Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

Impact of Di-(2-Ethylhexyl)-Phthalate on Metabolic Syndrome: Insights from Network Toxicology and Molecular Docking and Dynamics

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Background: Metabolic syndrome (MetS) is strongly associated with exposure to environmental pollutants, especially endocrine disruptors (EDCs). Di-(2-ethylhexyl)-Phthalate (DEHP), a typical EDC widely found in plastic products, has been shown to interfere with lipid metabolism and insulin signalling. However, the specific molecular mechanism by which it mediates MetS remains unclear.
Purpose: This study aimed to systematically investigate the molecular mechanisms underlying the effects of the ubiquitous environmental pollutant DEHP on MetS, thereby providing new insights into the role of environmental toxins in metabolic disorders.
Methods: MetS-related disease targets were searched using the GeneCards, OMIM, and TTD databases. DEHP-related targets were obtained from STITCH, SwissTargetPrediction, and ChEMBL. Constructed PPI networks of intersecting targets and visualized and screened core targets in Cytoscape 3.7.1. GO and KEGG pathway analyses were performed using the DAVID database to elucidate biological processes, cellular components, molecular functions, and key pathways ($p<0.05$). In addition, molecular docking and molecular dynamics simulations were used to analyze the interactions between compounds and targets further.
Results: 150 intersecting targets were identified between DEHP and MetS. The PPI network exhibited core targets, including TP53, ESR1, EGFR, TNF, and IL6. GO analysis showed entries in metabolic processes, transcriptional regulation, and redox reactions. The KEGG pathway showed significant enrichment in AGE-RAGE, FoxO, insulin resistance, and steroid hormone biosynthesis pathways. DEHP showed strong binding affinity to core targets: TP53 (−5.6 kcal/mol), ESR1 (−6.1 kcal/mol), EGFR (−5.4 kcal/mol), and IL6 (−4.8 kcal/mol). Molecular dynamics simulation further verified the results of molecular docking.
Conclusion: Our study highlights the interaction between environmental pollutants and metabolic dysfunction. These findings highlight the potential role of DEHP in exacerbating MetS and provide a basis for mitigating its health risks through targeted interventions. Further experimental validation is needed in the future to confirm these mechanistic insights.
Keywords: DEHP, metabolic syndrome, network toxicology, molecular docking

Introduction

Plastics are one of the indispensable and fundamental materials in modern society and are widely used in all aspects of daily life.[1] However, the chemical stability of plastics leads to their extensive accumulation in aquatic and terrestrial ecosystems, which in turn contributes to persistent environmental pollution.[2,3] The global production of plastic waste has reached 353 million tons per year and increased to 367 million tons in 2020.[4,5] As the consumption of plastics continues to rise, the future generation of plastic waste will show an increasing trend.[6] Various additives are often added during the production of plastics to achieve the desired physical properties.[7]

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Used as a plasticizer for plastics such as polyvinyl chloride (PVC), Di-(2-ethylhexyl)-Phthalate (DEHP) has become a core chemical additive in the plastics industry due to its low cost and excellent flexibility.[8] DEHP is mainly used in food packaging, children's products, and medical devices, which are involved in various aspects of life.[9,10] DEHP leaches out of the material over time and ultimately enters the environment, which has an undesirable effect on humans.[2,11] Exposure of newborns to DEHP during medical care has been found to begin after birth based on quantitative measurements of urinary DEHP metabolites.[12] PBPK (physiologically based pharmacokinetics) modelling has found that the cumulative distribution of DEHP in different organs and tissues may lead to various harmful health outcomes.[13]

Metabolic syndrome (MetS) is a common metabolic disorder characterized by a series of interrelated cardiovascular risk factors, including abdominal obesity, insulin resistance, hypertension, dyslipidemia, and disorders of glucose metabolism.[14,15] Recent studies have shown that environmental pollutants, especially plasticizer-like chemicals (eg, DEHP), may play an essential role in the development and progression of MetS.[16–18] DEHP acts as an endocrine disruptor (EDC) that may induce MetS through multiple biochemical pathways. It may interfere with hormone action through anti-androgenic or estrogenic mechanisms, thereby triggering early puberty.[19] Studies have also shown that DEHP can upregulate the expression of hepatic PPARγand SREBP-1c, promote lipid accumulation, reduce insulin sensitivity, and cause inflammation by activating the NF-κB pathway.[20] Since DEHP is widely present in the environment and can be exposed to humans, primarily through plastic products, an in-depth understanding of its potential health effects is of great public health importance.

Derived from Network Pharmacology, Network Toxicology is based on systems biology theory and analyzes biological systems using bioinformatics and network analysis methods.[21] Although studies have preliminarily revealed the association between DEHP and MetS, its complex multi-target mechanism of action has not been systematically analyzed. Therefore, this study aimed to systematically explore how DEHP exposure may affect the occurrence and development of MetS through multiple biological pathways and molecular targets using cyber toxicology techniques.[22] Establishing the molecular network between DEHP exposure and MetS will provide a theoretical basis for scientific research.

