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Orignal Article

Elucidating the Mechanism of Polyethylene Terephthalate Micro / Nanoplastics Inducing Gestational Diabetes Mellitus through Network Toxicology and Molecular Docking Analysis

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Abstract:
This study investigated polyethylene terephthalate-derived micro/nanoplastics (PET-MNPs), a predominant plastic pollutant in the circulatory system, employing network toxicology and molecular docking approaches to systematically elucidate their molecular mechanisms in gestational diabetes mellitus (GDM) pathogenesis. We identified 35 potential PET-MNPs-GDM interaction targets and demonstrated that PET-MNPs primarily disrupt insulin signaling through four key pathways: (1) cellular metabolic adaptation (amino acid starvation response), (2) hypoxic stress responses (HIF-1 signaling pathway), (3) vascular homeostasis (fluid shear stress and atherosclerosis pathways), and (4) proliferative signaling networks (oncogenic pathways). Network topology analysis pinpointed STAT1, PIK3R1, and PTPN11 as core regulatory nodes, with molecular docking confirming strong binding affinity between PET-MNPs and these targets. For the first time, this study establishes PET-MNPs as environmental metabolic disruptors that exacerbate GDM through multi-target and multi-pathway mechanisms, providing crucial theoretical insights into plastic pollution-metabolic disease relationships. Our findings underscore the urgent need for population-based epidemiological studies and targeted intervention strategies, highlighting significant public health implications for protecting vulnerable populations.

Key Words: PET-MNPs; GDM; Network toxicology; Molecular docking; PI3K/AKT pathway

Introduction

Plastics are widely used due to their convenience, yet they release substantial amounts of microplastics/nanoplastics (MNPs) throughout their lifecycle. Microplastics (MPs, 100-5000 nm) and nanoplastics (NPs, <100 nm) are ubiquitous environmental contaminants(Huang et al., 2024; Wiesinger et al., 2021). With particle sizes <5 mm, MNPs readily disperse through ecosystems and bioaccumulate in organisms, persisting long-term due to their resistance to degradation(Kozlov, 2024; Zhang et al., 2023). Notably, MNPs have been detected in various human tissues, including ocular structures(Zhong et al., 2024), brain and hepatic tissues(Nihart et al., 2025), pulmonary systems(Jenner et al., 2022), thrombi(Wang et al., 2024), seminal fluid(N. Li et al., 2024), and placental compartments(Garcia et al., 2024). While the toxicological implications remain unclear, MNP exposure raises critical public health concerns.

Polyethylene terephthalate (PET) accounts for 80% of global plastic production, with a global output of 33 million tons in 2015, dominates food/beverage packaging, textiles, personal care products, medical devices, and children's toys(Khairul Anuar et al., 2022). PET-derived MNPs represent the predominant plastic contaminants in human circulation, comprising 50% of blood MNPs(Leslie et al., 2022), 73.7% of arterial deposits(Liu et al., 2024), and 77% of cardiac tissue MNPs(Yang et al., 2023). This establishes PET-MNPs as the most prevalent

plastic contaminants in human biological systems.

Gestational diabetes mellitus (GDM), affecting 5-25% of pregnancies, represents a major global health burden due to its associated maternal-fetal complications. GDM significantly elevates the risk of hypertensive disorders, cesarean delivery, and preeclampsia, while conferring a 70% decade-risk for type 2 diabetes mellitus progression. Furthermore, offspring of GDM pregnancies exhibit 20%-50% increased susceptibility to obesity and metabolic dysfunction compared to non-GDM controls (Mora-Ortiz & Rivas-García, 2024).

While multifactorial in etiology, environmental contributors like MNPs remain underexplored. Emerging evidence implicates MNPs in oxidative stress, inflammatory cascades, metabolic dysregulation, cellular dysfunction, and epigenetic modifications(Ali et al., 2024; Khan & Jia, 2023). This study employs network toxicology and molecular docking to systematically investigate PET-MNPs mechanistic role in GDM pathogenesis.

Network toxicology integrates systems biology and bioinformatics to map compound-target-disease interactions through multi-omics data analysis(He et al., 2024). Molecular docking evaluates ligand-receptor binding affinities, where lower binding energies indicate greater stability. By synthesizing these approaches, we aim to: 1) Identify key PET-MNP molecular targets in GDM pathways; 2) Characterize toxicity mechanisms through protein interaction networks; 3) Validate high-affinity target binding through computational modeling. This theoretical framework advances understanding of environmental plastic toxicology while informing preventive strategies against pollution-related metabolic disorders.

1. Methods

The flowchart for this study is illustrated in Fig. 1.

