ORIGINAL RESEARCH ARTICLE

Network toxicology analysis of hair dye components and their association with breast and bladder cancers

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Abstract

This study employed a network toxicology approach to investigate the potential toxic effects and molecular mechanisms of hair dye components in relation to breast and bladder cancer. By integrating data from multiple databases and performing Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses, key targets and pathways were identified. Network and molecular docking analyses revealed that major hair dye chemicals may induce carcinogenesis through xenobiotic metabolism and interact with critical proteins involved in cancer pathways. These findings provide theoretical support for the health risks associated with hair dye exposure and offer insights into potential preventive strategies. *(Afr J Reprod Health 2025; 29 [12]: 204-216)*

Keywords: Network Toxicology, Molecular Docking, Hair Dye Safety, Carcinogenic Pathways, Toxicity Assessment

Résumé

Cette étude a employé une approche de toxicologie des réseaux pour investiguer les effets toxiques potentiels et les mécanismes moléculaires des composants des teintures capillaires en relation avec le cancer du sein et le cancer de la vessie. En intégrant des données provenant de multiples bases de données et en réalisant des analyses d'enrichissement Gene Ontology (GO) et Kyoto Encyclopedia of Genes and Genomes (KEGG), les cibles et voies moléculaires clés ont été identifiées. Les analyses de réseau et de docking moléculaire ont révélé que les principaux produits chimiques des teintures capillaires pourraient induire la carcinogenèse via le métabolisme des xénobiotiques et interagir avec des protéines critiques impliquées dans les voies cancéreuses. Ces résultats fournissent un support théorique concernant les risques sanitaires associés à l'exposition aux teintures capillaires et offrent des perspectives pour des stratégies préventives potentielles. *(Afr J Reprod Health 2025; 29 [12]: 204-216).*

Mots-clés: Toxicologie des Réseaux, Docking Moléculaire, Sécurité des Teintures Capillaires, Voies Carcinogéniques, Évaluation de la Toxicité

Introduction

The utilization of hair dye, a widely embraced cosmetic for achieving transformative hair alterations, relies on essential components such as p-Phenylenediamine (PPD), Resorcinol, and 3-Aminophenol. PPD, recognized for its adaptability in generating a spectrum of colors, binds to the hair shaft via oxidative reactions, giving rise to concerns about potential health implications, including skin reactions and suspected carcinogenicity.[1] Resorcinol, pivotal for color development, is effective but has raised red flags due to potential endocrine-disrupting and carcinogenic effects. Meanwhile, the examination of 3-Aminophenol, a vital element in the dyeing process, is underway to assess potential health effects, which encompass concerns such as skin irritation.

Recent research indicates potential connections between certain hair dye formulations and an increased risk of cancer, particularly bladder and breast cancers. Associations have been identified between exposure to P-Phenylenediamine (PPD) and Resorcinol and an elevated risk of bladder cancer, raising concerns about potential carcinogenic effects.[3] Investigations into breast cancer risk suggest a possible correlation between prolonged or frequent use of hair dye and an

increased risk of breast cancer.[4] The intricate interactions between hair dye chemicals and breast tissue underscore the need for further exploration to establish conclusive evidence.[5,6]

The extensive use of hair dye warrants a closer examination of its chemical constituents. It is imperative to comprehend the potential risks associated with P-Phenylenediamine (PPD), Resorcinol, and 3-Aminophenol, especially in light of preliminary findings hinting at a possible connection to cancers, such as bladder and breast cancers. Additional research is essential to elucidate the exact mechanisms behind these associations and to inform safe practices in the use of hair dye[7]. Emerging disciplines like network toxicology and molecular docking offer distinctive features and advantages in comprehending the potential carcinogenicity of hair dye components. Network toxicology, a fusion of network pharmacology and systems biology, establishes interconnected networks among chemicals, toxicity, and targets. [8,9] This method transforms intricate mechanisms into visually intuitive models, streamlining systematic analysis and prediction of the molecular mechanisms underlying the carcinogenicity of substances. Molecular docking, originally designed for drug development, is now applied to unveil the molecular foundation of toxic substances through compound-target interactions and affinity.[10] The stability of ligand-receptor binding conformations and interaction potential exhibits an inverse correlation with binding energy, indicating more favorable interactions with lower binding energy.[11] By leveraging the capabilities of network toxicology and molecular docking, we embarked on a quest to delve into the potential carcinogenicity of hair dye components, including PPD, Resorcinol, and 3-Aminophenol. This pioneering approach holds the potential for a thorough comprehension of the molecular complexities that underlie the identified associations, paving the way for informed decisions regarding hair dye safety and potential enhancements in formulations to ensure a safer cosmetic experience.

Particularly, P-Phenylenediamine (PPD), a prevalent oxidizing agent in hair dye, plays a pivotal role in color development via oxidation reactions with atmospheric oxygen or hydrogen peroxide. This results in the formation of colored oxidation products that adhere to the hair shaft, achieving the desired hue. However, PPD is associated with significant skin irritation potential, leading to allergic reactions such as redness and itching. Furthermore, research indicates a potential carcinogenic risk, particularly in instances of prolonged or high-concentration exposures, involving direct interactions with DNA and potentially elevating the risk of skin cancer.[12]

Resorcinol, a vital component in color development, engages in chemical reactions with oxidizing agents in hair dye, yielding colored compounds that effectively adhere to hair strands[1]. Despite its efficacy, Resorcinol is linked to endocrine-disrupting effects, prompting concerns about potential risks to the endocrine system. Prolonged or high-concentration exposure is associated with potential carcinogenicity, and the resulting toxicity primarily manifests through disruptions in hormonal balance. This disturbance has the potential to induce cellular damage and mutations.[13] 3-Aminophenol, another essential coloring agent, plays a role in color formation through oxidation reactions in hair dye. It contributes to stable color development by securely binding to hair strands. However, 3-Aminophenol has the potential to cause skin allergies, leading to symptoms such as redness and stinging. Prolonged or high-concentration exposure is also linked to potential cytotoxicity and carcinogenic risks.[14] Toxicity mechanisms encompass direct damage to the skin and cells, potentially eliciting adverse reactions through interactions with intracellular molecules.

