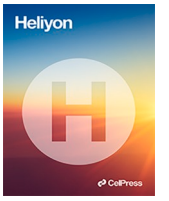
Heliyon 10 (2024) e31473

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Exploring the mechanisms underlying effects of bisphenol a on cardiovascular disease by network toxicology and molecular docking

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ARTICLE INFO

Keywords:
Bisphenol A
Cardiovascular disease
Mechanisms
Network toxicology
Molecular docking

ABSTRACT

Background: Globally, cardiovascular disease (CVD) has emerged as a leading cause of mortality. Bisphenol A (BPA), recognized as one of the most prevalent and widely distributed endocrine-disrupting chemicals (EDCs), has been consistently linked to the progression of CVD. This research centers on unraveling the molecular mechanisms responsible for the toxic effects of BPA exposure on CVD. Key targets and pathways involved in action of BPA on CVD were investigated by network toxicology. Binding abilities of BPA to core targets were evaluated by molecular docking.

Methods and results: Based on information retrieved from ChEMBL, DrugBank, and OMIM databases, a total of 27 potential targets were found to be associated with the influence of BPA on CVD. Furthermore, the STRING and Cytoscape software were employed to identify three central genes—ESR1, PPARG, and PTGS2—and to construct both the protein-protein interaction network and an interaction diagram of potential targets. Gene ontology (GO) and KEGG (Kyoto Encyclopedia of Genes and Genomes, KEGG) pathway enrichment analyses via WebGestalt revealed key biological processes (BP), cellular components (CC), molecular functions (MF), and pathways, such as the calcium signaling pathway, inflammatory mediator regulation of TRP channels, gap junction, adrenergic signaling in cardiomyocytes, cGMP-PKG signaling pathway, and cAMP signaling pathway, predominantly involved in BPA-induced CVD toxicity. By using molecular docking investigations, it proved that BPA binds to ESR1, PPARG, and PTGS2 steadily and strongly.

Conclusion: This study not only establishes a theoretical framework for understanding the molecular toxicity mechanism of BPA in cardiovascular disease (CVD) but also introduces an innovative network toxicology approach to methodically investigate the influence of environmental contaminants on CVD. This methodology sets the stage for drug discovery efforts targeting CVD linked to exposure to endocrine-disrupting chemicals (EDCs).

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https://doi.org/10.1016/j.heliyon.2024.e31473
Received 22 January 2024; Received in revised form 15 May 2024; Accepted 16 May 2024
Available online 17 May 2024

1. Introduction

Roughly one-third of all fatalities worldwide are caused by cardiovascular disease (CVD) [1]. Over the past ten years, there has been a 12.5 % increase in the number of CVD deaths worldwide [2]. CVD is influenced by personal factors, such as alcohol consumption, smoking, and diet. Furthermore, CVD also has traditional risk factors that include obesity, diabetes mellitus, and hypertension [3]. However, there is mounting evidence confirming that multiple environmental variables contribute to the development of CVD. Unfortunately, the overall impact of the environment on CVD has not been thoroughly assessed, and the underlying mechanisms also remain elusive.

Many consumer products contain large amounts of environmental contaminants such as endocrine-disrupting chemicals (EDCs) which are often and extensively utilized [4]. BPA is a water-soluble chemical that belongs to the class of diphenylmethane derivatives [5]. Numerous diseases and poor health are associated with widespread and chronic exposure to BPA through ingestion and skin contact, including multiple cancers [6], respiratory disease [7], nervous system developmental abnormalities [8] as well as poor adult reproductive and childhood health [9]. Additionally, BPA may lead to nervous system developmental abnormalities, such as migraine-like behaviors, enhanced fear memory [10–12]. Moreover, BPA is linked to conditional risk factors of CVD. There is a positive correlation observed between high levels of BPA and metabolic syndrome, insulin resistance, and obesity [13–15]. Though research based on the National Health and Nutrition Examination Survey (NHANES) shown the relationship between BPA exposure and cardiovascular disease was controversial, higher urine BPA levels were more likely to develop heart disease and hypertension [16,17] and was linked to an increased risk of cardiovascular mortality [18] and CVD [19].

Network toxicology is an innovative and promising approach for target discovery and originates from network pharmacology [20]. This approach systematically integrates multiple databases and constructs complicated networks among toxic targets, disease targets, and biological processes [21]. It can also reveal potential toxic-target-disease interactions as well as novel toxicology mechanisms. Network toxicology strategy and molecular docking were not applied to examine the fundamental pathways of BPA toxicity with respect to CVD. In the present study, candidate targets associated with effects of BPA on CVD were collected. Hub genes were identified and used to construct a protein-protein interaction network. Gene ontology (GO) and KEGG (Kyoto Encyclopedia of Genes and Genomes, KEGG) pathway enrichment shown key biological process (BP), cellular component (CC), and molecular function (MF) and pathways. Molecular docking revealed binding capacity of BPA to core target. Our research offered a rapid, strategic, and efficient method for thoroughly assessing the effect of toxic environmental pollutants, such as EDCs on CVD. Furthermore, this study will also facilitate drug discovery for the treatment of CVD.