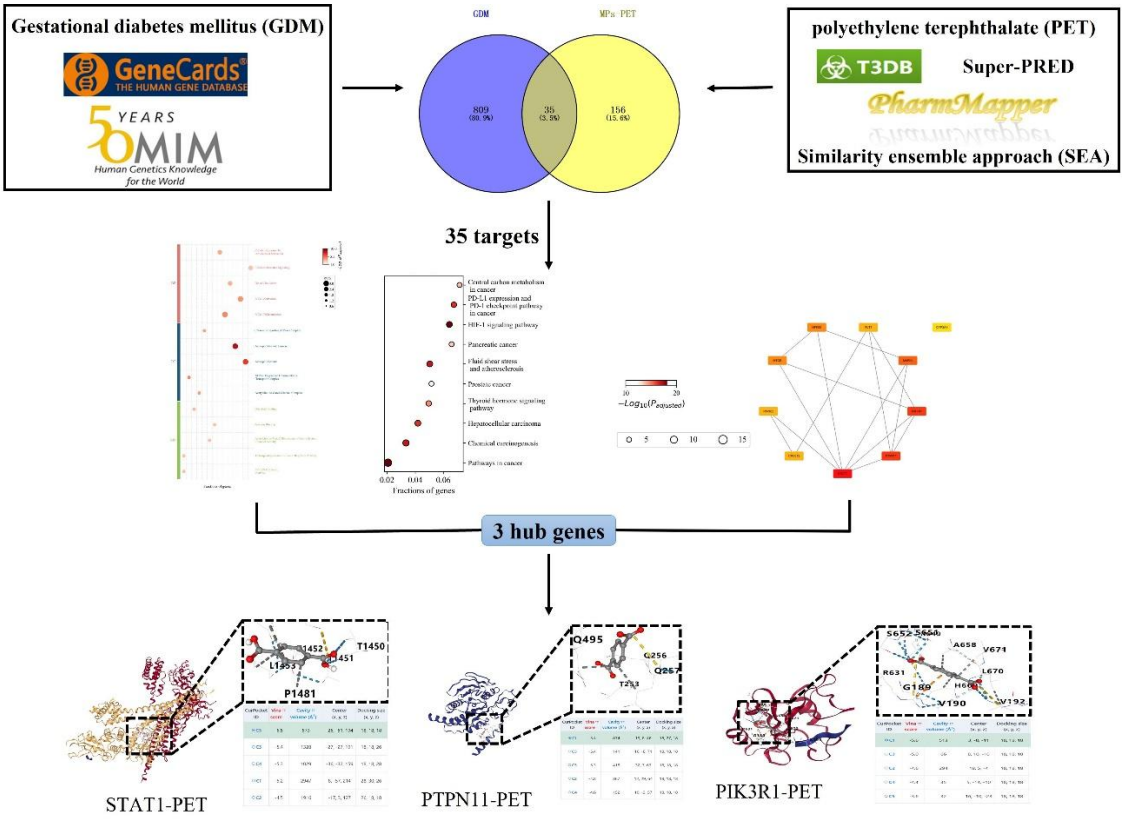


Figure 1 Flowchart of this study

2.1 Identification of PET-MNPs Targets

The SMILES and SDF structural information of polyethylene terephthalate (PET) was retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov). Potential human (Homo sapiens) targets of PET were systematically screened using the T3DB (https://www.t3db.ca/), SEA (https://sea.bkslab.org/), Super-PRED (https://prediction.charite.de/), and PharmMapper (https://lilab-ecust.cn/pharmmapper/index.html)

databases (Keiser et al., 2007; Liu et al., 2010; Nickel et al., 2014; Wishart et al., 2015). For Super-PRED, targets with a "Probability ≥ 50%" were retained, while PharmMapper results were filtered using a "Norm Fit ≥ 0.7" threshold. Target names were standardized via the UniProt database, and duplicate entries across the four databases were removed.

2.2 Acquisition of GDM-Related Targets

GDM-associated targets were extracted from the GeneCards (https://www.genecards.org/) and OMIM (https://www.omim.org/) databases using the keyword "GDM" and restricted to Homo sapiens. In GeneCards, targets with a relevance score ≥15 were selected. Duplicates between the two databases were merged and deduplicated. The intersection of PET-MNPs targets and GDM-related targets was identified as potential key mediators of PET-MNPs toxicity in GDM pathogenesis.

2.3 Construction of PPI Networks and Enrichment Analysis

Common targets shared between PET-MNPs and GDM were analyzed using the STRING database (https://cn.string-db.org/) to construct a protein-protein interaction (PPI) network with a high-confidence interaction threshold (confidence score ≥0.7). The network was visualized and analyzed using Cytoscape software, with key hub genes identified via the Maximal Clique Centrality (MCC) algorithm(Shannon et al., 2003).

2.4 GO and KEGG Enrichment Analysis

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses of the intersection targets were performed using the OmicVerse package to elucidate biological processes, molecular functions, cellular components, and signaling pathways associated with PET-MNPs-induced GDM (Zeng et al., 2024).

2.5 Molecular Docking and Visualization

Core target proteins were retrieved from UniProt, filtered for "reviewed" and "Homo sapiens" entries, and their 3D structures were obtained from the RCSB PDB database (https://www.rcsb.org/). Crystal structures were prioritized based on sequence completeness, ligand diversity, and resolution (<3.0 Å). The PET structure (SDF format from PubChem) was converted to mol2 format using Chem3D. Molecular docking between PET and core targets was performed via CB-Dock2 (https:// cadd. labshare.cn/cb-dock2/php/index.php), an Auto Dock Vina-based platform enabling automated binding site prediction and affinity scoring(Liu et al., 2022). Binding poses with the lowest binding energy (ΔG) were selected for visualization of intermolecular interactions.