These chemical constituents play crucial roles in the color development process of hair dye, but their associated toxicological concerns necessitate careful consideration. Ongoing research is essential to explore their precise mechanisms and potential carcinogenicity, ensuring a comprehensive understanding of their impact on human health.[15]

The upward trajectory in global hair dye consumption underscores the need for new strategies to assess its safety. The escalating usage emphasizes the urgency of investigating the potential toxicological mechanisms associated with the three aforementioned components. By utilizing network toxicology and molecular docking, we delve into the carcinogenic toxicity and potential mechanisms of hair dye formulations[16,17]. This approach not only provides an efficient and swift strategy for evaluating the toxicity of hair dye but also lays the groundwork for diagnosing diseases related to

exposure to such toxic substances. The amalgamation of network toxicology and molecular docking yields a comprehensive understanding of how these hair dye components may interact at the molecular level, elucidating potential carcinogenic pathways. This innovative methodology is pivotal in developing swift and efficient strategies for toxicity assessment, facilitating the timely identification of harmful effects.

Moreover, it serves as a research foundation for diagnosing diseases associated with exposure to these toxic substances, providing insights into the correlation between hair dye use and adverse health outcomes.By deciphering intricate molecular interactions and potential risks linked with hair dye components, our research aims to provide the public with profound scientific insights into product safety. This information is vital for consumers, enabling informed cosmetic decisions. Additionally, our findings guide industries towards innovation, shaping safer, reliable hair dye formulations. This research not only addresses current safety concerns but also lays the groundwork for future advanced solutions.

Methods

This study aims to investigate the relationship between the primary chemical components in hair dyes and the occurrence of bladder and breast cancer using the methods of computational toxicology. We adopt the following technical roadmap, detailed in Figure 1.

Commonly used chemical components in hair dyes

The most commonly used chemical components in hair dyes were obtained from databases such as PubMed, Google Scholar, and others database.

The toxicity of hair dye

We conduct literature searches using databases including PubMed, Google Scholar, China National Knowledge Infrastructure (CNKI), and others to retrieve diseases associated with hair dye. Identify tumor diseases relevant to include in this study.

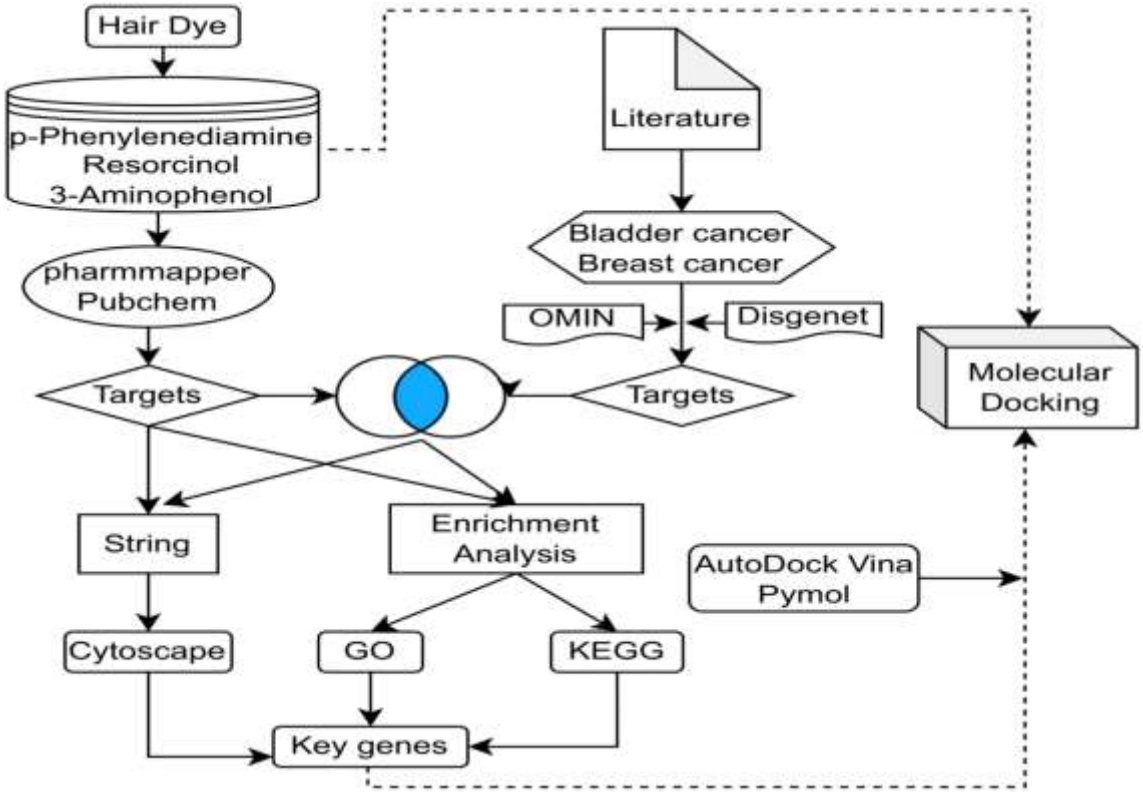


Figure 1: The research workflow diagram

Obtaining chemical component targets

The SMILES structures of the main components was retrieved from the PubChem database.[18] Targets of the three components were obtained in ChEMBL,[19] with organism set to Homo sapiens. The SMILES strings was transmitted to STITCH for supplementary information.[20] The SMILES were inputed into https://www.lilab-ecust.cn/pharmmapper/ for target prediction. The results from ChEMBL, STITCH, and PharmMapper[21] was integrated and the Uniprot database was utilized for name standardization.[22] We merged and deduplicated the results from the three sources separately. Furthermore, data from the Comparative Toxicogenomics Database (CTD) were incorporated to enhance the comprehensiveness and reliability of the target data.[23] By integrating information from these four databases, a comprehensive identification and validation of potential targets for chemical components can be achieved, providing a solid foundation for subsequent drug development and mechanistic studies.

Acquisition of disease-related targets

The disease-related target genes for bladder cancer and breast cancer were downloaded from Genecards[24] and OMIM[25] databases. Then, the intersection of targets between bladder cancer and breast cancer with the main chemical component targets of hair dye was obtained, serving as potential targets for the toxicity of hair dye.

