation antigen CD80	CD80
CD320 antigen	CD320
T-cell-specific surface glycoprotein CD28	CD28
C-C chemokine receptor type 2	CCR2
G1/S-specific cyclin-E2	CCNE2
G1/S-specific cyclin-E1	CCNE1
G1/S-specific cyclin-D2	CCND2
G1/S-specific cyclin-D1	CCND1
G2/mitotic-specific cyclin-B1	CCNB1
C-C motif chemokine 2	CCL2
Catalase	CAT
Caspase-9	CASP9
Caspase-3	CASP3
Carbonic anhydrase II	CA2
C5a anaphylatoxin chemotactic receptor	C5AR
Basigin	BSG
Baculoviral IAP repeat-containing protein 4	BRIC4
Breast cancer type 2 susceptibility protein	BRCA2
Breast cancer type 1 susceptibility protein	BRCA1
Baculoviral IAP repeat-containing protein 5	BIRC5
Baculoviral IAP repeat-containing protein 3	BIRC3
Bcl-2-like protein 11	BCL2L11
Bcl-2-like protein 1	BCL2L1
Bcl-2-related protein A1	BCL2A1
Apoptosis regulator Bcl-2	BCL2
Basal cell adhesion molecule	BCAM
Bcl-2-binding component 3	BBC3
Apoptosis regulator BAX	BAX
Bcl-2 homologous antagonist/killer	BAK1
Apoptotic protease-activating factor 1	APAF1
RAC-alpha serine/threonine-protein kinase	AKT1
Activator of 90 kDa heat shock protein ATPase homolog 1	AHSA1
Aryl hydrocarbon receptor	AHR
Type-1 angiotensin II receptor	AGTR1
Adiponectin receptor protein 2	ADIPOR2
Adiponectin receptor protein 1	ADIPOR1
ATP-binding cassette sub-family G member 2	ABCG2
Canalicular multispecific organic anion transporter 2	ABCC3
Alpha- and gamma-adaptin-binding protein p34	AAGAB

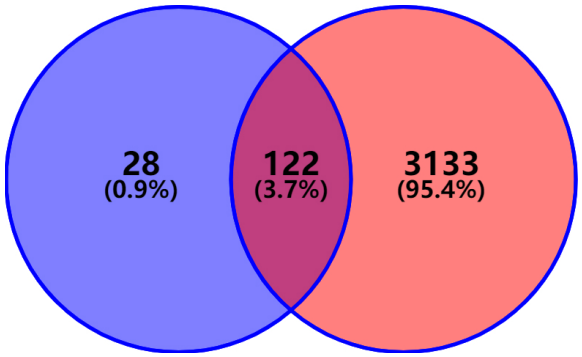


Fig. (2). Venn diagram of common target genes. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3.2. Construction and Analysis of PPI Network

The 122 shared genes were imported to STRING online database. The corresponding protein-protein interaction network contains 122 nodes (genes) and 2385 edges (interactions), representing the main interaction between resveratrol and type I endometrial cancer. The average degree score is 39.1, while the median value of node degree is 32. According to the current definition, two-folds of the median degree are regarded as hub genes, which are located in the central area of the network [22]. They are AKT1, TP53, IL6, TNF, VEGFA, JUN, MYC, CASP3, MAPK1/3/8, STAT3, CCND1, PTEN, PTGS2, CXCL8, MMP9, BCL2L1, IL1B, and CCL2 (Fig. **3**).

3.3. GO Biological Function and KEGG Pathway Enrichment Analysis

The 122 common genes were further analyzed in the gene ontology approach. There are 2374 biological processes (BP), 107