Methods

DEHP Composition and Target Acquisition

We first searched the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) for the chemical structure of DEHP and the canonical SMILES representation. Using the obtained SMILES symbols, we searched the STITCH database (http://stitch.embl.de/), SwissTargetPrediction database (http://swisstargetprediction.ch/) (Probability >0), and ChEMBL database (https://www.ebi.ac.uk/chembl/), specifying "Homo sapiens" as the target species.

MetS Related Targets Collection

Using "Metabolic syndrome" as the search term, we searched and collected MetS-related target genes in the GeneCards database (https://www.genecards.org/), OMIM database (https://www.omim.org/), and TTD database (https://db.idrblab.net/ttd/). All results were integrated into Excel, and data were merged and deduplicated to obtain a list of disease targets.

Protein–Protein Interaction (PPI) Network Analysis

Enter the common predicted targets of DEHP and MetS in the program corresponding to the protein interaction platform STRING (https://string-db.org),[23] The species was set as "Homo sapiens", and the minimum interaction score was set as "high confidence (0.700)" to obtain the PPI protein interactions map, which was simultaneously visualized using the Cytoscape 3.7.1 software was used for visualization.[24] Finally, topology analysis was performed using the Network Analyzer plug-in in Cytoscape 3.7.1 to assess the degree (DC), betweenness centrality (BC), and closeness centrality (CC) of the network nodes to filter out the core targets.

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

We entered the common targets into the DAVID database to elucidate the potential functions and enrichment pathways of MetS induced by DEHP exposure (https://david.ncifcrf.gov/).[25] The identifier was set to "OFFICIAL GENE SYMBOL", the

species was selected as "Homo sapiens", and other defaults were kept, and gene ontology (GO) functional analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis were performed. After downloading the relevant data, we logged into the Microbiome Visualization Cloud Platform (https://www.bioinformatics.com.cn/) and plotted the bar and bubble plots of the enrichment results. Items with $P < 0.05$ were considered statistically significant.

Molecular Docking

To confirm the effect of DEHP on core genes, molecular docking explored potential binding interactions. The 3D structures of the proteins were downloaded from the PDB database (https://www.rcsb.org/), while the PubChem database was used to download the 3D structural information of the compounds. The protein structures were obtained by searching the protein structure database, and after removing redundant structures such as small molecules and water, they were converted to pdbqt files using MGLTools. Download the small molecule structure file and process it into a pdbqt file using MGLTools. Construct the docking box so that it contains the entire protein. Use Autodock Vina 1.1.2 to dock the small molecule and protein. Receptor molecules with higher negative molecular docking binding energies are more stable in the docked conformation.

Molecular Dynamics Simulations

This study selected one set of protein-ligand complexes with the lowest molecular docking binding energies for molecular dynamics simulations using GROMACS 2022 software. The CHARMM36 force field was used for the proteins, and the ligand topology was constructed from the GAFF2 force field. The system was solvated using the TIP3P water model in a cubic box with periodic boundary conditions.[26] Particle mesh Ewald (PME) and Verlet algorithms were used to handle electrostatic interactions. Subsequently, 100,000 steps of isothermal isovolumic (NVT) equilibrium and isothermal isobaric (NPT) equilibrium were performed.[27] The van der Waals and Coulomb cutoffs were set to 1.0 nm. Ultimately, the system was subjected to 100 ns of molecular dynamics simulations at constant temperature and pressure.

Result

DEHP Affects the Target Identification of MetS

From the GeneCards database, we initially obtained 19,282 potential disease targets, and after four rounds of rigorous median screening, we finally screened 1205 disease targets (score>26.7). The OMIM database contains 650 disease-related gene targets. TTD contains nine disease targets. By querying the STITCH database, we identified potential targets for 10 compounds. Using the SwissTargetPrediction tool, we further predicted and obtained 100 potential compound targets. Finally, we collected 1165 compound targets from the ChEMBL database. After merging and de-weighting, we received 1772 MetS and 1177 DEHP targets. Venn diagram analysis was performed on DEHP and MetS targets, and 150 intersecting targets were finally obtained (Figure 1). A detailed list is provided in the Supplementary File.

Potential Target Interaction Networks and Core Gene Acquisition

PPI network analysis was performed on 150 potential action targets using the STRING database, and the results were imported into Cytoscape 3.7.1 software to construct a PPI network and obtain a PPI network graph. The network graph contains 127 nodes and 385 edges, and the darker color of the nodes indicates the more important the target is in the network (Figure 2).

To identify the core targets, we further refined the selection of core targets based on three key parameters: "degree", "betweenness centrality", and "closeness centrality". After two rounds of median screening, the core targets of Tumor Protein p53 (TP53), Estrogen Receptor 1 (ESR1), Epidermal Growth Factor Receptor (EGFR), Tumor Necrosis Factor (TNF), Interleukin 6 (IL6) were finally obtained. These may be potential key targets for DEHP to interfere with human metabolism (Table 1).

