Bioinformatic Characteristics and Therapeutic Mechanisms of Calycosin-Anti-Bisphenol A-related Osteosarcoma

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Research

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Abstract

Background

Environmentally, bisphenol A (BPA) is well-known as a pollutant caused human health risk, such as osteosarcoma (OS). OS, a deadly bone neoplasia, may occur in children and adults. Recently, the anti-OS pharmacotherapy prescribes limitedly. Interestingly, our previous experiments evidence that calycosin exerts the potential anti-OS action *in vitro*. Thus, in this report, we aimed to characterize and detail the therapeutic targets and mechanisms of calycosin-anti-BPA-related OS by means of network pharmacology and molecular docking analyses.

Results

In details, the bioinformatic data revealed the mapped, core targets, biological functions, molecular pathways of calycosin to treat BPA-related OS. The computational analysis indicated that molecular docking ability and characteristic of core targets in calycosin to treat BPA-related OS were identified. Meanwhile, all optimal functions and pathways of calycosin-anti-BPA-related OS were revealed, as detailed in pathway networks.

Conclusions

Taken together, the network pharmacology and structural biology findings illustrate the core biotargets, pharmacological functions and pathways of calycosin-anti-BPA-related OS. Potentially, these identified core targets may attribute to the scientific development of calycosin against BPA-related OS.

1 Background

OS, one kind of malignant bone cancers, may occur in adolescent that affect their growth and bone function [1]. Statistically, the incidence of OS is increasing yearly in China because of its huge population [2]. In medical etiology, the cause of OS may be associated with hereditary factor, food habit, and environmental exposure [3]. In recent decades, the environmental pollution is of great concerns for possible human health risk [4]. BPA, a manufactured material used widely, is a well-reported endocrine disrupting chemical that induces potential reproductive impairment, immunological and neurological dysfunctions, and tumorigenesis [5]. It is defined by International Agency for Research on Cancer and the National Toxicology Program that BPA may be a carcinogen, such as breast cancer and prostate cancer [6]. Furthermore, BPA is found with potential risk of developing of OS in experimental studies [7–8]. However, there is no related report of agent against BPA-induced OS, especially the natural compound.

Calycosin, a naturally-occurring ingredient, is reported with functionally protecting against antioxidation, neuroprotection, anti-cancers [8]. In details, calycosin is pharmacologically found with beneficial actions against malignant cancers, such as colorectal cancer [10], hepatocellular carcinoma [11]. In our reported study shows the calycosin-anti-osteosarcoma effect *in vitro*, characterized with pharmacological

mechanism [12]. However, the bioinformatic investigation of calycosin against BPA-induced OS remain unreported. Interestingly, a network pharmacology tool is effectively used for detection of hug biotargets and molecular mechanisms of agent to treat disease [13–14]. To attain the aim, this bioinformatic report was designed to detect and characterize network pharmacology approach to highlight all anti-BPA-induced OS targets and mechanisms of calycosin. Collectively, a flow diagram by use of network pharmacology method was planned and showed in Fig. 1.

2 Methods

2.1 Detection of genes of calycosin and BPA-related OS

A series of effective tools of TCMSP, SwissTargetPrediction, BATMAN TCM, SuperPred was applied for collecting anti-disease genes of calycosin, and BPA-related OS genes were also obtained based on the GeneCard, OMIM database. In further determination, all assayed genes of calycosin and BPA-related OS were re-tested via the online bioinformatics tool for mapping Venn diagram, and the intersection target of calycosin in treatment of BPA-related OS was obtained [15–16].

2.2 Detecting of core targets of alycosin in treatment of BPA-related OS

After assays, the mapped genes of calycosin and BPA-related OS were used to generate a protein-protein interaction (PPI) network of calycosin to treat BPA-related OS using STRING tool. And the tsv. data were determined via Cytoscape tool to collect the core targets. In details, the core targets were screened according to the Degree value using NetworkAnalyzer for the topological data [17–18].

2.3 Enrichment analysis of molecular pathways of core targets

By use of FunRich analysis, the core targets of calycosin to treat BPA-related OS were determined via Functional Annotation Bioinformatics Microarray Analysis (DAVID) for identifying pharmacological processes and pathways of calycosin in the treatment of BPA-related OS. On the basis of the -Log p-value, the bar diagram and Circos chart of biological processes and signalling pathways of calycosin to treat OS were created and demonstrated [19–20].

2.4 Construction of network visualization

Applying with Cytoscape software to assay the core targets, the data of gene ontology of biological process and pathway enrichment for calycosin to treat BPA-related OS. Further, the visualization graph of drug-target-gene ontology-biological process-pathway-disease was constructed [21–22].

2.5 Molecular docking verification

As reported previously [23], all core targets were verified by molecular docking, and the structure of calycosin compound was obtained from PubChem database. The related protein structure was collected from the PDB database. Applying with Chem Bio Office2010 software, the docked ligand molecule and the original ligand molecule, the rationality of the docking parameter setting can be determined and identified according to the root mean square deviation (RMSD). It was generally referenced that RMSD ≤ 4 Å was the threshold for the conformation of the ligand to match the conformation of the original ligand after molecular docking.

