PROTEOMIC INSIGHTS INTO THE HEALTH IMPACTS OF CIGARETTE SMOKING: ANALYZING NICOTINE, PAHS, AROMATIC AMINES, AND ALDEHYDES

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ABSTRACT

Cigarette smoking is a highly detrimental and dangerous habit that can lead to cancer. It contains numerous harmful compounds such as nicotine, polycyclic aromatic hydrocarbons (PAHs), aromatic amines, aldehydes, and various other compounds that are produced during smoking and enter the body. When these toxic substances enter the body, they can harm various systems, including the respiratory, cardiovascular, neurological, renal-urinary, reproductive, and ophthalmic systems. This study aims to identify the proteins that interact with nicotine, polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and aldehydes and to predict their potential impacts on the human body. We collected data for this investigation from the STITCH, STRING, UniProtKB, and NCBI databases. Next, we inputted the fasta sequences of identified proteins into OmicsBox to perform BLAST, GO Mapping, and functional annotation analysis. This study collected 330 sequences, consisting of 44 sequences for nicotine, 88 sequences for PAHs, 88 sequences for aromatic amine, and 100 sequences for aldehydes; finally, 205 sequences were obtained after the BLAST search. The functional annotation study revealed that these compounds significantly affect human health, especially biological processes, cellular components, and molecular functions. Our study also found that these compounds have numerous effects on signaling pathways, heart health, brain, reproductive system, liver functions, kidney functions, RNA and DNA binding, molecular apoptosis, carbohydrate and protein metabolism, mitochondrion, nucleoplasm, cytosol, and various cellular components. We have identified multiple genes stimulated by nicotine, PAHs, aromatic amines, and aldehydes, including BDKRB2, GPRC1C, MGLUR3, NNMT, ALDH1B1, ALDH7, DERA, CRABP2, ADH1A, ODC1, TLR6, JMJD1, and so on. Most of the genes are responsible for lung cancer, cardiovascular diseases, and alcohol-related cancer. The act of smoking cigarettes can have detrimental effects on individuals close to the smokers, even if they do not engage in smoking due to the transmission of harmful vapor via the air. Our study demonstrated that cigarette smoking is a highly prevalent and preventable cause of cancer, heart disease, and reproductive diseases, making it imperative for individuals to be knowledgeable and resolute in their efforts to stop it.

KEYWORDS: Cigarette smoking, Nicotine, PAHs, Aromatic amines, Aldehydes and Functional analysis.

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Introduction

Cigarette smoking is highly harmful and injurious to health as it contains various harmful chemical compounds. Though people know this, some people have a habit of cigarette smoking regularly. According to the U.S. National Cancer Institute, there are more than 7,000 chemicals found within tobacco smoke, 250 of which are identified to be harmful. Among these 250 harmful compounds, at least 69 can cause cancer. (NCI, 2017). When a person inhales the vapor of a cigarette, they inhale several harmful chemical compounds with it, such as nicotine, polycyclic aromatic hydrocarbons (PAHs), aromatic amines, aldehydes, and many more. (Soleimani *et al.*, 2022).

Nicotine is a naturally occurring chemical compound mainly found in tobacco products belonging to the alkaloid family and was first extracted by German physicians Wilhelm Heinrich Posselt and Karl Ludwig Reimann from tobacco plant (Das and Shafi, 2023). Though tobacco is referred to as a predominant source of nicotine additionally, it can also be found in several plants, such as tomatoes, aubergines, and potatoes (He *et al.*, 2024).

After consumption of nicotine, some effects and toxicity can appear immediately, such as irritation and burning sensation in the mouth and throat, nausea, increased salivation, vomiting, abdominal pain, and diarrhea (Mishra *et al.*, 2015). There are three significant mechanisms of action by which nicotine can act. These include ganglionic transmission, nicotinic acetylcholine receptors (nAChRs) on chromaffin cells via catecholamines, and central nervous system (CNS) stimulation of nAChRs (Rizkita *et al.*, 2024). Nicotine stimulates nAChRs, which have effects on cells that are important for the initiation

and progression of cancer (Mishra *et al.,* 2015). This carcinogenic compound harms the nervous system, cardiovascular system (CVS), respiratory system, renal system, metabolic system, ocular system, gastrointestinal system, and even reproductive system (Scherer and Scherer, 2024). Moreover, focusing on its short-term effects on the cholinergic system has some positive effects, such as working memory and executive function, and it may sometimes be neuroprotective (Swan and Lessov-Schlaggar, 2007).

Polycyclic aromatic hydrocarbons (PAHs) are naturally occurring non-polar carcinogenic chemical compounds primarily found in microorganisms, algae, phytoplankton, and several other organisms and enter the human body by cigarette smoking (El-Bouhy *et al.*, 2024). After entering the body, the detoxification of PAHs occurring in the liver by cytochrome P450 catalytic reactions and many oxidase enzymes via producing water-soluble epoxide glutathione conjugates (Patel *et al.,* 2020). PAHs have several toxic effects on humans, such as genotoxicity, embryotoxicity, phototoxicity, and immunotoxicity (Patel *et al.*, 2020).

During cigarette smoking, another pernicious lipid-soluble compound of tobacco enters the body called aromatic amines (Soleimani *et al.,* 2022). Aromatic amines are organic compounds that consist of an aromatic ring attached to an amine and are widely used and found in synthetic polymers, adhesives, rubber, pharmaceutical dyes, perfumes, explosives, and pesticides (Khoshraftar and Ghaemi, 2024). Aromatic amines can quickly enter the cells, severely affecting the normal cellular process. Additionally, several aromatic amines are marked as carcinogens to humans by the International Agency for Research on Cancer (Mazumder *et al.,* 2023). Some studies identified that aromatic amines exposure to humans increases the risk of urinary bladder cancer (Talaska, 2003).

Another harmful compound called aldehyde has been released with vapor during the burning of cigarettes (Soleimani *et al.,* 2022). Aldehyde is a class of organic compounds that shares a double bond with an oxygen atom, a single bond with the hydrogen atom, and a single bond with another atom or group of atoms (Asatryan *et al.,* 2024). Research showed that over 92% of cardiopulmonary disease risk increases due to just three aldehydes acrolein (88.5%), acetaldehyde (2.4%), formaldehyde (0.4%) (Ogunwale *et al.,* 2017). Several harmful and sometimes slightly beneficial effects are associated with nicotine, polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and aldehydes. Therefore, this study is focused on investigating and predicting the possible effects of cigarette smoking in humans by establishing the protein-protein network within the protein interacting with nicotine, polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and aldehydes.

Methodology

Network Retrieval

The STITCH 4.0 online server was used to investigate the interaction between nicotine, polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and aldehydes with the proteins of *Homo sapiens* (Ali *et al.,* 2017). This web server is known for validating chemical-protein interactions (CPI) utilizing many data sources. We re-examined the proteins interacting with nicotine, polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and aldehydes to identify protein-protein interactions within the same species. We used the STRING 9.1 web server (https://string-db.org/), which combines known and predicted protein interactions based on functional and physical associations, to identify these protein-protein interactions (PPIs) (Osman *et al.,* 2023).

Protein accession, amino acid sequences retrieval

The protein sequences for nicotine, polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and aldehydes were obtained from the UniProtKB protein database (https://www.uniprot.org/help/uniprotkb). The purpose was to identify the accession number, gene name, and amino acid number associated with the PCI and PPI. The amino acid sequences for nicotine, polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and aldehydes were obtained in the FASTA format from the NCBI protein database. We obtained 320 protein FASTA sequences for nicotine, polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and aldehydes.

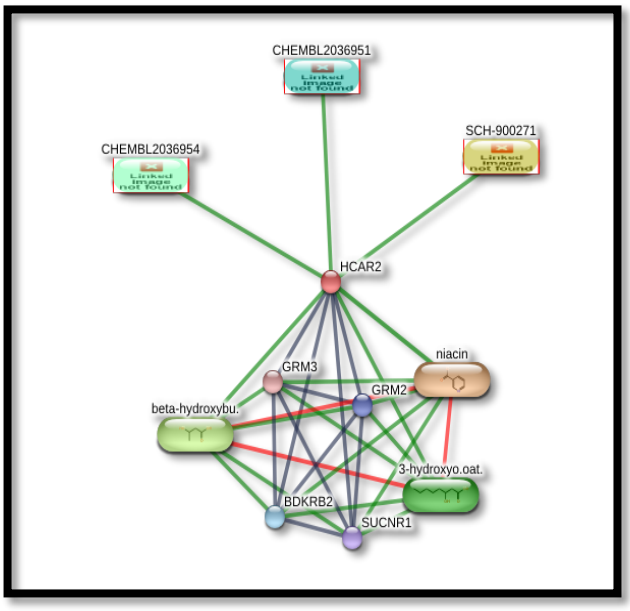
Functional annotation analysis

The Omicsbox program performed blast, functional annotation, and functional analysis of the query sequences. The cellular component, molecular function, and relationship within the biological process of the sequences were analyzed. The annotation parameters for the Omicsbox software are the selection of an appropriate search database, frequency and identity coverage of blast results along with the extension of the query-hit match, and validity of the annotations that have been transferred with the involvement of motif annotation. Enzyme codes (EC), InterPro IDs, and several pathways are the specific vocabularies that are supported by the Omicsbox software (Ali *et al.,* 2017). We identified several cancer-causing genes influenced by nicotine, PAHs, aromatic amines, and aldehydes.

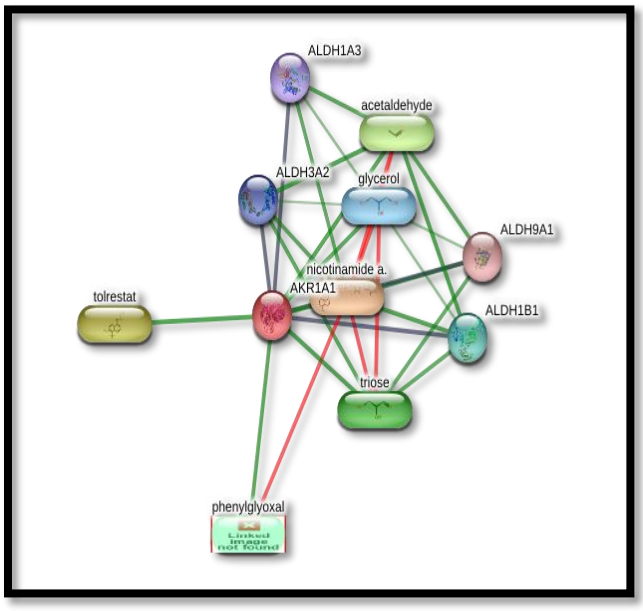
Results

Interaction Network

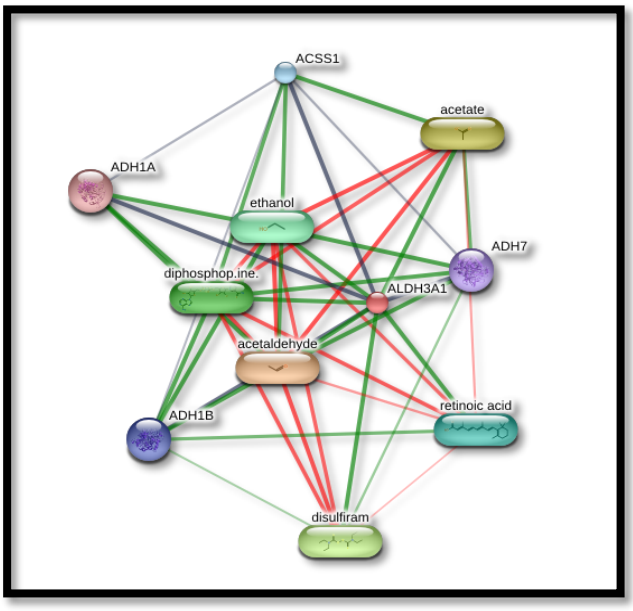
This study is mainly focused on identifying the possible effects of nicotine, polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and aldehydes on human health (*Homo sapiens*) via different bioinformatics tools. Our study found 30 potential proteins with their interaction networks by STITCH 4.0 among them, 4 proteins for nicotine, 8 proteins for polycyclic aromatic hydrocarbons (PAHs), 8 proteins for aromatic amines, and 10 proteins for aldehydes (Figure 1).



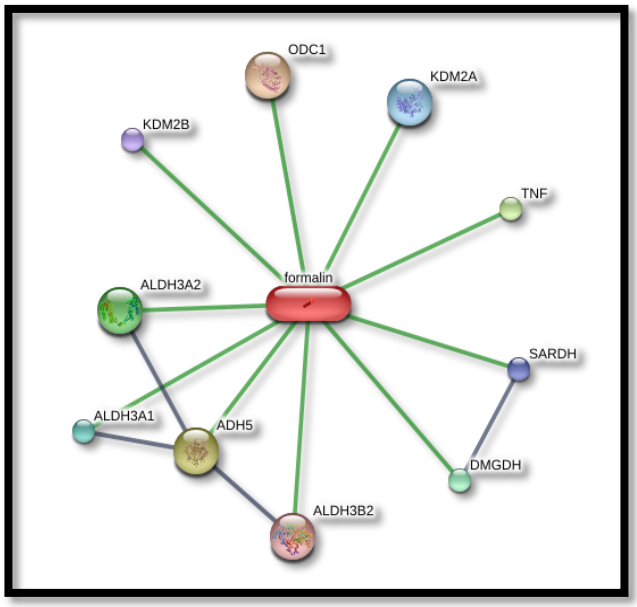
(A) Nicotine



(B) Polycyclic aromatic hydrocarbons (PAHs)



(C) Aromatic amines



(D) Aldehydes

Figure 1. Interactions of nicotine, polycyclic aromatic hydrocarbons (PAH), aromatic amines, and aldehyde with human proteins identified through STITCH 4.0

Identified 30 potential target proteins with their short descriptions, and interaction scores are mentioned in Tables 1, 2, 3, and 4.

Table 1. Proteins interacting with nicotine are identified through STITCH 4.0 with their short descriptions.

