

In Silico Prediction of Distinct HMW PAH-Associated Pathways in Allergic Rhinitis: Chemokine-Related Targets of BaP and Metabolic Enzyme Targets of BaA/DBA

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Abstract

Polycyclic aromatic hydrocarbons (PAHs), major atmospheric pollutants, have been associated with allergic respiratory disease, but the molecular links between individual PAHs and allergic rhinitis (AR) remain incompletely characterized. This in silico study explored predicted associations of three high-molecular-weight PAHs — benzo[a]pyrene (BaP), benzo[a]anthracene (BaA), and dibenz[a,h]anthracene (DBA) — with AR-related molecular networks. We integrated ADMET prediction (ADMETlab 2.0), multi-source target identification, network topology analysis (STRING and Cytoscape), functional enrichment (DAVID), and molecular docking (AutoDock Vina). ADMET analysis generated multiple toxicological alerts for all three compounds. Network analysis identified 191, 138, and 159 overlapping targets for the BaP – AR, BaA – AR, and DBA –

AR datasets, respectively. BaP-associated targets were preferentially enriched in chemotaxis and chemokine signaling, whereas BaA- and DBA-associated targets were more strongly enriched in xenobiotic and cytochrome P450-related metabolic pathways. Molecular docking yielded energetically favorable predicted poses between BaP and chemokine-related hub proteins (CCL2, CCL5, CXCL8, CXCL12, and CXCR4) and between BaA/DBA and metabolic hub proteins, including ABCB1, CYP1A2, and CYP3A4. Taken together, these analyses generate a hypothesis that BaP may be preferentially associated with chemokine-related inflammatory networks, whereas BaA and DBA may be associated with metabolic-enzyme networks that could influence endogenous inflammatory mediator metabolism or drug disposition. Given its computational scope, this study yields *in silico*-generated hypotheses and candidate targets warranting experimental validation.

Keywords: Polycyclic Aromatic Hydrocarbons; Allergic Rhinitis; Network Toxicology; Molecular Docking; *In Silico* Analysis

1. Introduction

Allergic rhinitis (AR) is an immunoglobulin E-mediated type I hypersensitivity reaction triggered by inhaled allergens. Pathologically, it is characterized by a Th2-biased immune response in the nasal mucosa. This response activates B lymphocytes to generate allergen-specific IgE, facilitates inflammatory-cell recruitment, and is associated with epithelial injury, glandular hyperplasia, and mucosal-barrier dysfunction (Zhang et al., 2021). The hallmark symptoms include paroxysmal sneezing, rhinorrhea, nasal pruritus, and congestion (Bousquet et al., 2020). AR affects hundreds of millions of people worldwide, impairs quality of life, and represents a substantial public-health burden (Colás et al., 2017; Cox, 2016). Although genetic predisposition and common environmental allergens, such as pollen and dust mites, are established contributors (Bernstein et al., 2024), epidemiological evidence also associates air-pollutant exposure with AR susceptibility and symptom severity (Li et al., 2022; Lu et al., 2022). Long-term exposure to specific PM_{2.5} constituents has likewise been associated with allergic diseases (Feng et al., 2023).

Polycyclic aromatic hydrocarbons (PAHs) are atmospheric contaminants generated mainly by incomplete combustion of organic materials (Srogi, 2007). Their lipophilicity and environmental persistence facilitate widespread distribution, bioaccumulation, and biological uptake (Abdel-Shafy & Mansour, 2016; Barbosa et al., 2023). Their carcinogenic and mutagenic effects are well documented (Holme et al., 2023; Liu et al., 2008), and epidemiological and experimental evidence has linked PAH exposure to immune dysregulation and allergic respiratory disease (Karimi et al., 2015; Yu et al., 2022). The selected high-molecular-weight PAHs differ structurally: BaA contains four fused aromatic rings, whereas BaP and DBA each contain five, and the three compounds have distinct ring-fusion geometries. These structural differences may alter molecular shape and target complementarity, providing a chemical rationale for comparing their predicted target profiles (Barbosa et al., 2023; Bukowska et al., 2022). Research has focused primarily on BaP, which has been associated with eosinophilic airway inflammation and aggravated nasal obstruction in experimental allergic models (Mizutani et al., 2007; Tajima et al., 2020). By contrast, the potential

molecular associations of BaA and DBA with AR remain poorly integrated and underexplored (Malik et al., 2013).

In this *in silico* study, we aimed to explore potential molecular associations of benzo[a]pyrene (BaP), benzo[a]anthracene (BaA), and dibenz[a,h]anthracene (DBA) with allergic rhinitis (AR). Our goal was to characterize the differential target profiles of these high-molecular-weight PAHs by integrating toxicity prediction, network toxicology, functional enrichment, and molecular docking. Specifically, we employed these computational approaches to map the predicted relationships between the PAHs and their potential targets. Through this comprehensive analysis, we sought to generate testable hypotheses and identify candidate targets associated with PAH-linked AR, thereby providing a computational framework for understanding environmental pollutant-immune interactions.

2. Methods

2.1. Integrated Network Toxicology-Based Analysis of PAHs

This study used an integrated computational approach to investigate three prototypical high-molecular-weight polycyclic aromatic hydrocarbons (HMW PAHs): benzo[a]pyrene (BaP), benzo[a]anthracene (BaA), and dibenz[a,h]anthracene (DBA). Their canonical SMILES strings were retrieved from the PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>). The ADMET properties were then predicted using the ADMETlab 2.0 platform (<https://admetmesh.scbdd.com/service/evaluation/cal>), providing exploratory pharmacokinetic and toxicological descriptors for subsequent target-prioritization analyses (Xiong et al., 2021).

2.2. Screening and Identification of Potential PAHs Molecular Targets

Potential molecular targets of the PAHs were screened using a triple-database cross-validation strategy. First, compound names were standardized and SMILES strings were obtained from PubChem. Parallel queries were then performed across three databases: 1) ChEMBL (<https://www.ebi.ac.uk/ChEMBL/>), using standardized compound names (e.g., "Benzo[a]pyrene") and a species filter for "Homo sapiens"; 2) SEA database (<https://sea.bkslab.org/>), by submitting the SMILES strings for screening against "HUMAN" targets; and 3) TargetNet database (<http://targetnet.scbdd.com/calcnnet/index/>), where SMILES strings were submitted to retain targets with a probability score greater than 0 ($\text{Prob} > 0$). The resulting target lists from all sources were integrated, and duplicates were removed. The combined list was then filtered through the UniProt database, restricting entries to 'Reviewed' proteins from 'Human' species, to obtain a non-redundant library of standardized target gene names (Coudert et al., 2023).

