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An *In Silico* Study on Target Gene Identification and Oral Health Conditions Linked to Coal Dust Exposure

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ABSTRACT

The second-largest coal-producing region in Indonesia is South Kalimantan. Coal mines have an impact on the accumulation of coal dust that flies into the residential areas of local communities. The prediction of coal dust exposure-induced genes and health conditions can be conducted through *in silico* study. This study is aimed to identify target genes and oral health conditions linked to coal dust exposure through an *in silico* study. Key coal compounds and oral health-related target genes were determined using network pharmacology analysis platforms. The datasets were downloaded from CTD database. GO and KEGG pathway enrichment analyses were performed using DAVID bioinformatics. PPI network was constructed using STRING. The disease-related genes integrative analysis was performed through CTD and HPA. Fifteen coal exposure markers were obtained to identify the gene interaction. The two main exposure markers were particulate matter and benzo(a)pyrene. There were 20 genes with more than 100 interactions selected as the coal dust exposure marker-related genes. Information on biological processes, cellular components, molecular functions, and pathway enrichment were obtained ($p<0.05$, FDR corrected). The PPI network was constructed. Target genes related to oral health conditions and coal dust exposure were found to be IL6, PTGS2, TNF, IL1B, CXCL8, MAPK3, TP53, RELA, CCL2, and HMOX1. The oral health conditions that were strongly linked to coal dust exposure were inflammation, necrosis, edema, pain, hyperplasia, and neoplasms. In conclusion, the main target gene identified was IL6, indicating a major role in inflammatory pathways affecting oral health conditions linked to coal dust exposure.

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INTRODUCTION

Coal is a sedimentary rock consists of organic and inorganic components (Kroon *et al*., 2020; Puspita *et al*., 2022). It was formed from biochemical and geochemical decomposition of various vegetations (Akbar *et al*., 2022). The high amount of coal and its easy processing are the main reasons of the utilization of this natural resource, especially for the energy production, fuel, industrial sector, export and domestic use (Ammar Azzam *et al*., 2019; Damayanti, 2018; Petrus *et al*., 2020; Rahman *et al*., 2019; Suhat *et al*., 2020). Coal in Indonesia is very potential (Petrus *et al*., 2020). Overall, the amount of coal in Indonesia reaches 49,44% that spreads across South Sumatra (38,01%), South Kalimantan (7,68%) and East Kalimantan (3,75%) (Rahman *et al*., 2020; Sira *et al*., 2021). Commodities of coal mining production in South Kalimantan reach 63,2 million tons (BPS-Statistics of Kalimantan Selatan Province, 2022; Pratidina *et al*., 2022).

One of the main issue involved in coal mining sector is the coal dust (Liu & Liu, 2020).

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The sequence of coal cutting, transportation and preparation processes produce inhalable coal dust with the diameter less than 10 μm and that could penetrate the terminal bronchiolus in gas exchange area of the lung. The main factors related to the harmful effect of the coal dust are the particle size, mineralogy, morphology, surface area, and the chemical composition of coal dust (Zazouli *et al*., 2021). Some research stated the characteristics of coal dust such as cytotoxic, pro-inflammatory and pro-fibrotic with complex development mechanism (Mu *et al*., 2022). It is one of the occupational health hazards that potentially induces disease development in human (Zhang *et al*., 2021). Beside the direct workplace exposure, prior research showed that the dust from coal mine could fly to the nearest residential area and potentially cause health problems to the local community (Kamanzi *et al*., 2023).

The existence of this air pollution raises the awareness to the oral health as one of the key components of overall health (Hart, 2020; Vo *et al*., 2020). Oral health conditions have the potential of multi-organs systemic implication and play an important role in systemic diseases (Fiorillo, 2019). Moreover, oral health conditions can imply the individual well-being and overall quality of life (Samaranayake, 2022; Vozza, 2021). However, there is no specific and comprehensive study of the coal dust impact to oral health conditions. The target genes and potential mouth diseases can be predicted through toxicology *in silico* study.