3 Results

3.1 Preliminary bioinformatics data of targets

After tests by online tools, the number of 245 BPA-related OS disease-genes were detected, and analytical 138 anti-disease genes of calycosin were determined. As shown in Venn graph, a total of 20 mutual genes of calycosin and BPA-related OS were identified before being highlighted in a interaction network of calycosin to treat BPA-related OS (Fig. 1A).

3.2 Findings of all core targets

The mutual genes were further assayed by Cytoscape software, and then the topological data showed that the median degree of freedom of the target was 3.667, and the maximum degree of freedom was 10. Therefore, the core target screening criteria range was set to 4–10. As a result, we identified total 9 core targets of calycosin to treat BPA-related OS, having EGFR, ESR1, HSP90AA1, MAPK14, ESR2, AR, BRCA1, PTGS2, CYP19A1. The findings illustrated in an interaction network (Fig. 1B) and Supplemental Table 1.

3.3 Enrichment analysis findings of core targets

All 9 core targets were used to determine the gene ontology enrichment and KEGG pathway enrichment analyses through *R* language-related packages. As results, the histogram and Circos circle chart of the biological process of the gene ontology were presented in Figure. 3A-B; and then the histogram and Circos circle chart of KEGG pathways were showed in Figure. 3C-D. The results suggested that the biological process of the gene ontology mainly involved in ossification, positive regulation of bone resorption, positive regulation of bone remodeling, regulation of inflammatory response, neuroinflammatory response, positive regulation of inflammatory response, interleukin-12 secretion, chronic inflammatory response, positive regulation of acute inflammatory response, positive regulation of interleukin-12 production, regulation of neuroinflammatory response, regulation of cytokine production involved in inflammatory response, cytokine production involved in inflammatory response, regulation of interleukin-12 production, regulation of macrophage chemotaxis, macrophage chemotaxis, regulation of

macrophage migration, macrophage migration, negative regulation of macrophage migration, positive regulation of macrophage chemotaxis, regulation of cytokine secretion involved in immune response, cytokine secretion involved in immune response, positive regulation of macrophage migration, neutrophil activation involved in immune response, neutrophil mediated immunity, negative regulation of leukocyte migration, negative regulation of I-kappaB kinase/NF-kappaB signaling, positive regulation of cytokine production involved in immune response, response to tumor necrosis factor, response to antineoplastic agent, regulation of signal transduction by p53 class mediator, signal transduction by p53 class mediator, cellular response to tumor necrosis factor, response to steroid hormone, intracellular estrogen receptor signaling pathway, cellular response to steroid hormone stimulus, intracellular steroid hormone receptor signaling pathway, regulation of intracellular estrogen receptor signaling pathway, steroid hormone mediated signaling pathway, hormone-mediated signaling pathway (Supplemental Table 2). The 26 KEGG pathways of the core targets ($P < 0.05$) were identified with involvement of IL-17 signaling pathway, Th17 cell differentiation, Endocrine resistance, Estrogen signaling pathway, Prolactin signaling pathway, Ovarian steroidogenesis, Progesterone-mediated oocyte maturation, Breast cancer, Prostate cancer, Proteoglycans in cancer, MicroRNAs in cancer, PD-L1 expression and PD-1 checkpoint pathway in cancer, VEGF signaling pathway, GnRH signaling pathway, C-type lectin receptor signaling pathway, PI3K-Akt signaling pathway, TNF signaling pathway, Relaxin signaling pathway, FoxO signaling pathway, Oxytocin signaling pathway (Supplemental Table 3).

3.4 Interaction network findings

The network visualization of calycosin-target-BP-KEGG-BPA/OS was determined and highlighted through Cytoscape software, as revealed in Figure. 4. The core targets enriched in the KEGG pathway were identified in red by R-language software, as detailed in Fig. 5.

3.5 Molecular docking findings

As shown in binding energy data (Fig. 6A), In EGFR (PDB ID: 5UGC), the RMSD of the original ligand 8BS was 3.889 Å, and the hydrogen bond with the 5UGC protein acted on the amino acid residue MET-793 (2.9 Å), and calycosin and the amino acid residue MET-793 (3.0 Å)) hydrogen bond formation (Fig. 6B). In ESR1 (PDB ID:1UOM), the RMSD of the original ligand PTI was 3.645 Å, which hydrogen bonded with 1UOM protein to the amino acid residues ASP-351(3.5 Å), GLU-353(2.7 Å), ARG-394(3.0 Å), calycosin formed a hydrogen bond with amino acid residues GLU-353(1.8 Å) (Fig. 6C). In HSP90AA1 (PDB ID: 4BQG), the RMSD of the original ligand 50Q was 3.105 Å, and the hydrogen bonded with the 4BQG protein to the amino acid residue ASP-93 (2.7 Å), and Calycosin and the amino acid residue SER-52 (3.5 Å)), TYR-139 (3.1 Å) formed a hydrogen bond (Fig. 6D). In MAPK14 (PDB ID: 3ZSG), the RMSD of the original ligand T75 was 3.789 Å, and its hydrogen bonded with the 3ZSG protein acts on the amino acid residues LYS-53 (3.2 Å), MET-109 (2.7 Å), calycosin and amino acids Residue MET-109 (3.4 Å) formed a hydrogen bond (Fig. 6E). In AR (PDB ID: 1T7F), the RMSD of the original ligand DHT was 0.0004796 Å,