2.3. Compilation of AR-Associated Targets

Targets associated with allergic rhinitis (AR) were systematically retrieved from four databases: DrugBank (<https://go.drugbank.com/>), GeneCards (<https://www.genecards.org/>), OMIM (<https://www.omim.org/>), and TTD (<https://db.idrblab.net/ttd/>), using "allergic rhinitis" as a standardized search query. To maximize relevance, GeneCards entries were screened to retain only those with a relevance score exceeding the median. Following data integration and removal of

redundant entries, a standardized AR target library was constructed, encompassing 1363 unique targets.

2.4. Intersection Analysis of PAHs and Allergic Rhinitis Targets

The overlap between predicted PAH targets and AR-associated targets was identified and visualized using the jvenn tool on the Weishengxin online platform (Bardou et al., 2014). Specifically, the PAH target library and the AR target library were uploaded separately. The platform's standard intersection analysis was then performed, generating an interactive Venn diagram. This diagram provided key statistical metrics and directly listed the common targets shared between the two sets. These shared targets were carried forward for exploratory network and enrichment analyses.

2.5. Establishment of the Protein-Protein Interaction (PPI) Network and Determination of Hub Targets

Based on the common targets identified in the Venn analysis, a human PPI network was constructed in the STRING database (confidence threshold > 0.4, <https://cn.string-db.org/>). The PPI network was imported into Cytoscape (Shannon et al., 2003) for multiparametric topological analysis. Significant targets were screened using the CytoNCA plugin based on degree centrality, closeness centrality, betweenness centrality, and local average connectivity (LAC). High-density functional modules were identified using the MCODE plugin (parameters: degree cutoff=2, k-core=2). The top 10 hub candidate genes were predicted by the MCC algorithm of the CytoHubba plugin. Ultimately, core hub genes were defined as the triple intersection of: 1) CytoNCA-significant targets, 2) MCODE core module genes, and 3) CytoHubba top 10 genes.

2.6. GO and KEGG Pathway Enrichment Analysis

Potential intersecting target genes between PAHs and AR were analyzed using the DAVID database (Huang da et al., 2009), with species restricted to Homo sapiens. Comprehensive functional annotation was conducted through Gene Ontology (GO) analysis encompassing biological processes, molecular functions, and cellular components, alongside pathway enrichment analysis via the Kyoto Encyclopedia of Genes and Genomes (KEGG) resource. Results were visualized using the integrated Weishengxin modules as bar charts and pathway-oriented bubble maps to summarize predicted functional associations and pathway patterns.

2.7. Molecular Docking Analysis of PAHs against Hub Targets

The crystal structures of the selected hub target protein were retrieved from the RCSB Protein Data Bank (<https://www.rcsb.org/>). Ligand structures of PAHs were standardized using PubChem. Prior to molecular docking, the target protein structure was preprocessed to remove all water molecules and co-crystallized ligands using PyMOL. Subsequently, hydrogen atoms and Gasteiger partial charges were applied to both the receptor protein and the ligand molecules using AutoDockTools. A grid box covering the entire putative binding pocket of the receptor was defined for docking simulations. Molecular docking simulations were conducted under rigid conditions using AutoDock Vina (Trott & Olson, 2010). Predicted ligand poses were examined with the PLIP online tool (<http://plip-tool.biotec.tu-dresden.de/>), and visualized in PyMOL.

3. Results

3.1. Predicted Toxicological Profiles of the Selected PAHs

ADMETlab 2.0 predicted high plasma protein binding for BaP, BaA, and DBA (PPB > 97%). The predicted volume of distribution (1.057 - 1.281 L/kg) and clearance (5.990 - 8.051 mL/min/kg) were compatible with broad tissue distribution and relatively slow elimination. The platform also generated alerts related to carcinogenicity, genotoxicity, drug-induced liver injury, skin sensitization, and eye irritation, with predicted activity involving the aryl hydrocarbon receptor and antioxidant response element pathways. Respiratory toxicity alerts were additionally predicted for BaP and DBA. These computational outputs were used as exploratory context for target prioritization.

3.2. Predicted BaP-Associated Targets and Pathways in AR

To characterize the predicted molecular overlap between BaP and AR, BaP-associated targets obtained from ChEMBL, SEA, and TargetNet ($n = 798$) were integrated with AR-related targets from DrugBank, GeneCards, OMIM, and TTD ($n = 1363$). Intersection analysis identified 191 shared candidate targets (Figure 1A). A PPI network of these targets was constructed using STRING (Figure 1B) and analyzed in Cytoscape (Figure 1C). Three complementary algorithms were applied: CytoNCA for centrality-based screening (Figure 1D), CytoHubba for ranking the top 10 genes (Figure 1E), and MCODE for module detection (Figure 1F). The consensus intersection of these outputs (Figure 1G) prioritized five hub targets: CCL2, CCL5, CXCL8, CXCL12, and CXCR4. Their predicted interaction subnetwork is shown in Figure 1H.

Functional enrichment analysis of the 191 shared candidate targets identified 154 enriched KEGG pathways and 856 GO terms, including 593 biological-process, 74 cellular-component, and 189 molecular-function terms. The leading biological-process terms included chemotaxis, inflammatory response, chemokine-mediated signaling, xenobiotic metabolism, and cellular chemotaxis; leading cellular-component terms included the cell surface, plasma membrane, endoplasmic reticulum membrane, and extracellular space; and leading molecular-function terms included heme binding, oxidoreductase activity, monooxygenase activity, C-C chemokine-receptor activity, and iron-ion binding (Figure 2A). The top KEGG pathways included chemokine signaling, viral protein interaction with cytokines and cytokine receptors, lipid and atherosclerosis, chemical carcinogenesis, and drug metabolism-cytochrome P450 (Figure 2B). These enrichment results nominate chemokine-related processes as candidate associations.

Within the selected docking protocol, BaP yielded favorable predicted binding scores with CCL2, CCL5, CXCL8, CXCL12, and CXCR4 (Figure 3). The predicted poses included hydrophobic, π -stacking, and π -cation interactions, and the most negative docking score was observed for CXCR4 (-11.5 kcal/mol). These scores support prioritization of the five proteins for further study, but they do not confirm direct binding, functional modulation, or chemokine dysregulation in nasal tissue.