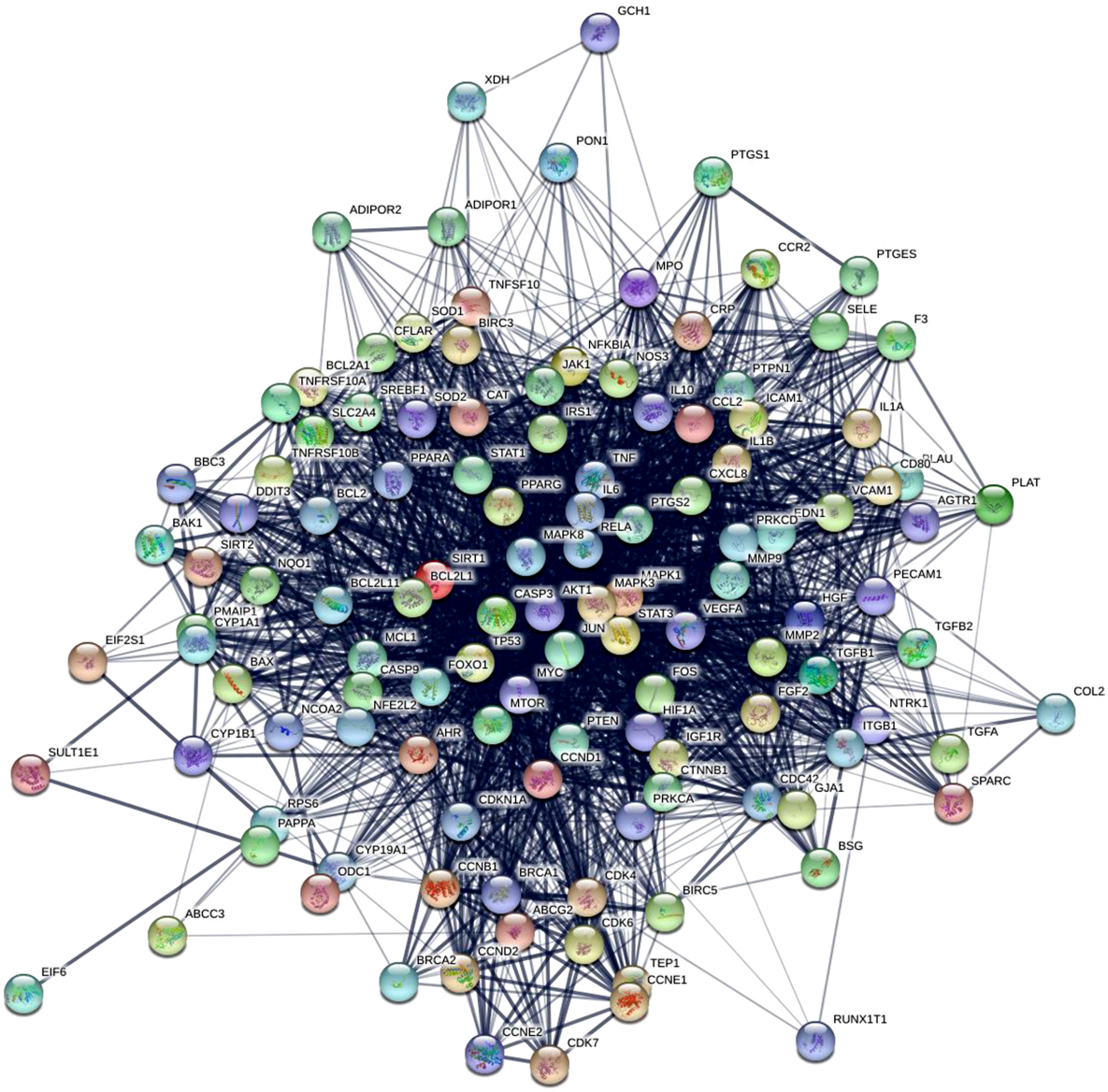


Fig. (3). Protein-protein interaction of common target genes. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

molecular functions (MF), and 49 cell components (CC) enriched after we set the threshold of adjusted P-value ≤ 0.05. The top 10 of each of the three items are illustrated in Fig. (**4a**) below.

156 related signaling pathways were obtained through KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway enrichment analysis. The top 20 significant pathways according to adjusted P-value are shown in Fig. (**4b**).

3.4. Compound-Target-Disease (CTD) Network Construction

We constructed the Resveratrol-common target genes-Type I endometrial cancer Network *via* Cytoscape in order to visualize and elucidate resveratrol's pharmacological potential in treating the most important sub-type of endometrial carcinoma. There are 122 nodes (in purple) representing common target genes and 2 additional nodes representing resveratrol (in pink) and type I endometrial cancer (in blue), respectively. 244 edges are also shown in Fig. (**5**) to demonstrate the association.

3.5. Molecular Docking Analysis

In order to evaluate the biological activity of selected proteins, the docking simulation between resveratrol and target proteins was applied *via* Autodock Vina. The targets were chosen because they were hub genes in the PPI network, which indicate a more important role in the interactive network.

The docking score contains 11 target proteins' affinity with resveratrol. Higher affinity was indicated by a lower score.The following 3 are predicted as most possibly bind with resveratrol: MAPK3 (-8.7 kcal/mol), TNF (-7.4 kcal/mol), and MAPK8 (-7.1 kcal/mol). Details of other targets are accessible in supplementary files. The results reveal that hydrogen bonding and hydrophobic interaction were the main forms of interaction. Resveratrol forms hydrogen bonds with MAPK8 at GLY-38, MET-111 and engages in hydrophobic action with multiple residues at LYS-55, VAL-40, ILE-32, LEU-168, ASN-156, ALA-53, LEU-110. Similarly, the hydrogen bonding with MAPK3 at ASN1-1, ASP-184, LYS-71, MET-125 while hydrophobic action at TYR-53, ALA-56, ALA-69, ASP-123, LEU-124, ILE-48, LEU-173. Another important target protein, TNF, also forms hydrogen bonds and hydrophobic action with resveratrol. Details of the visualisation of molecular docking can be seen in Fig. (**6**).

4. DISCUSSION

Network pharmacology offers multi-level perspectives for researchers to look into the relationship between drugs and diseases. The rapidly developed approach could allow pharmacologists and clinicians to come up with new ideas on the theoretical possibilities of certain natural or chemical components involved in disease intervention.

Endometrial cancer is the most prominent invasive neoplasm of the gynecological genital tract in today's Western world and China. As there are no preventive methods, screening tests strategies, or early detection methods in place, the number of new cases is expected to continue to rise rapidly over the years [4, 23]. In addition, a significant proportion of the patients are diagnosed at an advanced stage that requires chemotherapy following surgery, which some patients are intolerant to. This adds a financial burden to individuals and the government.

In the past 30 years, endometrial carcinoma has been roughly divided into 2 sub-types: type I and type II. Type I is hormone-receptor-positive, more common, less malignant, and hence has a better prognosis with an overall survival rate of 85% at 5 years [3, 4]. Type II is non-endometrioid with a poor prognosis (55% survival rate at 5 years) [4]. Although type I endometrial cancer has a good prognosis, it may be managed in a more economical and natural way.

Resveratrol is a natural polyphenol rich in a range of food, including grapes, mulberries, and blackberries. The non-flavonoid polyphenol possesses its anti-oxidant, anti-inflammatory, and neuroprotective properties in multiple biological processes, thereby potentially involving in the treatment of different diseases [24-26]. Recent studies have found that this polyphenol is involved in all three stages of cancer - carcinogenesis, tumor growth, and organ metastasis [27-29]. These studies have provided clues for the detection of the relationship between resveratrol and type I endometrial cancer. In our study, we identify resveratrol and its potential targets *via* network pharmacology to explore possible mechanisms underlying resveratrol's pharmacological effects on type I endometrial cancer.

A total of 122 common targets were screened out and presented in a visualized and interactive mode. Resveratrol generally exerts its effects of anti-tumorigenesis, anti-inflammatory, and regulative of tumor-associated signaling pathways on type I endometrial cancer. These effects were mainly reflected in the functions of hub nodes (important target genes located in the central area) in the network. Some of the important target genes have shown their key roles involving carcinogenesis.

VEGFA, a member of the VEGF family, is among the most important genes in the interaction. It is a proangiogenic factor, which is elevated in many cancers and is associated with angiogenesis and metastasis [30-33]. The angiogenic mechanism is related to hypoxia, which can be reversed by resveratrol [34]. This lays the foundation of resveratrol's anti-tumorigenesis action. MYC is the transcription factor that binds to the VEGFA promoter, promoting VEGFA production and its subsequent angiogenic effect [35]. In addition, TP53 acts as a tumor suppressor in many malignant diseases, inducing growth arrest or apoptosis of tumor cells. Prostaglandin G/H synthase 2 (PTGS2, also known as cyclooxygenase-2, COX-2) is positively associated with VEGF [36]. The regulation of cellular apoptosis is mediated by the repression of B-cell lymphoma 2 (BCL2). BCL2L1 is BCL-2-like protein 1, which inhibits the activation of caspases [37]. CASP3 are key genes that are involved in the activation cascade of caspases responsible for apoptosis. It is often elevated in endometrioid carcinoma, particularly in senior and advanced-stage patients, implicative of its involvement in the progressive deregulation of proliferation and apoptosis, leading to the progression from endometrial simple/complex hyperplasia to carcinoma [38]. Another tumor suppressor, PTEN, is frequently co-expressed with TP53 in endometrial cancer patients. The combination of the two antagonises the PI3K/AKT signaling pathway, thereby modulating cell cycle progression and cell survival in carcinoma patients. Resveratrol can induce miRNA-mediated regulation of PTEN in prostate cancer [39]. Therefore, it may also play a similar role in endometrial cancer, which has expression of TP53/PTEN [4, 34, 40-42].