Enrichment analysis of target proteins

ClusterProfiler, an R tool crafted for bioinformatics analysis, is mainly utilized for functional enrichment examination and visualization of high-throughput biological experiment data. This resource assists researchers in grasping the functional traits of a set of genes or proteins, encompassing their roles in biological processes, cellular components, and molecular functions. In this study, the ClusterProfiler package was applied to perform GO and KEGG enrichment analysis on the aforementioned intersection genes.

Construction of protein interaction network and screening of core targets

The relationship network was built using STRING for the intersection genes between breast cancer, bladder cancer, and the main compounds of hair dye.[26] Cytoscape was used for visual analysis to establish a protein-protein interaction network.[27] ClueGO provides an extensive perspective on biological pathways and functions linked with gene sets, fostering an enhanced comprehension of biological processes.[28] Simultaneously, the analysis was enriched by CluePedia through the integration of data from various databases, allowing for a more comprehensive investigation of gene functions. Functional enrichment analysis was conducted using the robust framework provided by ClueGO and CluePedia. Modules were first filtered using the MCODE plugin, followed by pathway analysis and visualization through ClueGO and CluePedia. Concurrently, key hub genes were identified using the CytoHubba plugin.[29] Analysis of the main clusters filtered by MCODE was also performed using ClueGO and Cluepedia.[30]

Molecular docking

Molecular docking, a potent tool reshaping drug discovery and therapy insights, was employed to explore the plausible binding of three chemical constituents in hair dye with core genes. AutoDock Vina [31,32] facilitated the docking process, and PyMOL.[33] was utilized for visual representation. The pdb files of key genes were retrieved from PDB,[34] followed by AutoDock Vina docking, culminating in visualization through PyMOL. The ligand's SMILES file from PubChem underwent conversion to pdb format using the online tool NovoPro (https://www.novopro.cn/tools/smiles2pdb).

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on request.

Results

The most common chemical components in hair dye

The three most common components in nearly all hair dyes—3-Aminophenol, p-Phenylenediamine, and resorcinol—were obtained from the databases mentioned in the methods. Their molecular formulas and SMILES files are provided in Table 1.

Table 1: Properties of three common hair dye components

Name	Compound CID	Isomeric SMILES	MW(g/mol)
3-Aminophenol	11568	C1=CC(=CC(=C1)O)N	109.13
p-Phenylenediamine	7814	C1=CC(=CC=C1N)N	108.14
Resorcinol	5054	C1=CC(=CC(=C1)O)O	110.11

**The molecular formulas, SMILES representations, and molecular weights (MW) of 3-Aminophenol, p-Phenylenediamine, and Resorcinol were obtained from the PubChem database (National Center for Biotechnology Information, https://pubchem.ncbi.nlm.nih.gov/).*

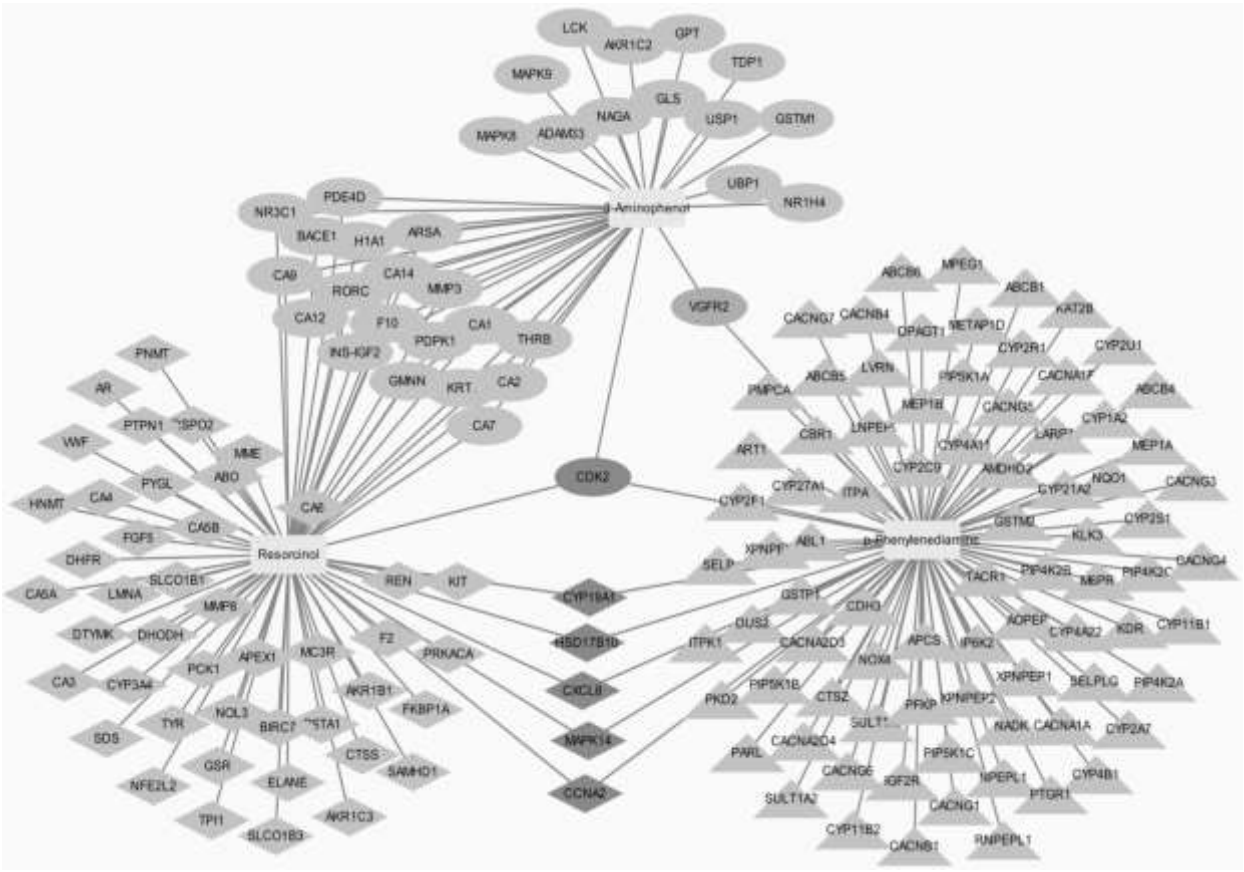


Figure 2: The relationship between the three chemical components and their targets. Yellow rectangles represent the chemical components, blue indicates targets unique to each component, magenta diamonds represent targets shared by p-Phenylenediamine and resorcinol, orange represents targets shared by 3-Aminophenol and resorcinol. CDK2 is a common target shared by all three components.