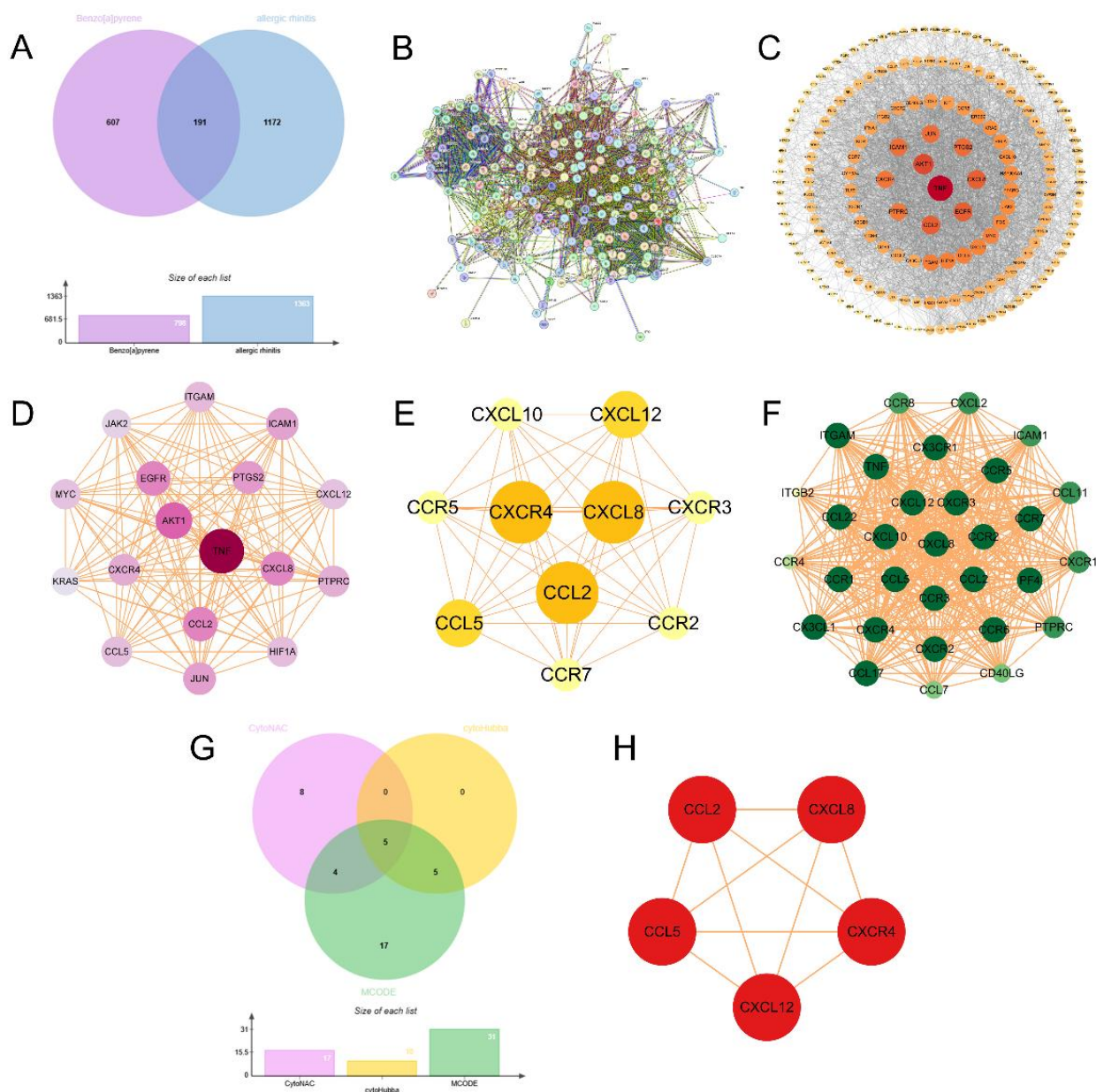


Figure 1. Computational Prioritization of BaP-Associated Targets in AR

Note: (A) Intersection analysis of BaP-associated targets (n = 798) and AR-related targets (n = 1363), yielding 191 shared candidate targets. (B-C) STRING PPI network and Cytoscape visualization. (D-F) CytoNCA centrality screening, CytoHubba ranking, and MCODE module analysis. (G-H) Consensus analysis prioritized CCL2, CCL5, CXCL8, CXCL12, and CXCR4 as chemokine-related hub targets.

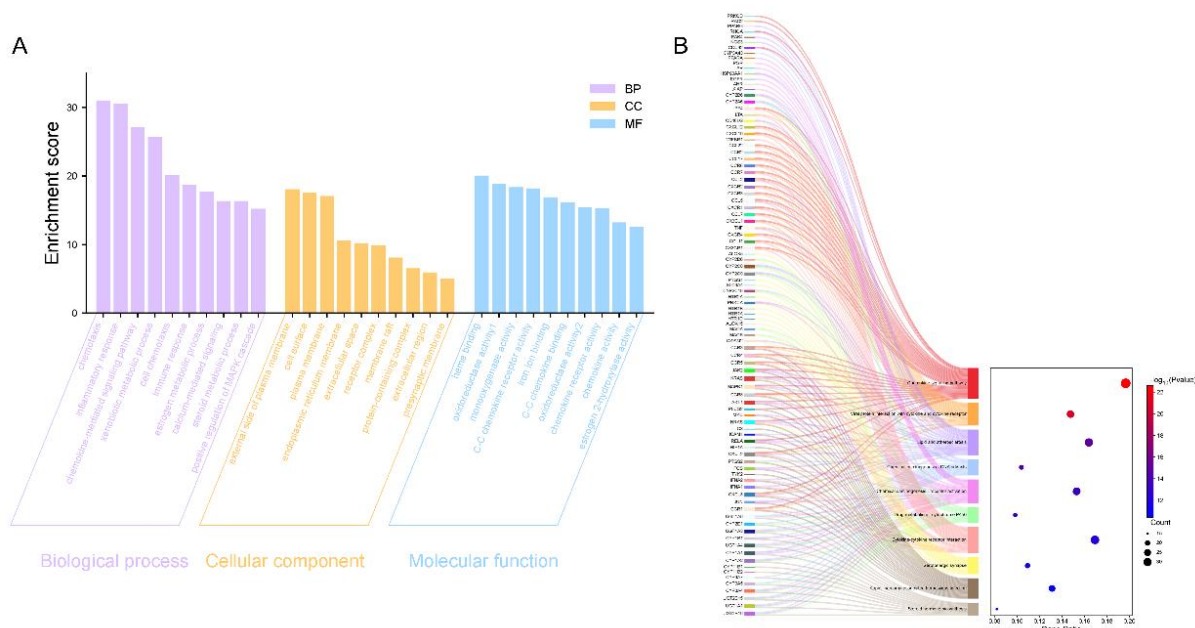


Figure 2. Functional Enrichment of Predicted BaP-AR Shared Targets

Note: (A) Top enriched GO terms for the 191 shared BaP-AR candidate targets across biological process, cellular component, and molecular function. (B) Top enriched KEGG pathways. The principal biological message is the computational enrichment of chemotaxis, inflammatory-response, and chemokine-signaling terms.