AKT1 encodes one of the three members of the human AKT serine-threonine protein kinase family, which are often referred to as protein kinase B alpha, beta, and gamma. They are phosphorylated by phosphoinositide 3-kinase (PI3K), and AKT/PI3K forms a key component of many signaling pathways involving in tumorigenesis [30, 43, 44]. MAPK1/MAPK3 belong to the Mitogen-activated protein kinases (MAPK) family, an important family of protein kinases involved in transmitting signals from the cell membrane to the nucleus. They play an important role in MAPK/ERK cascade, mediating diverse biological functions, including initiation of endometrial oncogenesis [45]. Mitogen-activated protein kinase 8 (MAPK8, also known as JNK1, c-Jun N-terminal kinases), acts to phosphorylate a number of transcription factors, including JUN, JDP2, ATF2, *etc*., thereby involved in the various biological process such as cell proliferation, differentiation, migration, transformation and programmed cell death [46]. C-C motif chemokine 2 (CCL2), a ligand for the C-C chemokine receptor (CCR2)

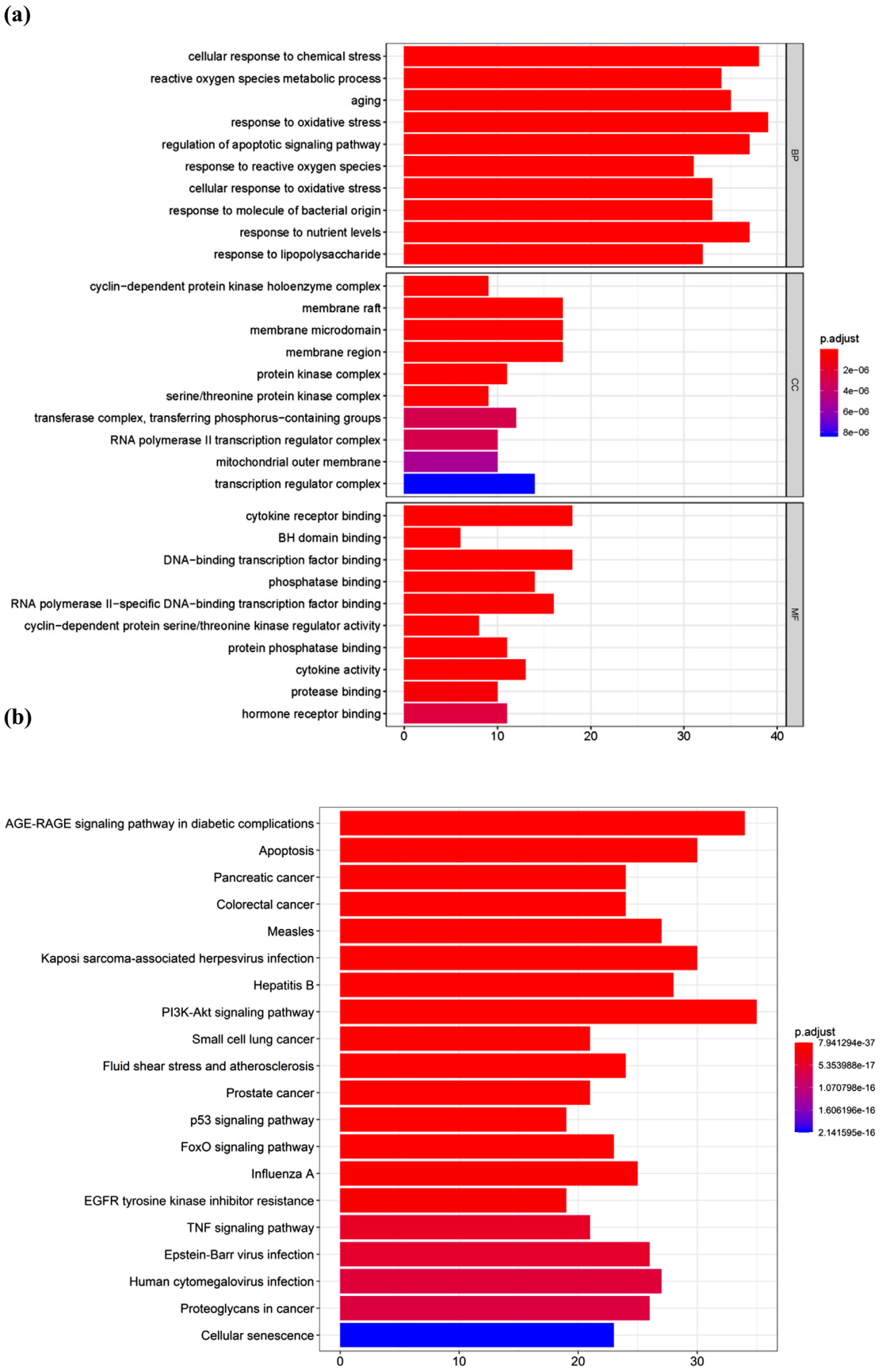


Fig. (4). (**a**) GO biological function analysis. (**b**) KEGG pathway enrichment analysis. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