Interacting Proteins	Short Descriptions	Score
BDKRB2	B2 bradykinin receptor is a G protein-coupled receptor (GPCR) that acts as a vasodepressor and regulates the cardiovascular system (CVS).	0.918
GRM2	Metabotropic glutamate receptor 2 has a role in the central nervous system (CNS), such as modulation of synaptic transmission and neuronal excitability.	0.917
SUCNR1	Succinate receptor 1 resists mitochondrial respiration in cancer cells.	0.917
GRM3	Metabotropic glutamate receptor 3 is co-released with glutamate and catabolized by glutamate carboxypeptidase II (GCPII).	0.916

Table 2. Proteins that interacted with Polycyclic Aromatic Hydrocarbons (PAHs) were identified using STITCH 4.0 mentioned in their short descriptions.

Interacting Proteins	Short Descriptions	Score
Nicotinamide a	Nicotinamide N-methyltransferase mediates lipofibroblast-myofibroblast transition and apoptosis resistance. The crosstalk between fibroblasts and tumor cells in oral squamous cell carcinoma is orchestrated by Stromal nicotinamide N-methyltransferase	0.980
Acetaldehyde	Deoxyribose-phosphate aldolase, DERA, 4.1.2.4, 2-deoxy-D-ribose 5-phosphate aldolase, Phosphodeoxyriboaldolase, Deoxyriboaldolase.	0.961
Triose	Triosephosphate isomerase, TIM, 5.3.1.1, Methylglyoxal synthase, 4.2.3.3, Triose-phosphate isomerase	0.956
ALDH1B1	Aldehyde dehydrogenase X**,** mitochondrial, 1.2.1.3, Aldehyde dehydrogenase 5, Aldehyde dehydrogenase family 1 member B1	0.932
Glycerol	Glycerol kinase, Glycerokinase, 2.7.1.30, ATP: glycerol 3-phosphotransferase	0.928
ALDH3A2	Aldehyde dehydrogenase family 3 member A2, 1.2.1.3, 1.2.1.94, Aldehyde dehydrogenase 10, Fatty aldehyde dehydrogenase, Microsomal aldehyde dehydrogenase	0.927
ALDH1A3	Retinaldehyde dehydrogenase 3, RALDH-3, RalDH3, 1.2.1.36, Aldehyde dehydrogenase 6, Aldehyde dehydrogenase family 1 member A3, ALDH1A3	0.921
ALDH9A1	4-trimethylaminobutyraldehyde dehydrogenase, TMABA-DH, TMABALDH, 1.2.1.47, Aldehyde dehydrogenase E3 isozyme, Aldehyde dehydrogenase family 9 member A1, 1.2.1.3, Formaldehyde dehydrogenase, 1.2.1.46, Gamma-aminobutyraldehyde dehydrogenase, 1.2.1.19, R-aminobutyraldehyde dehydrogenase, cleaved into: 4-trimethylaminobutyraldehyde dehydrogenase, N-terminally processed	0.921

Table 3. List of proteins that interact with aromatic amines identified by using STITCH 4.0 mentioned with their short descriptions.

Interacting Proteins	Short Descriptions	Score
Acetaldehyde	Deoxyribose-phosphate aldolase, DERA, 4.1.2.4, 2-deoxy-D-ribose 5-phosphate aldolase, Phosphodeoxyriboaldolase, Deoxyriboaldolase	0.998
Acetate	S-formylglutathione hydrolase, FGH, 3.1.2.12, Esterase D, Methylumbelliferyl-acetate deacetylase, 3.1.1.56	0.994
Ethanol	Alcohol dehydrogenase 1C, 1.1.1.1, Alcohol dehydrogenase subunit gamma	0.974
Retinoic acid	Cellular retinoic acid-binding protein 2, Cellular retinoic acid-binding protein II, CRABP-II	0.963
ACSS1	NAD-dependent protein deacetylase sirtuin-3, mitochondrial, hSIRT3, 2.3.1.286, Regulatory protein SIR2 homolog 3, SIR2-like protein 3	0.960
ADH1B	All-trans-retinol dehydrogenase [NAD (+)] ADH1B, 1.1.1.105, Alcohol dehydrogenase 1B, Alcohol dehydrogenase subunit beta	0.960
ADH7	All-trans-retinol dehydrogenase [NAD (+)] ADH7, 1.1.1.105, Alcohol dehydrogenase class 4 mu/sigma chain, 1.1.1.1, Alcohol dehydrogenase class IV mu/sigma chain, Gastric alcohol dehydrogenase, Omega-hydroxydecanoate dehydrogenase ADH7, 1.1.1.66, Retinol dehydrogenase	0.958
ADH1A	Alcohol dehydrogenase 1A, 1.1.1.1, Alcohol dehydrogenase subunit alpha	0.957

Table 4. List of proteins that interact with aldehydes identified by using STITCH 4.0 mentioned with their short descriptions.

Interacting Proteins	Short Descriptions	Score
ODC1	Ornithine decarboxylase, ODC, 4.1.1.17	0.943
ADH5	Alcohol dehydrogenase class-3, 1.1.1.1, Alcohol dehydrogenase 5, Alcohol dehydrogenase class chi chain, Alcohol dehydrogenase class-III, Glutathione-dependent formaldehyde dehydrogenase, FALDH, FDH, GSH-FDH, 1.1.1.-, S-(hydroxymethyl) glutathione dehydrogenase, 1.1.1.284	0.940
TNF	Tumor necrosis factor ligand superfamily member 18, Activation-inducible TNF-related ligand, AITRL, Glucocorticoid-induced TNF-related ligand, hGITRL	0.932
ALDH3A2	Aldehyde dehydrogenase family 3 member A2, 1.2.1.3, 1.2.1.94, Aldehyde dehydrogenase 10, Fatty aldehyde dehydrogenase, Microsomal aldehyde dehydrogenase.	0.929
DMGDH	Dimethylglycine dehydrogenase, mitochondrial, 1.5.8.4, ME2GLYDH	0.923
ALDH3A1	Aldehyde dehydrogenase, dimeric NADP-preferring, 1.2.1.5, ALDHIII, Aldehyde dehydrogenase 3, Aldehyde dehydrogenase family 3 member A1	0.923
KDM2A	Lysine-specific demethylase 3A, 1.14.11.65, JmjC domain-containing histone demethylation protein 2A, Jumonji domain-containing protein 1A, [histone H3]-dimethyl-L-lysine (9) demethylase 3A	0.920

SARDH	Sarcosine dehydrogenase, mitochondria, mitochondrial, SarDH, 1.5.8.3, BPR-2	0.918
KDM2B	Lysine-specific demethylase 3B, 1.14.11.27, F-box and leucine-rich repeat protein 10, F-box/LRR-repeat protein 10, JmjC domain-containing histone demethylation protein 1B, [Histone-H3]-lysine-36 demethylase 1B	0.916
ALDH3B2	Aldehyde dehydrogenase family 3 member B2, 1.2.1.3, Aldehyde dehydrogenase 8	0.914

In addition, each of these 30 proteins interacts with 10 other proteins, resulting in 300 interacting proteins. Figures 2, 3, 4, and 5 and Tables 5, 6, 7, and 8 describe these proteins.

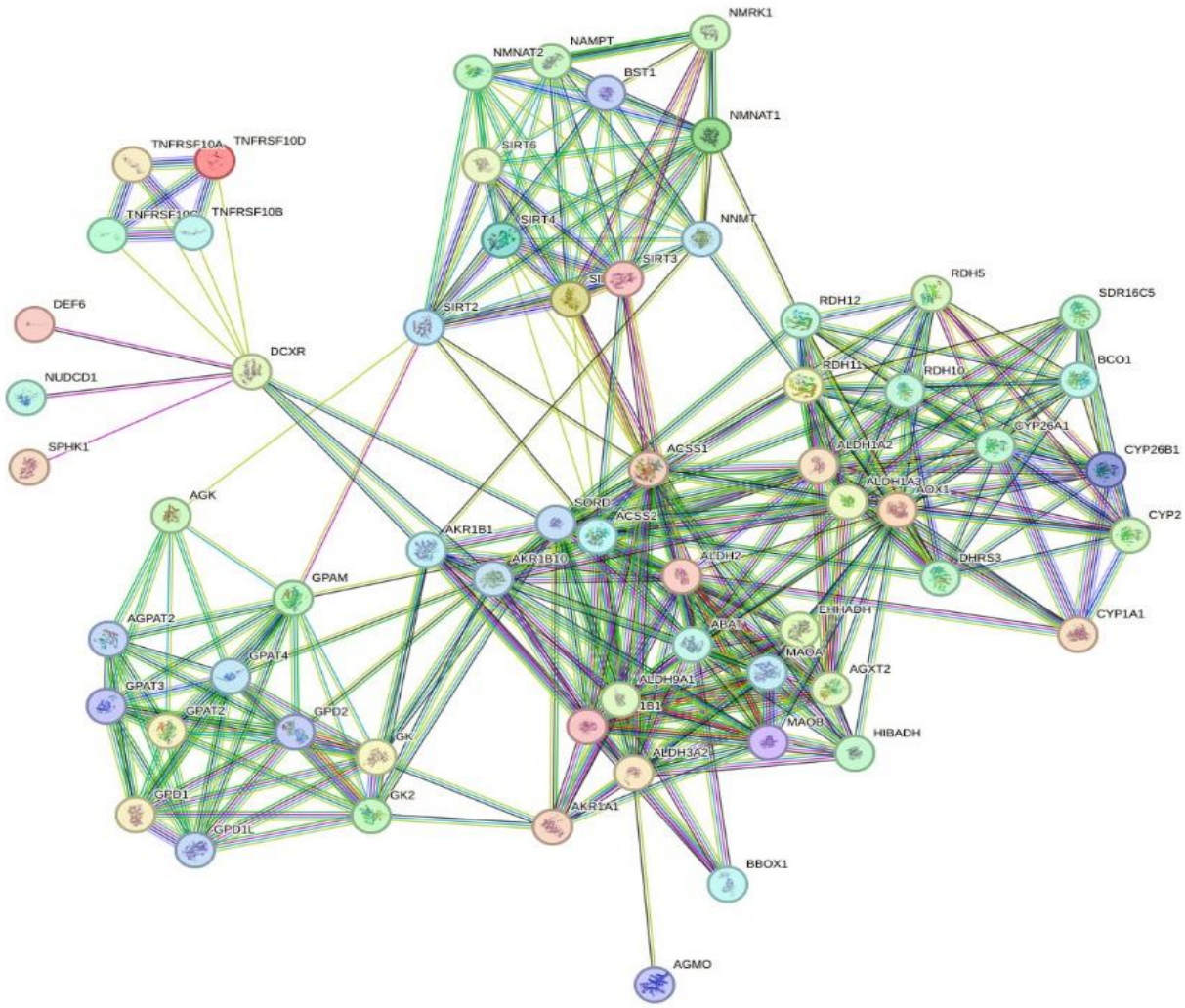


Figure 2. Protein-protein interaction (PPI) of nicotine identified via STRING 9.0.

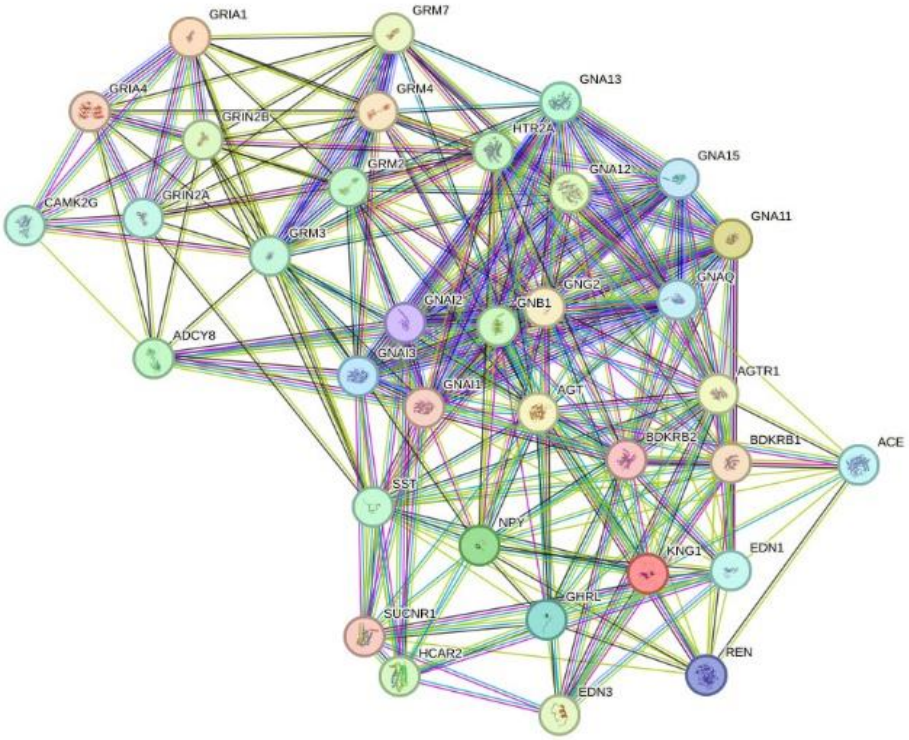


Figure 3. Protein-protein interaction (PPI) of polycyclic aromatic hydrocarbons (PAHs) identified via STRING 9.0.