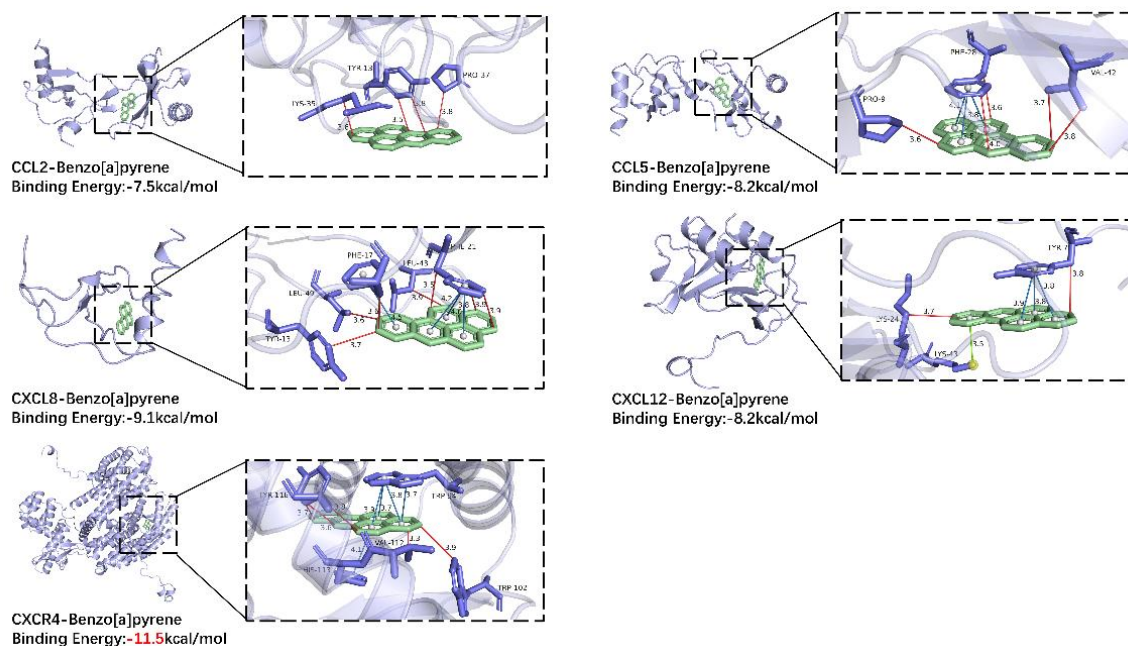


Figure 3. Predicted Docking Poses of BaP with Chemokine-Related Hub Proteins

Note: Representative computational docking poses of BaP with CCL2, CCL5, CXCL8, CXCL12, and CXCR4. Interaction annotations: hydrophobic (red), π -stacking (sky blue), π -cation (chartreuse).

3.3. Predicted BaA-Associated Targets and Pathways in AR

Using the same analytical approach, BaA-related targets (obtained from ChEMBL, SEA, and TargetNet; $n = 788$) were integrated with the previously described AR-related targets ($n = 1363$). A total of 138 potential BaA-AR association targets were identified through intersection analysis (Figure 4A). A protein-protein interaction (PPI) network was established based on these 138 targets

using the STRING database (Figure 4B), with subsequent visualization performed in Cytoscape (Figure 4C). The CytoNCA plugin was employed to filter nodes with betweenness centrality, closeness centrality, degree, and LAC values above the median (Figure 4D). We identified the top ten hub genes using the CytoHubba plugin (Figure 4E), and performed module clustering with MCODE (Figure 4F). The intersection of results derived from the three algorithms was illustrated using a Venn diagram (Figure 4G), yielding three core hub genes: ABCB1, CYP1A2, and CYP3A4. Their interaction network was subsequently visualized (Figure 4H).