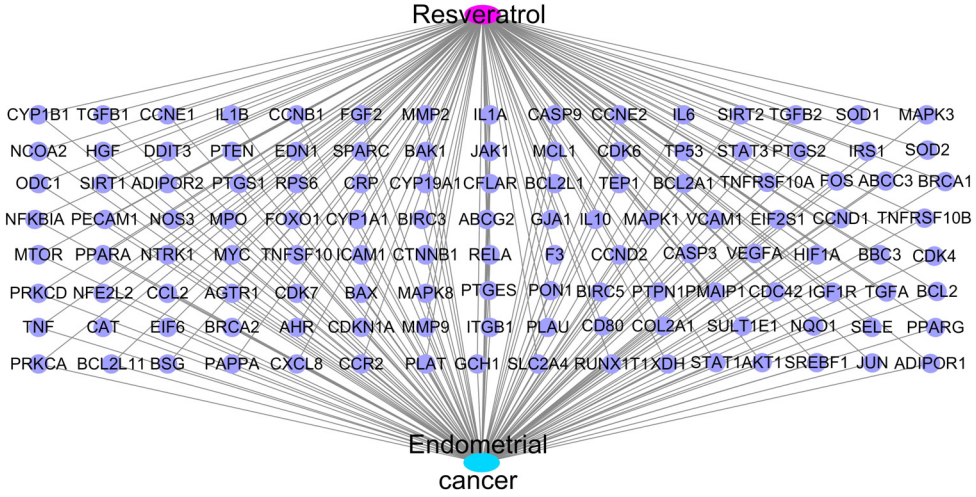
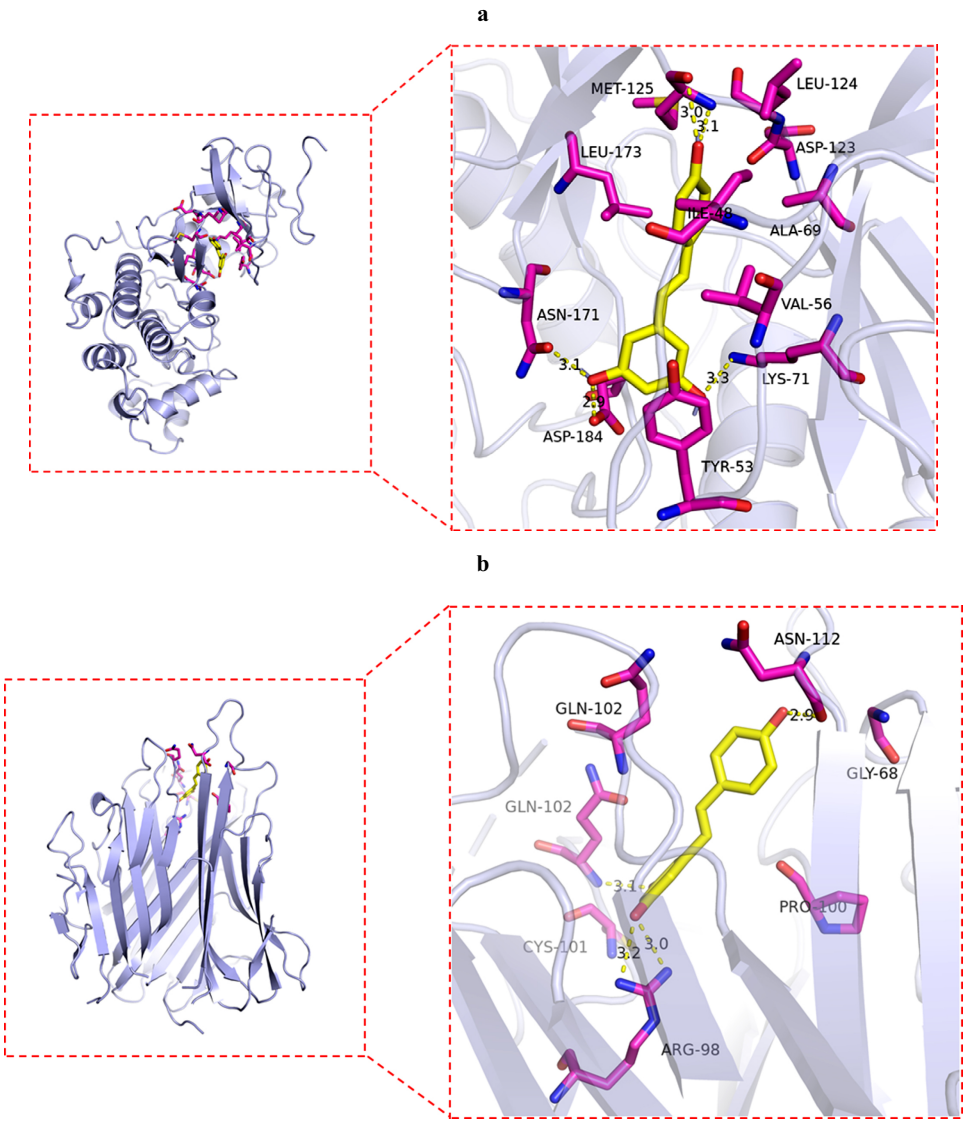


Fig. (5). Compound-Target-Disease network. Nodes represent shared target genes, resveratrol, and type I endometrial cancer. Edges represent the interaction between each of them. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



(Fig. 6) Contd….

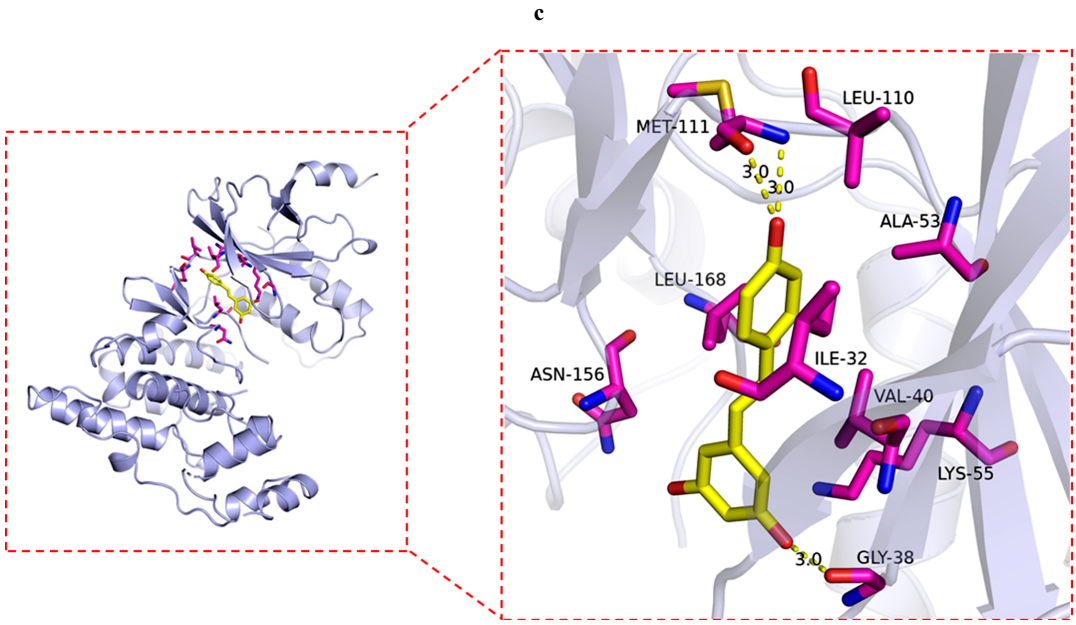


Fig. (6). Molecular models of resveratrol binding to its predicted protein targets. Proteins (**a**) MAPK3 (**b**) TNF (**c**) MAPK8 are shown optimal binding conformation with resveratrol. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