2. Methods

2.1. Prediction of potential targets of toxicity of BPA to CVD

To gather the structure and SMILES characters, "Bisphenol A″ was entered into PubChem (https://pubchem.ncbi.nlm.nih.gov/). Candidate targets of BPA were searched in the ChEMBL database (https://www.ebi.ac.uk/chembl/) and the species were restricted to "*Homo sapiens*" (Supplementary Table 1). Additionally, the DrugBank database (https://www.drugbank.com/) and the Online Mendelian Inheritance (OMIM) database (http://www.omim.org/) were employed to retrieve potential therapeutic targets related to CVD (Supplementary Table 2). The redundancy of the candidate targets was eliminated. The name of these targets was standardized in the Uniprot database (https://www.uniprot.org/). Finally, common targets of BPA's impact on CVD were obtained (Supplementary Table 3).

2.2. Construction of network and identification of hub genes

The STRING database (https://cn.string-db.org/) was used to construct a target-to-target, function-related, protein-protein interaction (PPI) network and export general data (tsv.) of candidate targets. The confidence score of protein interactions was set as >0.9. A network of molecular pathways of BPA toxicity to CVD was constructed using Cytoscape (v3.7.1) using general data. A set of hub genes was selected based on the maximal clique centrality (MCC) algorithm and Degree according to CytoHubba of Cytoscape software.

2.3. Gene function and pathway enrichment analysis of potential targets

GO analysis and KEGG pathway enrichment analysis of potential targets of BPA-induced toxicity on CVD were performed using the WebGestalt (http://www.webgestalt.org/option.php) database. The obtained results of GO enrichment analysis included BP, CC, and MF. Over-Representation Analysis (ORA) was set as the method of interest and the false discovery rate adjusted P-value <0.05 suggests statistical significance.

2.4. Molecular docking

Using CB-Dock2 (https://cadd.labshare.cn/cb-dock2/php/index.php) platform [22], molecular docking was conducted utilizing the protein targets of the chosen ligands. CB-Dock2 is a molecular docking tool based on AutoDock Vina analysis which can