The carcinogenic toxicity associated with three chemical components.

A literature review indicates an association between hair dye and various diseases. To rigorously investigate the relationship between hair dye and carcinogenic toxicity, we have chosen widely recognized bladder cancer and breast cancer as focal points. This selection aimed to comprehensively understand the potential impacts on health.

Target genes of the three chemical components

Through database retrieval, targets for the three chemical components were obtained, with 88, 69, and 34 targets respectively. After merging and removing duplicates, a total of 164 targets were identified. The component-target relationship diagram is depicted in Figure 2. 3-Aminophenol and resorcinol share numerous common targets, while relatively fewer common targets were observed with

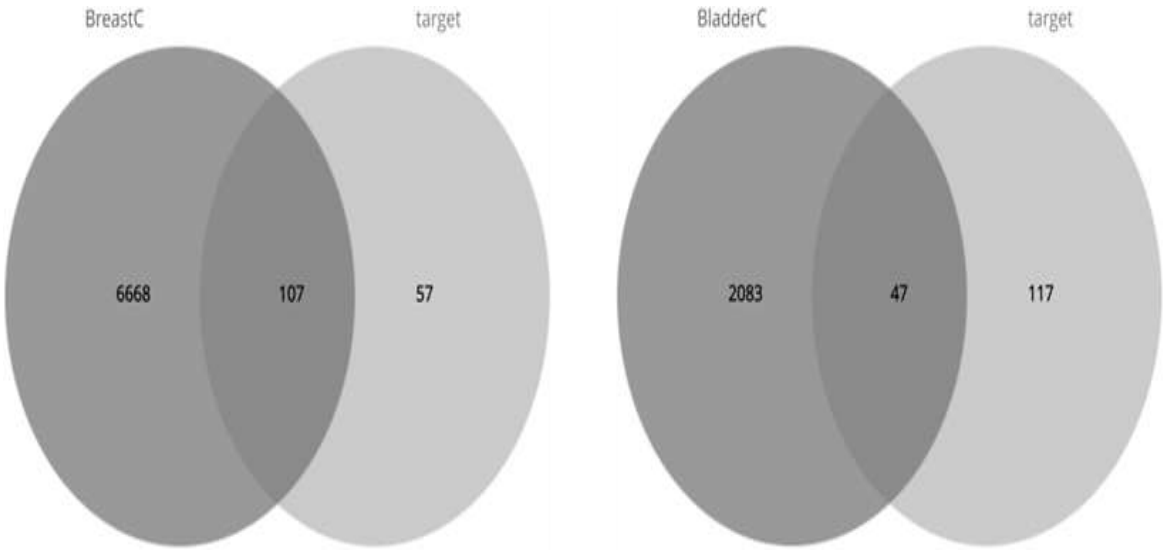


Figure 3: Intersection of targets between the three chemical components and disease-related genes

PPD. CDK2 is the only common target among the three.

Bladder cancer and breast cancer-related genes

The intersection of targets between the three chemical components and breast cancer was 107, while the intersection with bladder cancer was 47. There are 44 common genes between bladder cancer and breast cancer. These intersected genes served as the target genes for the next step of analysis. Figure 3

Enrichment analysis of target genes

The enrichment analysis results for breast cancer and bladder cancer-related target genes are shown in Figure 4. In order to comprehensively explore gene functions, ClueGO and CluePedia were employed. The enrichment results for breast cancer and bladder cancer reveal that both are primarily concentrated in chemical carcinogenesis, cellular response to xenobiotic stimulus, and metabolism of xenobiotics by the cytochrome P450 process (Figure 5A, Figure 5B). Among these, the processes related to chemical carcinogenesis include DNA adducts, reactive oxygen species, and receptor activation. Additionally, bladder cancer shows enrichment in fluid shear stress and atherosclerosis (Figure 5B).

Construction of protein interaction network and screening of core targets

After constructing the protein-protein interaction network (PPI) using STRING and visualizing it with Cytoscape, the resulting network exhibited a complex topology with nodes representing proteins and edges indicating interactions. Due to the striking similarity between the PPI networks associated with breast cancer and bladder cancer, we opted to merge them into a unified network for analysis. Utilizing the CytoHubba plugin for pivotal gene selection involved assessing genes with elevated degrees in the protein-protein interaction network.

A gene's degree signifies the quantity of connections it forms with other genes in the network. Genes with higher degrees are deemed more central or influential. This strategy enables the prioritization of key genes based on their connectivity, showcasing potential importance within the studied biological system. The resultant list of key genes with heightened degrees offers valuable insights into the network's structure, emphasizing pivotal elements in our analysis context as shown in Figure6A. The most central genes in the network, represented by the nodes with the highest degree, include genes CYP3A4, CYP1A2, GSTP1, CXCL8, CYP2C9, GPT, NFE2L2, ABCB1, REN and NQO1 (Figure