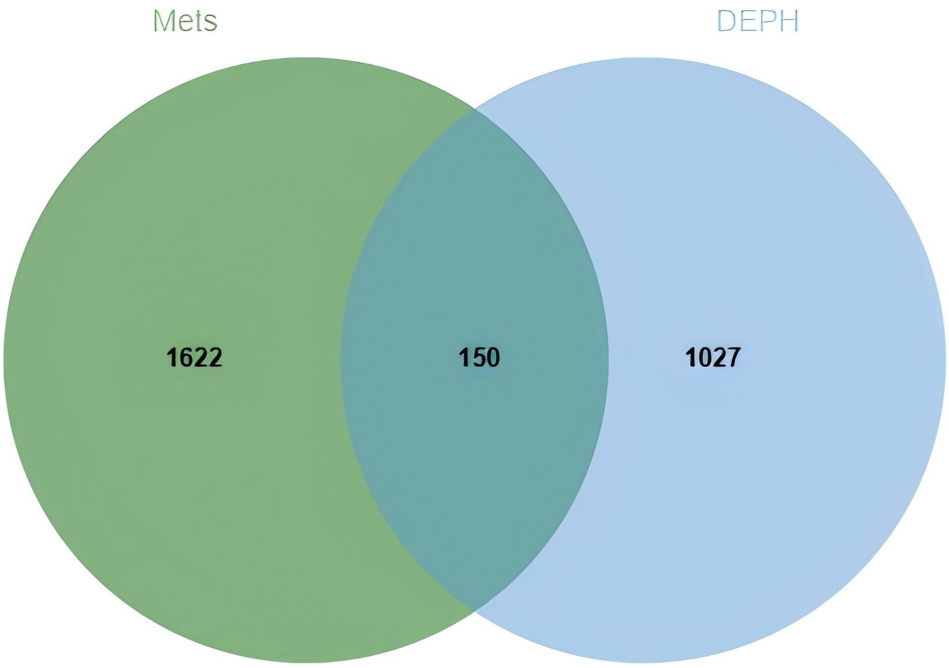

Figure 1 Venn diagram of common targets of DEHP and MetS.

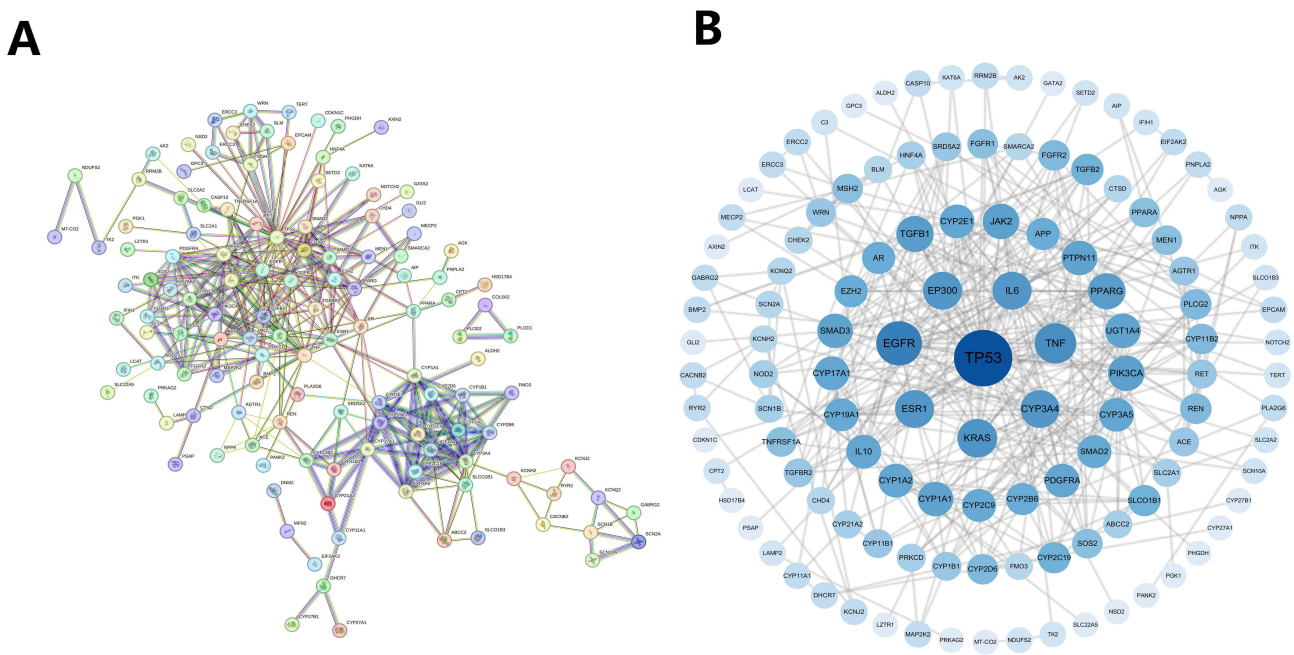

Figure 2 (**A**) PPI network of DEHP interfering with MetS target obtained by STRING. (**B**) PPI network processed by Cytoscape. The darker the color, the greater the degree value.