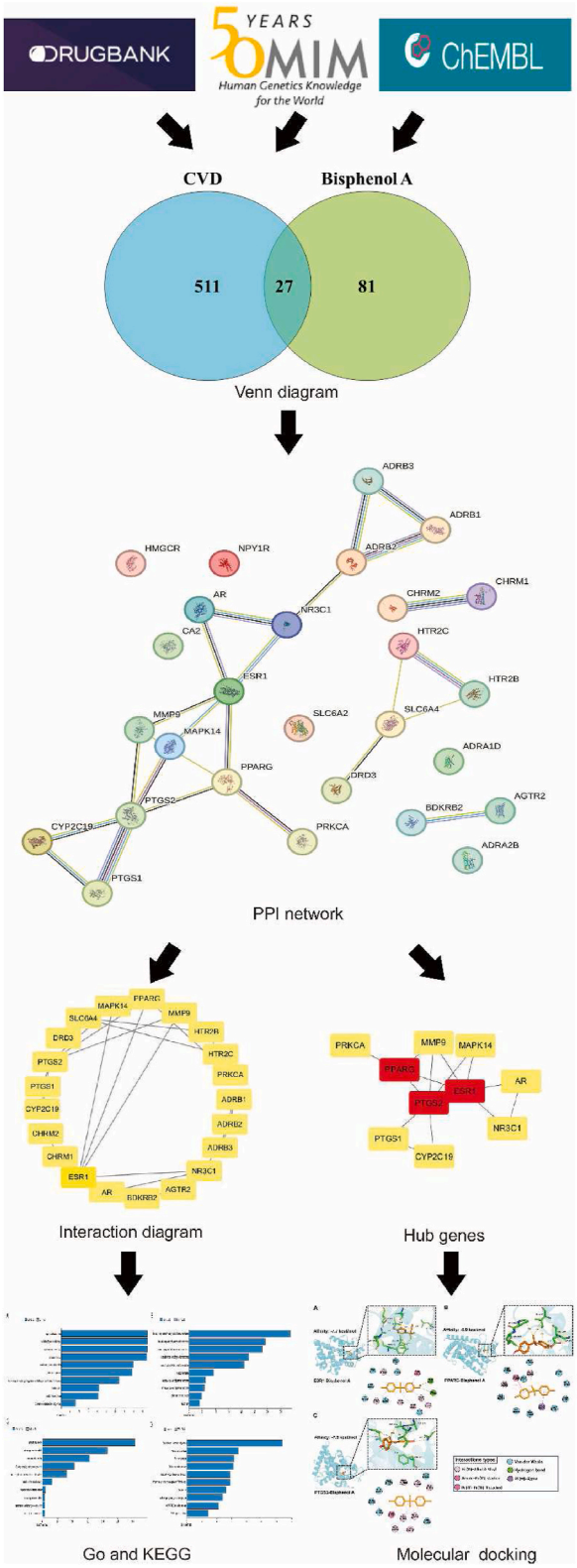

Fig. 1. A schematic diagram of network toxicology approach for investigating core targets, hub hubs, PPI network, interaction diagram, GO and KEGG enrichment of toxicity of BPA to CVD and molecular docking for the binding of BPA to core targets.

automatically identify and analyze the site where the ligand binds to the receptor. It enhances molecular docking accuracy and simplifies docking processes. After the 2D chemical structure of BPA was retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov), it was uploaded into the CB-Dock2 platform, charged with H atoms, and then subjected to free energy minimization. In addition, the protein crystal structures obtained from the PDB (https://www.rcsb.org/) database, were processed by adding hydrogen atoms and removing all water molecules. The binding affinity energy (kcal/mol) was computed using CB-Dock2, which projected the optimal docking model with the least amount of energy. We used the PyMol software (version: 2.5) and BIOVIA Discovery Studio Visualizer (version: 2021) software to uncover the details of ligand-receptor interactions. Fig. 1 shown the workflow of the present study.

3. Results

3.1. Identification of targets of BPA-induced CVD toxicity targets

A total of 538 known CVD targets were retrieved from the OMIM and DrugBank databases, and 108 BPA targets were obtained from ChEMBL.

. The Venn diagram was applied to visualize 27 common targets of BPA-induced CVD toxicity (Fig. 2). In the STRING database, the function-related PPI network of possible targets is constructed (Fig. 3).

3.2. Identification of hub genes

Potential targets were also uploaded into Cytoscape to plot the BPA-induced CVD toxicity network diagram (Fig. 4A). The hub genes were identified based on the degree of the MCC algorithm. ESR1, PPARG, and PTGS2 were finally determined as core targets of the impact of BPA on CVD (Fig. 4B).

3.3. GO and KEGG analysis

After analysis, the top 10 BP results were, regulation of tube diameter, regulation of blood vessel diameter, regulation of blood vessel size, regulation of tube size, vascular process in the circulatory system, regulation of blood pressure, G protein-coupled receptor signaling pathway, coupled to cyclic nucleotide second messenger, blood circulation, circulatory system process, and G protein-coupled receptor signaling pathway (Fig. 5A). Integral component of postsynaptic density membrane, integral component of postsynaptic membrane, intrinsic component of postsynaptic membrane, integral component of synaptic membrane, integral component of synaptic membrane, synaptic membrane, integral component of plasma membrane, intrinsic component of plasma membrane, plasma membrane region, and neuron part were identified as ten top CC (Fig. 5B). Epinephrine binding, adrenergic receptor activity, catecholamine binding, G protein-coupled amine receptor activity, G protein-coupled neurotransmitter receptor activity, neurotransmitter receptor activity, G protein-coupled receptor activity, signaling receptor activity, transmembrane signaling receptor activity and molecular transducer activity were identified as ten top MF (Fig. 5C). KEGG pathway enrichment analysis showed that signal pathways were mainly related to the regulation of lipolysis in adipocytes, serotonergic synapse, salivary secretion, calcium signaling pathway, neuroactive ligand-receptor interaction, inflammatory mediator regulation of TRP channels, gap junction, adrenergic signaling in cardiomyocytes, cGMP-PKG signaling pathway and cAMP signaling pathway (Fig. 5D).