contributes to the MAPK cascade [47]. Signal transducer and activator of transcription 3 (STAT3), activated by interleukin-6 (IL6), takes an active part in the oncogenesis of cancer after activation [48]. Endometrial cell lines and tissues from patients with endometrial cancer had higher levels of phosphorylated Stat3 protein [49]. Resveratrol can inhibit STAT3 *in vitro*, and hence we may extrapolate this to be one of the anti-tumor functions of resveratrol in suppressing the development of endometrial cancer [50]. Its regulative effect on cell cycle may be induced by expression of G1/S-specific cyclin-D1 (CCND1, also known as BCL1) [51].

Resveratrol also demonstrates inflammatory effects on tumor inhibition. Tumor necrosis factor (TNF, Uniprot ID: P01375) is a cytokine mainly secreted by macrophages and can induce cell death of tumor cells [52]. It is essential for the immunity and cellular homeostasis of human beings, playing a key role in angiogenesis by inducing VEGF production synergistically with interleukin-1 beta (IL1B) and IL6 [53, 54]. However, further *in vitro* experiment is needed to specify if the gene targeted by resveratrol is a general one, not TNF-a nor TNF-b.

GO, and KEGG pathway analyses were conducted for better studying the interaction among common target genes. The GO annotations showed that resveratrol's anti-tumor property mainly depends on cellular response to oxidative stress, and the enriched analysis demonstrates that biological processes mostly take place in the membrane, participating in activation and binding of a range of cell receptors and cascading downstream signaling pathway. KEGG analysis indicated that the AGE-RAGE signaling pathway, PI3K-Akt signaling pathway, FoxO signaling pathway, and apoptosis are likely to be the pathways of the interaction. The docking study demonstrates how resveratrol binds to its targets, and this may imply the possible mechanism of resveratrol's anti-tumor effect.

Previous studies have revealed that resveratrol inhibits carcinogenesis in a number of cancer cells [11, 14, 55-57]. However, our study is the first to analyze resveratrol and type I endometrial cancer in a systematic approach *via* network pharmacology. This study on resveratrol and type I endometrial cancer adds to a growing body of evidence that resveratrol is an important anti-tumor agent in the whole process of endometrial cancer carcinogenesis.

CONCLUSION

We have elucidated the possible underlying mechanism of resveratrol in treating type I endometrial cancer through network pharmacology-based study and in silico validation. However, further evidence from *in vitro* experiments is needed to explore the mechanism.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available on request from the corresponding author.

FUNDING

This study has been financially supported by Zhejiang Provincial Project for Medical and Health Science and Technology (Grant No. 2021441040).

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors acknowledge the financial support received from the Zhejiang Provincial Project for Medical and Health Science and Technology.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

REFERENCES

[1] Raglan, O.; Kalliala, I.; Markozannes, G.; Cividini, S.; Gunter, M.J.; Nautiyal, J.; Gabra, H.; Paraskevaidis, E.; Martin-Hirsch, P.; Tsilidis, K.K.; Kyrgiou, M. Risk factors for endometrial cancer: An umbrella review of the literature. *Int. J. Cancer,* **2019**, *145*(7), 1719-1730. http://dx.doi.org/10.1002/ijc.31961 PMID: 30387875

[2] Ma, Y.; Han, X. Research progress of molecular biology related to endometrial cancer. *J Medical Recapitulate,* **2020**, *26*(10), 1941-1945.

[3] Lu, K.H.; Broaddus, R.R. Endometrial cancer. *N. Engl. J. Med.,* **2020**, *383*(21), 2053-2064. http://dx.doi.org/10.1056/NEJMra1514010 PMID: 33207095

[4] Morice, P.; Leary, A.; Creutzberg, C.; Abu-Rustum, N.; Darai, E. Endometrial cancer. *Lancet,* **2016**, *387*(10023), 1094-1108. http://dx.doi.org/10.1016/S0140-6736(15)00130-0 PMID: 26354523

[5] Mueller, M.D.; Vigne, J.L.; Minchenko, A.; Lebovic, D.I.; Leitman, D.C.; Taylor, R.N. Regulation of Vascular Endothelial Growth Factor (VEGF) gene transcription by estrogen receptors alpha and beta. *Proc. Natl. Acad. Sci. USA,* **2000**, *97*(20), 10972-10977. http://dx.doi.org/10.1073/pnas.200377097 PMID: 10995484

[6] Applanat, M.P.; Buteau-Lozano, H.; Herve, M.A.; Corpet, A. Vascular endothelial growth factor is a target gene for estrogen receptor and contributes to breast cancer progression. *Adv. Exp. Med. Biol.,* **2008**, *617*, 437-444. http://dx.doi.org/10.1007/978-0-387-69080-3_42 PMID: 18497067

[7] Recchia, F.; Candeloro, G.; Desideri, G.; Necozione, S.; Rea, S. Estrogen and vascular endothelial growth factor (VEGF): Their role in breast cANCER (BC) carcinogenesis and disease progression in premenopause. **2011**, *29*(15), 540.