GO and KEGG Pathway Enrichment Analysis

The 150 DEHP and MetS intersecting targets were entered into the DAVID database for GO and KEGG enrichment analysis. Among them, 53 entries were obtained for cellular components (CC), 158 entries for molecular functions (MF), and 514 entries for biological processes (BP) (Figure 3). Among the BPs, metabolism, transcriptional regulation, insulin-like growth factor, etc. were mainly involved. Cellular components, on the other hand, focus on membrane-related structures and organelles, such as the

Table 1 Core Targets Screened from PPI

No.	Target	Degree	Betweenness Centrality	Closeness Centrality
1	TP53	40	0.333221	0.434783
2	ESR1	17	0.178449	0.41958
3	TNF	20	0.153101	0.427046
4	EGFR	25	0.085908	0.398671
5	CYP1A1	13	0.07436	0.364742
6	EP300	17	0.054889	0.382166
7	KRAS	18	0.049079	0.377358
8	IL6	17	0.040415	0.387097
9	PPARG	15	0.038333	0.376176
10	SMAD3	13	0.028606	0.371517

endoplasmic reticulum and mitochondria. Various redox reactions, steroid metabolism, and other functions are involved in molecular functions.

125 signalling pathways were obtained from KEGG analysis, from which the top 20 were selected for ranking ($p < 0.05$). Among the top 20 ranked signalling pathways, steroid hormone biosynthesis, AGE-RAGE signalling pathway in diabetic complications, FoxO signalling pathway, metabolic pathway, and insulin resistance showed significant enrichment (Figure 4).

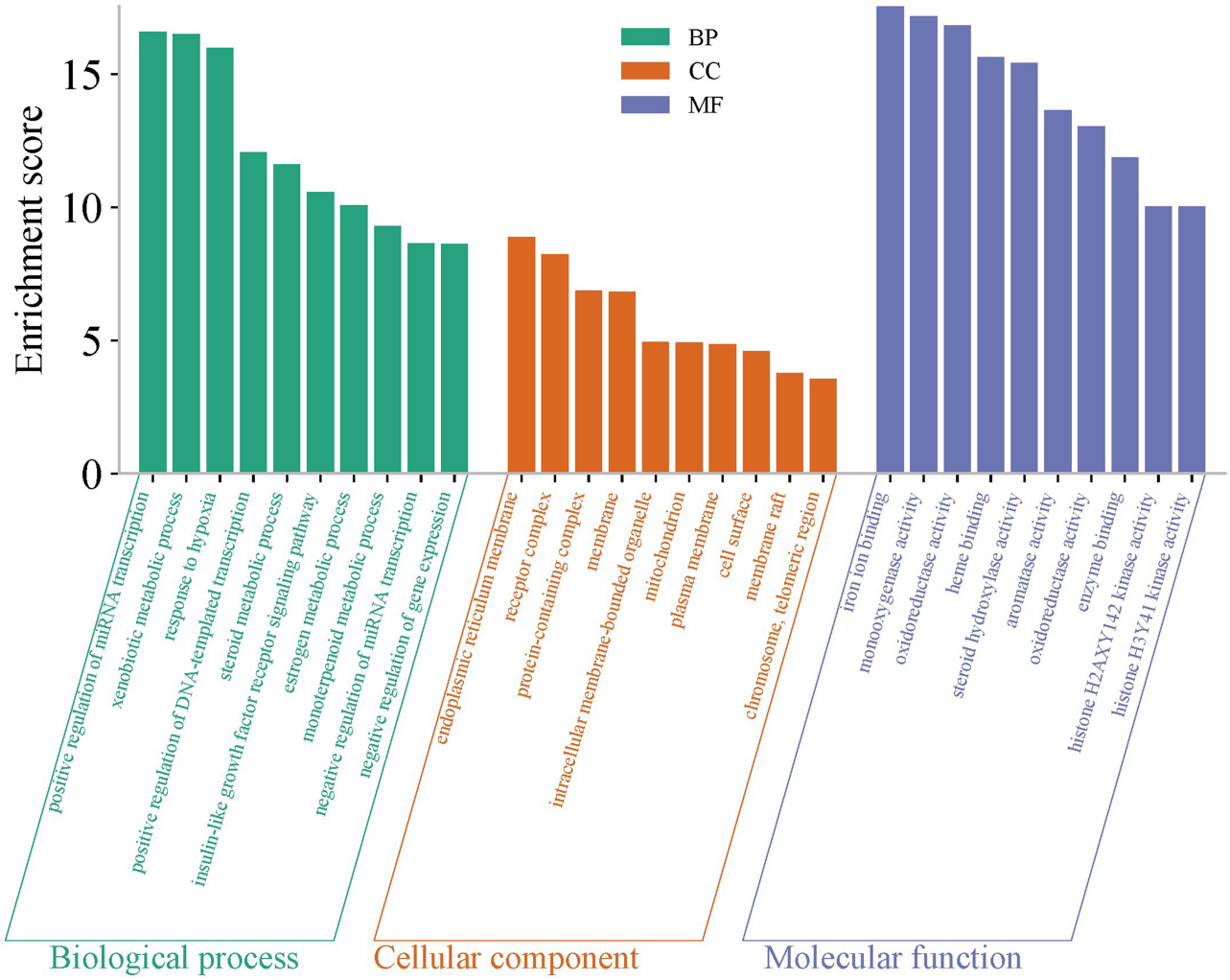

Figure 3 DEHP exposure interferes with the GO of MetS target genes (BP, CC, MF).