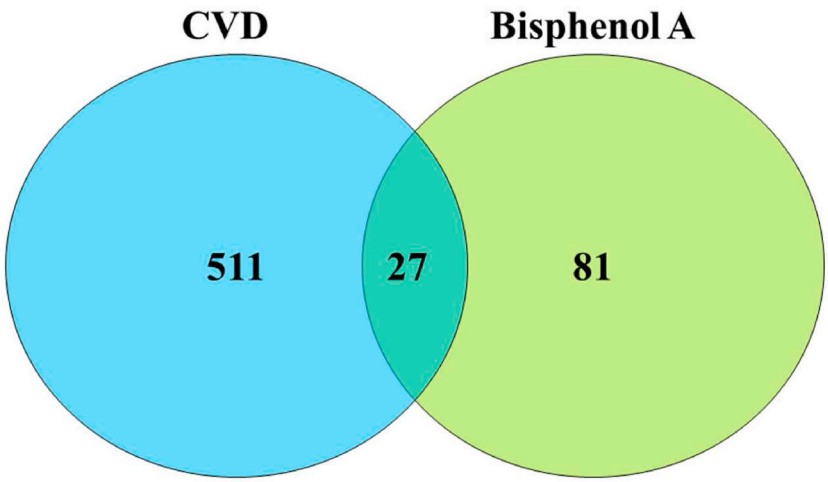

Fig. 2. Venn diagram of potantial targets of toxicity of BPA to CVD.

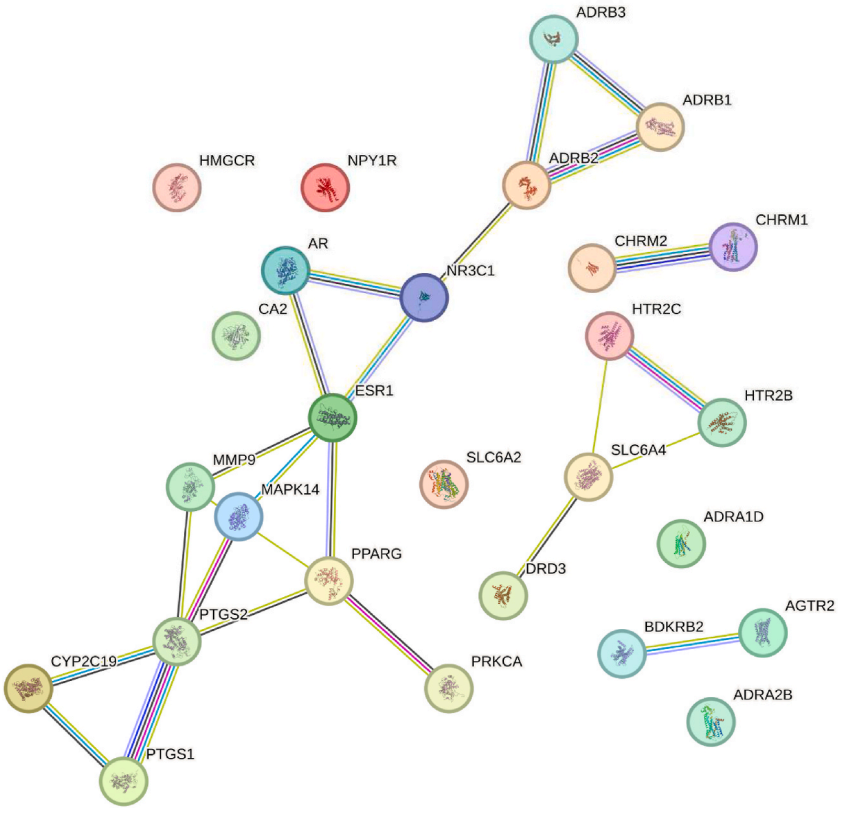

Fig. 3. The PPI network of common targets.

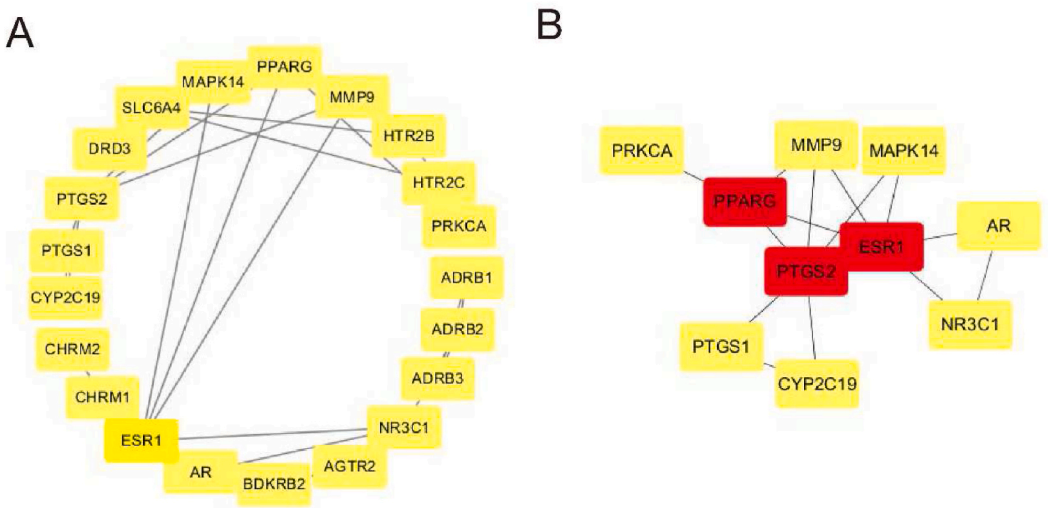

Fig. 4. Interaction diagram of common targets (A) and hub genes (B).