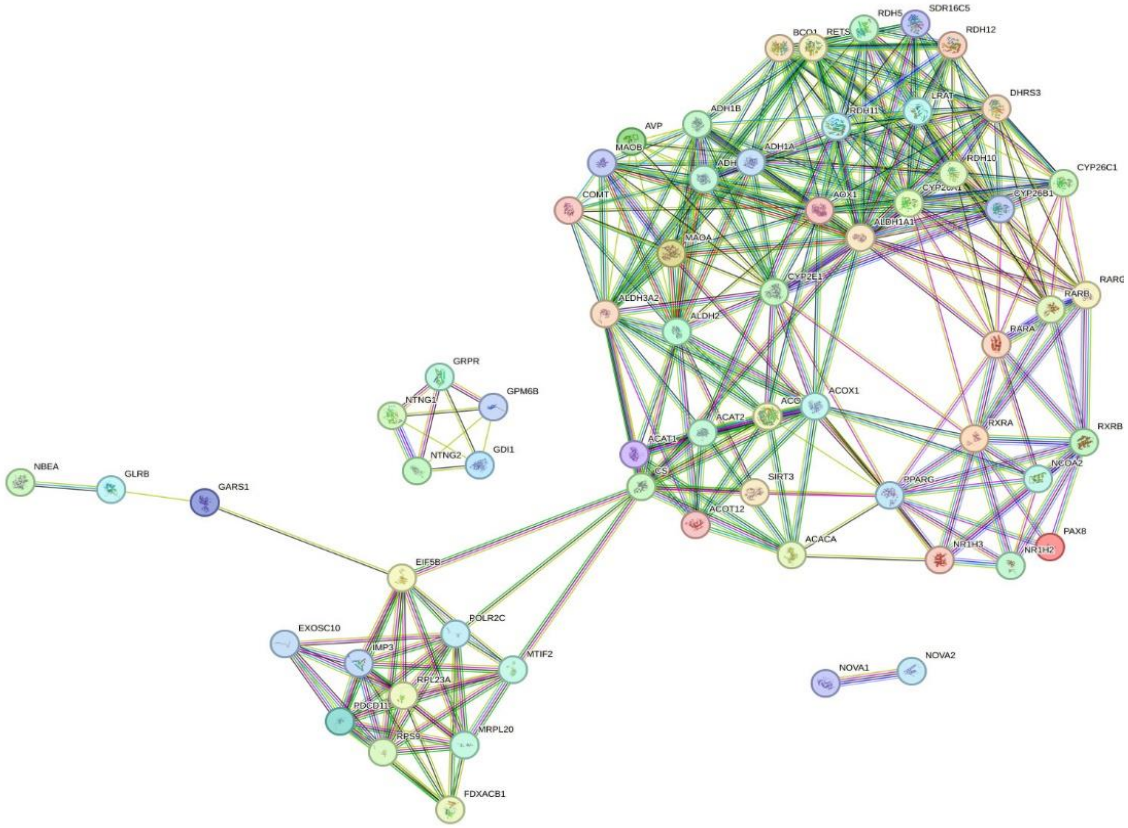


Figure 4. Protein-protein interaction (PPI) of aromatic amines identified via STRING 9.0.

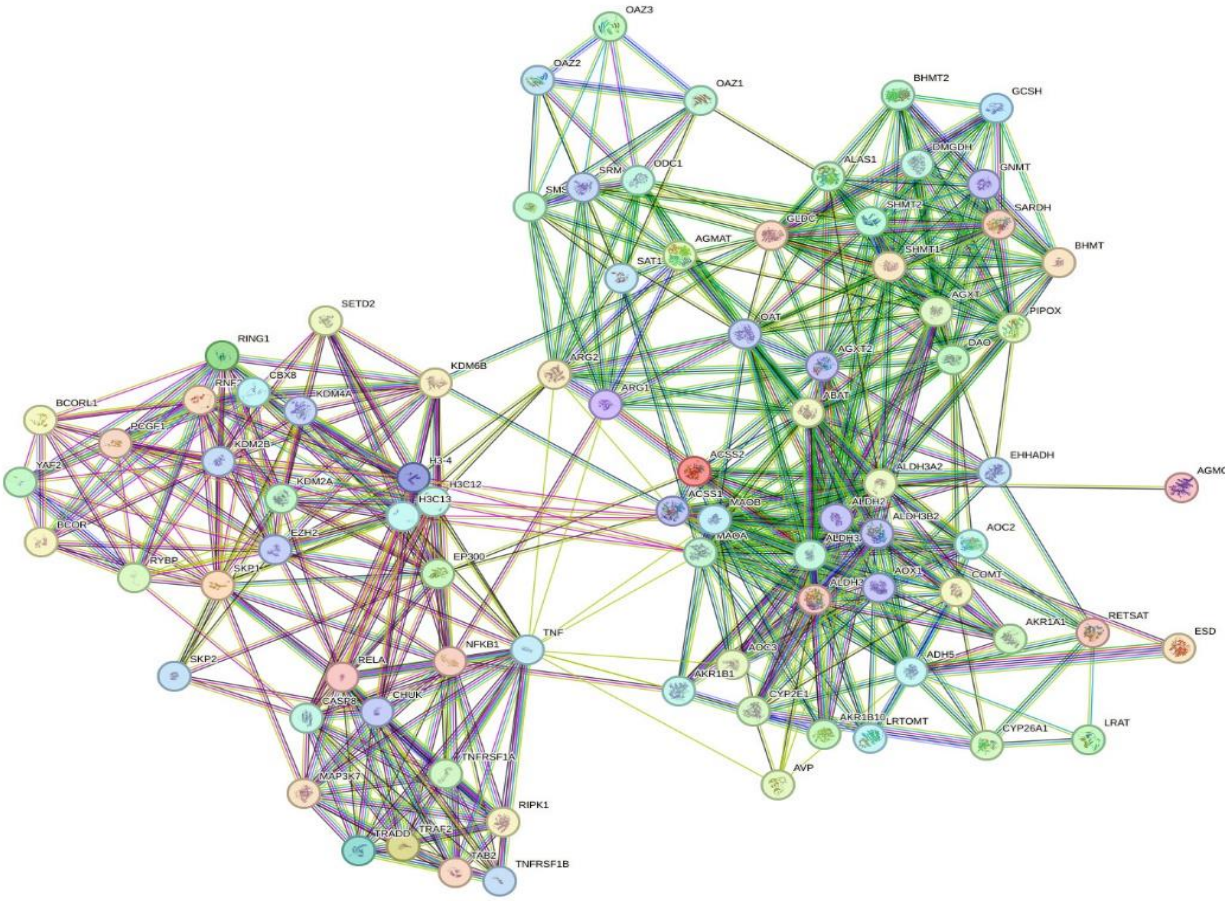


Figure 5. Protein-protein interaction (PPI) of aldehydes identified via STRING 9.0.

Table 5. Protein-protein interaction (PPI) of nicotine using STRING 9.1.

Sl. No.	BDKRB2	GRM2	SUCNR1	GRM3
1.	KNG1	HTR2A	NPY	GRM2
2.	AGT	GNAI1	HCAR2	GRIN2A
3.	GNAQ	GRIA1	REN	GNAI1
4.	AGTR1	GRM4	EDN1	GNAI2
5.	BDKRB1	GRM7	GNAI1	GNAI3
6.	GNB1	GRM3	EDN3	GRIN2B
7.	EDN1	GNG2	GNAI2	GRIA1
8.	GNA11	GNA12	GNA13	ADCY8
9.	GNA15	GNAI3	GHRL	GRIA4
10.	ACE	GRIA4	SST	CAMK2G

Table 6. Protein-protein interaction (PPI) of polycyclic aromatic hydrocarbons (PAHs) using STRING 9.1.

Sl. No.	Nicotinamide a.	Acetaldehyde	Triose	ALDH1B1	Glycerol	ALDH3A2	ALDH1A3	ALDH9A1
1.	SIRT1	CYP26A1	AKR1B1	AKR1B1	GPAM	EHHADH	RDH12	BBOX1
2.	NMNAT1	CYP26B1	SORD	ABAT	GPAT2	MAOB	RDH10	ACSS1
3.	NMNAT2	CYP26C1	AKR1B10	ACSS1	GPD1L	AKR1B1	CYP26A1	AKR1A1
4.	NMRK1	RDH10	NUDCD1	ALDH2	GPD1	MAOA	CYP26B1	EHHADH
5.	SIRT3	RDH12	SPHK1	AKR1A1	GK	AKR1A1	CYP26C1	ACSS2
6.	NNMT	DHRS3	TNFRSF10C	ACSS2	GK2	ACSS2	DHRS3	ABAT
7.	SIRT6	BCO1	TNFRSF10B	EHHADH	GPD2	AGMO	CYP1A1	AGXT2
8.	BST1	RDH11	TNFRSF10D	HIBADH	AGK	AKR1B10	RDH5	MAOB
9.	SIRT4	RDH5	TNFRSF10A	MAOA	AGPAT2	ACSS2	RDH11	HIBADH
10.	SIRT2	SDR16C5	DEF6	MAOB	GPAT4	ABAT	AOX1	MAOA

Table 7. Protein-protein interaction (PPI) of aromatic amines using STRING 9.1.

Sl. No.	Acetaldehyde	Acetate	Ethanol	Retinoic acid	ACSS1	ADH1B	ADH7	ADH1A
1.	CYP26A1	EXOSC10	NOVA1	NCOA2	SIRT3	ALDH2	ALDH2	ADH1B
2.	CYP26B1	RPL23A	GRPR	RARA	CS	ADH1A	AVP	ADH1C
3.	CYP26C1	FDXACB1	GLRB	RARB	ACAT1	CYP2E1	CYP2E1	ALDH2
4.	RDH10	MTIF2	GPM6B	PPARG	ACACA	ADH1C	COMT	AVP
5.	RDH12	EIF5B	NTNG2	NR1H3	ACOX1	AVP	CYP26A1	CYP2E1
6.	DHRS3	IMP3	NTNG1	RARG	ACOT12	AOX1	LRAT	ALDH1A1
7.	BCO1	MRPL20	GARS1	NR1H2	ACOX3	ALDH1A1	AOX1	AOX1
8.	RDH11	RPS9	NOVA2	RXRA	ACAT2	MAOA	ALDH1A1	CYP26A1
9.	RDH5	POLR2C	NBEA	RXRB	ALDH3A2	COMT	MAOA	MAOA
10.	SDR16C5	PDCD11	GDI1	PAX8	ALDH2	MAOB	RETSAT	LRAT

Table 8. Protein-protein interaction (PPI) of aldehydes using STRING 9.1.

Sl. No.	ODC1	ADH5	TNF	ALDH3A2	DMGDH	ALDH3A1	KDM2A	SARDH	KDM2B	ALDH3B2
1.	SRM	ESD	TNFRSF1A	EHHADH	BHMT	MAOB	SKP1	GLDC	SKP1	ALDH3B1
2.	OAZ1	ALDH2	NFKB1	MAOB	GNMT	MAOA	RELA	GNMT	PCGF1	ACSS2
3.	OAZ3	CYP26A1	TRAF2	AKR1B1	PIPOX	COMT	H3C13	SHMT1	RNF2	ABAT
4.	ARG2	CYP2E1	RIPK1	MAOA	SARDH	ACSS2	H3C12	PIPOX	RYBP	ACSS1
5.	AGMAT	AOX1	TRADD	AKR1A1	GLDC	ABAT	EP300	SHMT2	RING1	MAOA
6.	OAT	MAOB	CASP8	ACSS2	BHMT2	AKR1A1	SETD2	DAO	YAF2	AKR1A1
7.	SAT1	MAOA	TAB2	AGMO	SHMT1	ACSS1	H3-4	AGXT	BCORL1	MAOB
8.	ARG1	LRAT	MAP3K7	AKR1B10	GCSH	CYP2E1	KDM4A	DMGDH	BCOR	AOC2
9.	SMS	AVP	CHUK	ACSS2	SHMT2	LRTOMT	KDM6B	ALAS1	CBX8	AOC3
10.	OAZ2	RETSAT	TNFRSF1B	ABAT	ENSP491651	AOC2	SKP2	AGXT2	EZH2	CYP2E1

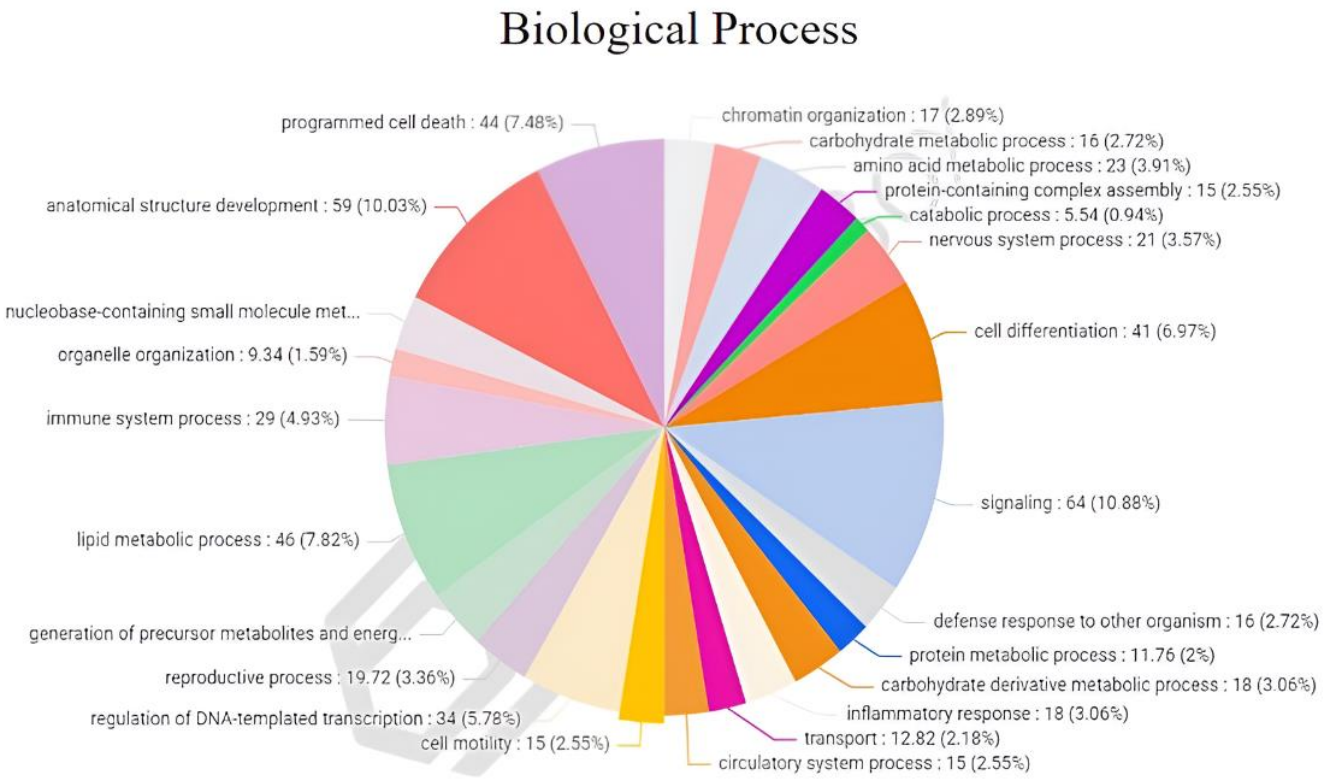
Protein accession, amino acid sequences retrieval, and functional annotation analysis

This study examined the interactions between proteins and chemicals, focusing on protein-chemical and protein-protein interactions. A total of 330 protein sequences were collected, with 44 sequences related to nicotine, 88 sequences related to polycyclic aromatic hydrocarbons (PAHs), 88 sequences related to aromatic amines, and 100 sequences related to aldehydes. The amino acid numbers, accession numbers, and fasta sequences were simultaneously obtained from the protein databases UniProtKB and NCBI. After doing the blast search, we found 205 proteins.