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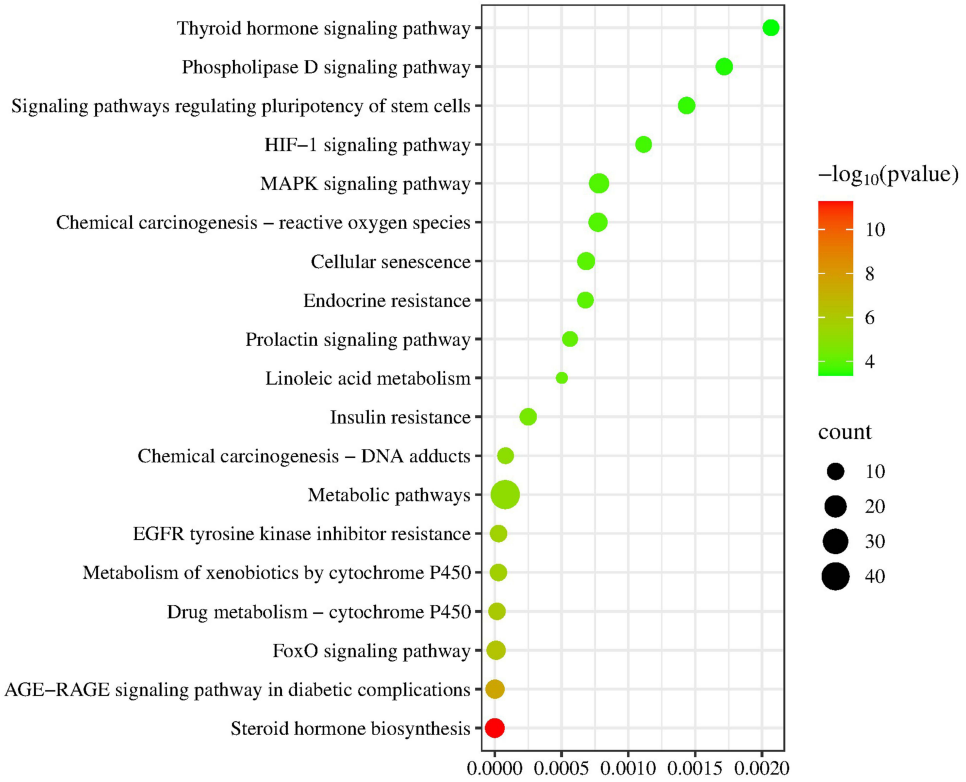

Figure 4 DEHP exposure interferes with the first 20 KEGG pathways of MetS target genes.

Molecular Docking of DEHP with MetS Core Target Proteins

Lower binding energy implies higher binding activity between large and small molecules. When the binding energy is less than −4.25 kcal/mol, it indicates a certain degree of affinity between the two. When the binding energy is further reduced to below −5 kcal/mol, it means a more significant affinity.[28] We performed molecular docking of the core targets of the screen, TP53, ESR1, EGFR, IL6, and DEHP (CHEMBL1242017). The Vina scores of TP53, ESR1, EGFR, and IL6 were −5.6 kcal/mol, −6.1 kcal/mol, −5.4 kcal/mol, and −4.8 kcal/mol, respectively (Figure 5). This indicates that these targets are highly bound and conformationally stable for DEHP. The detailed results of molecular docking are shown in Table 2.

Molecular Dynamics Simulations Validation

The equilibrium state of the simulated system was assessed using root mean square deviation (RMSD) (Figure 6A), and the ESR1-DEHP complex system reached equilibrium after about 65 ns and ultimately fluctuated above and below 2.1 Å, suggesting that the complex has a high structural stability. Further analysis showed that the radius of gyration (Rg) and solvent-accessible surface area (SASA) of the complex fluctuated less during the simulation (Figure 6B and C), suggesting that no apparent structural contraction or expansion occurred. The number of hydrogen bonds between small molecules and target proteins (Figure 6D) and between complex systems ranged from 0 to 2, suggesting the existence of stable hydrogen bonding interactions between the two. In addition (Figure 6E), the root-mean-square rise and fall (RMSF) values were relatively low (mostly below 3 Å), reflecting their overall low flexibility and high stability.