2. Result

3.1 Identification of PET-MNPs-Induced GDM Targets

A comprehensive identification of GDM-associated targets yielded a total of 884 entries, with 731 targets sourced from the GeneCards database and 180 from the OMIM database (Figure 2A). Regarding PET-MNPs, screening identified 191 potential targets, distributed as follows: 21 from T3DB, 84 through SEA analysis, 77 via Super-PRED, and 8 from PharmMapper (Figure 2B). Intersection analysis using a Venn diagram demonstrated 35 common targets implicated in PET-MNPs-induced GDM toxicity (Figure 2C).

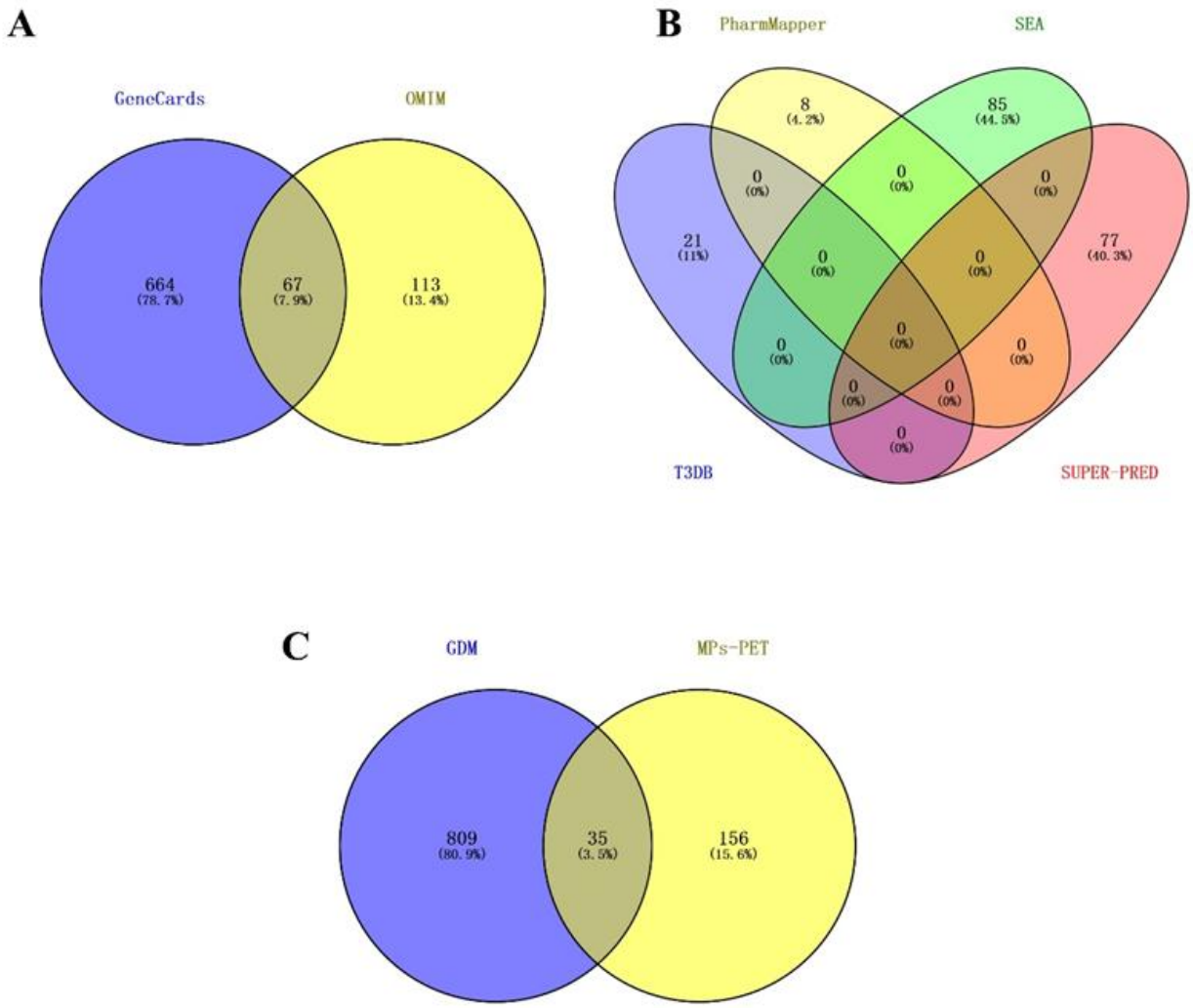


Figure 2. Prediction of PET-MNPs-GDM shared molecular targets. A Venn diagram of GDM-associated targets. B Venn diagram of PET-MNPs-related targets. C Venn diagram of overlapping PET-MNPs and GDM targets.