which hydrogen bonded with the 1T7F protein to the amino acid residues ASN-705 (2.7 Å), ARG-752 (3.0 Å), THR-877 (2.8 Å), calycosin formed a hydrogen bond with amino acid residue ARG-752 (2.1 Å) (Fig. 6F). In ESR2 (PDB ID: 2GIU), the RMSD of the original ligand FBR was 2.322 Å, which hydrogen bonded with the 2GIU protein to the amino acid residues GLU-305 (2.5 Å), LEU-339 (3.6 Å), calycosin formed a hydrogen bond with amino acid residue ILE-373 (2.6 Å) (Fig. 6G). In PTGS2 (PDB ID: 5IKR), the RMSD of the original ligand ID8 was 2.874 Å, and the hydrogen bond with the 5IKR protein acted on amino acid residues TYR-385 (2.0 Å), SER-530 (2.0 Å), calycosin formed a hydrogen bond with amino acid residue SER-530 (2.9 Å) (Fig. 6H). In CYP19A1 (PDB ID: 3S79), the RMSD of the original ligand ASD was 0.0004888 Å, which hydrogen bonded with the 3S79 protein to the amino acid residues ARG-115 (3.3 Å), MET-374 (2.8 Å), calycosin formed a hydrogen bond with the amino acid residue ARG-115 (3.1 Å) (Fig. 6I).

4 Discussion

In this bioinformatics study, we identified and elucidated the pharmacological activity and mechanism of calycosin to treat BPA-related OS. More interestingly, all core targets of calycosin to treat BPA-related OS were revealed, comprising EGFR, ESR1, HSP90AA1, MAPK14, ESR2, AR, BRCA1, PTGS2, CYP19A1. EGFR, if mutated, is reportedly found with the development of tumorigenesis [24]. Another evidence shows that BPA induces cancer cell proliferation via activation of EGFR activity [25]. ESR1, also known as estrogen receptor 1, is commonly found with mutation in many human cancer samples, such as breast cancer [26]. It is reported that high BPA exposure may be related to non-small cell lung cancer via changing ESR1 genetic polymorphism [27]. It is also reported in the literatures that in addition to affecting tumor cell survival, HSP90AA1 can act on the invasion and migration of cancer cells, and it is closely related to the poor prognosis of tumors [28]. HSP90AA1, functioning as a key effector of autophagy, is positively associated with the development of osteosarcoma chemoresistance [29]. MAPK14 acts as an integration point for multiple biochemical events, and it is involved in a group of cellular processes including cell differentiation and proliferation, gene transcription regulation [30]. Some of evidences suggest that MAPK14 activity activates the cancer cell migration, invasiveness and angiogenesis [31]. AR, an androgen receptor, is a drug target in cancers, such as prostate tumor, and the anti-cancer action is achived through regulating androgen receptor signaling [32]. It is reported that BPA regulates specific gene expression in human prostate cancer cells for androgen-dependent proliferation [33]. BRCA1, a nuclear phosphoprotein, exerts an action in maintaining genomic stability, and it also functions as a cancer suppressor [34]. It is found that BRCA1 may suppress the BPA-induced cell proliferation *in vitro* and *in vivo* [35]. The transcriptional profiling of PTGS signaling characterizes the key clue on the biological event of the tumor-related microenvironment, such as inflammatory infiltration [36]. However, there is no report regarding the association between PTGS and osteosarcoma, BPA. The clinical analysis suggests the potential impact of CYP19A1 in postmenopausal endocrine responsive breast cancer [37]. The study *in vitro* indicates that BPA induces cell proliferation and growth in human choriocarcinoma cell line [38]. As reveal in computational assaus, the pharmacological functions of to treat BPA-related OS were identified accordingly, such as ossification, positive regulation of bone resorption, positive regulation

of bone remodeling, regulation of inflammatory response, neuroinflammatory response, positive regulation of inflammatory response, interleukin-12 secretion, positive regulation of interleukin-12 production. These bioinformatic findings indicate that calycosin may play the anti-BPA-related OS action by modulating current molecular processes. In further investigation, the other KEGG enrichment analysis-based findings revealed all calycosin-anti-BPA-related OS, including IL-17 signaling pathway, Th17 cell differentiation, Endocrine resistance, Estrogen signaling pathway, Proteoglycans in cancer, MicroRNAs in cancer, PD-L1 expression and PD-1 checkpoint pathway in cancer, VEGF signaling pathway, GnRH signaling pathway□PI3K-Akt signaling pathway, TNF signaling pathway, FoxO signaling pathway. More markedly, our current computational evidences of GO-based molecular processes were consistent with the findings of KEGG signaling pathways of calycosin against BPA-related OS following bioinformatic analyses, contributing to the future clinical application of calycosin against BPA-related OS.

