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In silico insights into microplastic additive toxicity: Risks of pulmonary fibrosis and endocrine disruption

Km Shivangi[1], Jai Prakash Muyal[1]*, Amaresh Mishra[2, 3] & Shiv Shankar[4]*

[1]University School of Biotechnology, Gautam Buddha University, Greater Noida-201312, Uttar Pradesh, India

[2]IIT Bhilai Innovation and Technology Foundation (IBITF), IIT Bhilai, Chattisgarh-491001, India

[3]Department of Biotechnology & Microbiology, School of Sciences, Noida International University, Gautam Budh Nagar-201308, Uttar Pradesh, India

[4]Department of Environmental Science, University School of Vocational Studies and Applied Sciences, Gautam Buddha University, Greater Noida-201312, Uttar Pradesh, India

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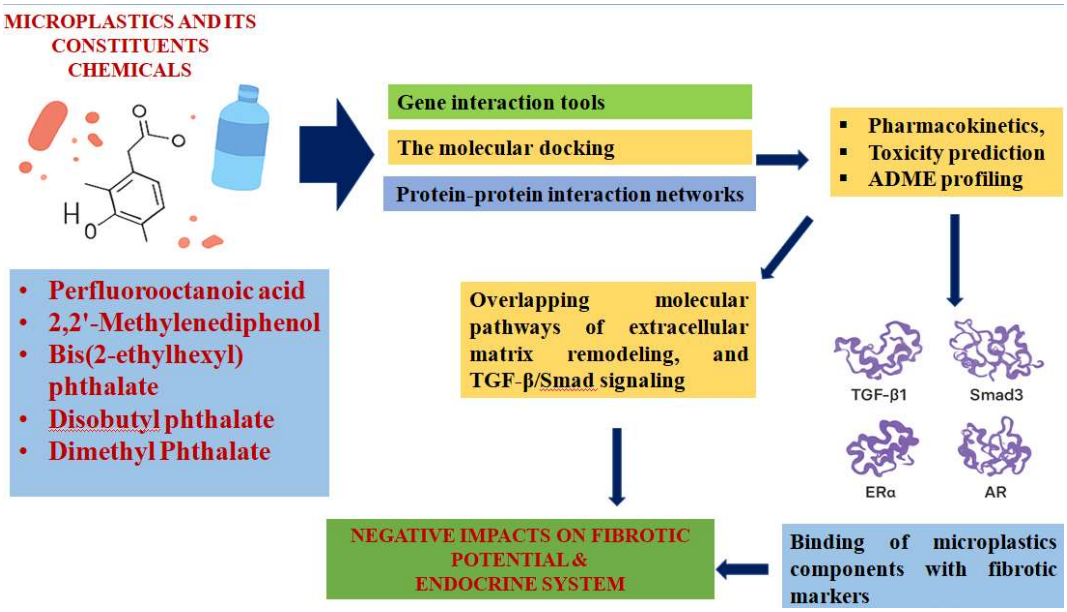
Microplastics and their constituent chemicals, such as phthalates, bisphenols, and flame retardants, have emerged as a significant toxin negatively affecting fibrotic potential and functioning of the endocrine system in human beings. With an objective to find out the principal molecular mechanisms and nature of interaction with key endocrine and fibrotic proteins, the impacts of five frequently used microplastic additives were studied. The molecular docking, protein-protein interaction networks, and gene interaction tools were employed to study the impacts. Pharmacokinetics, toxicity prediction, and ADME profiling and systemic risks were analysed using ProTox-II and Swiss ADME. The docking results revealed significant binding tendencies of microplastics components with fibrotic markers (TGF-β1, Smad3) and nuclear hormone receptors (ERα, AR). Network analysis indicated overlapping molecular pathways of extracellular matrix remodelling, and TGF-β/Smad signaling as key points of interaction. The present investigation indicated the strong connection between endocrine disruption and pulmonary fibrosis, mediated through shared signalling pathways. The present investigation revealed that microplastics and their additives exert adverse human health risks, demanding stringent environmental legislation and environmentally benign chemicals as a substitute for microplastic additives. *In silico* methods revealed significant insights into the molecular basis of ecotoxicity, emphasising the immediate requirement for further research to help interpret the chronic effects of microplastic pollution.

Keywords: Endocrine disruption, Fibrotic activities, *In silico* methods, Microplastics, Molecular docking