3.2 GO and KEGG Enrichment Analysis

GO enrichment analysis of the 35 overlapping targets was conducted using omicverse, revealing 164 enriched biological processes (BP), 21 cellular components (CC), and 67 molecular functions (MF). The top five most significant terms (ranked by p-value) from each category are presented in Figure 3. BP analysis highlighted the core targets' involvement in cellular response to amino acid starvation, calcium-mediated signaling, blood circulation, B cell activation, and B cell differentiation. CC analysis revealed enrichment in cation-transporting ATPase complex, azurophil granule lumen, azurophil granule, ATPase-dependent transmembrane transport complex, and acetylcholine-gated channel complex. MF analysis demonstrated functional associations with bile acid binding, ankyrin binding, acetylcholine-gated monoatomic cation-selective channel activity, 1-phosphatidylinositol-3-kinase regulator activity, and 3'-5' DNA helicase activity. The present systematic investigation identifies multiple pathogenic mechanisms by which PET-MNPs could induce GDM, including impaired nutrient sensing, altered ion transport, immune system activation, and dysregulated chromatin remodeling.

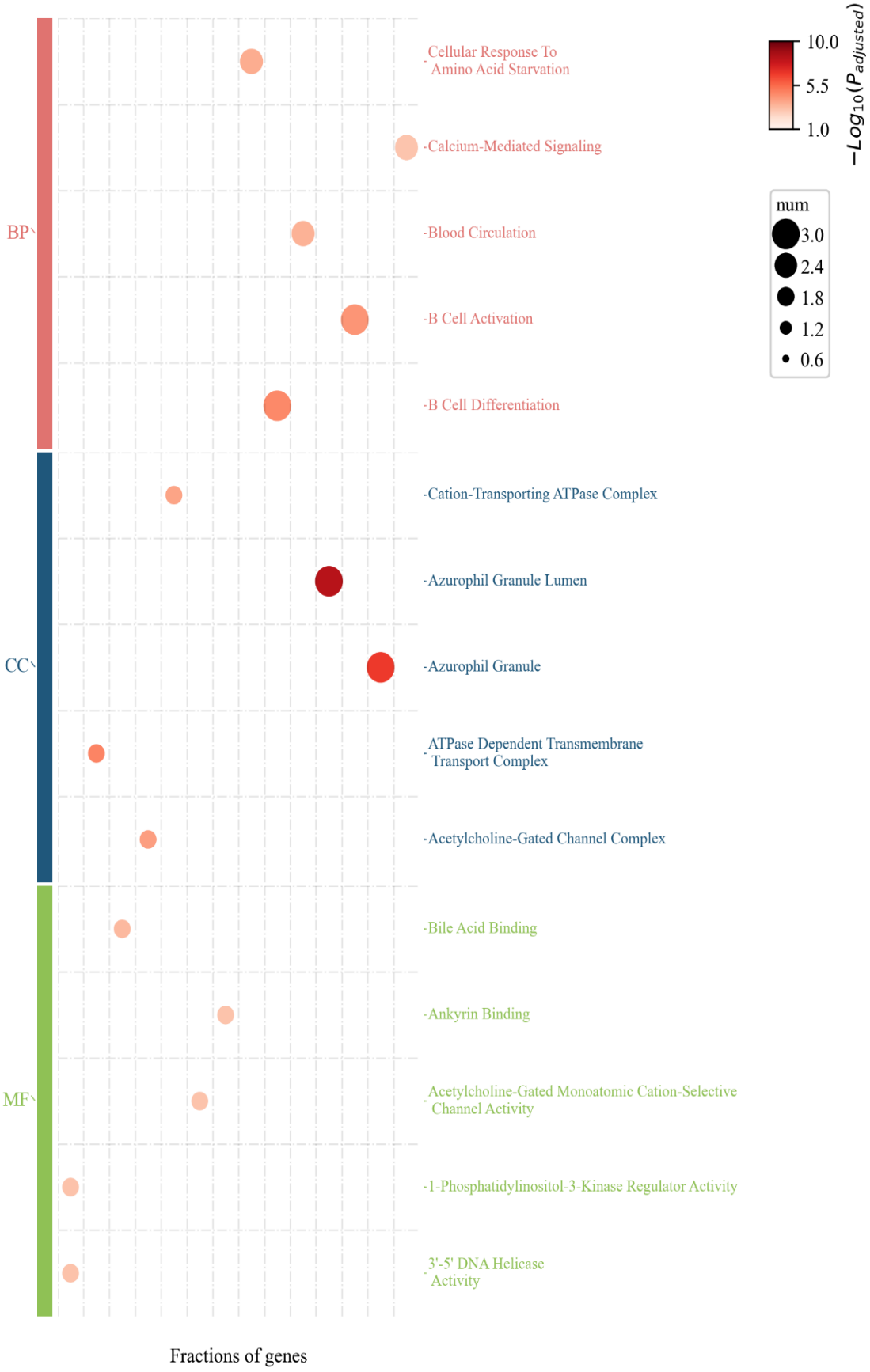


Figure 3. Systematic GO term analysis was performed on the 35 putative targets, with enriched terms stratified into: BP, CC, and MF categories. The five most significant terms per category (minimum adjusted p-value) are presented.