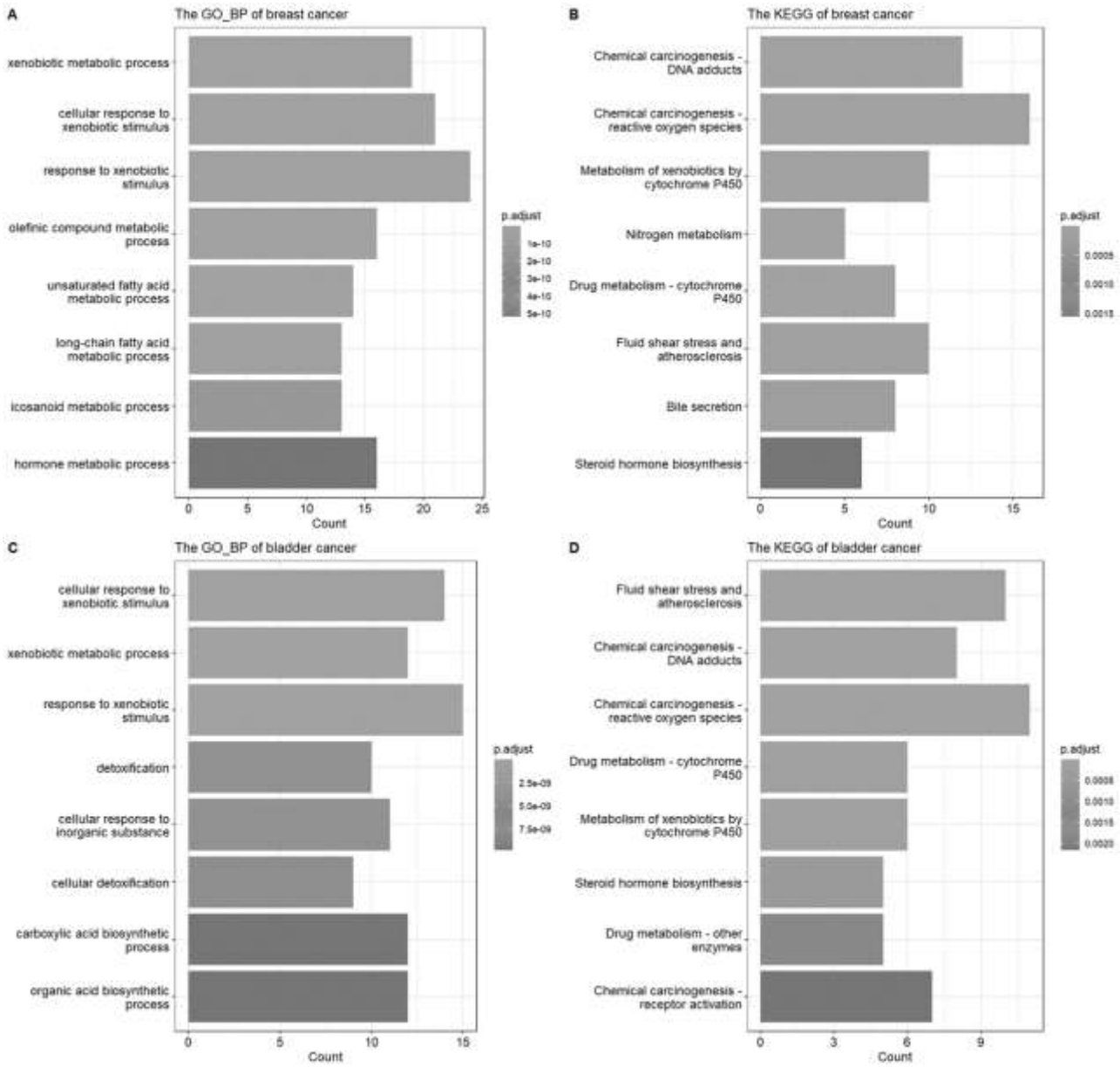


Figure 4: The enrichment analysis results for breast cancer and bladder cancer-related target genes A The GO enrichment result for breast cancer related targets B The KEGG enrichment result for breast cancer related targets C The GO enrichment result for bladder cancer related targets D The KEGG enrichment result for bladder cancer related targets

6B). The enrichment results for the core genes indicate their primary involvement in processes such as chemical carcinogenesis, gland development, and biological transformation, as illustrated in Figure 2. It can be observed that many core genes belong to a family, such as the CYP family and GST family, collectively participating in a specific metabolic pathway.

The MCODE plugin identified four distinct clusters within the protein-protein interaction network. These clusters are associated with crucial biological processes, including chemical carcinogenesis, bile secretion, inositol phosphate metabolism, and inflammatory mediator regulation of TRP channels. Each cluster represents a functionally enriched module, suggesting the network's organization around specific molecular pathways related to cancer development, metabolic processes, and inflammatory responses (Figure 7A-D). This comprehensive analysis provides insights