Microplastics, plastic debris less than 5 mm in diameter, are found throughout the environment and have drawn the attention of the researcher for its adverse impacts on environment and human health. Microplastics have been widely reported in air, water, and the food chain; therefore, human exposure is inevitable through inhalation, ingestion, or absorption. Microplastics contain chemical additives, namely bisphenols, phthalates, flame retardants, which are endocrine-disrupting chemicals (EDCs). Such additives, which should improve the performance of plastic, are also pollutants in the biological system, which may disrupt the hormone secretion, besides the cellular homeostasis, and may lead to negative health performances[1]. The main adverse effect of microplastic to human beings is endocrine disruption. The compounds present in microplastics have the ability to imitate, inhibit, or stimulate natural hormones, thus leading to imbalanced growth, metabolism, and reproduction. A compound, among others such as bisphenol A (BPA) or di(2-ethylhexyl) phthalate (DEHP), has been known to modulate the activities of estrogen and androgen receptors, thus triggering a cascade of biological effects on the body's health and local tissue. Moreover, these findings have recently been correlated with EDC exposure for the propagation and stimulation of fibrotic-like mechanisms, especially in lung tissues where such substances can also help in the advancement of persistent inflammation and fibrosis. Pulmonary fibrosis, with excessive ECM deposition and fibrosis of lung parenchyma[2, 3], has been associated with chronic inflammatory processes that nod to EDCs. Recent findings from research have indicated that certain EDCs are capable of modulating TGF-β-a key signaling molecule in the process of

*Correspondence:
E-mail: shiv.nature@gmail.com; jmuyal@gbu.ac.in



Graphical abstract

Table 1 — Selected microplastic additives and their canonical SMILES

Microplastic additives	Canonical smiles
Perfluorooctanoic acid	C(=O) (C(C(C(C(C(C(C(F)(F) F) (F)F) (F)F) (F)F) (F)F) (F)F) (F)F) O
2, 2'-Methylenediphenol	C1=CC=C(C(=C1) CC2=CC=CC=C2O) O
Bis(2-ethylhexyl) phthalate	CCCCC(CC)COC(=O) C1=CC=CC=C1C(=O) OCC(CC)CCCC
Diisobutyl phthalate	CC(C)COC(=O) C1=CC=CC=C1C(=O) OCC(C)C
Dimethyl Phthalate	COC(=O) C1=CC=CC=C1C(=O) OC

fibrosis. The development of fibroblast and myofibroblast through stimulation by TGF-β is needed in the pathogenesis of pulmonary fibrosis. Overall, in the context of chronic exposure, EDCs can aggravate the fibrotic mechanisms of parenchyma cells of the lungs by promoting pro-fibrotic gene expression and the formation of cytokines and pro-inflammatory agents. As the awareness of microplastics and their components increases, there is a need to elucidate the molecular mechanisms affecting the endocrine system and pulmonary fibrosis, which would be helpful in the basic understanding of the possible health risks[4, 5]. In the present study, an attempt is made to examine the synergistic impacts of five prevalent microplastic modifiers on both endocrine and pulmonary health, with emphasis given to their proportionate impact on endocrine disruptors and whether they affect fibrotic interactions in the pulmonary parenchyma. Attempts have been made in this research to identify compound-protein interactions targeting endocrine and fibrotic pathway proteins, predict cytotoxicity and ADME behavior, and perform docking experiments under *in silico* conditions. Additional insight into the macroscopic impacts of microplastic pollution on endocrine function and respiratory health is intended in this research, with particular focus on the possibility of lung fibrosis.

Materials and Methods

An *in silico* approach was employed to investigate the potential impacts of hazardous microplastic additives on pulmonary fibrosis and the human endocrine system. An attempt has been made to identify interactions between microplastic additives with selected endocrine/fibrosis-associated proteins, analyzing the toxicity and ADME properties of the additives; therefore, the genetic network interactions were analyzed, and molecular docking was performed to check the binding affinity and interaction with regulatory proteins of these pathways.

Selection of compounds and compound-protein interaction

Five potentially hazardous microplastic additives that act as endocrine disruptors were also selected based on their occurrence in environmental samples and their reportedly toxic effects. Available data from PubChem[6] was utilized to select these compounds.

They were based on the same databases listed in (Table 1) for the generation of their canonical smiles. In addition, the SMILES notation of each compound was analyzed with the support of the STITCH Database[7], which can estimate the potential interaction and detect further compound-protein interactions associated with endocrine disruption and fibrosis pathways.

Toxicity and ADME analysis and target prediction

Both of the compounds were investigated for their toxicity and ADME by using proTox-II[8] and SwissADME[9] tools. Pro Tox-II provides the test results about LD50, hepatotoxicity, carcinogenicity, and mutagenicity of both compounds. Data was recorded to determine the safety of selected additives comparatively. Swiss ADME determines pharmacokinetic properties, such as solubility, lipophilicity, and probability of blood-brain barrier permeation. SwissTargetPrediction[10] was also conducted in an effort to find potential human protein targets, putting special emphasis on endocrine-related and fibrosis-associated proteins. These investigations collectively provide a comprehensive understanding of the compounds' safety, pharmacokinetics, and target-specific interactions, guiding their potential therapeutic applications.

Selection of key target proteins

In view of the results of all the previous experiments, nine proteins were selected based on their relevance to endocrine disruption and pulmonary fibrosis (Table 2). Some protein structures were downloaded from the Protein Data Bank-PDB[11] for further discussion and molecular docking experiments. Four endocrine proteins were chosen based on their involvement in critical phenotypic effects related to endocrine regulation, while the fibrosis-related proteins are key drivers of signaling pathways involved in tissue scarring and extracellular matrix turnover. Further, considering Gene MANIA and the STRING database[12, 13], the design of the genetic and protein interactions of these proteins was pursued.