Discussion

The widespread use of DEHP in various plastic products has raised increasing concerns about environmental pollution and health risks, which continue to grow, as many studies have linked it to adverse health manifestations in humans.[29] DEHP has been detected at high frequencies and concentrations in soil, air, and water.[30,31] Plasticizers such as DEHP

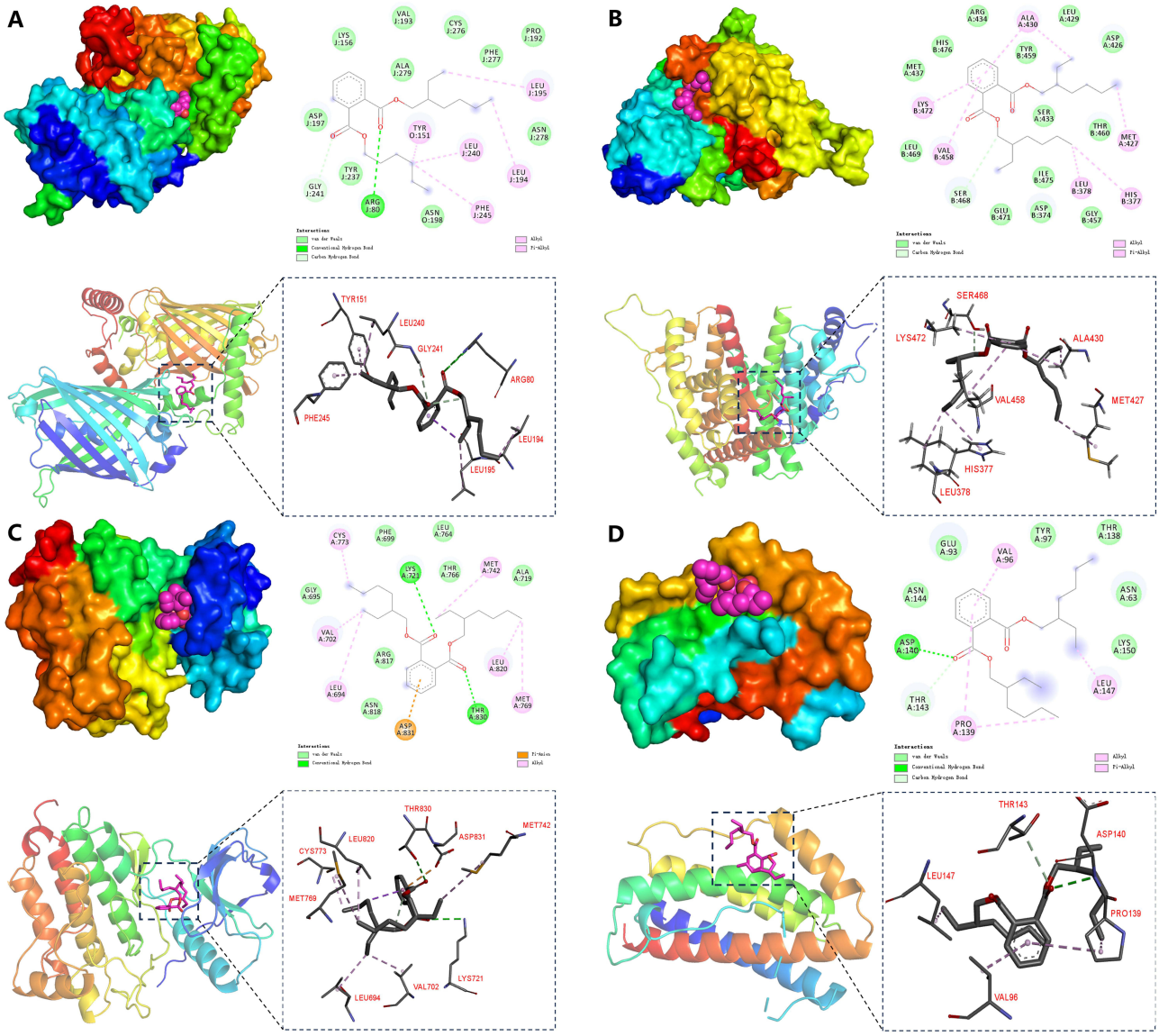

Figure 5 Two-dimensional and three-dimensional maps of molecular docking of DEHP with central targets (**A**) TP53-DEHP, (**B**) ESR1-DEHP, (**C**) EGFR-DEHP, (**D**) IL6-DEHP.

released from the slow degradation of discarded plastic products penetrate the soil,[32] and various persistent organic pollutants (POPs) are introduced into the aquatic environment, resulting in water contamination.[33] After contaminating the environment, DEHP enters the human body through the air, food, water, dermal contact, and medical devices and

Table 2 The Docking Results of Core Genes and DEHP Molecules

Core Gene	UniProt ID	PDB ID	Ligand	Docking Binding Energy (kcal/mol)	Interaction Type
TP53	P04637	7bwn	DEHP	−5.6	Van der Waals forces, hydrogen bonding, alkyl group, π-alkyl group
ESR1	P03372	2bj4	DEHP	−6.1	Van der Waals forces, carbon-hydrogen bonding, alkyl group, π-alkyl group
EGFR	P00533	1m14	DEHP	−5.4	Van der Waals forces, hydrogen bonding, π-anions, alkyl groups
IL6	P05231	1alu	DEHP	−4.8	Van der Waals forces, hydrogen bonds, carbon-hydrogen bonds, alkyl groups, π-alkyl groups