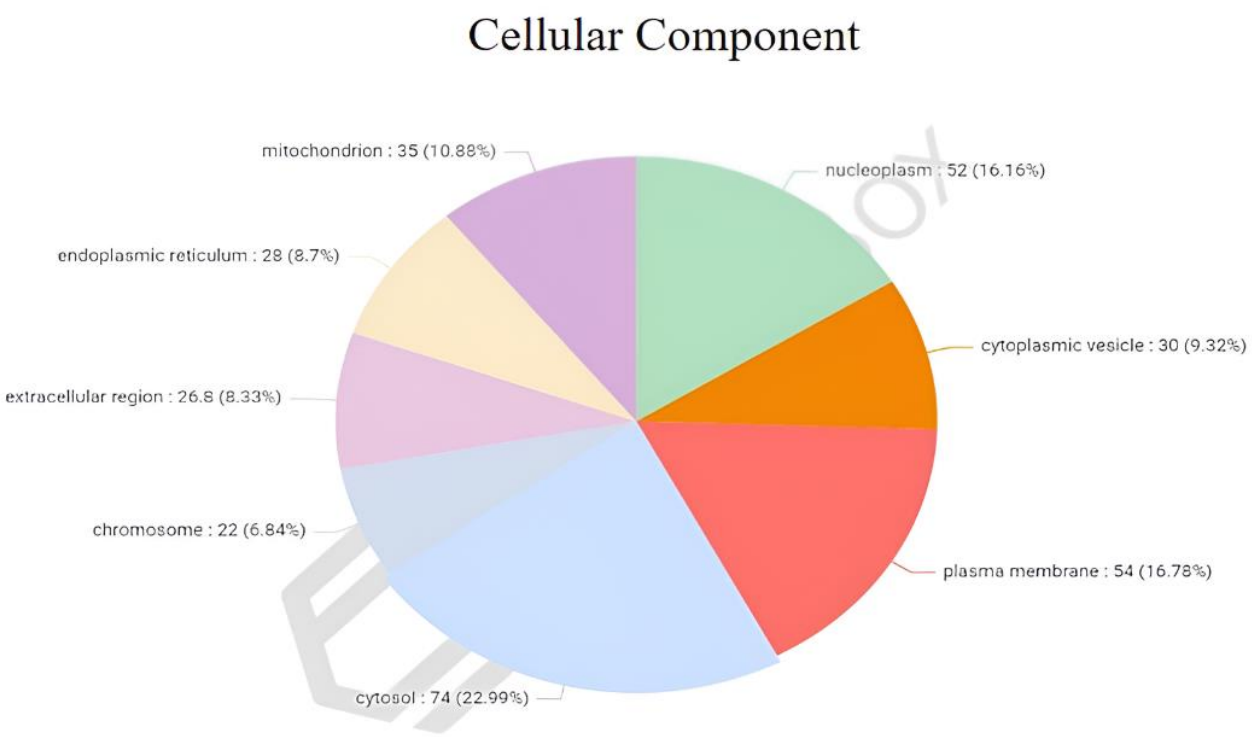
Functional analysis of 225 proteins they are interacting with these four compounds

Functional annotation analysis of combined proteins demonstrated that cigarette smoke has significant effects on biological processes such as signaling, cell differentiation, circulatory system, nervous system, anatomical structure development, amino acid metabolism process, immune system process, lipid metabolic process, and programmed cell death which is also known as apoptosis as well as many other major biological processes in *Homo sapiens* (Figure 6 a).

Alternately, we found that cigarette smoke severely affects the different cellular components of the human body, such as the plasma membrane, cytosol, mitochondrion, cytoplasmic vesicle, and so on (Figure 6 b). Instead, we found that cigarette smoke significantly affects human molecular functions, including transferase activity, molecular function regulator activity, molecular transducer activity, DNA binding, lipid binding, catalytic activity, and acting on a protein (Figure 6 c).



(a)



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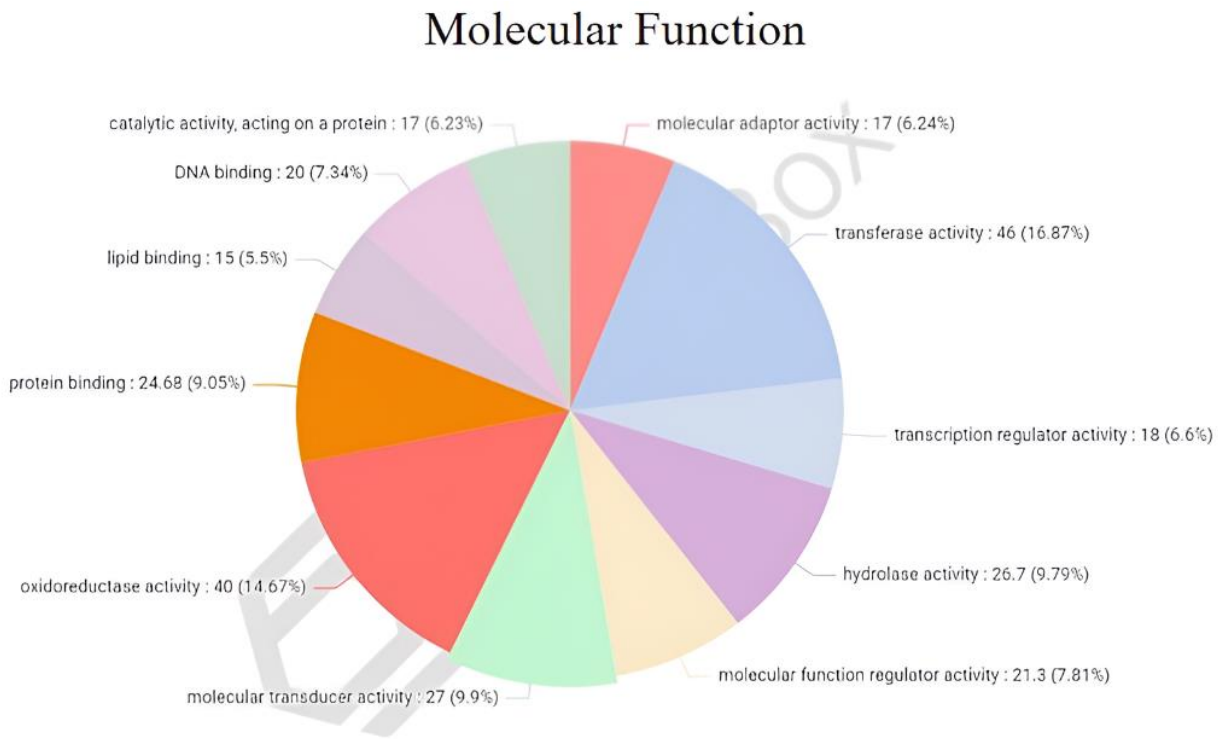
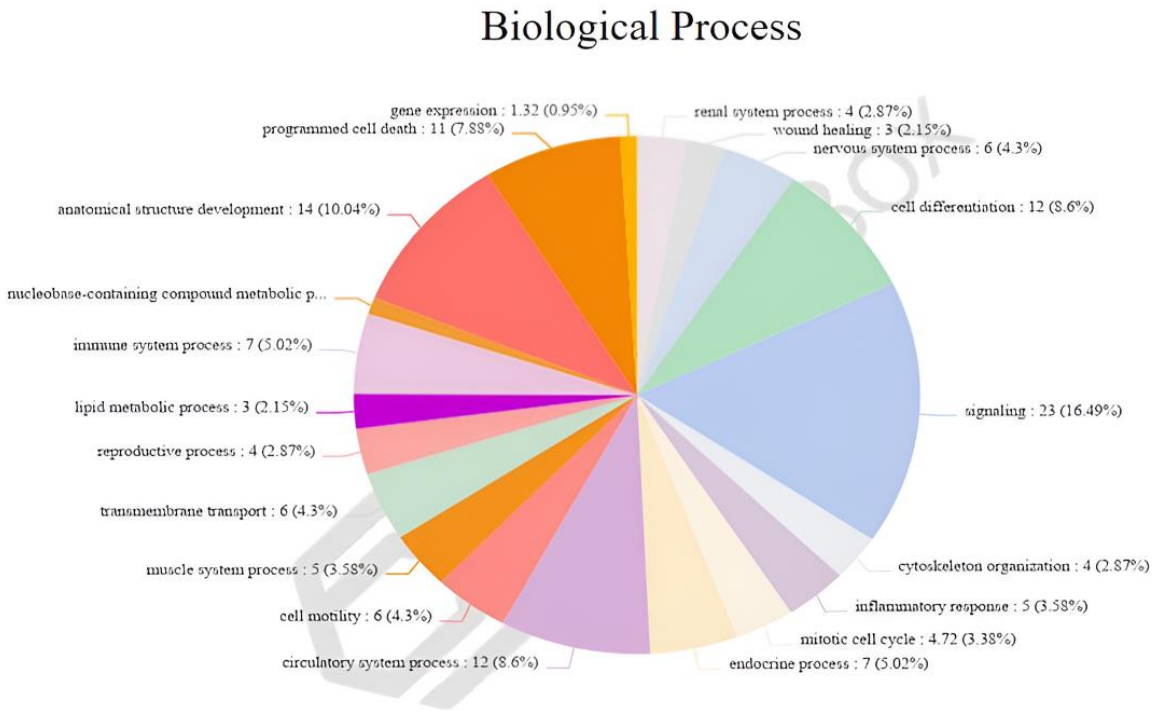


(c)

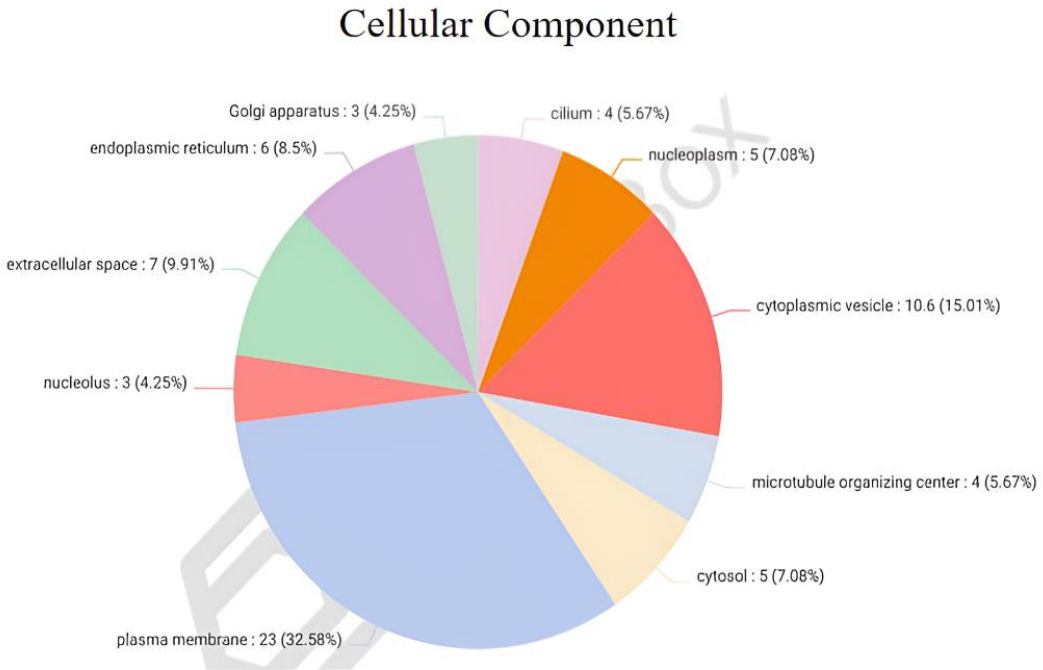
Figure 6. Functional annotation analysis showed the effects of cigarette smoking in various biological processes (a), localization of cellular components (b), and molecular functions (c) of different proteins in *Homo sapiens*.

Functional analysis of proteins that interacted with nicotine

Functional analysis of proteins that bind with nicotine exhibited that nicotine severely affects human biological processes, including the signaling pathways, the circulatory system, the endocrine system, cell differentiation, and programmed cell death it can cause uncontrolled growth of cells, which may result in tumors and ultimately can cause cancer (Figure 7 a). The cellular component analysis showed that nicotine heavily affects the plasma membrane, cytoplasmic vesicle, nucleoplasm, and extracellular space along with the nucleus (Figure 7 b). On the other hand, nicotine binds with several proteins with numerous molecular functions, which means this compound enormously influences these molecular functions including molecular transducer activity, GTPase activity, receptor-ligand activity, and cytoskeletal protein binding (Figure 7 c).