[8] Aoki, Y.; Kanao, H.; Wang, X.; Yunokawa, M.; Omatsu, K.; Fusegi, A.; Takeshima, N. Adjuvant treatment of endometrial cancer today. *Jpn. J. Clin. Oncol.,* **2020**, *50*(7), 753-765. http://dx.doi.org/10.1093/jjco/hyaa071 PMID: 32463094

[9] Nakata, R.; Takahashi, S.; Inoue, H. Recent advances in the study on resveratrol. *Biol. Pharm. Bull.,* **2012**, *35*(3), 273-279. http://dx.doi.org/10.1248/bpb.35.273 PMID: 22382311

[10] Celotti, E.; Ferrarini, R.; Zironi, R.; Conte, L.S. Resveratrol content of some wines obtained from dried Valpolicella grapes: Recioto and Amarone. *J. Chromatogr. A,* **1996**, *730*(1-2), 47-52. http://dx.doi.org/10.1016/0021-9673(95)00962-0 PMID: 8680595

[11] Jang, M.; Cai, L.; Udeani, G.O.; Slowing, K.V.; Thomas, C.F.; Beecher, C.W.; Fong, H.H.; Farnsworth, N.R.; Kinghorn, A.D.; Mehta, R.G.; Moon, R.C.; Pezzuto, J.M. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science,* **1997**, *275*(5297), 218-220. http://dx.doi.org/10.1126/science.275.5297.218 PMID: 8985016

[12] Delmas, D.; Lançon, A.; Colin, D.; Jannin, B.; Latruffe, N. Resveratrol as a chemopreventive agent: A promising molecule for fighting cancer. *Curr. Drug Targets,* **2006**, *7*(4), 423-442. http://dx.doi.org/10.2174/138945006776359331 PMID: 16611030

[13] Sexton, E.; Van Themsche, C.; LeBlanc, K.; Parent, S.; Lemoine, P.; Asselin, E. Resveratrol interferes with AKT activity and triggers apoptosis in human uterine cancer cells. *Mol. Cancer,* **2006**, *5*, 45. http://dx.doi.org/10.1186/1476-4598-5-45 PMID: 17044934

[14] Dann, J.M.; Sykes, P.H.; Mason, D.R.; Evans, J.J. Regulation of vascular endothelial growth factor in endometrial tumour cells by resveratrol and EGCG. *Gynecol. Oncol.,* **2009**, *113*(3), 374-378. http://dx.doi.org/10.1016/j.ygyno.2009.02.014 PMID: 19321194

[15] Hopkins, A.L. Network pharmacology. *Nat. Biotechnol.,* **2007**, *25*(10), 1110-1111. http://dx.doi.org/10.1038/nbt1007-1110 PMID: 17921993

[16] Li, S.; Zhang, B. Traditional Chinese medicine network pharmacology: Theory, methodology and application. *Chin. J. Nat. Med.,* **2013**, *11*(2), 110-120. http://dx.doi.org/10.1016/S1875-5364(13)60037-0 PMID: 23787177

[17] Zhou, Z.; Chen, B.; Chen, S.; Lin, M.; Chen, Y.; Jin, S.; Chen, W.; Zhang, Y. Applications of network pharmacology in traditional Chinese medicine research. *Evid. Based Complement. Alternat. Med.,* **2020**, *2020*, 1646905. http://dx.doi.org/10.1155/2020/1646905 PMID: 32148533

[18] Ru, J.; Li, P.; Wang, J.; Zhou, W.; Li, B.; Huang, C.; Li, P.; Guo, Z.; Tao, W.; Yang, Y.; Xu, X.; Li, Y.; Wang, Y.; Yang, L. TCMSP: A database of systems pharmacology for drug discovery from herbal medicines. *J. Cheminform.,* **2014**, *6*, 13. http://dx.doi.org/10.1186/1758-2946-6-13 PMID: 24735618

[19] Ogata, H.; Goto, S.; Sato, K.; Fujibuchi, W.; Bono, H.; Kanehisa, M. KEGG: Kyoto encyclopedia of genes and genomes. *Nucleic Acids Res.,* **2000**, *28*(1), 27-30.

[20] Shannon, P.; Markiel, A.; Ozier, O.; Baliga, N.S.; Wang, J.T.; Ramage, D.; Amin, N.; Schwikowski, B.; Ideker, T. Cytoscape: A software environment for integrated models of biomolecular interaction networks. *Genome Res.,* **2003**, *13*(11), 2498-2504. http://dx.doi.org/10.1101/gr.1239303 PMID: 14597658

[21] Garrido-Gomez, T.; Quiñonero, A.; Dominguez, F.; Rubert, L.; Perales, A.; Hajjar, K.A.; Simon, C. Preeclampsia: A defect in decidualization is associated with deficiency of Annexin A2. *Am. J. Obstet. Gynecol.,* **2020**, *222*(4), 376.e1-376.e17. http://dx.doi.org/10.1016/j.ajog.2019.11.1250 PMID: 31738896

[22] Li, S.; Zhang, Z.Q.; Wu, L.J.; Zhang, X.G.; Li, Y.D.; Wang, Y.Y. Understanding ZHENG in traditional Chinese medicine in the context of neuro-endocrine-immune network. *IET Syst. Biol.,* **2007**, *1*(1), 51-60. http://dx.doi.org/10.1049/iet-syb:20060032 PMID: 17370429

[23] Costas, L.; Frias-Gomez, J.; Guardiola, M.; Benavente, Y.; Pineda, M.; Pavón, M.A.; Martínez, J.M.; Climent, M.; Barahona, M.; Canet, J.; Paytubi, S.; Salinas, M.; Palomero, L.; Bianchi, I.; Reventós, J.; Capellà, G.; Diaz, M.; Vidal, A.; Piulats, J.M.; Aytés, Á.; Ponce, J.; Brunet, J.; Bosch, F.X.; Matias-Guiu, X.; Alemany, L.; de Sanjosé, S.; Screenwide, T. New perspectives on screening and early detection of endometrial cancer. *Int. J. Cancer,* **2019**, *145*(12), 3194-3206. http://dx.doi.org/10.1002/ijc.32514 PMID: 31199503

[24] Wang, W.; Wang, S.; Liu, T.; Ma, Y.; Huang, S.; Lei, L.; Wen, A.; Ding, Y. Resveratrol: Multi-targets mechanism on neurodegenerative diseases based on network pharmacology. *Front. Pharmacol.,* **2020**, *11*, 694. http://dx.doi.org/10.3389/fphar.2020.00694 PMID: 32477148

[25] Liu, T.H.; Tu, W.Q.; Tao, W.C.; Liang, Q.E.; Xiao, Y.; Chen, L.G. Verification of resveratrol inhibits intestinal aging by downregulating ATF4/Chop/Bcl-2/Bax signaling pathway: Based on network pharmacology and animal experiment. *Front. Pharmacol.,* **2020**, *11*, 1064. http://dx.doi.org/10.3389/fphar.2020.01064 PMID: 32754039

[26] Koushki, M.; Amiri-Dashatan, N.; Ahmadi, N.; Abbaszadeh, H.A.; Rezaei-Tavirani, M. Resveratrol: A miraculous natural compound for diseases treatment. *Food Sci. Nutr.,* **2018**, *6*(8), 2473-2490. http://dx.doi.org/10.1002/fsn3.855 PMID: 30510749