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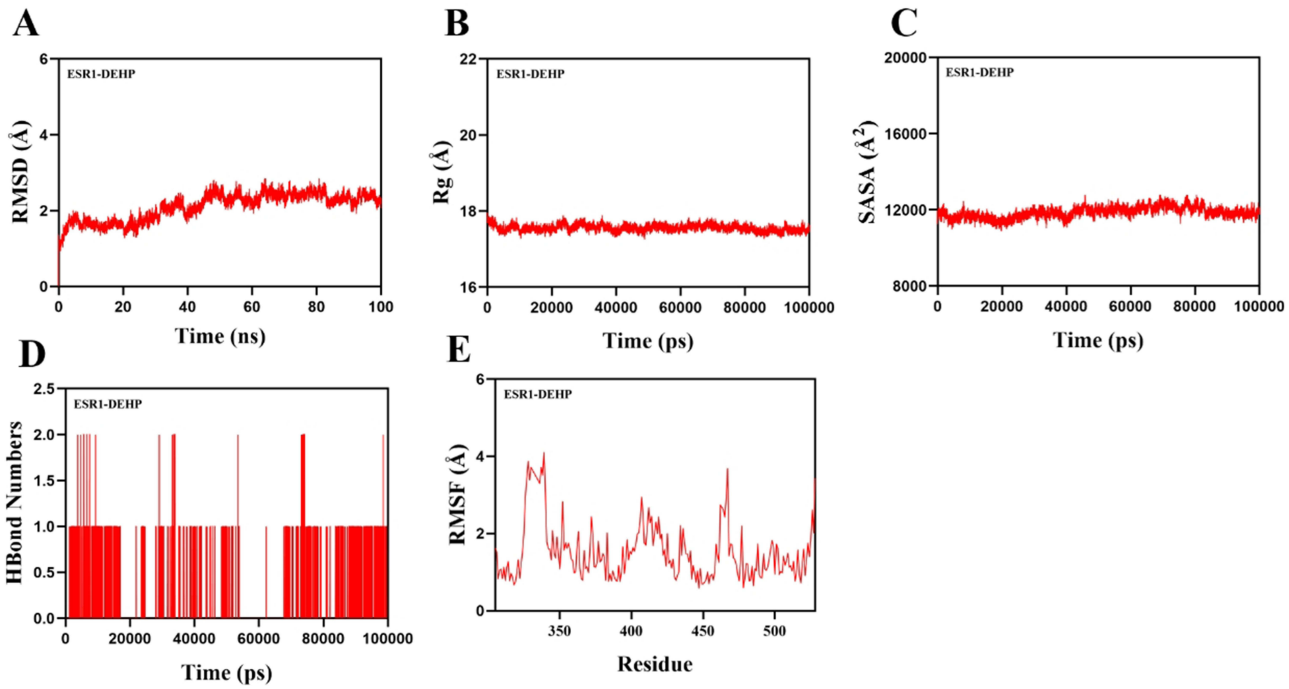

Figure 6 Molecular dynamics simulations of protein-ligand complexes. (**A**) Root mean square deviation, (**B**) Radius of gyration, (**C**) Solvent accessible surface area, (**D**) Number of hydrogen bonds, (**E**) Root-mean-square fluctuation.

accumulates in the body, potentially causing endocrine disruption to reproductive and immune systems with long-term health effects on health.[34]

In this study, we systematically explored the potential mechanisms by which DEHP exposure may contribute to the pathogenesis of MetS through network toxicology. By integrating DEHP and MetS-related genes, we identified 150 overlapping targets and revealed key biological pathways, providing new insights into the molecular interactions between environmental pollutants and metabolic disorders. PPI network and topological analyses highlighted key targets, such as TP53, ESR1, EGFR, TNF, and IL6, which may serve as central hubs for DEHP-induced metabolic disorders.

The TP53 gene encodes the tumor suppressor protein p53 and is traditionally thought to play an essential role in apoptosis and cancer suppression.[35] Emerging evidence emphasizes that certain activities are also involved in the homeostatic regulation of energy metabolism.[36,37] For example, p53 enhances gluconeogenesis in human and mouse hepatocytes.[38] DEHP activates p53 by inducing oxidative stress and inhibiting Mdm2, and the p53-dependent apoptotic pathway plays a key role in DEHP-induced hepatotoxicity.[39] Estrogen Receptor Alpha (ERα), encoded by the ESR1 gene, is a nuclear hormone receptor that plays a key role in regulating gene expression, cell proliferation, and differentiation. The function of ESR1 is closely related to metabolic processes. ESR1 directly regulates the obesity disparity gene MMAA to improve the prognosis of patients with hepatocellular carcinoma in terms of liver metabolism and tumor suppression.[40] ERα knockout mice have increased adipose tissue and insulin resistance, indicating that the E2/Erα signalling pathway is essential in adipose tissue.[41] Abnormalities in its function may lead to metabolic disorders and related diseases. EGFR genes play a key role in cell proliferation, differentiation, and survival. Recently, mutations in the EGFR gene have been found to affect metabolic processes.[42] EGFR-sensitive mutations cause metabolic reprogramming in tumor cells, such as enhancement of aerobic glycolysis and the pentose phosphate pathway, up-regulation of glutamine metabolism, and increased synthesis of lipids and adenosine, among many other metabolic pathways.[43] EGFR-mediated activation of adipose tissue macrophages promotes obesity and insulin resistance and thus encourages a low-grade inflammatory state in the MetS.[44] Animal studies suggest that EGFR may play an essential role in lipid metabolism in mice. EGFR inhibitors reduce serum lipid levels and hepatic steatosis in high-fat diet-induced obese mice.[45,46] The pro-inflammatory cytokines TNF and IL6 are known mediators of chronic low-grade inflammation in the MetS.[47] Metabolic