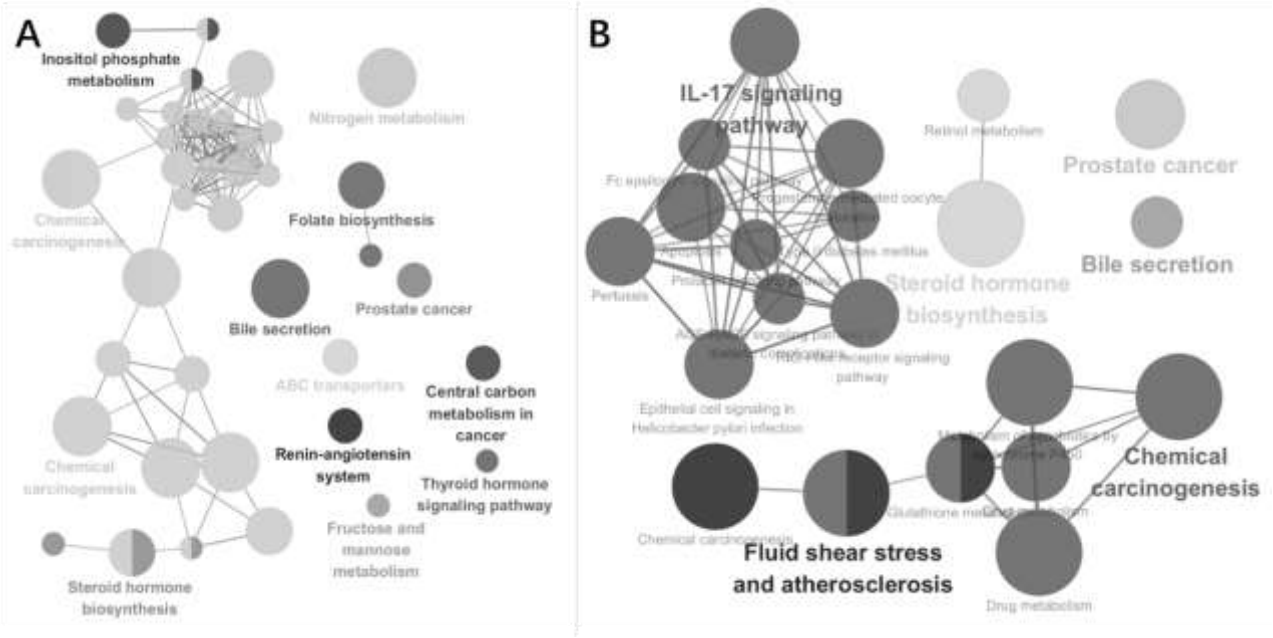
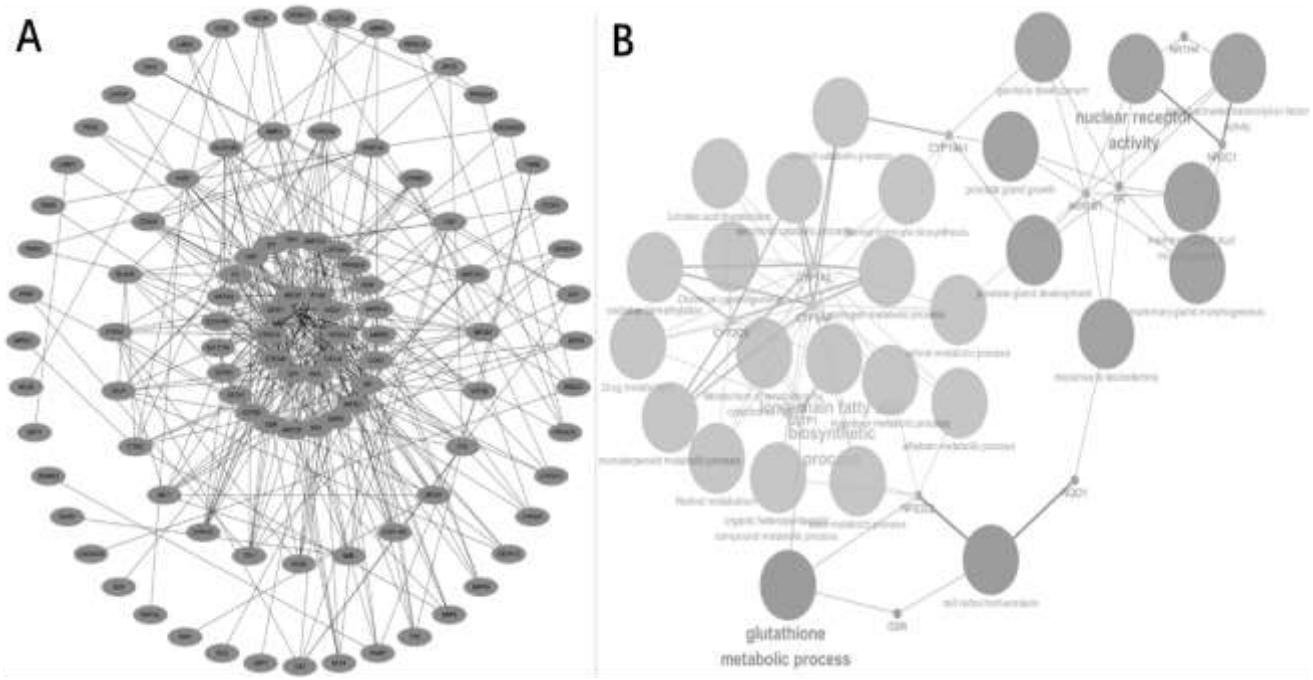
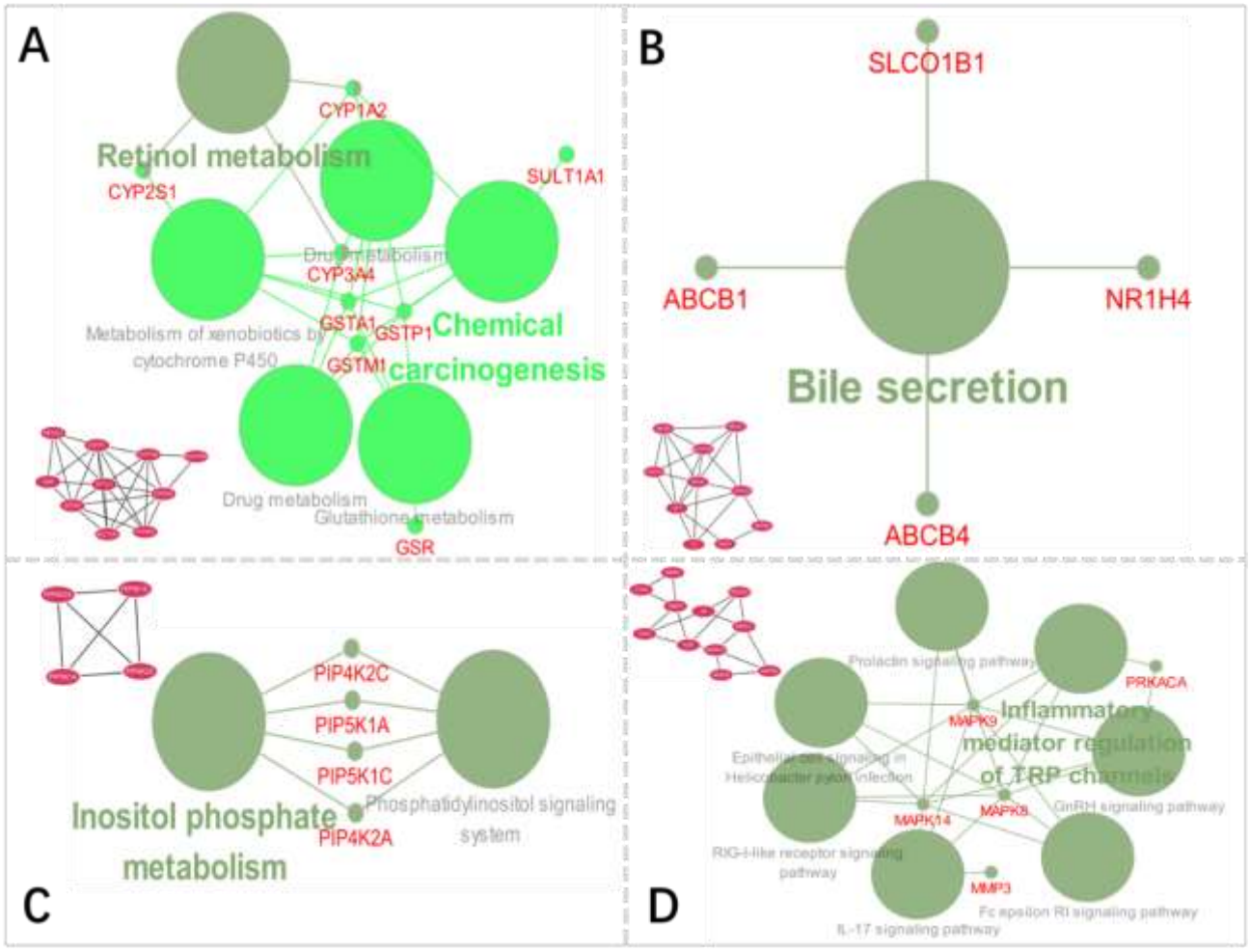