3.4. Molecular docking

Through the CB-Dock2 platform, the affinity of ESR1, PPARG, and PTGS2 to BPA was further investigated. The Vina score was calculated as an indication of binding affinity. Based on the receptor-ligand docking hypothesis, the docking energy is inversely proportional to binding affinity, with lower docking energy suggesting a greater binding affinity between the protein and the ligand. The results indicated that BPA had a binding affinity for ESR1 (PDB code: 5kra) of −7.7 kcal/mol. van der Waals's interactions with

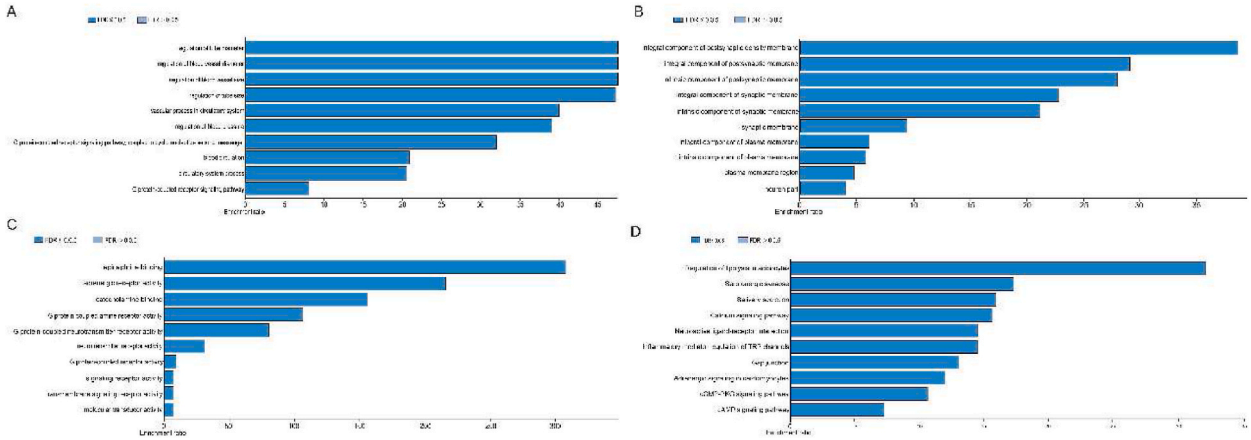

Fig. 5. GO and KEGG enrichment analysis of potential targets.

TRP383, MET421, LEU384, LEU349, THR347, LEU536, and LEU540 facilitated the binding of BPA to ESR1, as shown by 3D and 2D mapping. Furthermore, BPA displayed stable binding to ESR1 by forming hydrogen bonds with GLU353 and ARG394. Finally, pi (π)-alkyl and alkyl interaction bonds with LEU346, LEU391, LEU387, MET388, ALA350, and LEU525 residues were involved in the stable binding of BPA to ESR1. The binding of BPA to ESR1 also involved pi (π)-pi (π) T-shaped interaction bonds with PHE404 residue (Fig. 6A). The binding affinity of BPA for PPARG (PDB code: 1fm6) is −6.9 kcal/mol. Additionally, van der Waals interactions