(a)



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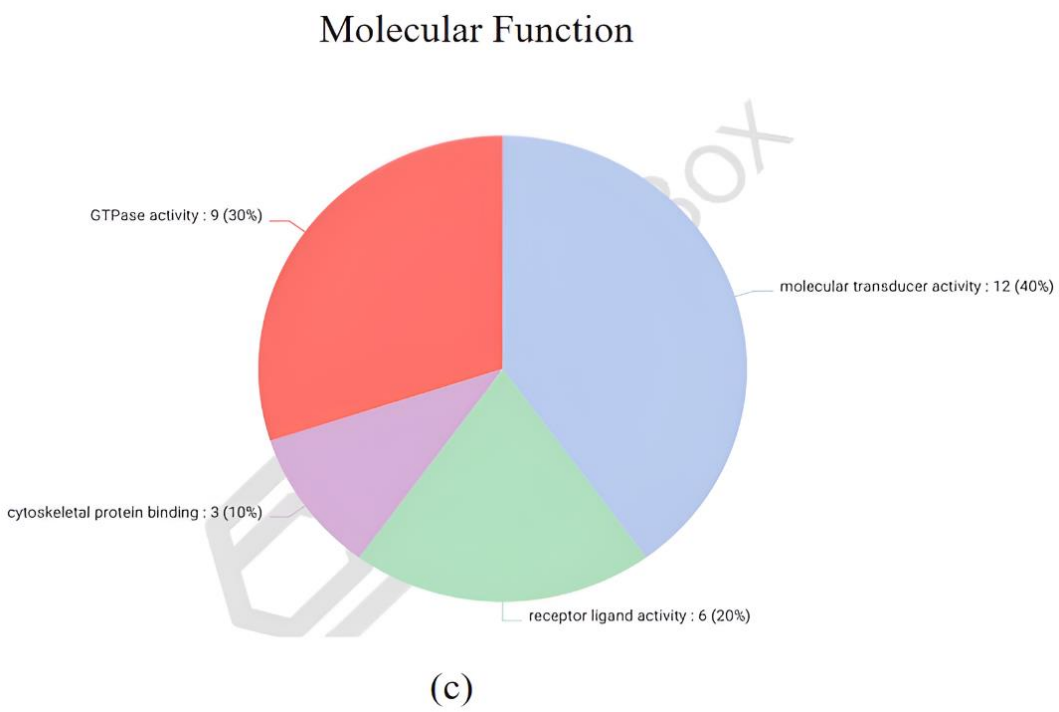
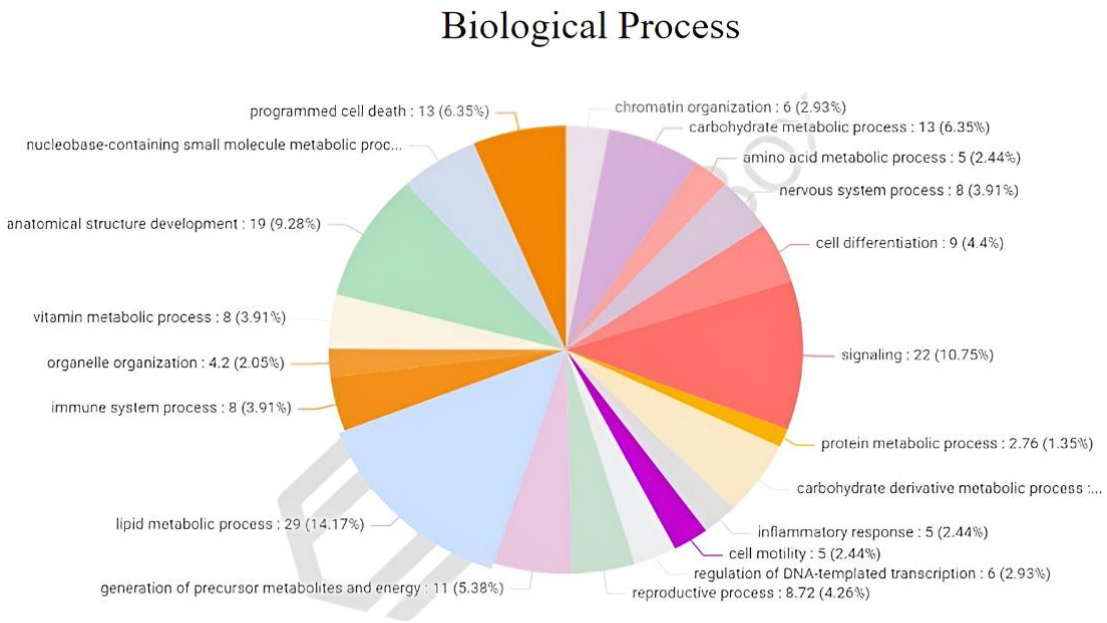


(c)

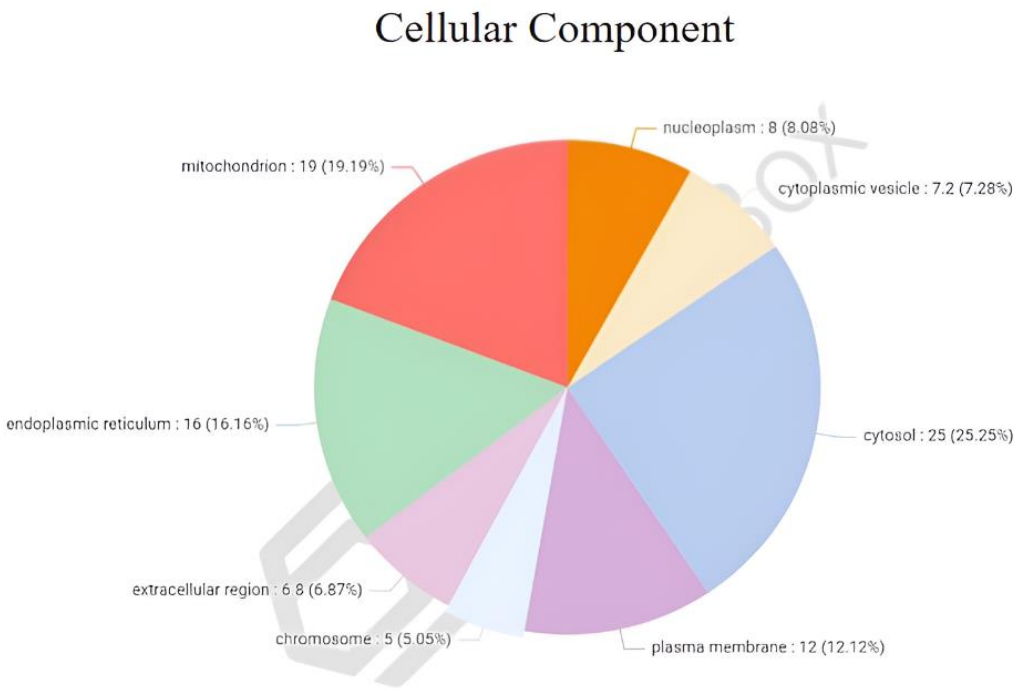
Figure 7. Functional annotation analysis showed the effects of nicotine in various biological processes (a), localization of cellular components (b), and molecular functions (c) of different proteins in *Homo sapiens*.

Functional analysis of proteins that interacted with polycyclic aromatic hydrocarbons (PAHs)

We found that Polycyclic aromatic hydrocarbons (PAHs) interact with 88 human proteins, and functional annotations showed that these proteins have numerous practical functions in biological processes, cellular components, and molecular functions of the human body. PAHs adversely affect several biological processes such as signaling, programmed cell death, cell differentiation, nervous system process, carbohydrate, lipid, and vitamin metabolism, generation of metabolites and energy, and some other significant biological processes (Figure 8 a). Polycyclic aromatic hydrocarbons (PAHs) have some effects on the cellular components of humans, such as cytosol, plasma membrane, endoplasmic reticulum, chromosomes, and many other cellular components (Figure 8 b). Polycyclic aromatic hydrocarbons have some significant effects on molecular functions, especially on oxidoreductase activity, transferase activity, and hydrolase activity, with some of the effects on many other molecular functions (Figure 8 c).



(a)



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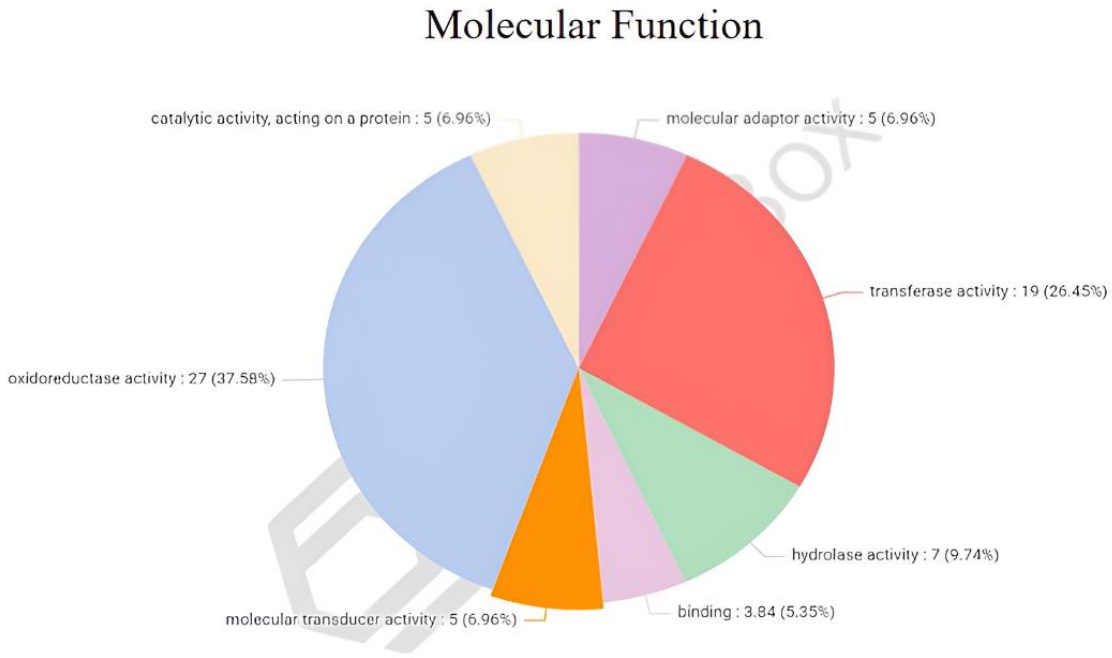


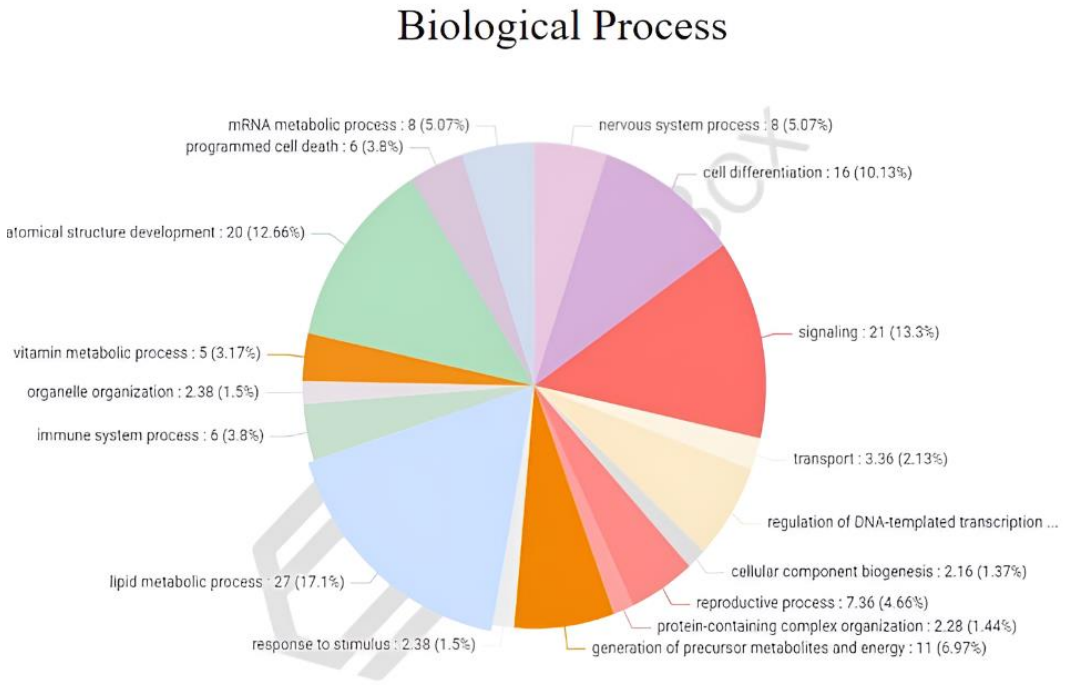
(c)

Figure 8. Functional annotation analysis showed the effects of Polycyclic aromatic hydrocarbons (PAHs) in various biological processes (a), localization of cellular components (b), and molecular functions (c) of different proteins in *Homo sapiens*.

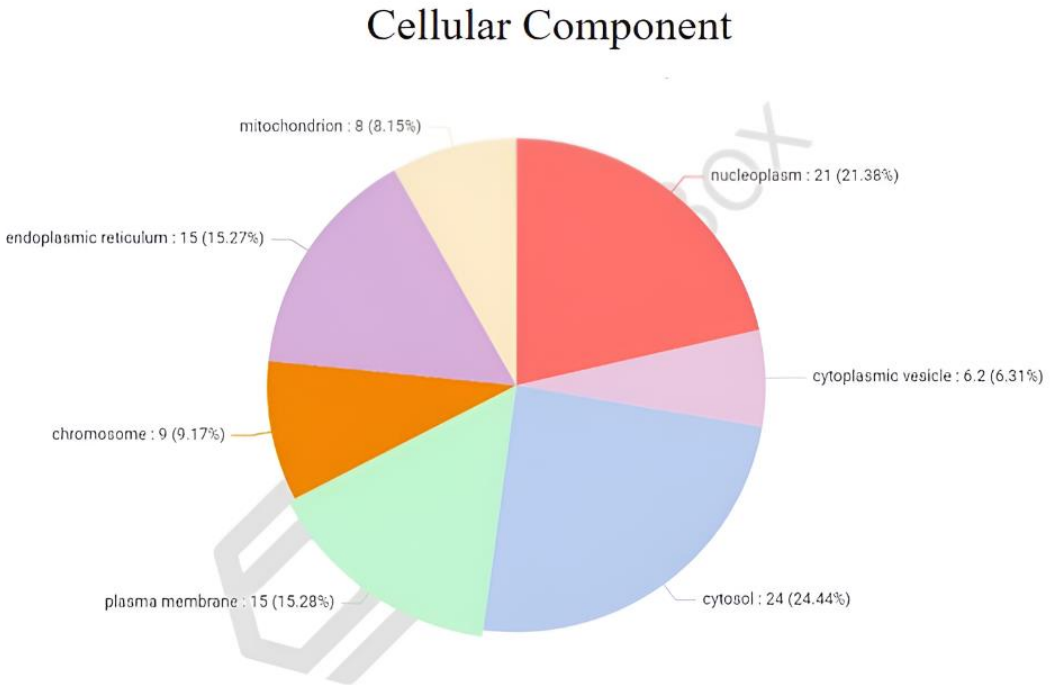
Functional analysis of proteins that interacted with aromatic amines

The stitch and string database analysis revealed that aromatic amines interacted with 88 human proteins. Further examination of these proteins revealed that they are crucial in various beneficial biological processes, cellular components, and molecular functions. Different studies already found that aromatic amines are carcinogenic chemicals and have various adverse effects on human health; that is why it is postulated that aromatic amines severely affect the functions of these

respective proteins. We found that aromatic amines significantly affect biological processes, including signaling, cell differentiation, anatomical structural development, immune response, lipid metabolism, mRNA metabolic process, and several influential biological processes (Figure 9 a). These compounds can disrupt average cellular organization as they affect some cellular components, including nucleoplasm, cytosol, endoplasmic reticulum, plasma membrane, chromosomes, and several crucial elements of the human cell (Figure 9 b). At the molecular level, aromatic amines can damage human health because aromatic amines can affect some molecular functions, including oxidoreductase activity, lipid binding, RNA binding, and DNA binding of human health (Figure 9 c).