5 Conclusion

In conclusion, our current computational report highlights the pharmacological biotargets, biological processes, molecular mechanisms of calycosin to treat BPA-related OS. In future medical significance, current bioinformatic findings will be applied in clinical practice against osteosarcoma, including BPA-related OS.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

Bin Liu and Zhenchao Yuan designed the research; Jiachang Tan, Zhenjie Wu, Jun Chen, Hao Mo conducted the data analyses; Jiachang Tan, Bin Liu and Zhenchao Yuan wrote the draft of initial manuscript; Bin Liu and Zhenchao Yuan contributed to the interpretation of the data and preparation of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets obtained and analyzed in the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflicts of interest in present study.

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Figures

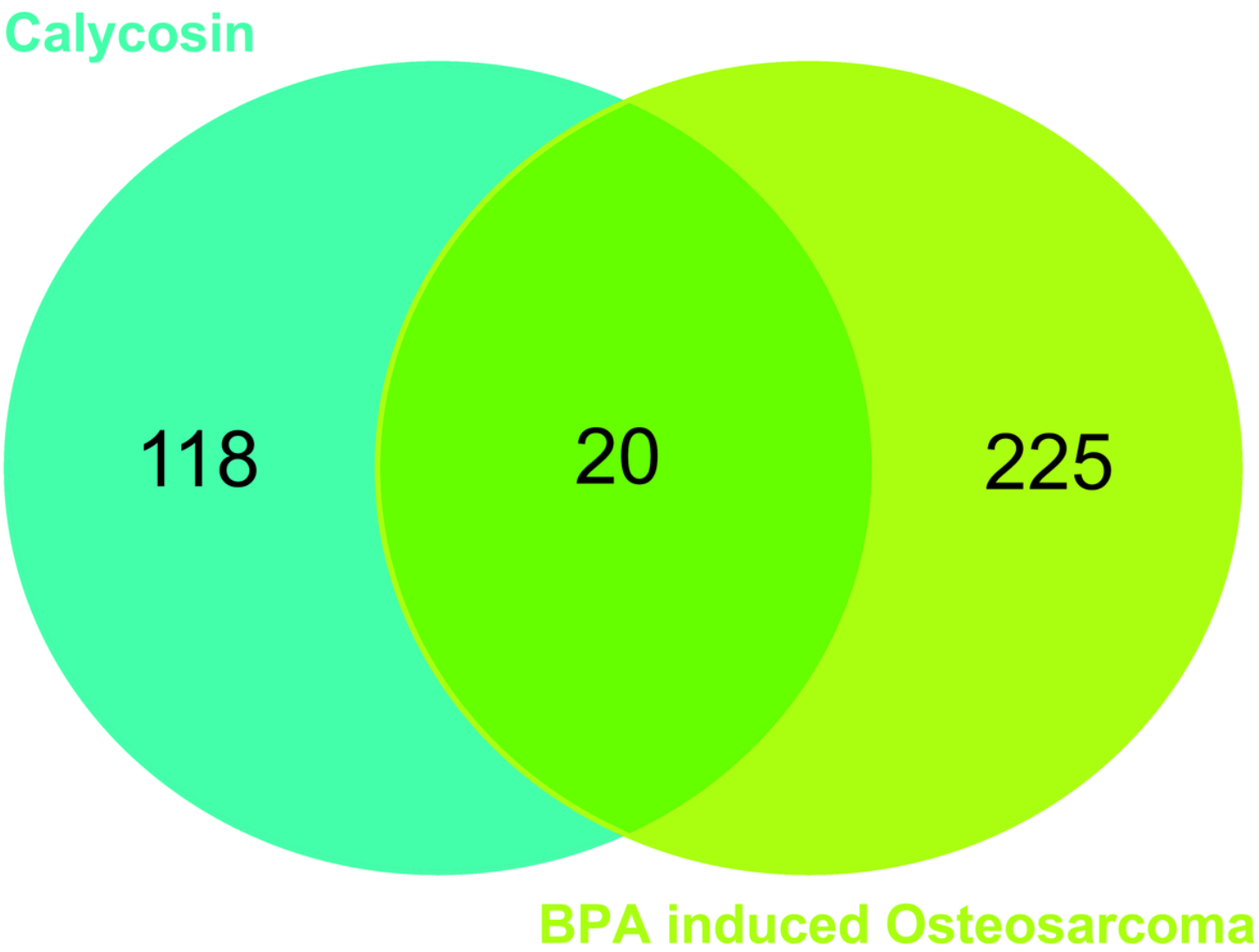

Figure 1

As showed in Venn assay, all candidate, mapped targets of calycosin and BPA-related OS were identified accordingly.