[27] Ko, J.H.; Sethi, G.; Um, J.Y.; Shanmugam, M.K.; Arfuso, F.; Kumar, A.P.; Bishayee, A.; Ahn, K.S. The role of resveratrol in cancer therapy. *Int. J. Mol. Sci.,* **2017**, *18*(12), E2589. http://dx.doi.org/10.3390/ijms18122589 PMID: 29194365

[28] Han, Y.; Jo, H.; Cho, J.H.; Dhanasekaran, D.N.; Song, Y.S. Resveratrol as a tumor-suppressive nutraceutical modulating tumor microenvironment and malignant behaviors of cancer. *Int. J. Mol. Sci.,* **2019**, *20*(4), E925. http://dx.doi.org/10.3390/ijms20040925 PMID: 30791624

[29] Vervandier-Fasseur, D.; Latruffe, N. The potential use of resveratrol for cancer prevention. *Molecules,* **2019**, *24*(24), E4506. http://dx.doi.org/10.3390/molecules24244506 PMID: 31835371

[30] Kazi, A.A.; Koos, R.D. Estrogen-induced activation of hypoxia-inducible factor-1α, vascular endothelial growth factor expression, and edema in the uterus are mediated by the phosphatidylinositol 3-kinase/Akt pathway. *Endocrinology,* **2007**, *148*(5), 2363-2374. http://dx.doi.org/10.1210/en.2006-1394 PMID: 17272396

[31] Guo, J.; Chen, M.; Ai, G.; Mao, W.; Li, H.; Zhou, J. Hsa_circ_0023404 enhances cervical cancer metastasis and chemoresistance through VEGFA and autophagy signaling by sponging miR-5047. *Biomed. Pharmacother.,* **2019**, *115*, 108957. http://dx.doi.org/10.1016/j.biopha.2019.108957 PMID: 31082770

[32] Stuchi, L.P.; Castanhole-Nunes, M.M.U.; Maniezzo-Stuchi, N.; Biselli-Chicote, P.M.; Henrique, T.; Padovani Neto, J.A.; de-Santi

Neto, D.; Girol, A.P.; Pavarino, E.C.; Goloni-Bertollo, E.M. *VEGFA* and *NFE2L2* gene expression and regulation by microRNAs in thyroid papillary cancer and colloid goiter. *Genes (Basel),* **2020**, *11*(9), E954.
http://dx.doi.org/10.3390/genes11090954 PMID: 32824922

[33] Lu, Y.; Qin, T.; Li, J.; Wang, L.; Zhang, Q.; Jiang, Z.; Mao, J. MicroRNA-140-5p inhibits invasion and angiogenesis through targeting VEGF-A in breast cancer. *Cancer Gene Ther.,* **2017**, *24*(9), 386-392.
http://dx.doi.org/10.1038/cgt.2017.30 PMID: 28752859

[34] Kazi, A.A.; Koos, R.D. Estrogen-induced activation of hypoxia-inducible factor-1alpha, vascular endothelial growth factor expression, and edema in the uterus are mediated by the phosphatidylinositol 3-kinase/Akt pathway. *Endocrinology,* **2007**, *148*(5), 2363-2374.
http://dx.doi.org/10.1210/en.2006-1394 PMID: 17272396

[35] Chen, H.; Liu, H.; Qing, G. Targeting oncogenic Myc as a strategy for cancer treatment. *Signal Transduct. Target. Ther.,* **2018**, *3*, 5.
http://dx.doi.org/10.1038/s41392-018-0008-7 PMID: 29527331

[36] Tsujii, M.; Kawano, S.; Tsuji, S.; Sawaoka, H.; Hori, M.; DuBois, R.N. Cyclooxygenase regulates angiogenesis induced by colon cancer cells. *Cell,* **1998**, *93*(5), 705-716.
http://dx.doi.org/10.1016/S0092-8674(00)81433-6 PMID: 9630216

[37] Bruey, J.M.; Bruey-Sedano, N.; Luciano, F.; Zhai, D.; Balpai, R.; Xu, C.; Kress, C.L.; Bailly-Maitre, B.; Li, X.; Osterman, A.; Matsuzawa, S.; Terskikh, A.V.; Faustin, B.; Reed, J.C. Bcl-2 and Bcl-XL regulate proinflammatory caspase-1 activation by interaction with NALP1. *Cell,* **2007**, *129*(1), 45-56.
http://dx.doi.org/10.1016/j.cell.2007.01.045 PMID: 17418785

[38] Peiró, G.; Diebold, J.; Baretton, G.B.; Kimmig, R.; Löhrs, U. Cellular apoptosis susceptibility gene expression in endometrial carcinoma: Correlation with Bcl-2, Bax, and caspase-3 expression and outcome. *Int. J. Gynecol. Pathol.,* **2001**, *20*(4), 359-367.
http://dx.doi.org/10.1097/00004347-200110000-00008 PMID: 11603220

[39] Dhar, S.; Kumar, A.; Rimando, A.M.; Zhang, X.; Levenson, A.S. Resveratrol and pterostilbene epigenetically restore PTEN expression by targeting oncomiRs of the miR-17 family in prostate cancer. *Oncotarget,* **2015**, *6*(29), 27214-27226.
http://dx.doi.org/10.18632/oncotarget.4877 PMID: 26318586

[40] Berchuck, A.; Kohler, M.F.; Marks, J.R.; Wiseman, R.; Boyd, J.; Bast, R.C., Jr The p53 tumor suppressor gene frequently is altered in gynecologic cancers. *Am. J. Obstet. Gynecol.,* **1994**, *170*(1 Pt 1), 246-252.
http://dx.doi.org/10.1016/S0002-9378(94)70414-7 PMID: 8296829

[41] Okamoto, A.; Sameshima, Y.; Yamada, Y.; Teshima, S.; Terashima, Y.; Terada, M.; Yokota, J. Allelic loss on chromosome 17p and p53 mutations in human endometrial carcinoma of the uterus. *Cancer Res.,* **1991**, *51*(20), 5632-5635.
PMID: 1913680

[42] Schultheis, A.M.; Martelotto, L.G.; De Filippo, M.R.; Piscuglio, S.; Ng, C.K.; Hussein, Y.R.; Reis-Filho, J.S.; Soslow, R.A.; Weigelt, B. TP53 mutational spectrum in endometrioid and serous endometrial cancers. *Int. J. Gynecol. Pathol.,* **2016**, *35*(4), 289-300.
http://dx.doi.org/10.1097/PGP.0000000000000243 PMID: 26556035