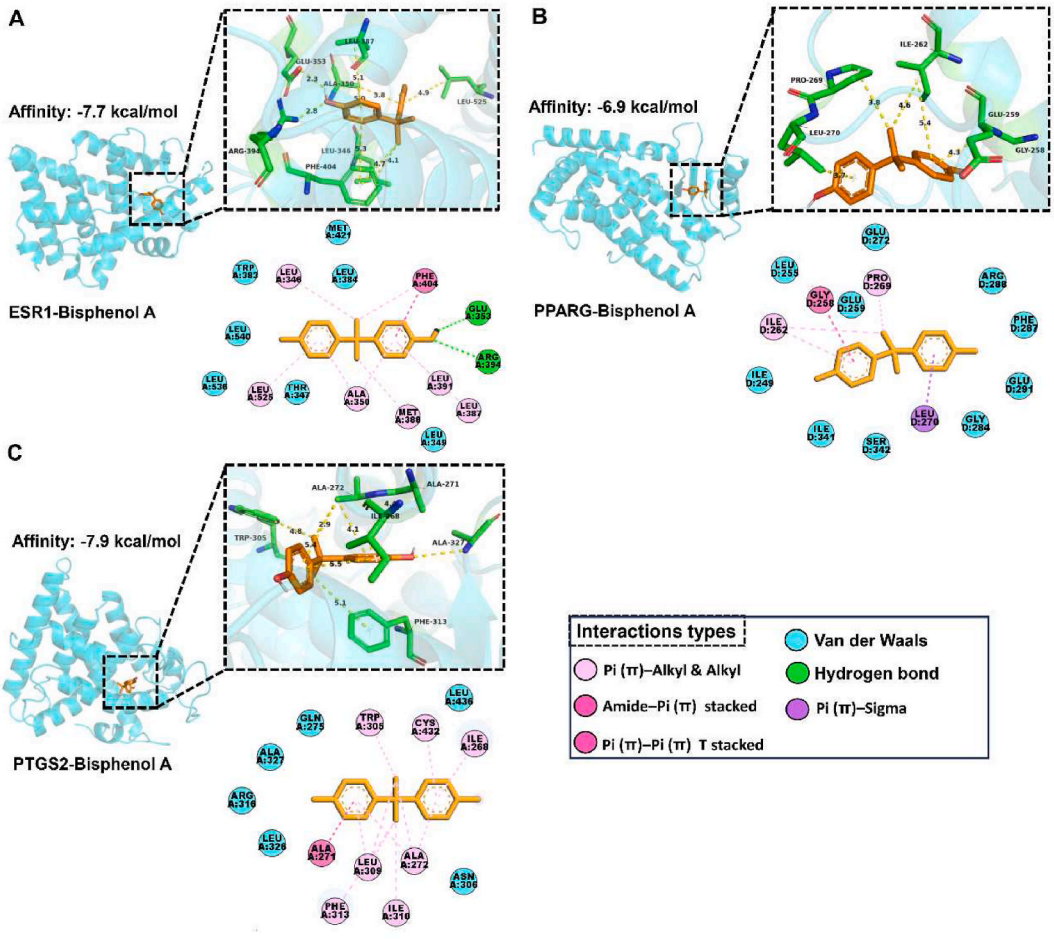

Fig. 6. Molecular models of the binding of BPA to core targets, including ESR1 (A), PPARG (B), and PTGS2 (C).

involving GLU272, ARG288, PHE287, GLU291, GLY284, SER342, ILE341, ILE249, GLU259, and LEU255 residues were shown to mediate BPA binding to PPARG in both 3D and 2D maps. Moreover, BPA binding to PPARG was mediated by pi (π)-alkyl and alkyl interaction bonds with ILE262 and PRO269 residues as well as pi (π)-Sigma interaction bonds with LEU270 residue. Finally, BPA binding to PPARG was mediated by Amide-pi(π) stacked with GLY258 residue (Fig. 6B). The BPA has a binding affinity of −7.9 kcal/mol to PTGS2 (PDB code: 5f19). BPA's interaction with PTGS2 was revealed to be mediated by van der Waals interactions with residues of LEU458, ASN306, LEU326, ARG316, ALA327, and GLN275, using 3D and 2D maps. In addition, BPA's stable binding to PTGS2 was linked to pi (π)-alkyl and alkyl interaction bonding to TRP305, CYS432, ILE268, ALA272, ILE310, LEU309, and PHE313 residues. Finally, BPA binding to PTGS2 was mediated by Amide-pi(π) stacked with ALA271 residue (Fig. 6C).

4. Discussion

This research used data collected from the Durgbank, OMIM, and ChEMBL databases to identify 27 candidate targets involved in BPA-induced CVD toxicity. The STRING platform and Cytoscape software were employed to generate the BPA-induced CVD toxicity network diagram and PPI network. The top 10 KEGG pathways, CCs, MFs, and BPs of potential targets were discovered. In addition, ESR1, PPARG, and PTGS2 were found to be the core targets for BPA-induced toxicity in cardiovascular disease. All three of the key core proteins showed stable binding to BPA, suggesting that this binding is involved in the molecular mechanism of BPA-induced toxicity to CVD.

Future computer models have been increasingly employed to determine toxicity pathways. A thorough examination of the molecular mechanisms of a substance's harmful effects may help uncover useful treatment targets [23]. BPS-induced prostatic toxicity has been evaluated by network toxicology analysis. In addition, network toxicology strategy was used to assess toxicity and mechanisms of ATBC-induced brain toxicity [24]. Furthermore, hepatotoxicity, carcinogenicity, mutagenicity and testicular injury induced by metformin chlorination byproducts and cantharidin were also reported to explored by network toxicology [25,26]. However, the underlying molecular mechanisms of environmental pollutants, such as BPA on CVD remain elusive. Because of wide exist of BPA and high prevalence of CVD, this research will promote drug discovery for CVD treatment.