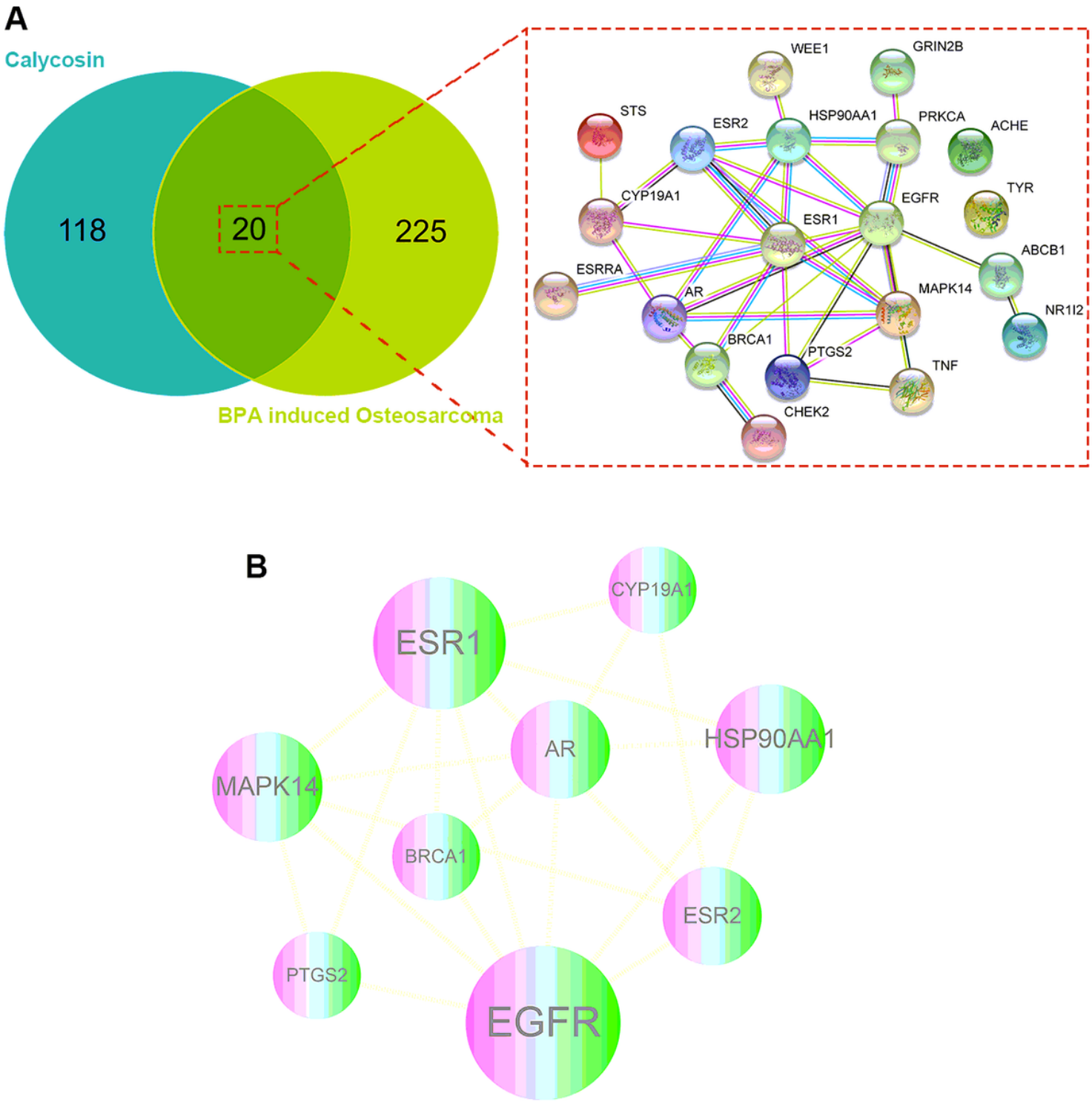

Figure 2

After further bioinformatics analysis, the targets of calycosin and BPA-related OS were identified to produce a mapped network of calycosin to treat BPA-related OS. And then all core targets of calycosin to treat BPA-related OS were identified accordingly.