Protein interaction network and Genetic analysis have revealed significant crosstalk between the two protein groups, suggesting that endocrine disruption may contribute to fibrosis systemically through common pathways, such as TGF-β/Smad signaling and MMP activation. The combined analysis suggested the impact of microplastic additives on the loss of homeostasis at the endocrine level. Moreover, microplastic additives have a strong tendency to worsen the fibrosis via interwoven molecular networks. Such investigations suggest that microplastics and their additives cause general adverse biochemical effects and particular endocrine disruption and fibrotic pathways.

Molecular docking studies

The binding affinity and the estimation of each microplastic additive and endocrine target protein interaction modes were done through molecular docking simulations, followed by pathway interaction studies. AutoDock Vina[14] docking calculations were done based on the protein active sites and their interaction. Ligand structures were optimized and the target protein preprocessed to make sure that unnecessary ligands or water molecules would not interfere with the docking process. Binding affinities were then analyzed using docking, which was then followed up by visualization software, such as PyMOL, Discovery Studio[15, 16], which could be used in order to visualize the binding-specific interactions, for example, hydrogen bonds or hydrophobic contacts, which indicated the strength of binding of particular compounds and, finally, their ability to modify protein activity.

Table 2 — Selected proteins with their PDB IDs

Protein Name	Type	PDB ID
Estrogen Receptor Alpha (ERα)	Endocrine	1ERE
Androgen Receptor (AR)	Endocrine	1I37
Thyroid Hormone Receptor Beta (THRβ)	Endocrine	3GWS
Peroxisome Proliferator-Activated Receptor Gamma (PPARγ)	Endocrine	3DZY
Transforming Growth Factor Beta 1 (TGF-β1)	Fibrosis	3KFD
TGF-β Receptor 1 (TGFBR1)	Fibrosis	1PY5
Smad3	Fibrosis	1MJS
Matrix Metalloproteinase 2 (MMP-2)	Fibrosis	1QIB
Epidermal Growth Factor Receptor (EGFR)	Fibrosis	1IVO

Results

Our research reports twofold impacts of microplastic additives on endocrine disruption and pulmonary fibrosis by making use of the complicated *in silico* research approaches for investigating these relations at the molecular plan. Findings have particularly been remarkable since they also let account for a large research gap, thus revealing the influence of microparticles on endocrine cascades and fibrosis pathways, which are generally researched independently in the field of research. A complementary approach of molecular docking with the predictions of toxicity and analysis of the genetic network reveals more comprehensive information on the toxicity of the microplastics and their additives.

Selection of microplastic additives and their interactions

Five microplastic additives selected for the studies are perfluorooctanoic acid, 2, 2'-methylenebisphenol, Di-N-Butyl phthalate, Bis(2-ethylhexyl) phthalate, and Dimethyl phthalate due to their widespread environmental presence and documented toxicity. Compounds present in the air, soil, and water give a wide range of applicability to both ecological and human health effects. The compounds' endocrine-disrupting potential was further supported by data from PubChem and STITCH databases. Similarly, functional relationships between the chemicals and essential proteins known to be involved in apoptosis, metabolism, and inflammation were found within the network. (Fig. 1) Placing these chemicals in the limelight of biological pathways regulating cell survival, immune modulation, and energy metabolism, thus gives perspectives on the mechanisms of toxicity and effects on health. DEHP has also been shown to cause mitochondrial oxidative stress via TXNIP signaling pathway resulting in pulmonary dysfunction in mice and has the potential to provide associated links between endocrine-disrupting chemicals and human diseases[3].

Toxicity prediction and toxicological targets

One notorious example of a persistent organic pollutant with impressive chemical stability that is becoming widespread in the environment is perfluorooctanoic acid, which is known to have severe health effects in mammals through various routes of exposure, including ingestion, inhalation, and skin contact. The information that has been gained from this research using ProTox-II indicates that Perfluorooctanoic acid is the most toxic, with a

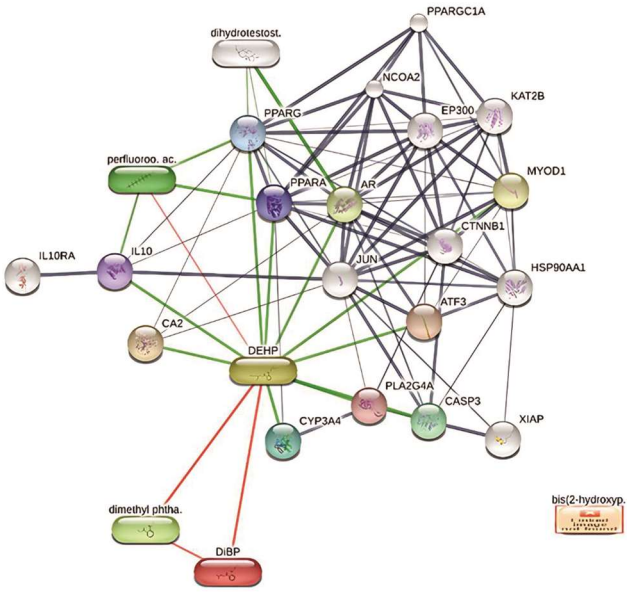


Fig. 1 — Interaction network of microplastic-derived hazardous chemicals with proteins. This network illustrates the interactions of DEHP, DiBP, dimethyl phthalate, bis(2-hydroxyphenyl) methane, and perfluorooctanoic acid with proteins involved in apoptosis (CASP3), inflammation (IL10), metabolic regulation (PPARG, PPARA), and other critical cellular processes. Green edges represent activation relationships, red edges denote inhibition, and blue edges indicate binding interactions