(a)



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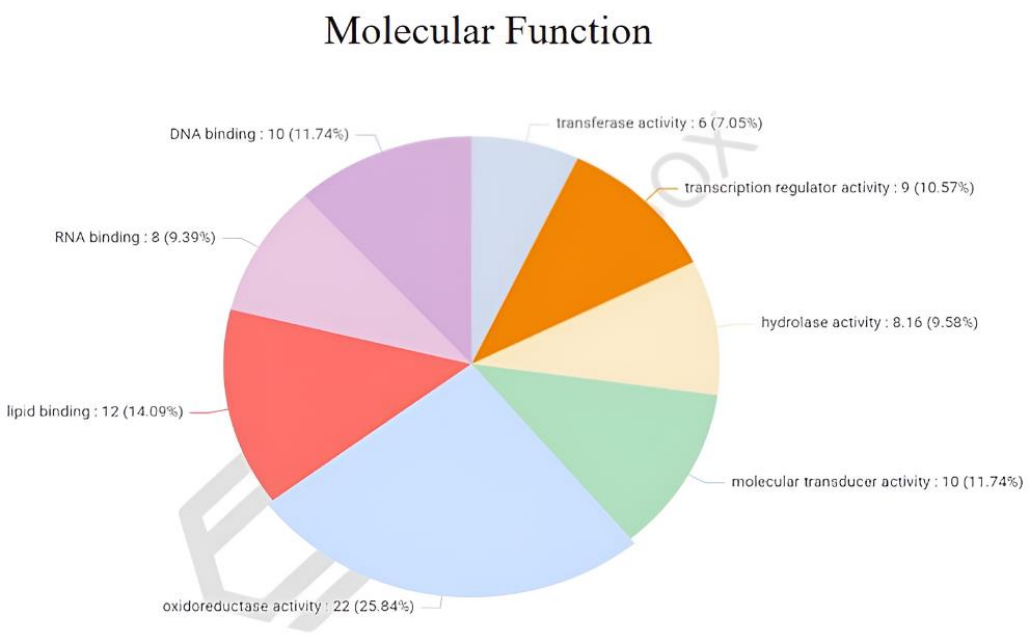
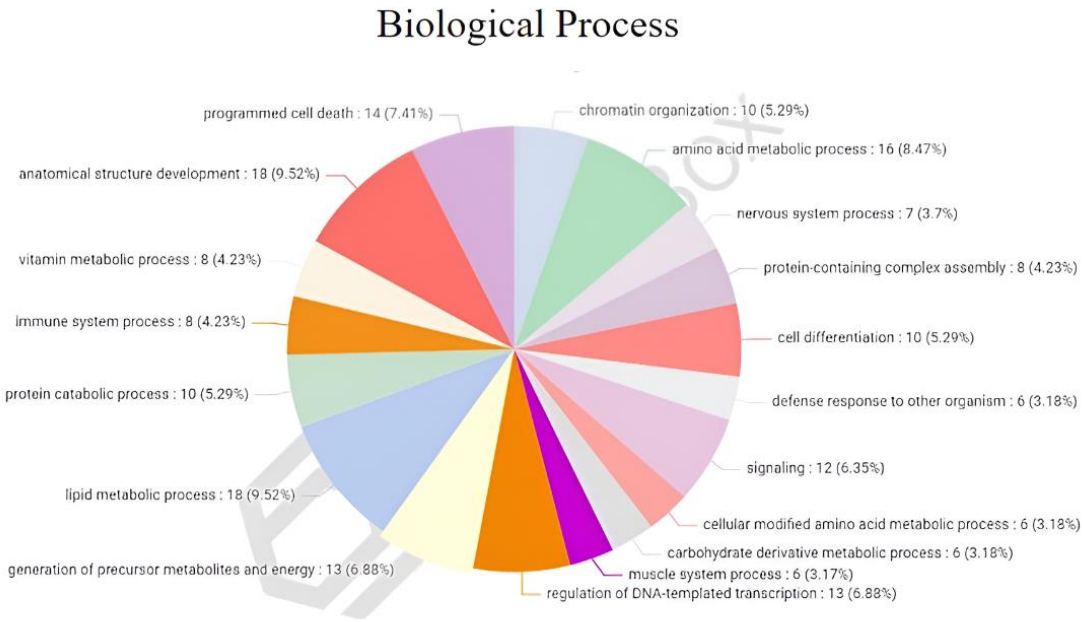


(c)

Figure 9. Functional annotation analysis showed the effects of aromatic amines in various biological processes (a), localization of cellular components (b), and molecular functions (c) of different proteins in *Homo sapiens*.

Functional analysis of proteins that interacted with aldehydes
Like the other three compounds, aldehydes interact with 100 essential human proteins in human health. However, we have discovered that these carcinogenic compounds also impact various biological processes in the human body, including signaling, nervous system function, cell differentiation, lipid metabolism, generation of precursor metabolites and energy, anatomical structure development, and programmed cell death (Figure 10 a). They impact various cellular components in humans, such as the mitochondrion, nucleoplasm, cytosol, plasma membrane, and cytosolic vesicle (Figure 10 b). Molecular functions are fundamental and complex processes in the human body. Even in these tasks, aldehydes impact transferase activity, oxidoreductase activity, and molecular adaptor activity (Figure 10 c).



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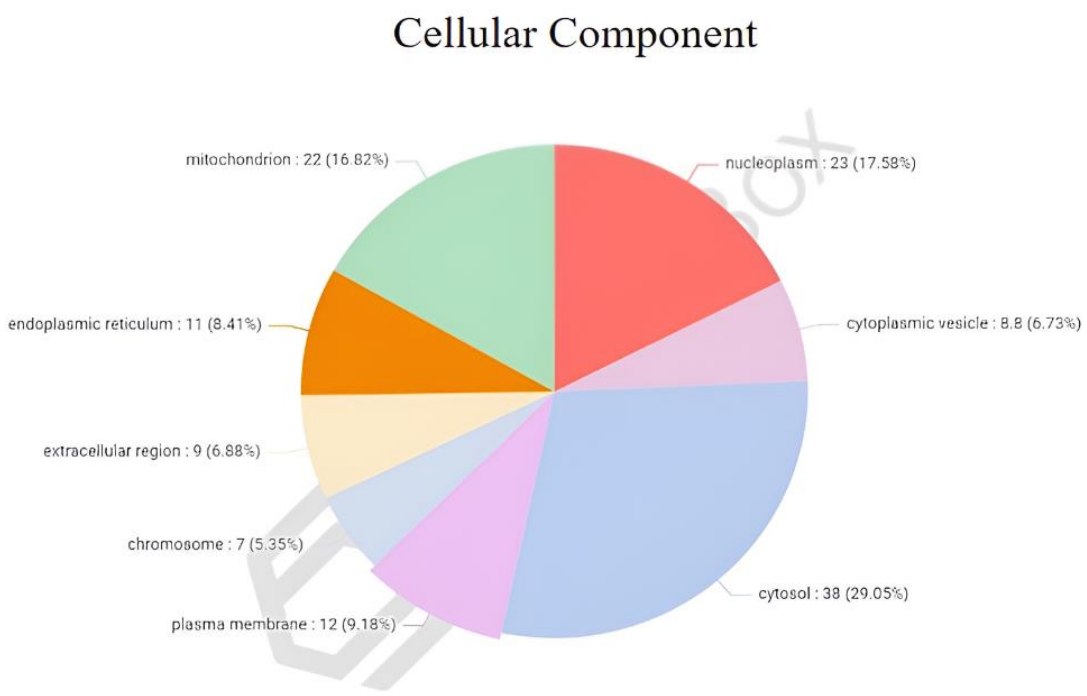

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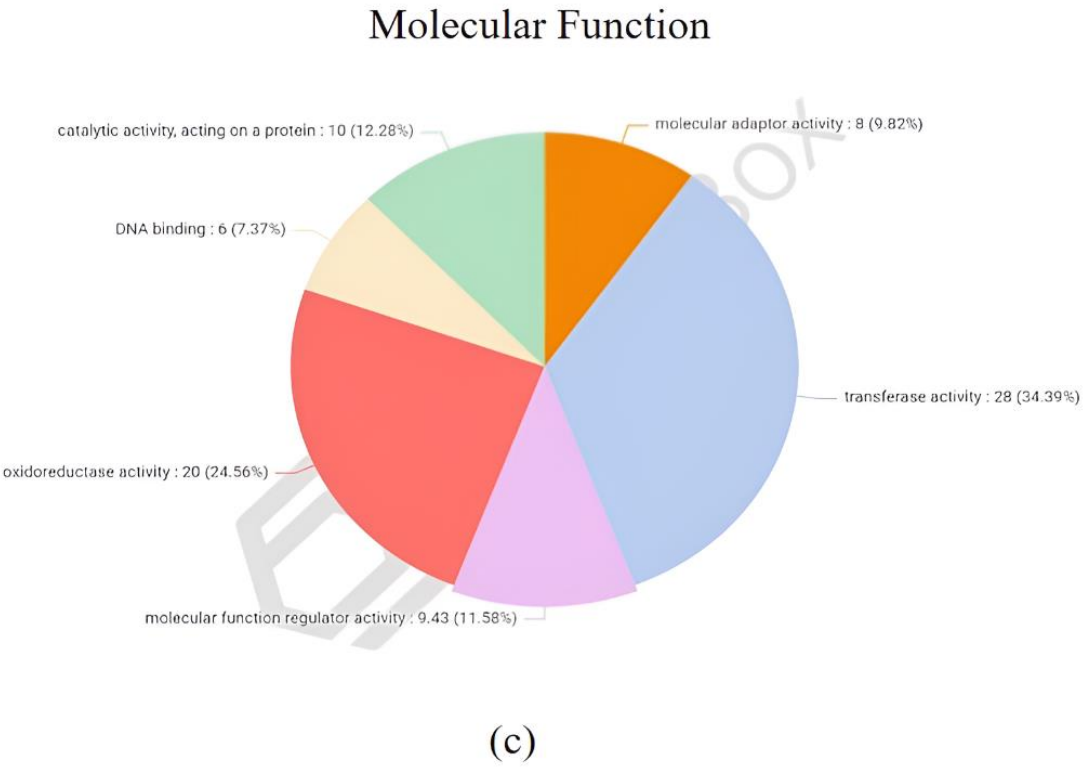

(c)

Figure 10. Functional annotation analysis showed the effects of aldehydes in various biological processes (a), localization of cellular components (b), and molecular functions (c) of different proteins in *Homo sapiens*.

Venn diagram

We conducted the Venn diagram analysis to observe the common proteins among all four compounds. A total of 330 proteins were identified for nicotine, polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and aldehydes in our bioinformatics analysis. No proteins were identified to be shared among nicotine, polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and aldehydes. We identified a single protein that is common to both nicotine and polycyclic aromatic hydrocarbons, another protein that is common to nicotine and aldehyde, and one protein that is shared among nicotine, polycyclic aromatic hydrocarbons (PAHs), and aldehyde. Additionally, we found seven proteins that are common to polycyclic aromatic hydrocarbons (PAHs) and aromatic amines, six proteins that are common to polycyclic aromatic hydrocarbons (PAHs) and aldehydes, and eight proteins that are common to aromatic amines and aldehyde. Furthermore, we discovered five proteins shared among polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and aldehydes, except one protein still needs to be identified in the OmicsBox database. The identified common proteins are mentioned in Figure 11 and Table 10**.**

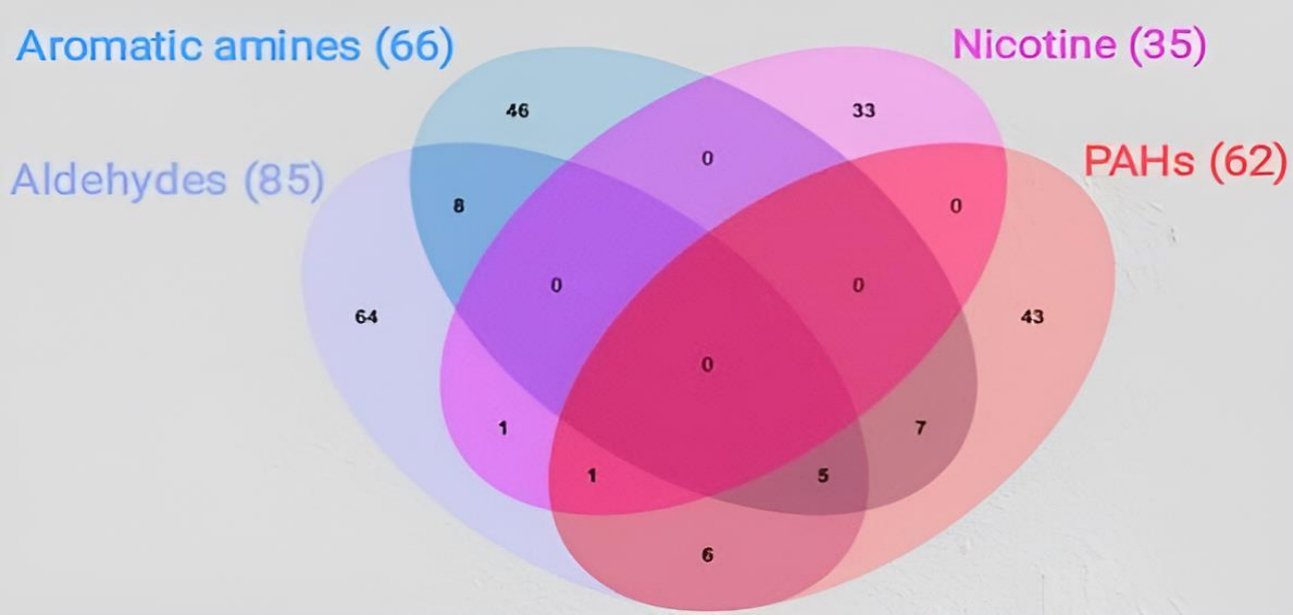

Figure 11. Identification of commonly targeted proteins through the Venn diagram in *Homo sapiens*.