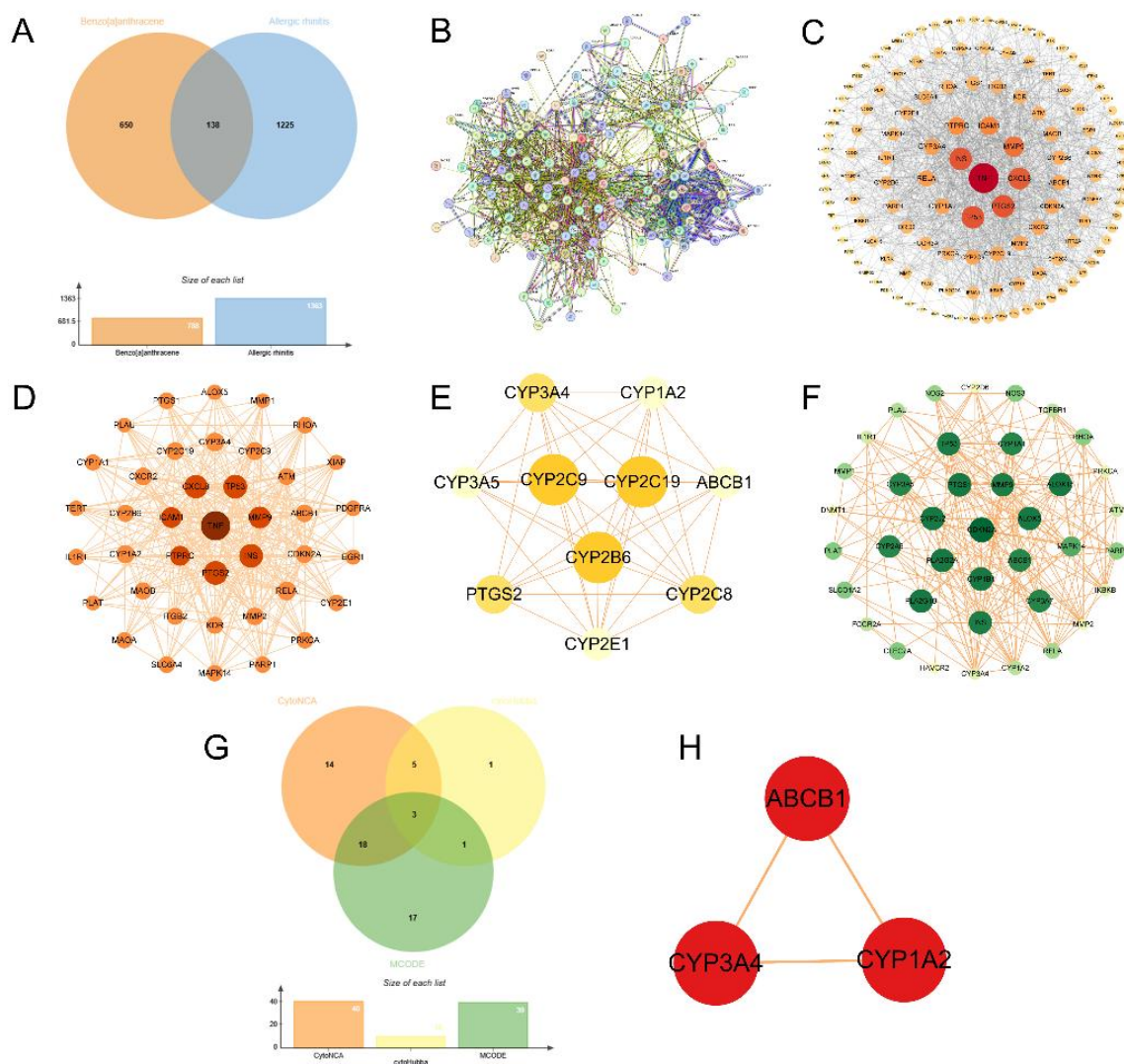


Figure 4. Computational Prioritization of BaA-Associated Targets in AR

Note: (A) Intersection of BaA-associated targets (n = 788) and AR-related targets (n = 1363), yielding 138 shared candidate targets. (B-F) PPI construction, network visualization, centrality screening, hub ranking, and module analysis. (G-H) Consensus analysis prioritized ABCB1, CYP1A2, and CYP3A4 as metabolic hub targets.

Enrichment analysis of the 138 shared candidate targets identified 124 enriched KEGG pathways and 649 GO terms, comprising 450 biological-process, 56 cellular-component, and 143 molecular-function terms. Leading biological-process terms included xenobiotic metabolism, inflammatory response, steroid metabolism, the cytochrome P450 epoxygenase pathway, and long-chain fatty acid biosynthesis; leading cellular-component terms included the cell surface, plasma membrane, endoplasmic reticulum membrane, and membrane raft; and leading molecular-function terms

included heme binding, iron-ion binding, oxidoreductase activity, monooxygenase activity, and estradiol 2-hydroxylase activity (Figure 5A). The top KEGG pathways included lipid and atherosclerosis, serotonergic synapse, arachidonic-acid metabolism, linoleic-acid metabolism, and chemical carcinogenesis (Figure 5B). These results prioritize metabolic and inflammatory pathways as computationally associated with the BaA-AR target overlap.

BaA yielded favorable predicted docking scores with ABCB1, CYP1A2, and CYP3A4, with values below -9 kcal/mol under the selected protocol (Figure 6). The predicted poses included hydrophobic, π -stacking, and π -cation contacts, and the most negative score was observed for CYP1A2 (-13.2 kcal/mol). These computational results identify candidate protein-ligand interactions for future testing.

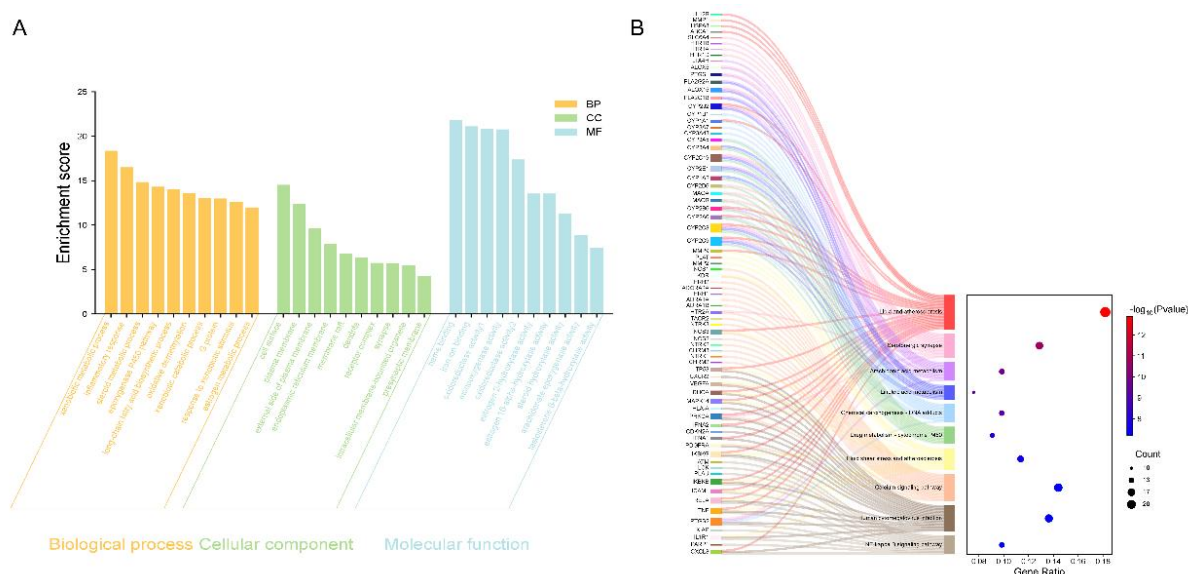


Figure 5. Functional Enrichment of Predicted BaA-AR Shared Targets

Note: (A) Top enriched GO terms for the 138 shared BaA-AR candidate targets. (B) Top enriched KEGG pathways. The principal biological message is enrichment of xenobiotic, lipid, arachidonic-acid, steroid, and cytochrome P450-related metabolic processes.