KEGG pathway analysis identified 124 significantly enriched pathways ($p<0.05$), with the top 10 most statistically significant pathways presented in Figure 4. Core PET-MNPs-GDM targets were predominantly mapped to: (1) Pathways in cancer, (2) HIF-1 signaling pathway, (3) Fluid shear stress and atherosclerosis, (4) Chemical carcinogenesis, (5) Hepatocellular carcinoma, and (6) PD-1 checkpoint pathway in cancer. These findings suggest PET-MNPs may exacerbate GDM pathogenesis through convergent mechanisms involving oncogenic signaling, hypoxia response, hemodynamic stress adaptation, and immune checkpoint regulation, revealing previously unappreciated parallels between plastic particle toxicity and cancer-associated metabolic dysregulation.

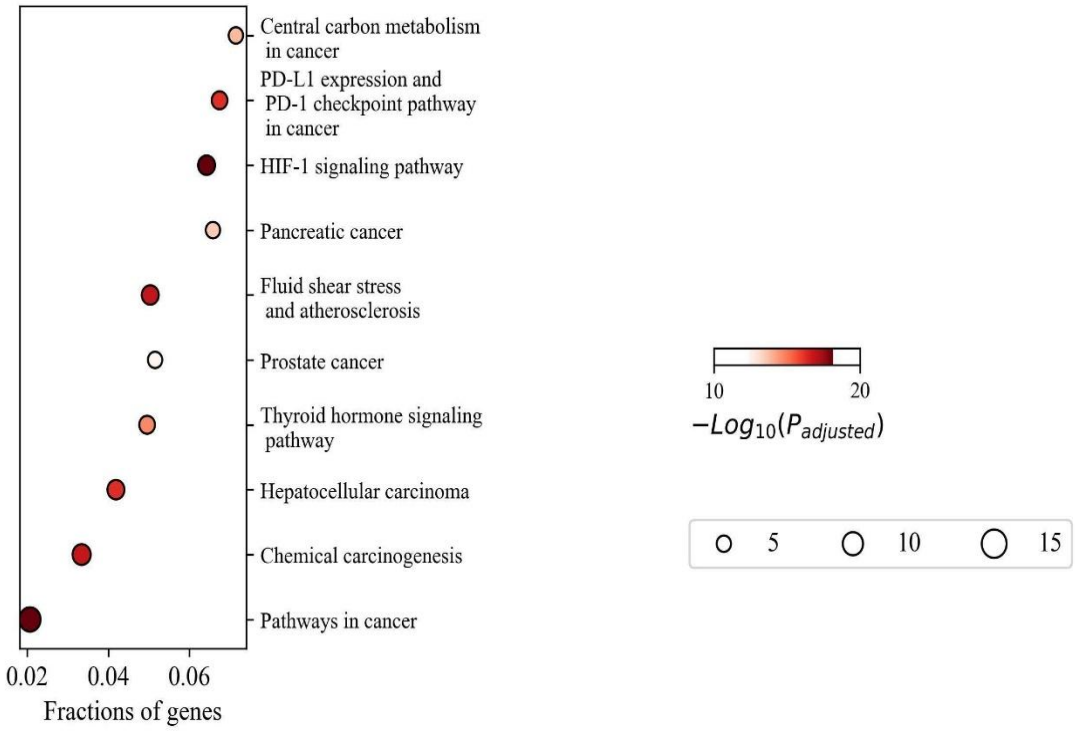


Figure 4 KEGG enrichment analysis showing the top 10 pathways with the lowest adjusted p values.

3.3 Core Target Identification and Network Analysis

To elucidate the molecular interplay between PET and GDM targets, we established a protein-protein interaction (PPI) network. The 35 shared targets were analyzed using the STRING database, yielding a high-confidence interaction network (interaction score >0.700) consisting of 34 proteins connected by 24 interactions (Figure 5A). Subsequent topological analysis in Cytoscape employing the Maximal Clique Centrality (MCC) algorithm identified STAT1, PIK3R1, and PTPN11 as core regulatory hubs, suggesting their pivotal roles in PET-MNPs-induced GDM pathogenesis (Figure 5B).