Figure 5: Visualization results of CluePedia for breast cancer (A) and bladder cancer (B). The figure illustrates the significant associations and interactions found in the respective cancer types, highlighting key pathways involved in their pathogenesis.



A The visualization of the graph follows a radial layout, where nodes are arranged from the center outward based on decreasing degree. Additionally, the color intensity increases with higher degrees, with red indicating nodes with the highest degrees in the protein-protein interaction network.
B The CluePedia results for the top 20 core genes Figure 6 Core genes and their ClueGO results.

Figure 6: The core genes and their ClueGO results



The red oval-shaped gene network represents four clusters.

Figure 7: Module discovery in the PPI network using the MCODE plugin., Along with CluePedia results for main modules.

into the network's modular structure and its potential implications in the context of the chemical toxicity of hair dye formulations. The detailed examination also reveals that each cluster is predominantly associated with a specific gene family.

The results for molecular docking

The outcomes of molecular docking uncover the interactions between the three chemical constituents present in hair dye and essential genes, offering valuable insights into their binding affinities. As depicted in Figure 8, we observe the configurations with the lowest binding energy for 3-Aminophenol, p-Phenylenediamine, and Resorcinol in association with critical genes like CYP3A4, CYP1A2, and GSTP1. These interactions provide indications of potential binding modes and the strength of affinity between the hair dye components and these pivotal genes. The varied colors denote distinct chemical constituents, emphasizing their specific interactions with particular genes. The molecular docking results reveal significant similarities in the binding sites of the three chemical components with key genes, with instances where two or all three components bind to a single site on the protein. Additionally, at times, a protein may have binding sites for all three chemical components simultaneously.

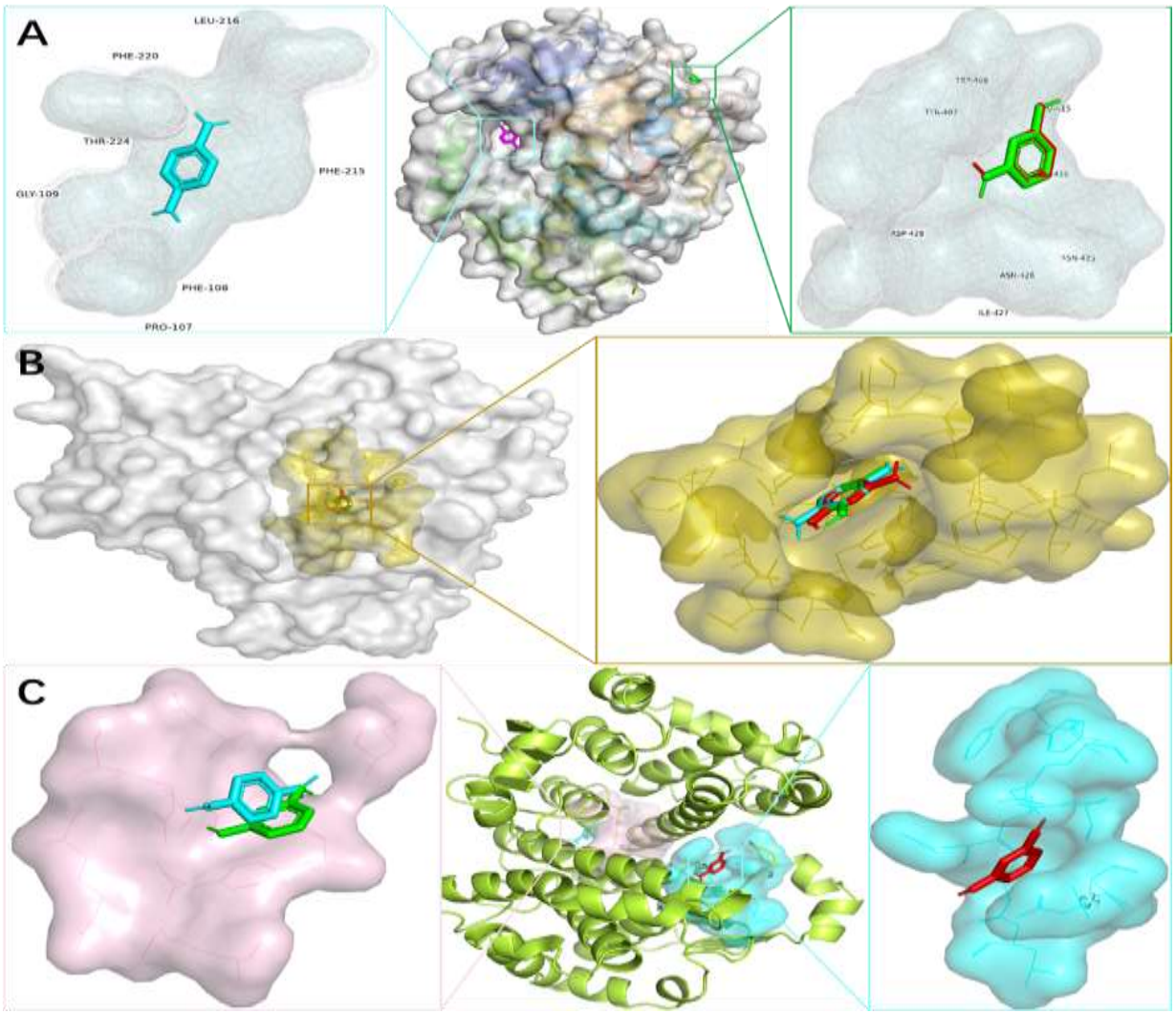


Figure 8: Molecular docking results of the three chemical components in hair dye with several key genes in their lowest binding energy form. Magenta represents 3-Aminophenol, cyan represents p-Phenylenediamine, and green represents Resorcinol. (A) Interaction of the three components with CYP3A4, (B) Interaction of the three components with CYP1A2, (C) Interaction of the three components with GSTP1.