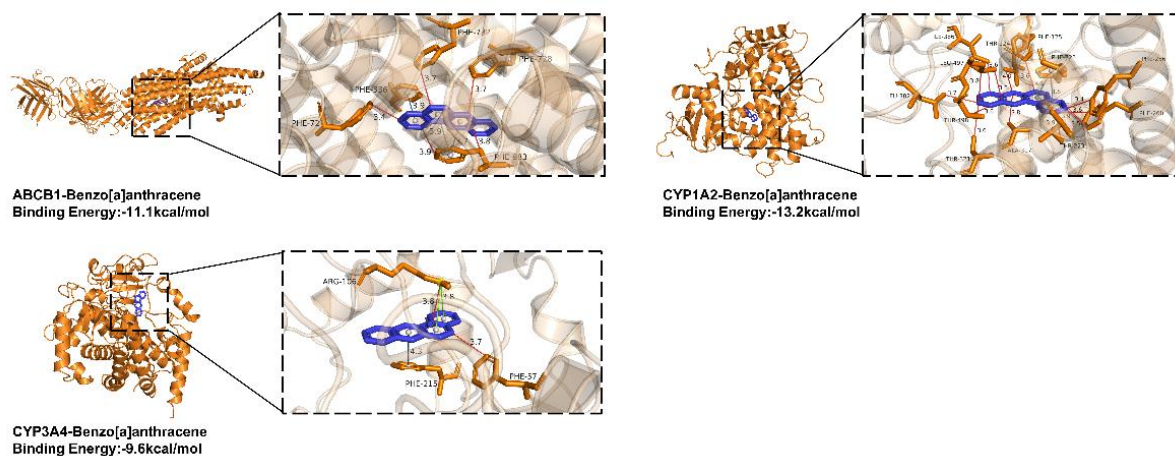


Figure 6. Predicted Docking Poses of BaA with Metabolic Hub Proteins

Note: Representative computational docking poses of BaA with ABCB1, CYP1A2, and CYP3A4. Interaction annotations: red for hydrophobic interactions; sky blue for π -stacking; chartreuse for π -cation interactions.

3.4. Predicted DBA-Associated Targets and Pathways in AR

DBA-associated targets (obtained from ChEMBL, SEA, and TargetNet; $n = 891$) were combined with AR-related targets ($n = 1363$). A total of 159 potential DBA–AR interaction targets were identified through intersection analysis (Figure 7A). We constructed a protein-protein interaction (PPI) network from the 159 candidate proteins with the STRING database (Figure 7B) and visualized it using Cytoscape (Figure 7C). Consistent with the methodology used in the benzo[a]anthracene investigation, a combination of topological and functional module analyses was performed, including node centrality screening via CytoNCA (Figure 7D), hub gene identification using CytoHubba (top 10 genes, Figure 7E), and module detection with MCODE (Figure 7F). The consensus core targets derived from the three algorithms were identified using a Venn diagram (Figure 7G), yielding six key hub genes: ABCB1, CYP1A2, CYP3A4, CYP2C9, CYP2C19, and UGT1A1. The interaction subnetwork among these genes was explicitly depicted (Figure 7H).

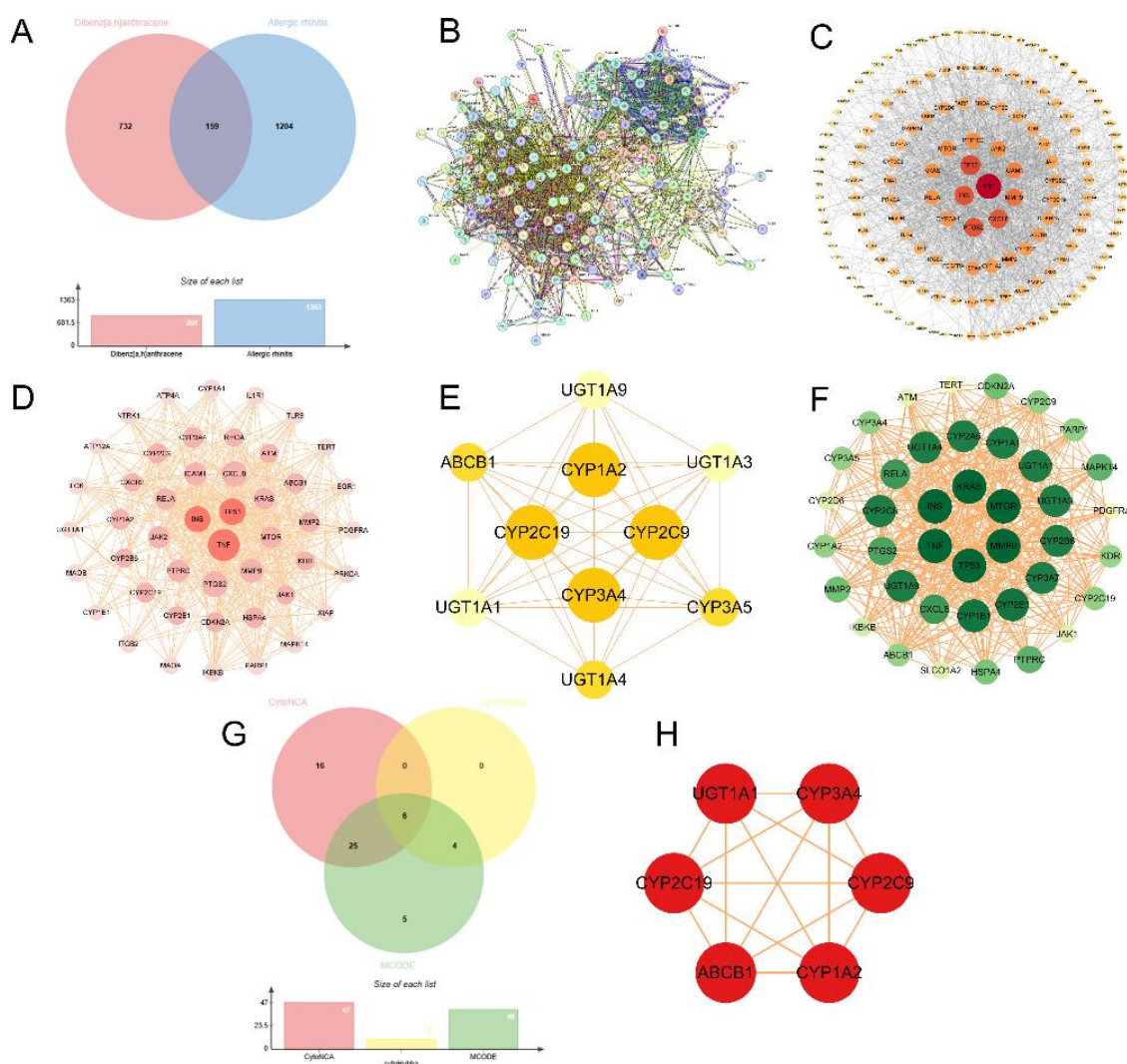


Figure 7. Computational Prioritization of DBA-Associated Targets in AR

Note: (A) Intersection of DBA-associated targets ($n = 891$) and AR-related targets ($n = 1363$), yielding 159 shared candidate targets. (B-F) PPI construction, network visualization, centrality screening, hub ranking, and module analysis. (G-H) Consensus analysis prioritized ABCB1, CYP1A2, CYP3A4, CYP2C9, CYP2C19, and UGT1A1 as metabolic hub targets.