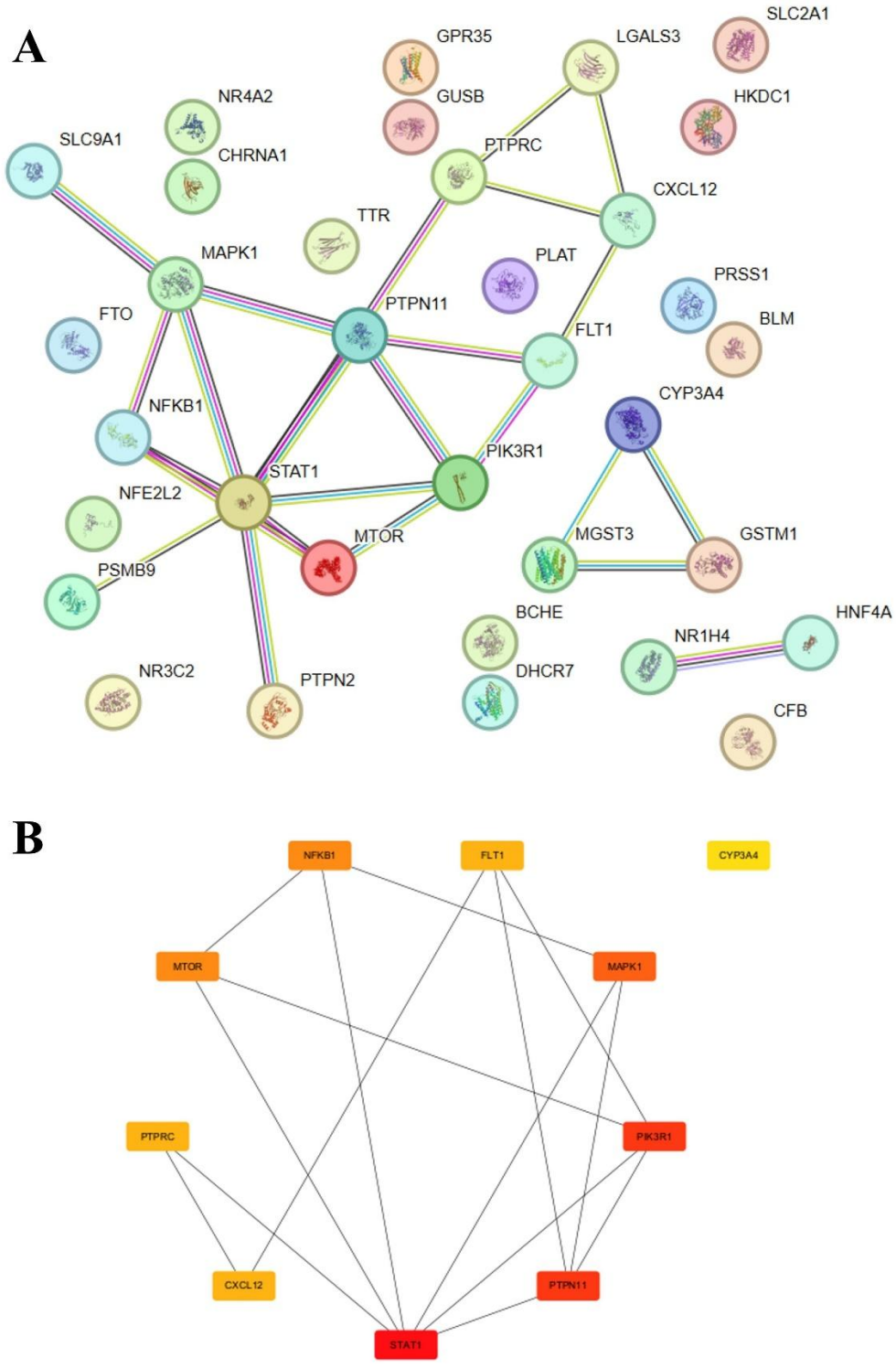
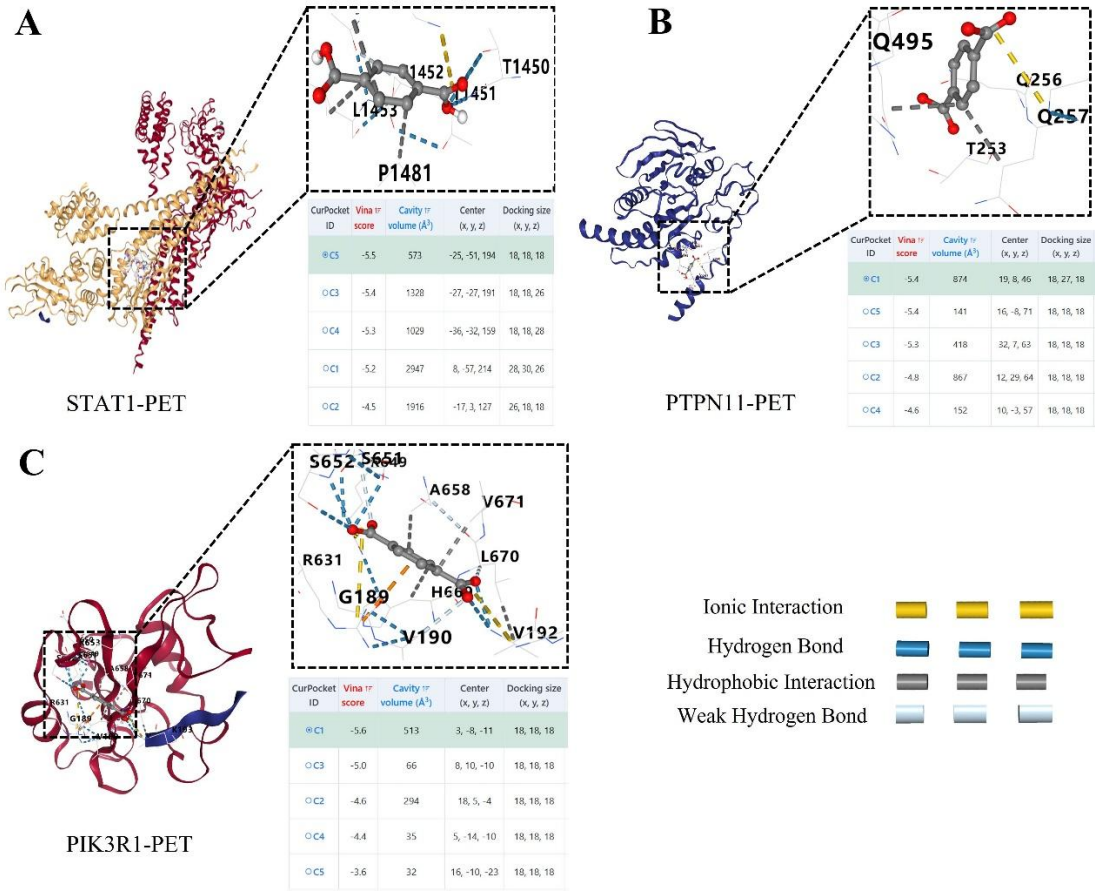