[43] Manning, B.D.; Cantley, L.C. AKT/PKB signaling: Navigating downstream. *Cell,* **2007**, *129*(7), 1261-1274.
http://dx.doi.org/10.1016/j.cell.2007.06.009 PMID: 17604717

[44] Memarzadeh, S.; Zong, Y.; Janzen, D.M.; Goldstein, A.S.; Cheng, D.; Kurita, T.; Schafenacker, A.M.; Huang, J.; Witte, O.N. Cell-autonomous activation of the PI3-kinase pathway initiates endometrial cancer from adult uterine epithelium. *Proc. Natl. Acad. Sci. USA,* **2010**, *107*(40), 17298-17303.
http://dx.doi.org/10.1073/pnas.1012548107 PMID: 20855612

[45] Yang, Y.; Bao, W.; Sang, Z.; Yang, Y.; Lu, M.; Xi, X. Microarray pathway analysis indicated that mitogen-activated protein kinase/extracellular signal-regulated kinase and insulin growth factor 1 signaling pathways were inhibited by small interfering RNA against AT-rich interactive domain 1A in endometrial cancer. *Oncol. Lett.,* **2018**, *15*(2), 1829-1838.
PMID: 29399196

[46] Murata, T.; Shinozuka, Y.; Obata, Y.; Yokoyama, K.K. Phosphorylation of two eukaryotic transcription factors, Jun dimerization protein 2 and activation transcription factor 2, in Escherichia coli by Jun N-terminal kinase 1. *Anal. Biochem.,* **2008**, *376*(1), 115-121.
http://dx.doi.org/10.1016/j.ab.2008.01.038 PMID: 18307971

[47] Wu, F.; Zhang, W.; Li, L.; Zheng, F.; Shao, X.; Zhou, J.; Li, H. Inhibitory effects of honokiol on lipopolysaccharide-induced cellular responses and signaling events in human renal mesangial cells. *Eur. J. Pharmacol.,* **2011**, *654*(1), 117-121.
http://dx.doi.org/10.1016/j.ejphar.2010.11.022 PMID: 21147091

[48] Yamamoto, T.; Sekine, Y.; Kashima, K.; Kubota, A.; Sato, N.; Aoki, N.; Matsuda, T. The nuclear isoform of protein-tyrosine phosphatase TC-PTP regulates interleukin-6-mediated signaling pathway through STAT3 dephosphorylation. *Biochem. Biophys. Res. Commun.,* **2002**, *297*(4), 811-817.
http://dx.doi.org/10.1016/S0006-291X(02)02291-X PMID: 12359225

[49] Chen, C.L.; Hsieh, F.C.; Lieblein, J.C.; Brown, J.; Chan, C.; Wallace, J.A.; Cheng, G.; Hall, B.M.; Lin, J. Stat3 activation in human endometrial and cervical cancers. *Br. J. Cancer,* **2007**, *96*(4), 591-599.
http://dx.doi.org/10.1038/sj.bjc.6603597 PMID: 17311011

[50] Yu, L.J.; Wu, M.L.; Li, H.; Chen, X.Y.; Wang, Q.; Sun, Y.; Kong, Q.Y.; Liu, J. Inhibition of STAT3 expression and signaling in resveratrol-differentiated medulloblastoma cells. *Neoplasia,* **2008**, *10*(7), 736-744.
http://dx.doi.org/10.1593/neo.08304 PMID: 18592012

[51] Saxena, N.K.; Vertino, P.M.; Anania, F.A.; Sharma, D. leptin-induced growth stimulation of breast cancer cells involves recruitment of histone acetyltransferases and mediator complex to CYCLIN D1 promoter *via* activation of Stat3. *J. Biol. Chem.,* **2007**, *282*(18), 13316-13325.
http://dx.doi.org/10.1074/jbc.M609798200 PMID: 17344214

[52] Nie, H.; Zheng, Y.; Li, R.; Guo, T.B.; He, D.; Fang, L.; Liu, X.; Xiao, L.; Chen, X.; Wan, B.; Chin, Y.E.; Zhang, J.Z. Phosphorylation of FOXP3 controls regulatory T cell function and is inhibited by TNF-α in rheumatoid arthritis. *Nat. Med.,* **2013**, *19*(3), 322-328.
http://dx.doi.org/10.1038/nm.3085 PMID: 23396208

[53] Blaser, H.; Dostert, C.; Mak, T.W.; Brenner, D. TNF and ROS crosstalk in inflammation. *Trends Cell Biol.,* **2016**, *26*(4), 249-261.
http://dx.doi.org/10.1016/j.tcb.2015.12.002 PMID: 26791157

[54] Nakahara, H.; Song, J.; Sugimoto, M.; Hagihara, K.; Kishimoto, T.; Yoshizaki, K.; Nishimoto, N. Anti-interleukin-6 receptor antibody therapy reduces vascular endothelial growth factor production in rheumatoid arthritis. *Arthritis Rheum.,* **2003**, *48*(6), 1521-1529.
http://dx.doi.org/10.1002/art.11143 PMID: 12794819

[55] Aggarwal, B.B.; Bhardwaj, A.; Aggarwal, R.S.; Seeram, N.P.; Shishodia, S.; Takada, Y. Role of resveratrol in prevention and therapy of cancer: Preclinical and clinical studies. *Anticancer Res.,* **2004**, *24*(5A), 2783-2840.
PMID: 15517885

[56] Tomé-Carneiro, J.; Larrosa, M.; González-Sarrías, A.; Tomás-Barberán, F.A.; García-Conesa, M.T.; Espín, J.C. Resveratrol and clinical trials: The crossroad from *in vitro* studies to human evidence. *Curr. Pharm. Des.,* **2013**, *19*(34), 6064-6093.
http://dx.doi.org/10.2174/13816128113199990407 PMID: 23448440

[57] Harikumar, K.B.; Kunnumakkara, A.B.; Sethi, G.; Diagaradjane, P.; Anand, P.; Pandey, M.K.; Gelovani, J.; Krishnan, S.; Guha, S.; Aggarwal, B.B. Resveratrol, a multitargeted agent, can enhance antitumor activity of gemcitabine *in vitro* and in orthotopic mouse model of human pancreatic cancer. *Int. J. Cancer,* **2010**, *127*(2), 257-268.
PMID: 19908231