Enrichment analysis of the 159 shared candidate targets identified 147 enriched KEGG pathways and 726 GO terms, comprising 482 biological-process, 70 cellular-component, and 174 molecular-function terms. Leading biological-process terms included xenobiotic metabolism, estrogen metabolism, steroid metabolism, inflammatory response, and the cytochrome P450 epoxygenase pathway; leading cellular-component terms included the cell surface, plasma membrane, endoplasmic reticulum membrane, and membrane raft; and leading molecular-function terms included heme binding, oxidoreductase activity, iron-ion binding, and monooxygenase activity (Figure 8A). The leading KEGG pathways included lipid and atherosclerosis, chemical carcinogenesis, metabolism of xenobiotics by cytochrome P450, and serotonergic synapse (Figure 8B). These results prioritize metabolic-enzyme networks as computationally associated with the DBA-AR target overlap.

DBA yielded favorable predicted docking scores with ABCB1, CYP1A2, CYP3A4, CYP2C9, CYP2C19, and UGT1A1, with values below -9 kcal/mol under the selected protocol (Figure 9). The predicted poses included hydrophobic, π -stacking, and π -cation contacts, and the most negative score was observed for CYP1A2 (-14.2 kcal/mol). These computational scores support target prioritization but do not establish direct binding, altered catalytic activity, or a causal role in AR.

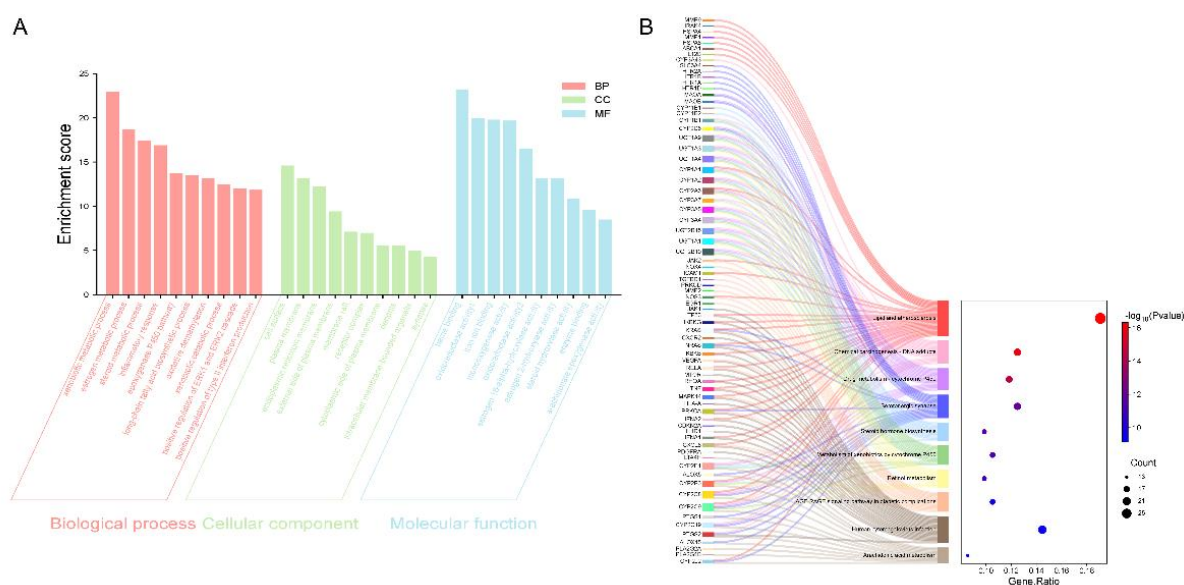


Figure 8. Functional Enrichment of Predicted DBA-AR Shared Targets

Note: (A) Top enriched GO terms for the 159 shared DBA-AR candidate targets. (B) Top enriched KEGG pathways. The principal biological message is enrichment of xenobiotic, steroid, estrogen, and cytochrome P450-related metabolic processes.

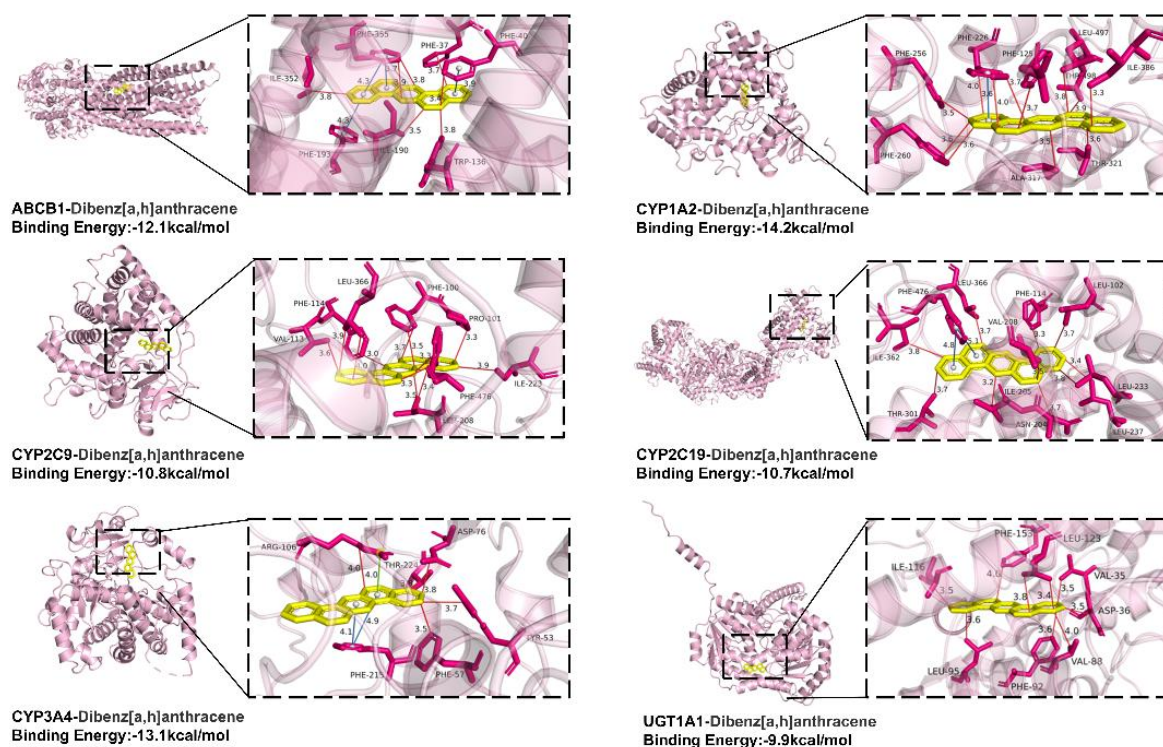


Figure 9. Predicted Docking Poses of DBA with Metabolic Hub Proteins

Note: Representative computational docking poses of DBA with ABCB1, CYP1A2, CYP3A4, CYP2C9, CYP2C19, and UGT1A1. Interaction annotations: hydrophobic (red), π -stacking (sky blue), π -cation (chartreuse).