The most prevalent subtype of breast cancer is caused by a mutation in the protein known as estrogen receptor alpha (ERα), which is encoded by ESR1 [27]. Numerous disorders, including cardiovascular disease, metabolic syndrome, neurodegeneration, inflammation, and osteoporosis, are also brought on by abnormal ERα signaling [28]. It has been demonstrated that ERα mediates the protective effects of E2 against hypertension induced by angiotensin II [29,30]. In pulmonary arterial hypertension (PAH) MODELS, ERα is downregulated, and the effect of E2 on the right ventricular hypertrophy in PAH is regulated by an ERα specific agonist [31]. Moreover, bone morphogenetic protein receptor type 2 expression was negatively regulated by ERα, a factor that is critical in heritable PAH [32]. In low-density lipoprotein receptor-deficient mice, endothelial ERα deficiency provided protection against atherosclerosis [33]. In female mice, atherosclerosis caused by excessive cholesterol was reversed by hepatocyte ERα, which also regulated cholesterol transport and arterial lipid buildup [34]. Pharmacological inhibition of ERα also exerted protective effects on atherosclerotic lesions in ApoE KO male mice [35]. In female rabbits, myocardial damage caused by ischemia/reperfusion was reduced by ERα activation [35]. ERα improved transverse aortic constriction-induced cardiac dysfunction in ovariectomized female mice [36]. It was found that in end-stage human dilated cardiomyopathy, the levels of ERα mRNA and protein were increased [37].

PPARG, also known as peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ), is a major factor in the development of type 2 diabetes (T2DM). Thiazolidinediones as PPAR-γ agonists are clinically utilized for T2DM treatment [38]. PPARG His477His polymorphism predicted the likelihood of developing coronary heart disease [39]. PPAR-γ activators may increase HDL-C and decrease triglyceride concentration leading to the amelioration of atherosclerosis [40–42]. Evidence from clinical and experimental studies suggested that TZDs could lower blood pressure [43,44]. The largest clinical trial showed a TZD – pioglitazone dramatically lowered blood pressure, all-cause mortality, and myocardial infarction [45]. After percutaneous coronary revascularization, PPAR-γ activation may enhance endothelium repair, inhibit the proliferation and migration of vascular smooth muscle cells, and prevent restenosis [40]. PPAR-γ antagonist depressed cardiac ischemia-reperfusion injury in rats [46]. The PPARγ agonist pioglitazone also prevented right heart failure and corrected pulmonary hypertension [47].

PTGS2 (also called COX-2) is a vital enzyme in the cardiovascular system and is suppressed by nonsteroidal anti-inflammatory medications like aspirin [48]. COX-2 is primarily expressed in regions of vascular inflammation and disease but is largely missing in platelets and only weakly expressed in blood vessels. COX-2 inhibition increased thrombosis and decreased bleeding time in mice [49]. Additionally, COX-2 blockage promoted atherosclerosis and raised blood pressure [50–52].

KEGG enrichment analysis indicated central several signaling pathways in CVD that were involved in the impact of BPA on CVD. In smooth muscle cells and cardiomyocytes, cyclic AMP (cAMP) and the resulting calcium fluxes are the most well-studied receptor-regulated signaling processes [53]. Calcium influx into cardiomyocytes triggers a huge release of calcium, which in turn activates the contractile mechanism of the myocyte. The main calcium effector primarily targets calmodulin, which in turn activates myosin light-chain kinase and phosphorylates myosin light-chain, ultimately leading to muscular contraction in smooth muscles. Cardiomyocyte contractile dysfunction and arrhythmias are triggered by the dysregulation of calcium fluxes [54]. The knockdown of Cav1.2 (the cardiovascular system's most widely expressed calcium channel) in mice causes severe cardiac abnormalities and early death at the embryonic stage [55]. These knockout models also exhibited substantial arrhythmias and bradycardia with numerous channelopathies being linked to Cav1.2. Furthermore, Cav1.2 dysfunction was implicated in Timothy syndrome and Brugada syndrome [56,57]. Abnormal function of calcium fluxes can contribute to hypertension in smooth muscle cells [58]. Produced by guanylate cyclase (GC), cyclic guanosine monophosphate (cGMP) activates protein kinase G (PKG) and is crucial for cardiac remodeling [59]. Heart failure exhibiting both preserved and reduced ejection fractions (HFpEF and HFrEF) is associated with cGMP-PKG