predicted LD50 of 518 mg/kg, and likely to be both neurotoxic and hepatotoxic. These results are consistent with the established bioaccumulative and persistent environmental risks of the substance, which highlighted its considerable health risks across many systems. In other studies, chronic exposure to PFOA was observed to induce inflammatory bowel disease-like injuries in the mouse colon, disrupt stem cell activity, and alter lipid metabolism. It also contributes to the inflammatory reactions, which facilitate the activation of NLRP3 inflammasome, pyrin domain-containing 3 (NLRP3), and cell apoptosis[17]. Bis(2-ethylhexyl) phthalate (DEHP) was of moderate toxicity with an LD50 of 1340 mg/kg and was closely linked to immunotoxicity and endocrine disruption. Its pretense to being a hormone and interference with the functioning of the immune system made it an endocrine disruptor, as corroborated by its prior status as an endocrine disruptor. The varied LD50 of Diisobutyl phthalate (DiBP) was 1190 mg/kg indicating that it is predicted to be both neurotoxic and hepatotoxic. It gives an indication that there were tremendous risks to liver and nervous system health in acute exposure to 2, 2, 2, 2'-Methylenediphenol, which had a predicted LD_{50} of 4880 mg/kg. Even

though its acute toxicity is relatively low, mild neurotoxic and immunotoxic results were revealed, that ought to be followed by research in the area of its chronic toxicity. The lowest is dimethyl phthalate with the predicted LD50 of 6800mg/kg, which is recommended to pose relatively low adverse effects in the acute phase (Fig. 2). It was, however, flagged as having potential immunotoxic and hepatotoxic effects, meaning concerns over its implications as to its long-term exposure. Many studies have suggested that DEHP can assist women of reproductive age develop endometriosis and other hormonally related illness[18-21]. Cobellis *et al.* showed that there is a positive correlation between the presence of endometriosis and plasma DEHP levels, which may be due to DEHP playing a contributing role in the development of endometriosis. All these results have reaffirmed the different toxicological backgrounds of microplastic additives and, therefore, warranted the introduction of focused risk evaluation and risk reduction methods to minimize their effects on health and nature.

Compound target prediction

These compounds often targeted the secondary sites of species-specific modifications, besides nuclear receptors, enzymes, and G-protein-coupled receptors. Enzymes chiefly reacted with perfluorooctanoic acid and Dimethyl Phthalate, along with the signaling proteins of oxidoreductases and kinases by 2, 2'-methylenediphenol and Bis(2-ethylhexyl) phthalate, DEHP. Diisobutyl phthalate expressed the capability of targeting both hormonal and cellular signaling pathways, balancing nuclear and G-protein-coupled receptors as illustrated in (Fig. 3). These results point out the potential of the compound to cause endocrine disruption and to interfere with fundamental signaling and enzymatic pathways.

Target Selection

In order to choose vital molecular targets, the results of the analysis of STITCH network and Swiss Target Prediction were selected as they had shown strong interaction with the endocrine system. The results from the STITCH analysis had implicated endocrine-associated pathways, and for the majority of the compounds under investigation, including diisobutyl phthalate, 2, 2'-Methylenediphenol, perfluorooctanoic acid, bis(2-ethylhexyl) phthalate (DEHP), and dimethyl phthalate, many important interactions between estrogen and androgen receptors