inflammation is characterized by elevated serum levels of pro-inflammatory cytokines, predominantly IL-6 and TNF-α, which are derived from chronically inflamed adipose tissue and are associated with oxidative stress.[48,49] Inhibition of IL-6 and TNF-α alleviates hypertension, hyperuricemia, dyslipidemia, and insulin resistance in MetS rats induced by a high-fat diet.[50] DEHP exposure may exacerbate their expression, further contributing to oxidative stress and metabolic dysfunction. These findings suggest that DEHP disrupts metabolic homeostasis by targeting multifunctional nodes involved in inflammation, hormonal signalling, and cellular stress responses.

Our KEGG pathway enrichment analysis showed that DEHP exposure disrupts multiple key metabolic homeostatic pathways, including steroid hormone biosynthesis, AGE-RAGE signalling, FoxO signalling, and insulin resistance. ESR1 is a steroid hormone receptor, and DEHP interferes with adipocyte differentiation and lipid storage by enhancing ESR1 activity, leading to abnormal adipose tissue distribution and inducing insulin resistance.[51] EGFR, on the other hand, induces the expression of inflammatory factors TNF and IL6 through activation of the NF-κB signalling pathway.[52] In the inflammatory response, the sustained activation of the AGE-RAGE pathway further induces pathological processes such as inflammation, oxidative stress, and insulin resistance, significantly increasing the risk of MetS-associated cardiovascular complications.[53,54] The metabolic disruptions induced by DEHP are dependent on FoxO1. DEHP-induced metabolic disturbances depend on the overexpression of FoxO1, which drives hepatic gluconeogenesis and lipid accumulation.[18] Abnormal enhancement of FoxO signalling further contributes to disturbed energy metabolism and exacerbates the phenotype of MetS, and inhibition of FoxO1 reverses the metabolic disturbances induced by DEHP.[55] The disruption of these metabolic pathways is a direct driver of lipid accumulation and insulin resistance, which are central pathological features of MetS.

Although the present study revealed the potential mechanism of action of DEHP exposure and MetS through network toxicology, molecular docking, and kinetic simulations, there are still some limitations. First, cyber toxicology analysis is highly dependent on data from public databases, which may have data bias or incompleteness and cannot fully reflect the complex biological processes in the human body. Second, the results of molecular docking and kinetic simulations are computer simulations, which are difficult to adequately model the complex metabolic environment and its dynamic changes in the body. Finally, DEHP's metabolizing ability and sensitivity differ in different populations (eg, children, pregnant women, and the elderly). It is also impossible to clarify the effect of DEHP exposure dose or exposure route on MetS. This is likewise a direction in which future research needs to focus on breakthroughs. Our findings emphasize the urgent need to regulate the use of DEHP, especially in products with a high risk of human exposure (eg, medical devices and food packaging). Future work should prioritize in vivo and in vitro validation of key targets. Epidemiological studies should also be conducted in different populations to establish dose-response relationships between DEHP exposure and MetS, to clarify the differential effects of DEHP in specific populations, and to track the impact of long-term DEHP exposure to MetS so that these heterogeneities can be fully assessed. In addition, there is an urgent need to find safer and more environmentally friendly alternatives and to systematically evaluate the differences in environmental persistence, bioaccumulation, and health risks between alternatives and DEHP. These directions will deepen the mechanistic understanding of the association between DEHP and MetS and provide a scientific basis for environmental health policy and precision medicine.

Conclusion

In this study, we revealed through network toxicology that DEHP exposure may promote MetS by regulating key target proteins (eg, TP53, ESR1, EGFR) and interfering with lipid metabolism, insulin signalling pathway, and inflammatory response. These findings not only elucidate the metabolic toxicity mechanism of DEHP but also provide new perspectives for understanding the association between environmental pollutants and metabolic diseases. Identification of DEHP-associated biomarkers of metabolic disorders may be helpful for early diagnosis and personalized intervention, especially in populations chronically exposed to plasticizers. It points the way for subsequent toxicological studies and provides a scientific basis for improving public health policy and clinical practice.

Data Sharing Statement

The data supporting the findings of this study are available from the corresponding author, Dr. Maoyuan Wang, upon reasonable request.

Ethics Approval and Informed Consent

The data used are de-identified public datasets that cannot be traced back to any individual and do not involve direct interaction with human subjects. According to Article 32, Item 1 of the Measures for Ethical Review of Human Life Science and Medical Research (February 18, 2023, China), this type of research meets the conditions for exemption from ethical review.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the study has no conflicts of interest.

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