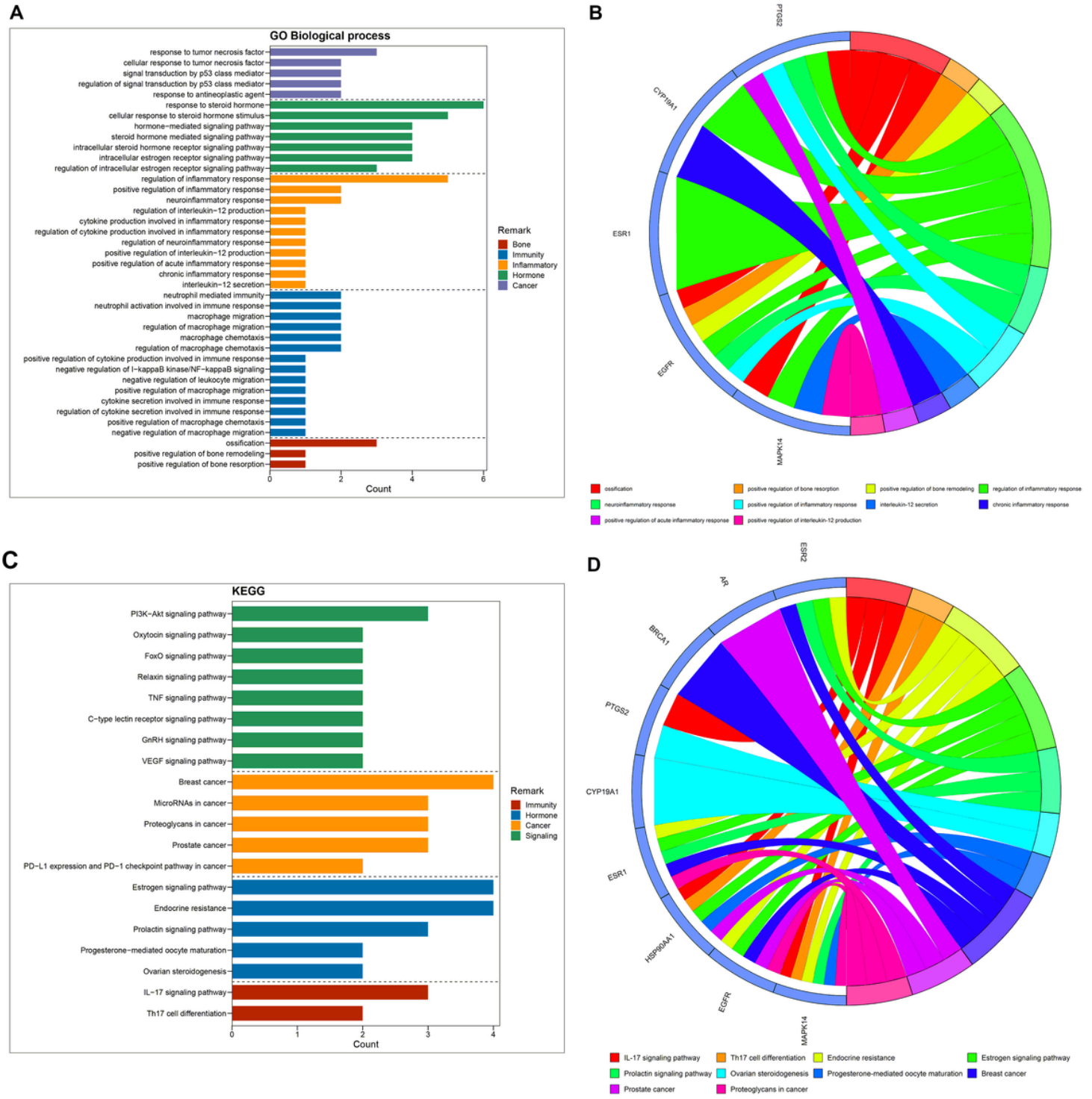

Figure 3

After enrichment analyses, all top functional processes, molecular mechanisms of calycosin to treat BPA-related OS were screened and highlighted.