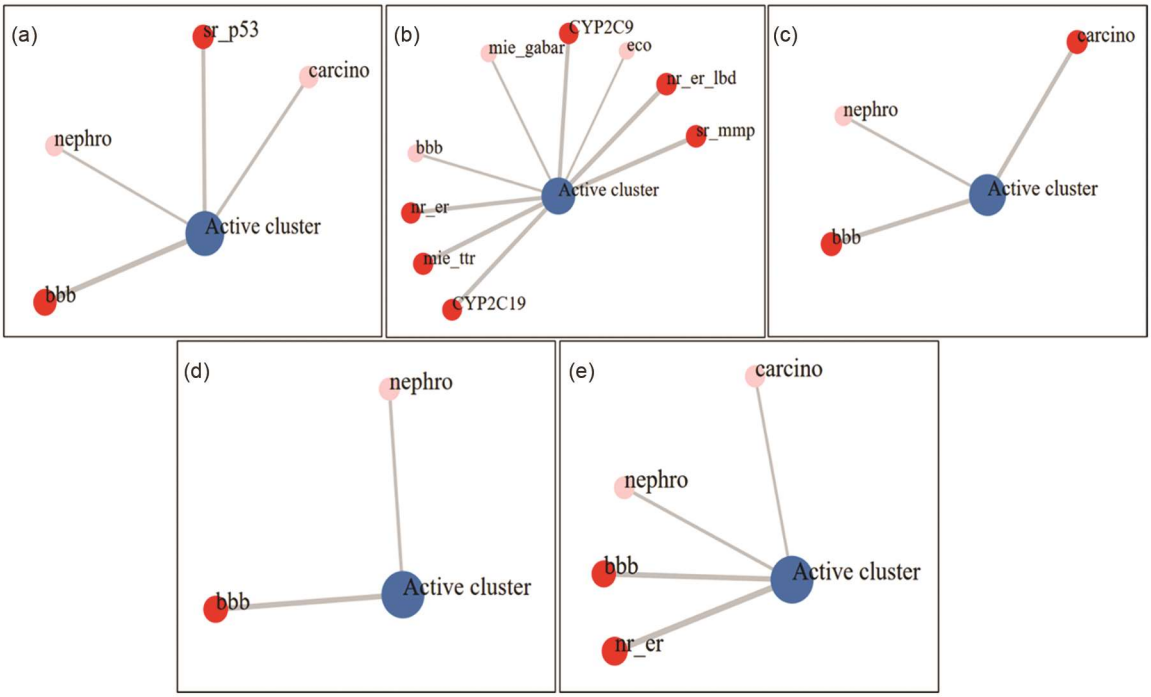


Fig. 2 — Toxicological profile of five compounds using ProTox-II. (a) Perfluorooctanoic acid; (b) 2, 2'-Methylenediphenol; (c) Bis(2-ethylhexyl) phthalate; (d) Diisobutyl phthalate; and (e) Dimethyl Phthalate. The central node ("Active cluster") represents the compound being studied, and the red nodes depict predicted toxicity endpoints such as carcinogenicity (carcino), nephrotoxicity (nephro), blood-brain barrier permeability (bbb), and specific molecular interactions (*e.g.*, sr_p53, CYP2C9, *etc.*)

were present. These results have consequently led to the selection of Aromatase: CYP19A1 - A pivotal enzyme in estrogen biosynthesis, Estrogen Receptor Alpha: ERα, Thyroid Hormone Receptor Beta: THRβ - A crucial regulator of metabolic and developmental processes, and Androgen Receptor: AR - Key hormonal signaling mediators generally disrupted by endocrine-disrupting chemicals, along with PPARγ: A nuclear receptor involved in adipogenesis and lipid metabolism, all of which interact directly with these substances.

Swiss ADME analysis

The pharmacokinetic properties of the selected microplastics additives were determined using Swiss ADME, with a focus on the ability of these chemicals to cross the blood-brain barrier, human intestinal absorption, and interaction with P-glycoprotein.

Figure 4 represents the plotted results in a form of WLOGP versus TPSA graph, indicating essential ADME features: Absorption, Distribution, Metabolism, and Excretion. This result implies that the Disobutyl phthalate, Dimethyl Phthalate, and 2, 2'-

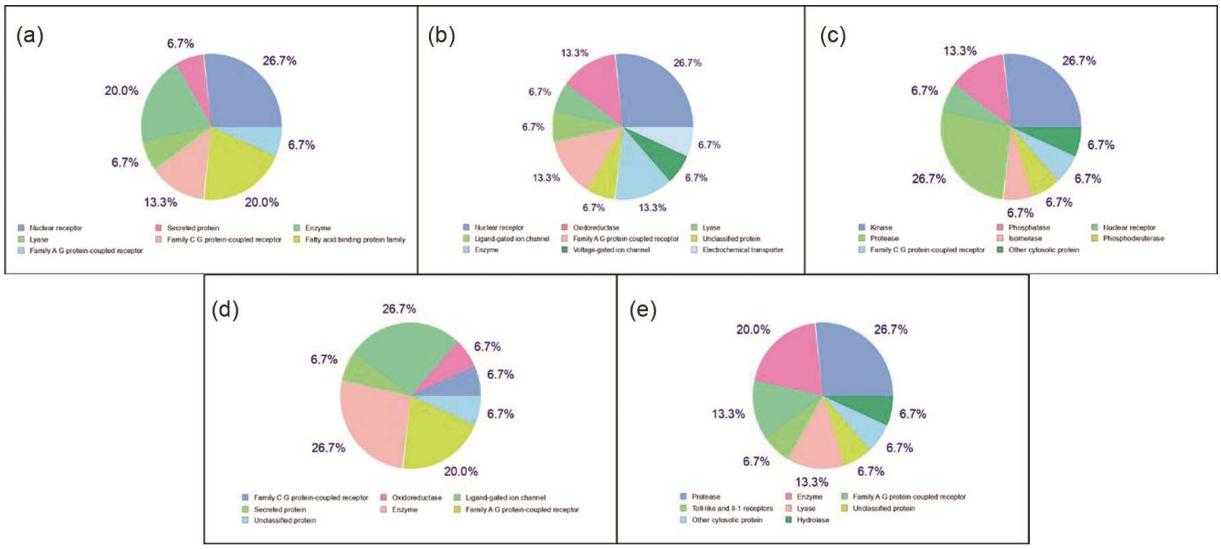


Fig. 3 — The image shows the pie chart for possible targets of the five compounds (a) Perfluorooctanoic acid; (b) 2, 2'-Methylenediphenol; (c) Bis(2-ethylhexyl) phthalate; (d) Diisobutyl phthalate; and (e) Dimethyl Phthalate], the different colors show the different family of proteins that the compounds target