Figure 5. PET-MNPs - GDM core targets acquisition. A PPI network of the 35 potential targets shared between PET-MNPs exposure and GDM. B MCC illustrate the intricate interactions among the 10 core targets.

3.4 Molecular Docking Validation

Molecular docking analysis performed using CB-Dock2 demonstrated significant binding interactions between PET and core regulatory targets. The computational simulations revealed: 1. STAT1-PET complex formation with a binding energy of -5.5 kcal/mol, stabilized through multiple intermolecular forces including three hydrogen bonds, three hydrophobic interactions, and one ionic bond (Figure 6A). 2. PTPN11-PET interaction exhibiting a binding affinity of -5.4

kcal/mol, primarily mediated by two hydrophobic interactions and one ionic interaction (Figure 6B). 3. PIK3R1-PET binding showed the strongest interaction energy (-5.6 kcal/mol), involving an extensive network of five conventional hydrogen bonds, three ionic interactions, three hydrophobic contacts, and three weaker hydrogen bonds (Figure 6C). These robust molecular interactions, particularly the high-affinity binding observed with PIK3R1, suggest PET may functionally impair these core regulatory proteins. The multiple interaction modalities identified support the hypothesis that PET could serve as a persistent molecular disruptor in GDM pathogenesis during chronic exposure scenarios.



CurPocket ID	Vina score	Cavity volume (Å³)	Center (x, y, z)	Docking size (x, y, z)
C5	-5.5	573	-25, -51, 194	18, 18, 18
C3	-5.4	1328	-27, -27, 191	18, 18, 26
C4	-5.3	1029	-36, -32, 159	18, 18, 28
C1	-5.2	2947	8, -57, 214	28, 30, 26
C2	-4.5	1916	-17, 3, 127	26, 18, 18

CurPocket ID	Vina score	Cavity volume (Å³)	Center (x, y, z)	Docking size (x, y, z)
C1	-5.4	874	19, 8, 46	18, 27, 18
C5	-5.4	141	16, -8, 71	18, 18, 18
C3	-5.3	418	32, 7, 63	18, 18, 18
C2	-4.8	867	12, 29, 64	18, 18, 18
C4	-4.6	152	10, -3, 57	18, 18, 18

CurPocket ID	Vina score	Cavity volume (Å³)	Center (x, y, z)	Docking size (x, y, z)
C1	-5.6	513	3, -8, -11	18, 18, 18
C3	-5.0	66	8, 10, -10	18, 18, 18
C2	-4.6	294	18, 5, -4	18, 18, 18
C4	-4.4	35	5, -14, -10	18, 18, 18
C5	-3.6	32	16, -10, -23	18, 18, 18

Figure 6. Molecular docking results of PET with target proteins: (a) Docking of PET with STAT1, (b) Docking of PET with PTPN11, (c) Docking of PET with PIK3R1. The Fig. shows the binding positions of the PET molecule within the surface cavities of each protein and the interactions with the residues.

3. Discussion

This investigation employed an integrative network toxicology approach to elucidate the molecular mechanisms linking PET-MNPs exposure to gestational diabetes mellitus (GDM). Through systematic bioinformatic analysis of six complementary databases (T3DB, SEA, Super-PRED, PharmMapper, GeneCards, and OMIM), we identified 35 putative molecular targets associated with PET-MNPs-induced GDM. Subsequent protein-protein interaction network analysis, conducted using STRING with Cytoscape visualization, identified three critical hub genes (STAT1, PIK3R1, and PTPN11) exhibiting maximal network centrality. Molecular docking simulations revealed stable binding conformations between PET-MNPs and these hub proteins, with energetically favorable interaction profiles. These computational findings suggest that PET-MNPs may exert diabetogenic effects through direct modulation of these central regulatory proteins, providing mechanistic insights into environmental nanoparticle-induced metabolic dysregulation during pregnancy.