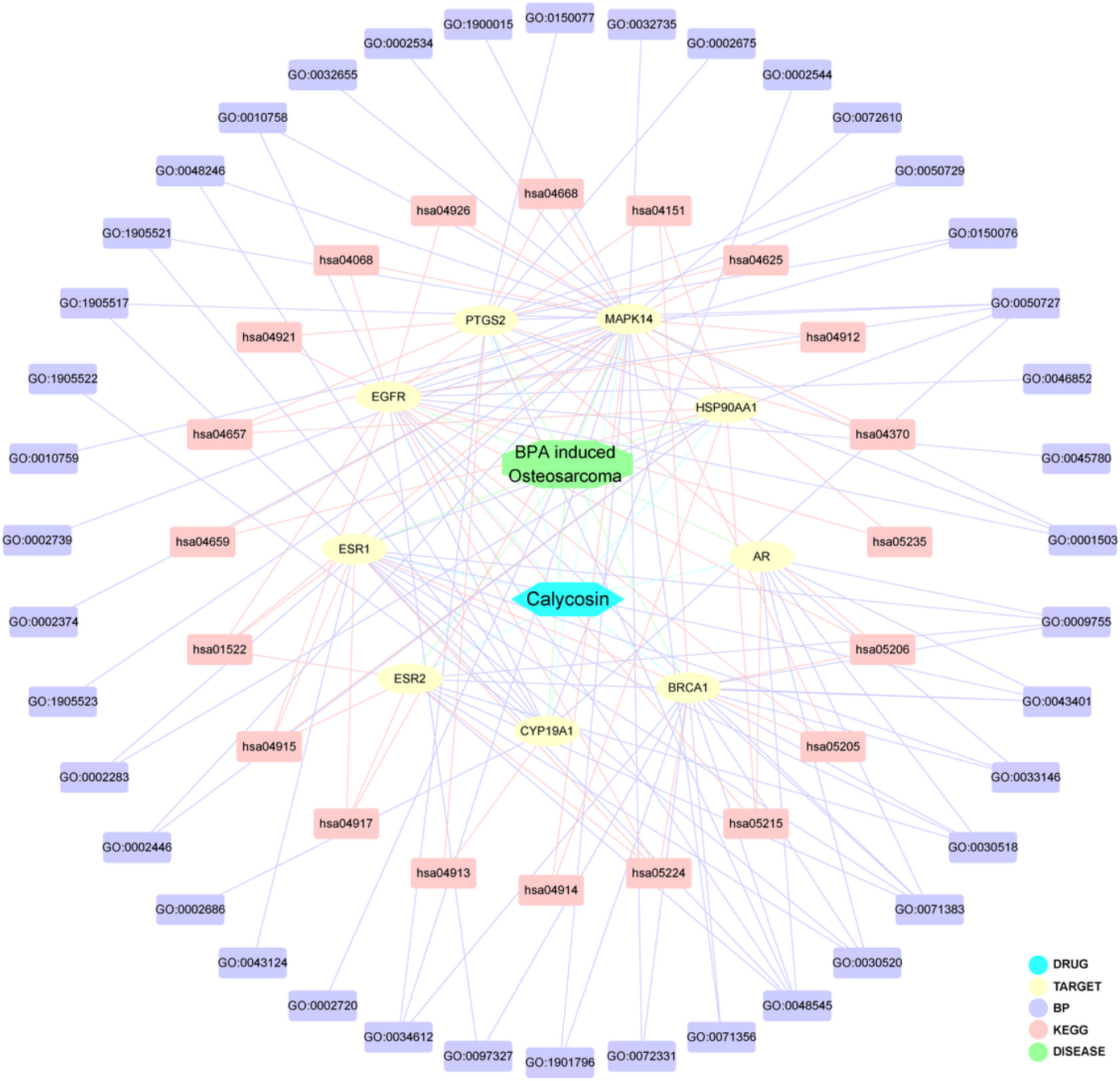

Figure 4

A network visualization of calycosin-target-BP-KEGG-BPA/OS was determined and highlighted.