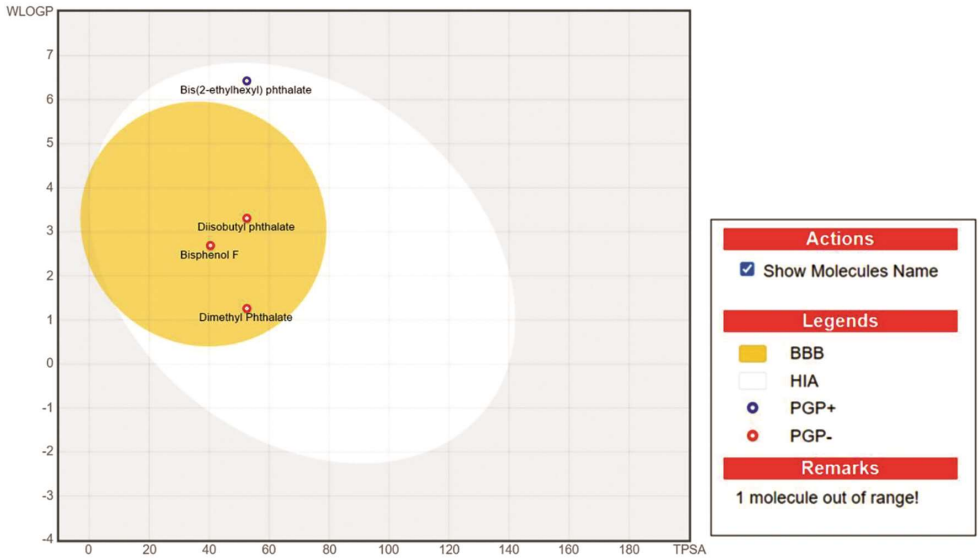


Fig. 4 — SwissADME analysis of the selected compounds, illustrating their WLOGP vs. TPSA profile. The yellow region represents BBB-permeable compounds, while the white region indicates HIA-permeable compounds. Markers indicate interaction with P-glycoprotein (PGP+ for substrates, PGP- for non-substrates)

Methylenediphenol BBF have fallen within the BBB-permeablearea, yellow, showing they will more readily permeate the blood-brain barrier. Also, under their PGP status view, it has been established that these compounds are not substrates of the efflux PGP; however, only Bis 2 2-ethylhexyl phthalate DEHP has fallen outside the BBB-permeable window, which could imply a very minimal potential for permeation across the blood-brain barrier. It also shows a positive relationship with PGP PGP+, which suggests possible efflux specificity of compounds to the substrate, apart from the fact that all the compounds fall within the HIA-permeable window white, suggesting probable efflux as well.

Molecular docking studies

Molecular docking studies using Autodock Vina were performed to compute the interaction between four selected compounds and four key endocrine proteins, namely ESR1, AR, PPARG, and THRB. Overall, docking simulations indicated that all four compounds had binding interactions which were considerably strong with target proteins. This is depicted in varying affinities and interacting networks. For ESR1, the affinities of the compounds hovered between -7.8 kcal/mol and -9.0 kcal/mol, and both compounds showed consistency in hydrogen bonding and hydrophobic interactions with ESR1 residues (Fig. 5a-d). For AR, affinities were slightly