Table 9. Common protein found through Venn diagram.

Accession number	Protein name	Full name of the protein	Gene name	Amino acid length
Nicotine-Aldehydes				
KAI4033008.1	SST	Somatostatin	SST	116
Nicotine-PAHs-Aldehydes				
CAC24841.1	AGT	Alanine-glyoxylate aminotransferase 2	AGXT2, AGT2	514
PAHs-Aromatic amines				
NP_059125.2	BCO1	Beta-carotene 15,15'-dioxygenase	BCO1, BCDO,	547
NP_620419.2	SDR16C5	Epidermal retinol dehydrogenase 2	SDR16C5, RDHE2	309
NP_899230.2	CYP26C1	Cytochrome P450	CYP26C1	522
NP_063938.1	CYP26B1	Cytochrome P450 26B1	CYP26B1, CYP26A2	512
NP_742034.1	RDH10	Retinol dehydrogenase 10	RDH10, SDR16C4	341

NP_004744.2	DHRS3	Short-chain dehydrogenase-3	DHRS3, RDH17	302
KAI4064898.1	acetaldehyde	Deoxyribose-phosphate aldolase	DERA, CGI-26	318
PAHs-Aldehydes				
NP_061147.1	ACSS2	Acetyl-coenzyme A synthetase	ACSS2, ACAS2	701
NP_001004320.1	AGMO	Alkylglycerol monooxygenase	AGMO, TMEM195	445
NP_001619.1	AKR1B1	Aldo-keto reductase	AKR1B1, ALDR1	316
NP_001189342.1	AKR1A1	Aldo-keto reductase family	AKR1A1, ALDR1	325
NP_001957.2	EHHADH	Peroxisomal bifunctional enzyme	EHHADH, ECHD	723
AAA74449.1	ABAT	4-aminobutyrate aminotransferase	ABAT, GABAT	500
PAHs-Aromatic Amines-Aldehydes				
NP_036371.1	SIRT3	NAD-dependent protein deacetylase sirtuin-3	SIRT3, SIR2L3	399
NP_000889.3	MAOB	Amine oxidase	MAOB	520
NP_000774.2	CYP26A1	Cytochrome P450	CYP26A1, CYP26	497
NP_000231.1	MAOA	Amine oxidase	MAOA	527
Aromatic amines-Aldehydes				
NP_060220.3	RETSAT	All-trans-retinol 13	RETSAT, PPSIG	610
AAA96830.1	ALDH2	Aldehyde dehydrogenase	ALDH2, ALDM	517
NP_000764.1	CYP2E1	Cytochrome P450	CYP2E1, CYP2E	493
NP_001975.1	acetate	S-formylglutathione hydrolase	ESD	282
AAA68927.1	COMT	Catechol O-methyltransferase	COMT	271
NP_001356067.1	ALDH3A2	Aldehyde dehydrogenase family 3	ALDH3A2, ALDH10, FALDH	485
AAD13529.1	LRAT	Lecithin retinol acyltransferase	LRAT	230
NP_000481.2	AVP	Vasopressin-neurophysin 2-copeptin	AVP, ARVP, VP	164

Disease-causing genes

We found several genes that are activated by nicotine, PAHs, aromatic amines, and aldehydes, including BDKRB2, GPRC1C, MGLUR3, NNMT, ALDH1B1, ALDH7, DERA, CRABP2, ADH1A, ODC1, TLR6, JMJD1, and SARDH (Table 10). Bradykinin B2 receptor (BDKRB2) is a kinin protein responsible for cervical cancer in women (Zhou *et al.,* 2019), alternately BKR2 is responsible for subcutaneous and submucosal edema (Zając *et al.,* 2023). Aldehyde dehydrogenase 1B1 (ALDH1B1) is a mitochondrial enzyme responsible for alcoholism and several neurological diseases (Singh *et al.,* 2015), alternately the GK gene causes neonatal hypoglycemia (Barbetti *et al.,* 2009). CGI-26 is responsible for vitreoretinal degeneration in males (Huopaniemi *et al.,* 1999), the CRABP2 gene is responsible for cardiovascular disease (Salazar *et al.,* 2007), and the TNFSF18 gene causes etiopathogenesis of autism spectrum disorder (Bilgiç *et al.,* 2024).

Table 10. Genes interacting with nicotine, polycyclic aromatic hydrocarbons (PAH), aromatic amines, and aldehydes are responsible for cancer.

Compounds	Nicotine	Polycyclic aromatic hydrocarbons (PAHs)	Aromatic Amines	Aldehydes
Interacting genes	BDKRB2 BKR2 GRM2 GPRC1B MGLUR2 SUCNR1 GPR91 GRM3 GPRC1C MGLUR3	NNMT DERA CGI-26 TPI1 TPI ALDH1B1 ALDH5 ALDHX GK ALDH3A2 ALDH1A3 ALDH6 ALDH9A1 ALDH4 ALDH7 ALDH9 ALDH3	DERA CGI-26 ESD ADH1C ADH3 CRABP2 SIRT3 ADH1B ADH2 ADH7 ADH1A ADH1	ODC1 ADH5 ADHX FDH TNFSF18 GITRL TLR6 ALDH3A2 ALDH10 FALDH DMGDH ALDH3A1 ALDH3 KDM3A JMJD1 JMJD1A KIAA0742 SARDH KDM3B JMJD1B KIAA1082 ALDH3B2 ALDH8

Nicotine, PAHs, aromatic amines, and aldehydes are responsible for numerous human diseases by affecting their interactive human proteins and genes

This study found that nicotine interacts with several human genes and proteins, including BDKRB2, KNG1, GNA11, ACE, HTR2A, NPY, REN, SST, and CAMK2G. These proteins are involved in regulating different essential human body processes and affect numerous body functions. In humans, nicotine causes the release of adrenaline, which raises blood pressure and heart rate and has a role in the development of heart disease. Long-term nicotine consumption is associated with coronary artery disease (COD), stroke, and peripheral arterial disease (PAD) (Ahmad *et al.,* 2014).

However, PAHs interact with multiple proteins, such as nicotinamide a, deoxyribose-phosphate aldolase, ALDH1A3, Sorbitol dehydrogenase (SORD), Sphingosine kinase 1 (SPHK1), TNFRSF10C, DEF6, EHHADH, MAOA, and MAOB, and play crucial roles in regulating different physiological processes in the human body. The human immune system produces the enzyme nicotinamide N-methyltransferase. It inhibits adhesion molecule activity, ROS production, and nitric oxide synthase expression to aid in inflammatory clearance. It is commonly recognized that PAHs cause cancer. According to the International Agency for Research on Cancer (IARC), several PAHs are carcinogenic to humans. Extended exposure can raise the chance of developing several malignancies, such as lung, skin, bladder, and kidney cancer (Tarafdar *et al.,* 2020).

Additionally, we have discovered that 8 genes interact with aromatic amines, which play a significant role in several processes and disorders within the human body. Aromatic amines have been connected to several significant illnesses, including skin toxicity, reproductive problems, kidney toxicity, and malignancies, including those of the bladder, liver, and leukemia. Numerous aromatic amines are known to cause cancer and can have a role in the onset of other illnesses, particularly cancer especially bladder and liver cancer (Golka *et al.,* 2004). Aldehydes can interact with 8 particular human genes (**Table 11**) that encode various proteins with distinct activities in the human body. Numerous illnesses, such as malignancies, respiratory disorders, neurotoxic effects, skin irritation, and reproductive toxicity, have been related to aldehydes, especially formaldehyde and acetaldehyde. These chemicals are recognized as respiratory irritants and are associated with both acute and chronic respiratory conditions as well as potentially leading to cognitive and neurological impairments like Alzheimer's disease (AD), and Parkinson's disease (PD) (Corradi *et al.,* 2003; Fitzmaurice *et al.,* 2014).

Table 11. Proteins that bind to nicotine, polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and aldehydes are associated with disorders resulting from the dysfunction of these proteins and their specific processes.

Proteins	**Abnormalities**	**Respective mechanisms**
Interactions with nicotine		
BDKRB2	Skeletal muscular fibroblasts	Cytoskeletal formation
KNG1	Parkinson's disease	Nervous system
GNA11	Negatively regulating cell growth	Signaling pathway
ACE	Mental illness and substance misuse in adulthood	Nervous system
HTR2A	Mood disorders	Nervous system and reproductive system
NPY	Anxiety, depression, alcoholism, schizophrenia, and post-traumatic stress disorder	Nervous system
REN	Control blood pressure	Circulatory system
SST	Reduces gastric secretion	Endocrine process
CAMK2G	Heart failure and arrhythmia	Signaling pathway
Interactions with PAHs		
Nicotinamide a	Expression of adhesion molecules	Immune response process
Acetaldehyde	Atherosclerosis by Oxidation of LDL79, 80, 81, 82, 83	Circulatory system
ALDH1A3	Breast cancer	Signaling pathway
SORD	Hereditary neuropathy	Nervous system
SPHK1	Breast cancer and lung metastasis	Signaling pathway
TNFRSF10C	TRAIL-induced apoptosis	Programmed cell death
DEF6	Inactivation of T cells and myeloid cells	Immune system
EHHADH	Bladder cancer	Signaling pathway
MAOA	Alzheimer's disease, aggression, panic disorder, bipolar disorder, major depressive disorder, and attention deficit hyperactivity disorder	Nervous system
Interactions with aromatic amines		
EXOSC10	Liver cancer	Signaling pathway
RPL23A	p53-dependent cell cycle arrest	Cell differentiation
EIF5B	Lung cancer	Signaling pathway
NTNG2	Protein stability and cell surface expression	Cellular component biogenesis
GARS1	Production of glycine--tRNA ligase	Anatomical structure development
NBEA	Autism and epilepsy linked neurokeratin	Nervous system
GDI1	Genetic disorders	Hereditary system
COMT	Detoxification of stress hormones, influencing estrogen, dopamine, norepinephrine, and epinephrine	Endocrine process
Interactions with aldehydes		
ODC1	Decarboxylation of ornithine to putrescine	Amino acid metabolic process
TNF	Psoriatic arthritis, rheumatoid arthritis, ulcerative colitis, and Crohn's disease. It can also kill certain tumor cells	Immune response process
KDM2A	Expression of malignancy-related genes in esophageal squamous cell carcinoma	Molecular function
SARDH	Neurologic problems, growth failure, enlarged liver, cardiomyopathy, vision or hearing problems, and skeletal abnormalities	Amino acid metabolic process
SRM	Cell growth and differentiation	Cell differentiation
SAT1	Dengue virus targets RBM10, deregulating host cell splicing, and innate immune response	Immune response and molecular function
ESD	Retinoblastoma and Wilson's disease	Molecular function
LRAT	Mutations in the human LRAT gene cause retinal pathology	Molecular function

Discussion

Cigarette smoking susceptibility causes numerous diseases in the endothelium and oxidative stress, which is caused by the reactive oxygen and reactive nitrogen particles released from cigarette smoke (Csordas and Bernhard, 2013). Another study by Bernhard *et al.* (2007) revealed that cigarette smoking busts the human body's defense system and repair mechanisms, leading to cellular damage, including modifications and broken human proteins. Correspondingly, cigarette smoke heavily affects the plasma membrane of sperm cells and finally causes the apoptotic spermatozoa (Belcheva *et al.,* 2004). Also, this bad habit is responsible for RBC hemolysis by increasing 2,2′-azo-bis-(2-amidino-propane) dihydrochloride, and this proportion was 21.6% higher than in non-smokers (Asgary *et al.,* 2005). Likewise, Somborac-Bačura *et al.* (2013) demonstrated that cigarette smoke is responsible for endoplasmic reticulum anxiety, which may cause excess apoptosis and be accountable for the epithelial barrier's leakage and chronic obstructive pulmonary disease.

On the other hand, Hoffmann *et al.* (2013) and Aravamudan *et al.* (2014) observed that long-term cigarette smoke causes mitochondrial structure alterations, including fusion, branching, and quantity of cristae. Cigarette smoking strongly decreased the activity of liver function enzymes such as serum glutamic-pyruvic transaminase (SGPT), serum glutamic-oxaloacetic transaminase (SGOT), and alkaline phosphatase (ALP) in the blood (Atta *et al.,* 2019). Inflammation is a crucial factor for tissue repair, but cigarette smoking adversely affects the inflammation process by reducing the human body's molecular function and regulator activity (Gonçalves *et al.,* 2011). Likewise, (Lee and Pausova, 2013) found that cigarette smoking has numerous effects on DNA binding capacity and is responsible for DNA methylation as well as epigenetic alteration and several genetic diseases. Alternately, lipid transport is a crucial process in regulating homeostasis, but cigarette smoke affects lipid accumulation and binding and defects the lipid transport process.

Similarly, Grando *et al.* (2014) demonstrated that nicotine activates the nicotinic acetylcholine receptors responsible for several tumorigenic pathways in human cells. Alternately, nicotine may cause several cardiovascular diseases by releasing synaptic neural and systemic catecholamine, increasing heat rate, and affecting the sympathetic outflow by binding with brainstem regulatory centers as well as cardiac fibrosis and remodeling (Benowitz and Gourlay, 1997; Ialongo *et al.,* 2020). Instead, nicotine affects epithelial cell differentiation and malignant oral keratinocytes as well as inhibits cell growth by apprehending the cell cycle of the G_0/G_1 stage by increasing the articulation of $p21^{WAF1/CIP1}$ (Lee *et al.,* 2005; Kim *et al.,* 2012). Otherwise, smoking has several silent effects on hormone secretion which is mediated by pharmaceutical actions of cigarette smoke, and these effects are evident in testicular, thyroid, adrenal, pituitary, as well as insulin secretions (Kapoor and Jones, 2005).