STAT1, a member of the signal transducer and activator of transcription family, functions as a critical regulator in diabetes pathogenesis. It orchestrates the expression of genes implicated in

cellular proliferation, fibrosis, inflammatory responses, and oxidative stress, thereby modulating metabolic homeostasis and tissue dysfunction during diabetes development(Chen et al., 2020). Experimental evidence demonstrates that MNPs exposure induces systemic inflammation, insulin resistance, and hyperglycemia in murine models(Huang et al., 2022; Yang et al., 2024). These effects are consistent with the pathophysiological changes observed in GDM, suggesting that exposure to MNPs may modulate STAT1 signaling and promote the progression of GDM. Therefore, systematic investigation of PET-MNPs-mediated modulation of STAT1 functional activity represents a crucial research direction for understanding their mechanistic role in GDM pathogenesis.

PIK3R1, also termed p85α, as a regulatory subunit of PI3K, PIK3R1 governs insulin signaling by mediating PIP3-dependent AKT activation, which regulates glucose transport (via GLUT4), glycogen synthesis, and lipid metabolism(Huang et al., 2018; Tsay & Wang, 2023). Upregulated PIK3R1 expression in GDM patients and MNPs-induced hepatic steatosis/insulin resistance in mice underscore its role in metabolic dysregulation(Hu et al., 2019; Roh et al., 2024). PET-MNPs may impair PI3K/AKT signaling, disrupting glucose homeostasis and placental nutrient transport in GDM.

PTPN11, also known as SHP2 due to its Src homology 2 (SH2) domain, serves as a pivotal hub for intracellular and extracellular signal transduction. It interacts with membrane-bound receptors, including receptor tyrosine kinases (RTKs), cytokine receptors, and integrins, to propagate extracellular signals into key downstream pathways such as RAS-RAF-MEK-ERK, PI3K-AKT, JAK-STAT, and PD-L1/PD-1, thereby modulating cellular differentiation, survival, and proliferation(Chen et al., 2024). As highlighted earlier, the PI3K-AKT axis critically influences glucose and lipid metabolism, which exhibit a bidirectional relationship with diabetes pathogenesis. Consequently, SHP2, as a central signaling modulator, contributes to diabetic progression by regulating glycolipid homeostasis through PI3K-AKT signaling. Reactive oxygen species (ROS), essential mediators of cellular growth and signal transduction, reversibly regulate SHP2 activity(Machado et al., 2017). In diabetic nephropathy, ROS-SHP2 interactions exacerbate renal fibrosis, while ROS-induced oxidative modifications of diabetes-related proteins further drive metabolic dysfunction(J. Li et al., 2024; Zhang et al., 2020). Notably, MNPs, including PET-MNPs have been shown to induce ROS overproduction, which may dysregulate SHP2 signaling(Das, 2023). Such dysregulation could amplify SHP2 activity, accelerating GDM pathogenesis. Investigating PET-MNPs-triggered ROS-mediated SHP2 activation pathways may unveil novel mechanisms underlying GDM development, offering critical insights into environmental pollutant-driven metabolic disruptions during pregnancy.

GO and KEGG analyses implicated PET-MNPs in pathways including amino acid starvation response, HIF-1 signaling, fluid shear stress/atherosclerosis, and oncogenic pathways. Key mechanistic links include: HIF-1 signaling, hypoxia-inducible signaling exacerbates oxidative stress and gluconeogenesis, potentiating insulin resistance. Amino acid starvation, disrupted nutrient sensing impairs mTORC1-regulated β-cell function and placental amino acid transport. Fluid shear stress, hemodynamic alterations promote endothelial dysfunction and ROS overproduction, aggravating GDM-associated vascular complications. Oncogenic pathways, shared metabolic reprogramming features between cancer and GDM highlight PET-MNPs potential to disrupt glucose-fueled anabolic processes.

The current computational predictions, though mechanistically insightful, underscore critical knowledge gaps requiring empirical investigation. Systematic validation should include: (1) longitudinal murine exposure studies to assess STAT1/PIK3R1/PTPN11 modulation under physiologically relevant PET-MNPs concentrations, and (2) human cohort studies addressing real-world exposure variables such as co-pollutant interactions and transplacental transmission kinetics.

4. Conclusion

This study employed network toxicology and molecular docking to elucidate PET-MNPs' role in GDM pathogenesis. Integrated multi-database analysis identified three core targets (STAT1, PIK3R1, PTPN11) mediating GDM progression.

Pathway enrichment revealed PET-MNPs disrupt metabolic homeostasis through HIF-1 signaling, nutrient sensing, hemodynamic stress, and oncogenic pathway activation. These findings underscore the urgent need for environmental remediation while providing a mechanistic framework linking microplastics to gestational metabolic disorders.

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6. Declaration of Interests

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.

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