4. Discussion

Allergic rhinitis (AR) is a prevalent inflammatory respiratory disease whose occurrence and severity have been associated with environmental pollution (Li et al., 2022). PAHs are persistent organic pollutants generated by incomplete combustion and are detected in particulate matter, vehicle exhaust, tobacco smoke, and other environmental media (Låg et al., 2020). PAH exposure has also been linked to altered regulatory T-cell function, providing biological plausibility for effects on allergic immune responses (Hew et al., 2015). Consistent with this, epidemiological evidence supports an association between PAH exposure and respiratory diseases in children, particularly asthma development and impaired respiratory function, with pediatric populations showing heightened susceptibility due to their smaller body size and immature immune systems (Wang et al., 2023). Nevertheless, epidemiological associations with mixed air pollution do not establish the contribution of an individual PAH to specific clinical AR phenotypes.

BaP, BaA, and DBA are environmentally relevant high-molecular-weight PAHs with distinct fused-ring structures. BaP, a classical PAH comprising five fused benzene rings, has been reported to possess carcinogenic and mutagenic properties. It was reported that BaP exposure was associated with nasal mucosal damage and respiratory irritation in an experimental model (Liu et al., 2024). Early investigations revealed that short-term intranasal BaP administration in guinea pig models of AR did not exacerbate rhinitis symptoms; however, prolonged treatment (22 weeks) was associated with aggravated nasal obstruction in an AR model (Mizutani et al., 2007). In vitro studies reported

that BaP enhanced basophil activation and stimulated IL-4 secretion in pollen-allergic subjects independently of allergen exposure (Lubitz et al., 2010). Additional *in vivo* studies have also associated BaP exposure with elevated mucus secretion and nasal tissue remodeling (Liu et al., 2024). These observations support investigating potential molecular links between BaP exposure and AR. However, they do not validate the specific target relationships predicted in the present analysis. The BaP-associated network prioritized CCL2, CCL5, CXCL8, CXCL12, and CXCR4. Chemokines and their receptors are relevant to clinically meaningful AR features because they coordinate inflammatory-cell trafficking, immune-cell recruitment, and epithelial-barrier responses (Li et al., 2022). In particular, CXCR4 has been implicated in mediating epithelial autophagy and compromising nasal epithelial barrier integrity via the CXCR4/miR-125b/FoxP3 pathway (Zheng et al., 2020). Thus, the predicted hub set offers a plausible molecular bridge to nasal inflammatory-cell infiltration and barrier dysfunction.

For BaA and DBA, existing case-control studies have reported an association between exposure to these compounds and the incidence of asthma (Al-Daghri et al., 2013; Jung et al., 2014); however, their potential association with AR remains unexplored. The analyses prioritized ABCB1 and several CYP enzymes and highlighted xenobiotic metabolism, arachidonic-acid metabolism, steroid metabolism, and cytochrome P450 epoxide metabolism pathways. In addition to xenobiotic and drug metabolism, CYP-associated networks participate in the processing of endogenous lipids and steroid hormones that can influence inflammatory signaling (Guengerich et al., 2016). The resulting hypothesis is therefore broader than drug disposition alone: BaA- or DBA-associated metabolic perturbation could theoretically alter endogenous inflammatory-mediator balance. Loratadine, for example, undergoes CYP3A4-mediated metabolism (Wang et al., 2025; Yumibe et al., 1996; Zhang et al., 2026), making altered drug handling a clinical possibility. Moreover, studies suggest that CYP1A2 may be involved in the metabolism of montelukast—a leukotriene receptor antagonist used in AR management—and that altered CYP1A2 activity could modulate its metabolic clearance (Filppula et al., 2011). CYP1A2 and CYP3A4, which were prioritized by the present analysis, have been reported to be involved in the metabolism of certain anti-allergy medications. Whether BaA or DBA binding could alter the catalytic activity of these enzymes and thereby affect drug disposition remains a testable hypothesis.

This study has several limitations. First, all findings are derived from computational predictions and depend on database completeness, target-prediction algorithms, enrichment backgrounds, network thresholds, available protein structures, and docking assumptions. Second, docking scores do not establish direct binding, target activation or inhibition, tissue exposure, or causal biological effects. Third, no clinical samples, nasal-mucosal measurements, exposure–response data, cell experiments, animal models, CYP activity assays, or pharmacokinetic analyses were included. Fourth, the analysis did not account for PAH mixtures, metabolites, exposure dose and route, temporal patterns, or interindividual variability. Accordingly, the proposed pathways should be viewed as hypothesis-generating and require independent experimental and clinical validation.

In summary, the integrated computational analysis generated a dual-pathway hypothesis: BaP-associated targets were preferentially linked to chemokine-related networks, whereas BaA- and DBA-associated targets were preferentially linked to metabolic-enzyme networks. This framework

may help prioritize biomarkers and experimental questions. Importantly, these findings represent computational hypotheses and candidate targets that warrant experimental validation.

5. Conclusion

Using computational toxicology, multi-algorithm network analysis, functional enrichment, and molecular docking, this study identified distinct predicted target patterns for three high-molecular-weight PAHs in relation to AR. BaP-associated targets were enriched in chemokine-related pathways and included CCL2, CCL5, CXCL8, CXCL12, and CXCR4, whereas targets associated with BaA and DBA were enriched in metabolic pathways and included CYP1A2, CYP3A4, and other metabolic proteins. These findings provide *in silico* hypotheses concerning inflammatory-cell recruitment, epithelial-barrier regulation, endogenous mediator metabolism, and possible drug-disposition effects.

Author Contributions:

Yue He: Writing-original draft, Formal analysis, Visualization. Yibo He: Writing-original draft, Formal analysis, Visualization. Junfeng Xi: Formal analysis, Data curation. An Chang: Writing-review & editing, Data curation. Zeyu Guo: Writing-review & editing, Formal analysis. Xianzhi Liu: Formal analysis, Data curation. Jiayu Li: Formal analysis, Data curation. Jiaxuan Li: Formal analysis, Data curation. Zhao Wang: Writing-original draft, Methodology, Supervision, Funding acquisition. Dong Chen: Writing-original draft, Methodology, Supervision, Funding acquisition. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement:

Not applicable.

Data Availability Statement:

The datasets supporting the findings of this study are fully available within the paper and its supplementary information files. Requests for additional details can be directed to the corresponding author.

Conflict of Interest:

The authors declare no conflict of interest.

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