Nicotine has toxic effects on the lungs and penetrates the lung's plasma membrane, which leads to the permeability of the membrane (Thelestam *et al.,* 1980). Likewise, nicotine increases extracellular vesicle formation at its outer layer and cytosol, which causes the tightening of the soft muscle cells and controls the formation of pulmonary hypertension (Zhu *et al.,* 2019). Another study found similar findings and Black *et al.,* (2001) demonstrated that nicotine has sensitive effects on the vasculature of the human skin and leads to the damage of endothelium-mediated reduction of vascular tension of human skin. Nicotine elevates smoking by enhancing its binding to the β_2-mediating nicotinic acetylcholine receptors in the human brain (Esterlis *et al.,* 2013). Alternately, nicotine improved the secretion of platelet-derived growth which may cause modifications of the structure of cytoskeletal association (Cucina *et al.,* 2000). Although nicotine binds with numerous human proteins that have specific functions to regulate body functions, our study identified these possible functions by functional analysis. It demonstrated that nicotine heavily affects human biological processes, cellular components, and molecular functions.

PAHs disrupt specific signaling pathways such as MAPK, immune responses, neurological responses, and other pathways by affecting the human body's endocrine system and the estrogen signaling pathway (Zhang *et al.,* 2016). PAHs developed the PAH-DNA adducts and reactivated the aryl hydrocarbon receptor, leading to cell and murine embryo cell death (Detmar *et al.,* 2006). Likewise, PAHs severely affect the functional differentiation of living organisms and the maturation of blood monocyte-derived dendritic cells, which cause immunotoxicity (Laupeze *et al.,* 2002). In the formation of gray matter in the left hemisphere, PAHs significantly inhibit the formation of this matter and cause several neural diseases, such as attention deficit, behavioral disturbances, and injured neural cells (Tang *et al.,* 2003). Another study by Hu *et al.* (2015) suggested that PAHs were responsible for insulin resistance and β-cell disorder of pancreas cells; the leading cause of this is the supportive behavior of PAHs on some carbohydrate metabolic processes or syndromes.

Further studies found that PAHs have various effects on plasma membranes because this compound breaks their cellular integrity, finally leading to cellular death (Meador, 2008). Likewise, PAHs affect cellular calcium absorption into the endoplasmic reticulum and ATP hydrolysis via different manners, such as dose-dependent PAHs intake, disruption of intracellular calcium absorption, and defects in calcium-mediated signaling (Krieger *et al.,* 1995). Another study demonstrated that PAHs are responsible for chromosomal abnormalities, a sophisticated part of carcinogenesis (Agova *et al.,* 2005). The crucial findings related to the adverse effects of PAHs are Aldo-keto reductases activated by the carcinogen compounds PAHs in the cell lines of the human lung (Penning, 2014). PAHs are also responsible for Asthma because they mainly affect the lung cells, Wang *et al.,* (2019) demonstrated that PAHs and the epoxide hydroxylase 1 gene are involved in asthma's formation, provoking, and pathogenic modifications.

Aromatic amines can disrupt the normal immune responses of the human immune system due to their severe effects on the immune response process (Cho and Uetrecht, 2017). Similarly, this carcinogenic chemical affects cell differentiations and ATP production by removing electrons from the respiratory cycle (Neumann, 2007). Another study found that aromatic amines

severely affect the chromosomal structure and DNA structure, disrupting DNA single strands and breaking DNA double strands (Barnes *et al.,* 2018). Aromatic amines play a significant role in the development of bladder cancer. According to Vineis and Pirastu (1997), the exposure of humans to aromatic amines and the subsequent risk of bladder cancer is mainly influenced by metabolic polymorphisms and the N-acetyltransferase genotype. Another study suggests that when aromatic amines undergo metabolism, they bind to DNA and create DNA mutations responsible for cancer development, including skin cancer. (Turesky, 2002). An additional investigation revealed that the AOX and XOR enzymes are molybdenum hydroxylases, which facilitate the reduction of numerous chemical groups and the oxidative degradation of diverse heteroaromatic chains and aldehydes (Rendić *et al.,* 2022).

The pie chart indicates that aldehydes exert influences on signaling pathways. Another investigation by Averill-Bates and Tanel (2024) observed that the levels of aldehydes have risen due to the expanding understanding that links these acute aldehydes to a broad spectrum of pathophysiology, such as neurodegenerative diseases, multiple lung disorders like chronic asthma, atherosclerosis, and specific types of cancers. Alternately, exposure to formaldehyde can cause mild headaches as well as potentially lead to permanent neurotoxicity along with brain tumors. Low amounts of acute exposure result in stimulation, even with greater concentrations, causing peripheral nervous system atrophy (Abdu *et al.,* 2014). A separate investigation has demonstrated that lipid aldehydes are generated through lipid peroxidation inside human sperm. This leads to a decline in sperm mobility and cell destruction. The researchers suggested that this type of aldehyde is the primary indicator for detecting oxidative damage in men's reproductive cells. (Moazamian *et al.,* 2015).

The harmful effects of aldehydes can disrupt the structure of a typical cell and its cellular components. Another study found that aldehyde dehydrogenases (ALDHs) are crucial enzymes that detoxify harmful aldehydes by facilitating their conversion into non-reactive acids via oxidation. However, the presence of aldehydes hinders the formation of this enzyme, leading to cellular damage and contributing to the development of cardiac disorders (Chen *et al.,* 2010). Meanwhile, Sapkota and Wyatt (2015) aldehydes can create persistent and volatile additives when combined with nucleophilic target molecules such as DNA, lipids, and proteins. This adduction can disrupt cellular activities and potentially damage proteins, nucleic acids, and lipids. Likewise, membrane vesiculation and myelin figures arise due to aldehydes' inability to prevent lipids' mobility in highly flexible membranes. However, exocytic activity occurs when aldehydes are fixed (Seckler *et al.,* 2020).
Aldehydes phospho-transferase pathway component promotes the formation of 4-HNE inside the cells. 4-HNE is an enzyme associated with xenobiotic metabolism and can potentially induce mitochondrial damage (Sharma *et al.,* 2022). Following functional annotation, we note that nicotine, polycyclic aromatic hydrocarbons (PAH), aromatic amines, and aldehydes substantially impact biological processes, cellular components, and molecular activities. These factors have the potential to result in severe health complications such as cancer, neurological impairment, disruption of signaling pathways, infertility, and various other ailments.

The Bdkrb2 gene, which is expressed in the aorta of the cardiovascular system, is a gene that causes cancer. The presence of nicotine significantly enhances the production of Bdkrb1 protein, as demonstrated by Al Hariri *et al.* (2016). Macrocytosis is a heterogeneous medical illness characterized by abnormal mast cells. It is usually acquired rather than inherited, and survival rates differ depending on the age at which it develops. A Gallardo *et al.* (2021) study revealed that the GRM2 gene is responsible for macrocytosis, and its expression can be altered by exposure to nicotine. The incidence of oral cancers is highest among individuals who consume alcohol and tobacco. These cancers are associated with the mGluR2 and mGluR3 receptors connected to Gai/o proteins. Activation of Gai/o proteins inhibits adenylyl cyclase and decreases cAMP synthesis, ultimately resulting in the development of oral cancer (Rigi-Ladiz *et al.,* 2019).

A different investigation has shown that NNMT affects the growth and ability to form tumors in both respiratory and mouth carcinoma cells. Both cigarette smoking and PAHs impact this gene (Seta, 2017). On the other hand, aldehyde dehydrogenases (ALDHs) comprise catalysts that rely on NAD(P)+ as a cofactor. They catalyze the conversion of naturally occurring and externally introduced aldehydes into their respective acids. However, Chen *et al.* (2011) they demonstrated that ALDH1B1, ALDH9A1, and ALDH3A2 exhibit elevated expression in human epithelium malignancies. In contrast, ALDH1B1 has significant expression in carcinoma among all malignant cells. However, Soucek *et al.* (2010) they demonstrated that ADH1C was recognized as a distinct risk factor for the formation of alcohol-related cancers in persons who consume large amounts of alcohol. Although cigarette smoking has numerous effects on human health and several carcinogenic compounds released from tobacco burning, including nicotine, PAHs, aromatic amines, and aldehydes, these compounds influence carcinogenic genes in human health.

Guanine nucleotide-binding protein subunit alpha-11 is a protein that binds with nicotine, and Asada *et al.* (2003) showed that it has a role in activating the hormone gonadotropin receptors, which has a deleterious effect on cell development. Likewise, Manyema *et al.* (2018) found that the angiotensin-converting enzyme (ACE) is released through the neural process and has a role in long-term health issues, psychiatric disorders, and substance abuse during adulthood. However, there is a significant effect for mental disorders caused by the specific variant of HTR2A protein, and there is a relationship with experiences of sexual and physical assault that influences suicide attempts as well (Sprooten *et al.,* 2009). Likewise, renin is a digestive enzyme responsible for regulating blood pressure and maintaining optimal amounts of K^+ and Na^+ in the human body. However, nicotine has significant effects on renin and can make maintaining blood pressure difficult.

Nevertheless, PAHs considerably diminish this enzyme's efficiency (Lappas and Permezel, 2011). On the contrary, we found that PAHs interact with aldehyde dehydrogenase 1 family member A3 (ALDH1A3) and sphingosine kinase 1

(SPHK1) genes that code for two proteins that regulate the plasminogen-stimulating pathway to promote metastasis and invasion (Bharadwaj *et al.,* 2024). An additional interactive gene is member 10C of the tumor necrosis factor receptor superfamily (TNFRSF10C), an inhibitory receptor that impedes programmed cellular death and cytotoxicity (Johnstone *et al.*, 2008). Monoamine oxidase A (MAO-A) and Monoamine oxidase B (MAO-B) are enzymes the MAOA and MAOB genes synthesized, respectively. When exposed to polycyclic aromatic hydrocarbons (PAHs), the MAOA and MAOB genes undergo mutations, resulting in monoamine oxidase deficiency, also known as Brunner syndrome. MAO-A is also linked to various other conditions, such as Alzheimer's disease, aggressiveness, anxiety, and bipolar disorder (Van Rhijn *et al.*, 2022; Xia *et al.*, 2018).

Exosome complex component 10 (EXOSC10) is a gene responsible for the immune disorder, Meng *et al.* (2023) exhibited that the human hormone EXOSC10 is an adverse prognostic indicator of liver cancer. Netrin-G2 is a gene that codes for a protein that creates cellular components. It has a detrimental impact on protein integrity and the synthesis of proteins on the cell membrane (Dias *et al.,* 2019). Alternately, the Ras-related protein Rab-5A is a gene with molecular functions. Aromatic amines cause mutations of this gene. D'Adamo showed that this gene mutation is prevalent in this particular gene and does not appear to affect gene expression, thus not leading to any observable changes in an organism's physical characteristics (phenotype). This study also found that aromatic amines bind with an enzyme of the nervous system, namely catechol O-methyltransferase; it controls how the brain reacts to stress and Wiegand *et al.,* (2021) demonstrated that it has a role in the breakdown and elimination of stress hormones, affecting the levels of testosterone, norepinephrine, dopamine, and epinephrine in the human body.

The gene ODC1 encodes an enzyme involved in the metabolic process of amino acids. It synthesizes polyamines, specifically putrescine, spermidine, and spermine, by converting ornithine into putrescine through decarboxylation (Prokop *et al.*, 2021). Tumor necrosis factor ligand superfamily member 18 (TNF 18) is a protein of the human immune system that plays a role in inflammatory disorders such as psoriatic and inflammatory bowel diseases. It also induces apoptosis in specific tumor cells (Jang *et al.,* 2021). Lysine demethylase 2A (KDM2A) is a gene that encodes a protein and has molecular activities. It has two distinct functions in modulating the proliferation of genes associated with malignancies in squamous cell carcinoma of the esophagus (Wang *et al.*, 2022). Spermidine synthase (SRM) is an enzyme responsible for synthesizing the polyamine precursor spermidine, which plays a crucial role in maintaining the pH level in the human body. Spermidine is a widely distributed polycationic mediator involved in cell proliferation and differentiation. However, the activity of the SRM enzyme is greatly affected by aldehydes (Nakanishi and Cleveland, 2021). The S-formylglutathione hydrolase gene encodes an enzyme belonging to the serine hydrolase family. This enzyme is utilized as a marker of gene expression for retinal tumors and Wilson's syndrome, as well as has several molecular functions (Kumar *et al.,* 2021). This study conclusively demonstrated the detrimental effects of cigarette smoking on human health and its impact on animals and the environment.

Conclusion

Cigarette smoking is a threat to humankind as it has several atrocious effects on human beings. Cigarette smoking is not only harming smokers; it can also harm the people around them. Sometimes nicotine, polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and aldehydes act as mutagens; if parents consume cigarettes, it can cause genetic defects in their children. Cigarette smoking should be strongly prohibited. Tobacco and other sources that produce nicotine, polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and aldehydes should be avoided, and stay aware of the risk of cancer-causing compounds. Our study demonstrated that these four types of carcinogenic compounds are strongly connected with more than 200 proteins, and these proteins have crucial functions in maintaining human biological processes, cellular components, and molecular functions. We analyzed many research studies that have already been conducted and found that these compounds have no beneficial functions in the human body. As nicotine, polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and aldehydes can harm human health and even cause cancer, these compounds should be marked as hazardous, and people should be careful about using these compounds. This study identified 10 genes associated with nicotine, 17 genes associated with PAHs, 12 genes associated with aromatic amines, and 23 genes associated with aldehydes. These genes are responsible for many forms of human tumors and malignancies. In our investigation, we discovered that 9 genes have interactions with nicotine, 10 genes with PAHs, 8 genes with aromatic amines, and 8 genes with aldehydes. These genes encode different proteins and are associated with various human health disorders. This study definitively established the harmful consequences of cigarette smoking on human health, as well as its repercussions on creatures and the natural world. By avoiding cigarette smoking, we can avoid cancer, which is caused by nicotine, polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and aldehydes.

Ethical approval

The authors have complete confidence that publishing this manuscript will not cause any ethical concerns

Data availability

The data used to support the findings of this study are available from the submitting or corresponding author on request.

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Conflicts of interest

The authors declare there is no conflict of interest.

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