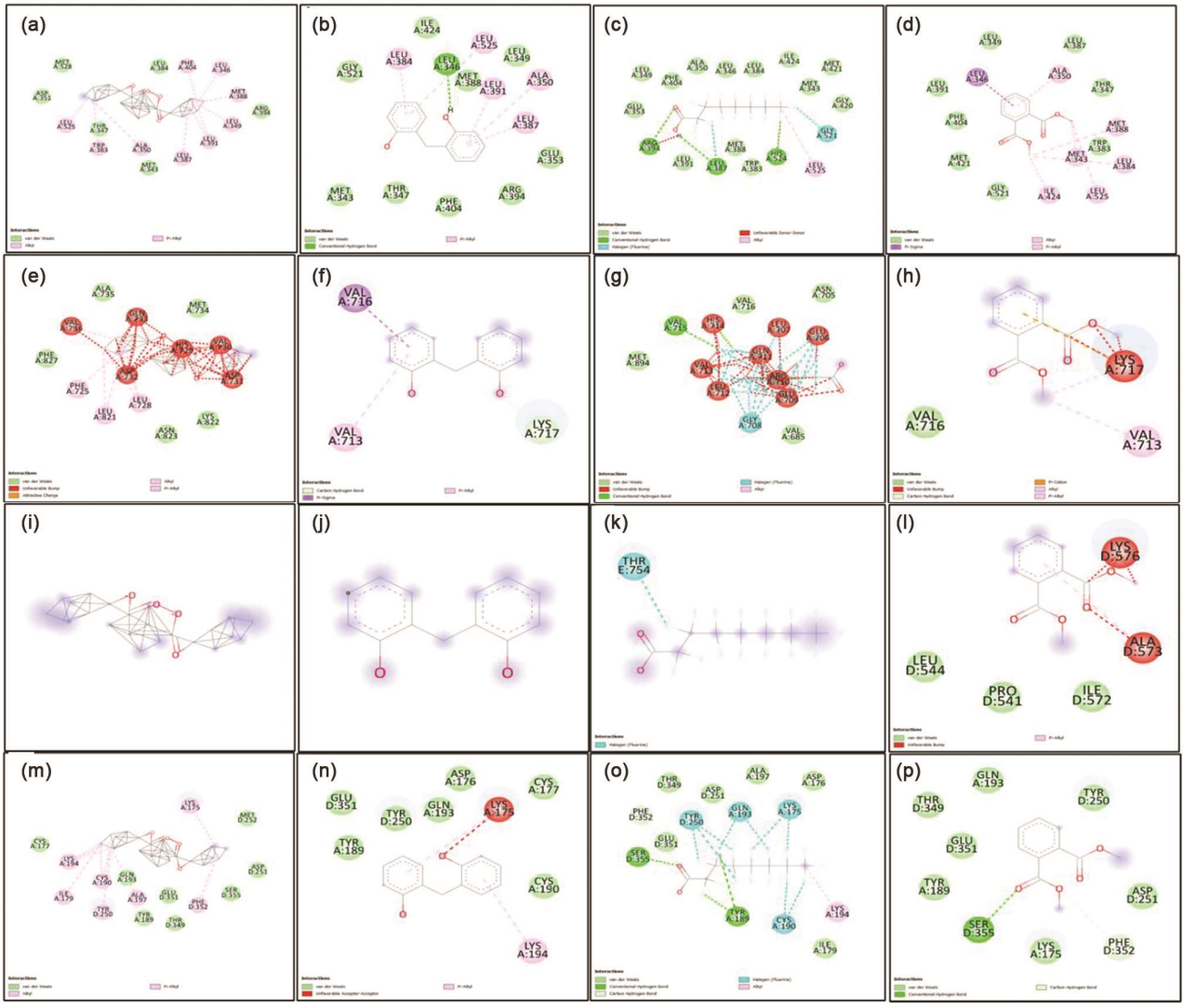


Fig. 5 — Docking results visualizing the interactions of four compounds with endocrine proteins. (a-d) Docking of compounds with ESR1, showing hydrogen bonding and hydrophobic interactions. (e-h) Interaction profiles of compounds with AR, depicting key residues involved in protein binding. (i-l) Docking interactions with PPARG, highlighting stable binding conformations. (m-p) Docking with THRB, showing selective binding to the protein's active sites. Figure generated using Discover Studio