Discussion

The widespread use of hair dye has raised concerns about its potential toxicity, yet the intricate mechanisms driving this toxicity remain elusive. The exploration of enriched processes offers valuable insights into the potential health consequences associated with the chemical constituents present in hair dyes. Special attention is given to pathways related to chemical carcinogenesis and xenobiotic metabolism. The revelation of enriched pathways linked to chemical carcinogenesis prompts inquiries into a plausible association between the components of hair dye formulations and processes implicated in cancer development. Within this framework, the engagement of gene families, particularly Cytochrome P450 (CYP) and Glutathione S-transferase (GST), assumes a pivotal role. Noteworthy genes, such as CYP1A2, CYP3A4, and GSTP1, emerge as significant contributors to xenobiotic metabolism, providing insights into their potential roles in the breakdown and detoxification of chemicals present in hair dyes.

The essential roles of the CYP and GST gene families in cellular metabolism and detoxification are underscored, particularly with the pivotal involvement of CYP enzymes, notably

cytochrome P450, in drug and hormone metabolism.[35] GST enzymes, governed by the GST family, contribute significantly to cellular detoxification by facilitating the conjugation of glutathione with toxic substances.[36,37] Both gene families are integral in defense against oxidative stress, detoxification of external chemicals, and the maintenance of cellular homeostasis. Their collaborative actions emphasize their indispensability in fundamental biological processes. Furthermore, the synergistic interactions among these core genes imply potential coordination, especially in specific metabolic pathways. For instance, the CYP and GST families, commonly implicated in cellular metabolism and detoxification, may cooperate in drug metabolism, detoxification of harmful substances, and related biochemical transformations. This cooperative interplay is likely crucial for normal physiological functions and defense mechanisms against toxicity in organisms. This nuanced perspective enhances our comprehension of the potential repercussions of hair dye components on the intricate regulatory processes governed by these gene families.

The molecular docking results indicate that the three chemical components can simultaneously bind to one or multiple binding sites on key genes, suggesting that these components may exert synergistic effects on different biological pathways and molecular mechanisms. If the three chemical components easily bind to the active sites of enzymes involved in intracellular detoxification reactions, possibly the active centers, it may lead to reduced enzymatic activity. This could result in compromised detoxification processes, potentially leading to an accumulation of toxic substances within the body. The diminished enzymatic activity may disrupt normal cellular functions, affecting various metabolic pathways and biological processes.[38,39]

That is to say, the three main chemical components in hair dye may potentially exert their effects by binding to enzymes associated with detoxification, including members of the Glutathione S-transferase (GST) family and key genes such as CYP1A2 and CYP3A4 from the Cytochrome P450 family. This binding could result in the inhibition or reduction of the activity of these enzymes. Such inhibition may lead to a decrease in the cell's detoxification capability, making cells more susceptible to damage from external harmful substances.[40] Additionally, it may impact normal metabolic pathways and the cellular redox balance, increasing the likelihood of oxidative stress. All these factors may be associated with the occurrence of tumors. If the three chemical components bind to the active centers of key detoxification enzymes, it may lead to a weakening of detoxification functions. This diminished detoxification capacity could result in the accumulation of harmful substances in the bladder. Such accumulation may cause damage to cells and increase the risk of developing bladder cancer.

Study strengths and limitations

This study's strength lies in its integrative approach, combining network toxicology and molecular docking to systematically identify key mechanisms by which hair dye chemicals may contribute to carcinogenesis. The focus on xenobiotic metabolism pathways and specific interactions with detoxification enzymes provides novel insights into potential toxicity mechanisms. However, as a computational study, these predictions require experimental validation in biological systems. The research also does not address potential synergistic effects of chemical mixtures in commercial products or individual genetic variations that may influence susceptibility.

These findings suggest regulatory agencies should consider more stringent safety assessments of hair dye components, particularly regarding long-term carcinogenic risks. For public health practice, the results highlight the need for greater consumer awareness and industry investment in developing safer alternatives. Healthcare providers should be informed of these potential risks when counseling frequent hair dye users.

Future research should prioritize experimental validation and investigate how genetic differences in metabolic enzymes might affect individual risk profiles.

Conclusion

This study unveils the molecular interactions and toxicological implications of the primary chemical components in hair dye. It contributes to a comprehensive understanding of the impact of hair dye components on human health. The research lays the theoretical foundation for comprehending the

molecular mechanisms underlying hair dye-induced bladder and breast cancer. Simultaneously, it establishes a crucial groundwork for the prevention and treatment of diseases associated with exposure to the key chemical components in hair dye, providing additional options for concerned individuals. Furthermore, the methods employed in this study expedite the elucidation of the toxicity of environmental chemicals with undefined characteristics, advancing our understanding of potential health risks in a broader context.

Disclosure statement

The authors report there are no competing interests to declare.

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Conflict of interests

The authors declare no competing interests.

Contribution of authors

Li Yin: Conceptualization, Methodology, Writing - Original Draft , Review & Editing, and Funding acquisition. Yuanyuan Wang: Writing - Original Draft, Software and Visualization. Shuhui Xu and Hanyue Xue: Software and Visualization. Yifei Qin, Yang Bai and Zhixiang Yin: Data curation, Writing- Original draft preparation. Yuanyuan Wang and Hanyue Xue are co-first authors.

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