signaling dysfunction [60,61]. cAMP or cGMP can be hydrolyzed by phosphodiesterase (PDE) into their corresponding inactive 5′-monophosphate forms. Through the cAMP pathway, PDE1 inhibition produces acute inotropic, lusitropic, and arterial vasodilatory effects in mammals with and without HF [62]. PDE1A regulates pathological hypertrophy through the cGMP/PKG-dependent mechanism in *vivo* and *in vitro* experiments. Transient receptor potential-canonical-derived Ca2+ activates PDE1C, which hydrolyzes cAMP and promotes cardiomyocyte apoptosis [63,64]. The overexpression of PDE2A reduces cAMP, which attenuates norepinephrine-induced cardiomyocyte hypertrophy [65]. However, PDE2A inhibition also ameliorates norepinephrine-induced cardiac hypertrophy in rats [66]. In various situations, cAMP and cGMP may have opposing effects. The increase of β adrenergic stimulation promotes PDE2A hydrolyzing cAMP and cGMP [67]. PDE5 specifically hydrolyzed cGMP produced by soluble guanylyl cyclase. PDE5 inhibitors have been shown to treat Group 1 pulmonary arterial hypertension by inducing nitric oxide production and vasodilation [68]. PDE5 inhibition provides protection against pressure overload-induced cardiac hypertrophy, ischemia-reperfusion injury, and doxorubicin-toxicity by blocking catabolism of cGMP [69–71]. The PDE5-cGMP-PKG pathway exerts cardiac protection via the inhibition of necrosis and apoptosis in the ischemia-reperfusion model [72]. The primary modulator of cardiovascular function is the adrenergic system. Cardiomyocytes express a low level of adrenaline receptors, whereas vascular smooth muscle expresses them at a high level. Consequently, α1-adrenergic receptors substantially promote vascular constriction, which raises blood pressure. It has been well documented that beta-adrenergic receptor antagonists are well primary therapeutic agents for hypertension and heart failure [73]. TRP superfamily represents a large family of non-selective cation channels of Ca2+-permeability. TRP is not only activated by receptor stimulation but also by other various physicochemical stimuli, including inflammation, oxidative stress, pressure, sheer stress, and mechanical stretch. Aneurysms, hypertension, cardiac hypertrophy/myopathy, and cardiac arrhythmia have all been linked to TRP channels [74,75]. The gap junction coupling participates in the organization of the tissue and accurate development. In the heart, gap junctions offer pathways for intercellular current flow, thereby facilitating coordinated action potential propagation. Based on existing research, it appears that abnormalities in the gap junction may contribute to the development and maintenance of different types of cardiac arrhythmias [76,77]. It is evident that the toxicity of BPA in cardiovascular disease is compounded by the close cross-talk of various signaling pathways. Further research is needed to determine how other signaling pathways, such as adipocyte lipolysis, serotonergic synapses, salivary secretion, and neuroactive ligand-receptor interaction, contribute to the toxicity of BPA in cardiovascular diseases.

5. Conclusion

In conclusion, our work provided a thorough molecular docking analysis and network toxicology analysis of the potential toxicity of BPA in CVD. Three hub genes (PTGS2, PPARG, and ESR1) as well as 27 putative targets were found to be connected to the toxic effects of BPA in CVD. The top 10 BP, CC and MF linked to effects of BPA on CVD were identified. The key pathway enrichment analyses revealed the mechanism of action of BPA through targets related to pathways such as the calcium signaling pathway, inflammatory mediator regulation of TRP channels, gap junction, adrenergic signaling in cardiomyocytes, cGMP-PKG signaling pathway, and cAMP signaling pathway. Molecular docking analyses confirmed stable and robust binding of BPA to ESR1, PPARG, and PTGS2. Our study presented a systematic understanding of molecular mechanisms involved in the toxicity of BAP in CVD and provided a foundation for drug discovery. In addition, this work encourages the application of molecular docking and network toxicology to the examination of the toxicity and potential molecular pathways of environmental pollutants, like EDCs, in CVD. In the future, it is imperative to conduct experimental validation to corroborate the findings derived from the network-based “in silico” analysis. Large-scale prospective studies hold the potential to elucidate the definitive association between BPA and CVD. Additionally, animal and cell models can serve to validate the identified potential targets and pathways.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Funding

This work was supported by Wenzhou Science & Technology Bureau (grant no. 2023Y1720).

Data availability

Data will be made available on request.

CRediT authorship contribution statement

Lina Xie: Writing – original draft, Visualization, Software, Formal analysis, Data curation. **Bingwu Huang:** Validation, Methodology, Formal analysis. **Xuyong Zhao:** Validation, Investigation. **Ning Zhu:** Writing – review & editing, Validation, Supervision,

Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e31473.

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