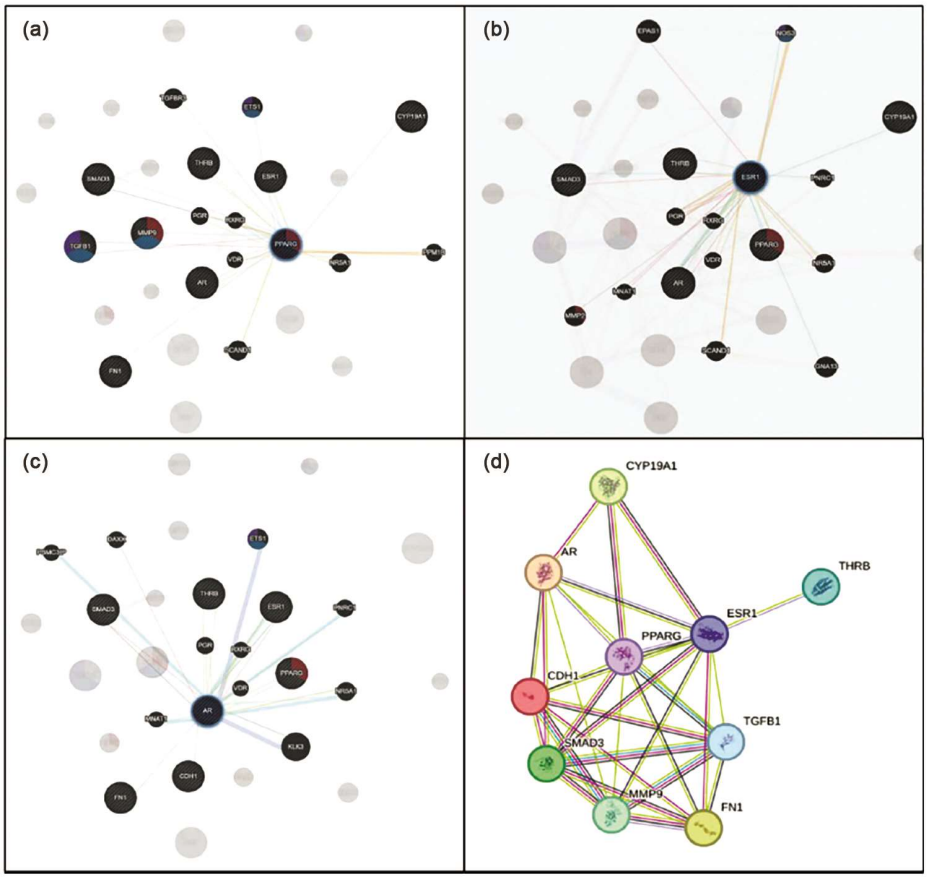


Fig. 6 —The image depicts gene-level interactions, including co-expression, co-localization, and shared pathways. Key hubs such as (a) ESR1; (b) AR; (c) PPARG show strong associations with fibrotic genes like TGFβ1, SMAD3, and MMP9, reflecting the interconnectedness of endocrine signaling and fibrosis; and (d) Illustrates protein-level associations between the same genes, highlighting functional interactions using STRING. Central proteins (ESR1, AR, and PPARG) strongly connect to fibrosis-related proteins (TGFβ1, SMAD3, and FN1), suggesting shared molecular mechanisms driving endocrine disruption and fibrosis progression

low, around -6.9 kcal/mol to -8.2 kcal/mol, with the compounds depicting several interactions with some important residues involved in the activation of this protein (Fig. 5e-h). Binding affinities between PPARG were -7.1 kcal/mol to -8.5 kcal/mol, indicating the importance of this protein in ligand activation (Fig. 5i-l). Finally, THRB docking showed a selective and energetically favored binding pattern, with its affinity spanning from -8.7 kcal/mol to -7.0 kcal/mol (Fig. 5m-p). The most striking observation was that DiBP could not be docked due to its poor interaction storyline in STRING analysis and the low toxicity established by ADME analysis. This suggests that DiBP is less likely to be an effective endocrine disruptor or have therapeutic activity.

Gene interaction and Protein network analysis of endocrine and fibrotic genes

ESR1, AR, PPARG, and THRB are genes related to endocrinos, while TGFbeta1, SMAD3, CDH1, FN1, and MMP9 are genes related to fibrosis. In Figure 6, GeneMANIA and the STRING network have identified a complex and interconnected relationship between ESR1, AR, PPARG, THRB, TGFbeta1, SMAD3, CDH1, FN1, and MMP9 during analysis, finding the best features of convergence between the endocrine and fibrotic signaling processes. ESR1, AR, and PPARG have been shown by Gene Ontology to be core to the interaction network in the GeneMANIA network; this has strong associations with several fibrotic genes, including TGF-B1, SMAD3, and MMP9, as well as in the process of extracellular matrix remodeling and fibrotic progression. Thus, it has also been described that the central PPI network of ESR1, AR, and PPARG is characterized, showing a high degree of connectivity with fibrotic proteins such as TGF-β1/SMAD3, highlighting well the three proteins as important regulators in fibrosis pathways. Furthermore, GDH1

exhibits close associations with SMAD3 and FN1 in the epithelial-to-mesenchymal transition (EMT) and fibrosis differentiation. Moreover, strong correlations between MMP9 and matrix-remodeling activities were noticed. These network investigations taken as a whole reveal functional similarities and overlapping pathways in the fibrotic and endocrine systems. These may be of help in the management of disorders related to fibrosis and disruption of the endocrine system. Of major importance, these two networks involve very valuable information about potential biological therapeutic targets and emphasize the importance of the interaction between the fibrotic and endocrine pathways.

Discussion

The present study concluded with interpreting the correlation between microplastics and endocrine disruption, as well as particular additives like DEHP and perfluorooctanoic acid, and the pattern of their interaction with the most important hormone receptors, such as estrogen receptor alpha (ERα) and androgen receptor (AR). The results depict that microplastics may affect endocrine variables via biochemical pathways, having adverse effects on human health and the natural environment. The present study outlines a two-way disruption hypothesis in light of the obtained results and interprets, for the first time, a two-way effect on fibrotic processes, taking into special consideration proteins like TGF-β1 and Smad3. Results of the study proffer a multi-pronged global view on adverse health impacts of microplastics, unlike other research attempts that only pursued multiple impacts of endocrine disruption without considering its eventual relationship to injury and healing processes separately. It raises the possibility of acquiring chronic illnesses such as fibrosis and the possibility of hormone disruption brought on by microplastics. The study provides a critical insight into the concurrent degradation of microplastics by verifying connections between endocrine and fibrotic targets using advanced computational tools, such as molecular docking and network analyses. These studies, in essence, involve regulatory measures to reduce the release of hazardous microplastic additives in a natural environment; therefore, considering the need for environmentally sound chemical substitutes of microplastics, the study justifies the same. This is an important signal to academics and policy makers that they have to take all-encompassing measures to deal with the intricate features of environmental pollutants such as microplastics. A more in-depth investigation of the health impacts of microplastics and the emphasis on resolving environmental policy and human health priorities, however, is further underlined by growing concerns about environmental contamination.

Conflicts of interest

All authors declare no conflicts of interest.

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