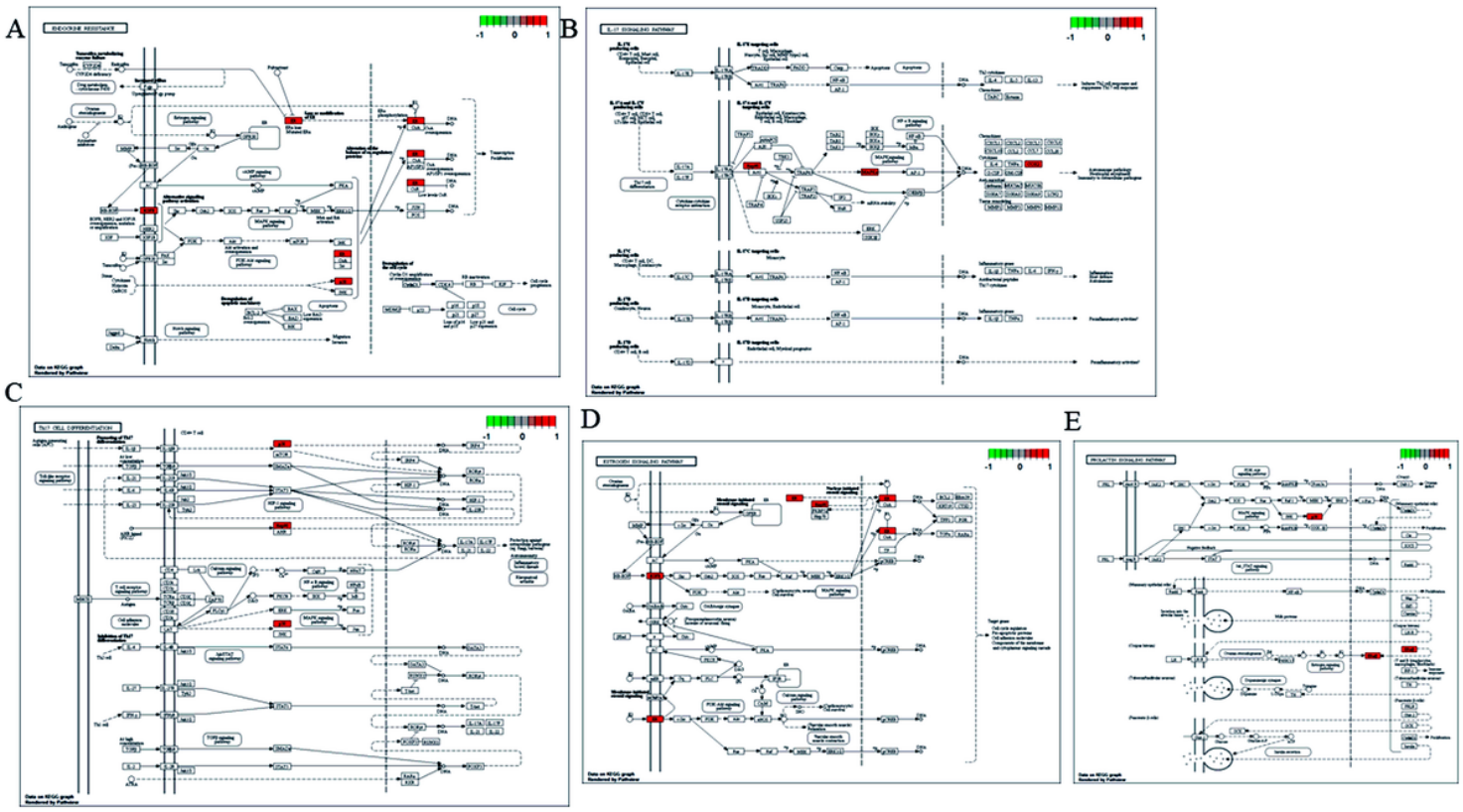

Figure 5

The core targets enriched in the KEGG pathway were identified in red by R-language software.

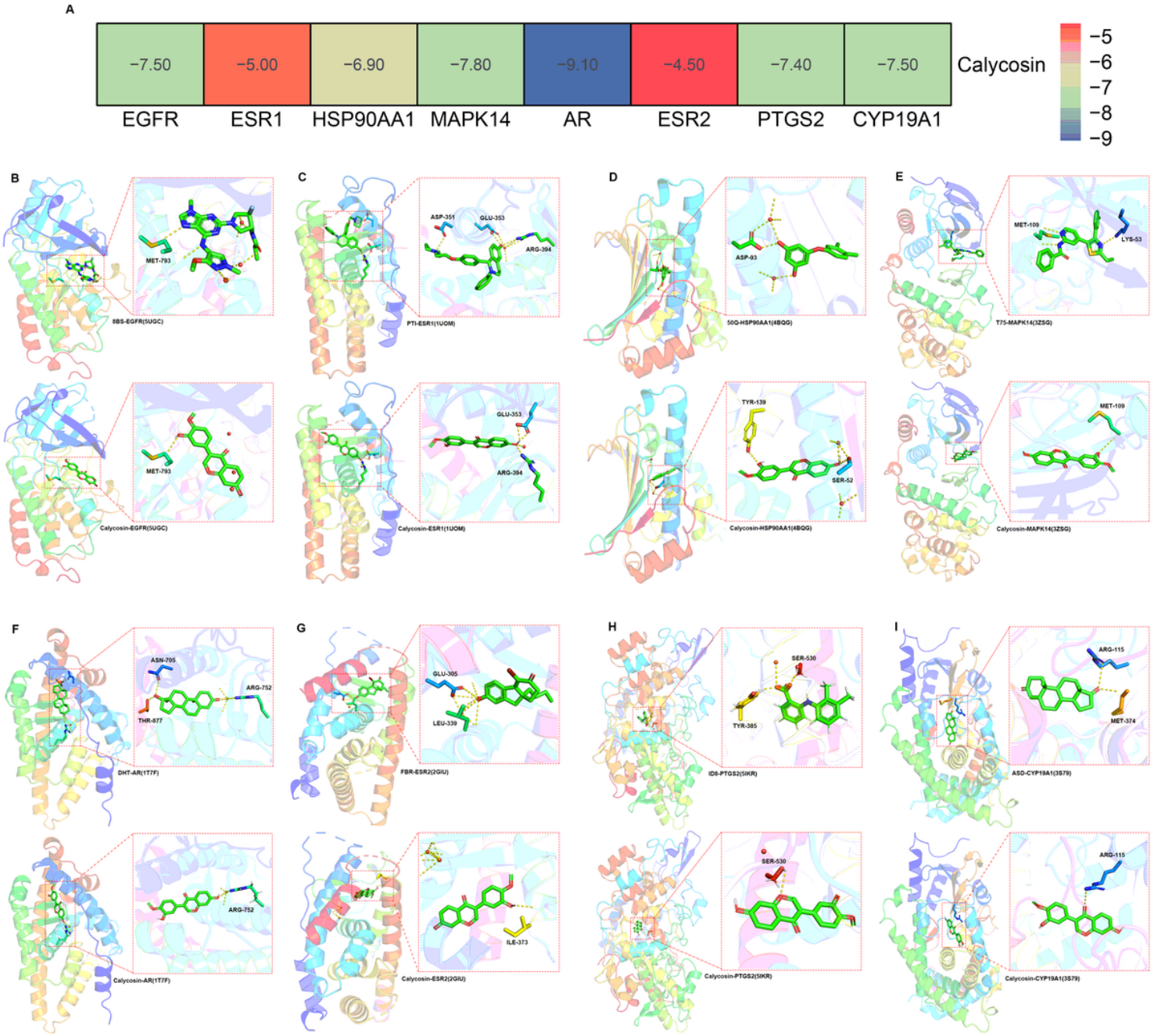

Figure 6

Molecular docking findings of calycosin to treat BPA-related OS.

Supplementary Files

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