Toxicology *in silico* study is a term that refers to the utilization of various computational tools to collect, analyze, model, simulate and predict toxicokinetic properties or potential toxicity of a chemical substance from its molecular structure (Cronin *et al*., 2023; Hernandez, 2021; Myatt *et al*., 2022; Pandey *et al*., 2022). *Comparative Toxicogenomic Database* (CTD) is a manually curated literature-based public resources that provides the information of chemical compound, gene interaction, phenotype, Gene Ontology (GO) terms, and disease-pathway relation to increase the understanding of the impact of environmental exposure on human health conditions (Alarabi *et al*., 2023; Chai *et al*., 2021; Sendra *et al*., 2021; Stanic *et al*., 2021). The objective of this study is to identify target genes and oral health conditions linked to coal dust exposure.

MATERIAL AND METHODS

Datasets Download

Genes and proteins were obtained in Comparative Toxicogenomics Database (http://ctdbase.org/ (accessed on 9 March 2024)) in March 2024. Relevant information of the coal dust exposure were collected. Specifically, there were 15 exposure markers of the coal dust exposure. For CTD database, the gene interaction includes the increase and decrease of mRNA expression. Gene interactions quantification was based on the published literature curation using a hierarchial interaction type vocabulary which characterizes common biochemical, regulatory, and physical chemical-genes/protein interactions. Genes with more than 100 interactions were considered as genes with high interaction (Jiang *et al*., 2022).

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway Enrichment Analysis

After searching for the gene interactions of the coal dust exposure in CTD database, genes with more than 100 interactions were chosen as coal dust-related genes. In order to explore the molecular and biological functions, GO and KEGG functional annotation pathway enrichment analysis were performed in DAVID Bioinformatics website (https://david.ncifcrf.gov/tools.jsp). The biological process, molecular function and cellular component analyses were conducted; FDR (False Discovery Rate) correction and $p<0.05$ were chosen as the threshold in the analysis of this study.

Protein-Protein Interaction (PPI) Network and Hub Genes Identification

Protein-Protein Interaction (PPI) Network was performed using STRING functional protein association networks (https://string-db.org/ (accessed on 10 March 2024)). Various life aspects such as the regulation of gene expression, transmission of biological signal, metabolism of energy & material, and cell cycle regulation can be understood through most protein interactions in biological system. The Protein-Protein Interaction (PPI) information were downloaded. Selection was made based on high interaction score. Active interaction scores were based on textmining, experiments, neighborhood, gene fusion, databases, co-occurrence and coexpression. The interaction score of ≥0.4 was chosen as the selection criterion. Furthermore, interactive protein count from STRING was analyzed and visualized using Cytoscape 3.10.1. Hub genes were defined as highly node-connected genes in a module and considered functionally significant. In this study, 10 highest hub genes were chosen. The hub genes were filtered based on the value degree as the parameter using the Cytohubba plug-in of the Cytoscape. Darker performance color represents larger value degree.

Identification of Oral Health Conditions-Related Genes Linked to Coal Dust Exposure

In order to understand the main consequence of oral health linked to coal dust exposure, co-interaction genes analysis was performed. Co-interaction quantification was based on the inference score which counted as log-transformed product from two common-neighbor statistics. The first statistic calculates the chemical-disease connectivity and gene counts in order to generate the inference. The second statistic calculates each of the genes connectivity in order to generate the inference. Gene-disease interaction data was obtained from CTD database. The potential tissue-specific effects were evaluated using human gene expression diagrams from the Human Protein Atlas (HPA) website (https://www.proteinatlas.org/). The RNA expression of the hub genes were observed by selecting the proximal digestive tract group which consisted the oral mucosa, salivary gland, esophagus and tongue. RNA expression shows the consensus data that were fueled by RNA sequencing approach which had mRNA transcripts detection ability from tissue sample. The nTPM (transcripts per million) values indicates the detected transcripts rate for a given gene.

RESULTS AND DISCUSSION

Identification of Coal Dust Exposure-Related Gene Datasets

After comprehensive search for the information of coal dust exposure in CTD database, the total number of 15 exposure markers were obtained. Those markers are particulate matter, acenaphthylene, benz(a)anthracene, benzo(a)pyrene, benzo(b)fluoranthene, 1,12-benzoperylene, benzo(k)fluoranthene, chrysene, 1,2,5,6-dibenzanthracene, fluoranthene, fluorene, indeno(1,2,3-cd)pyrene, naphthalene, phenanthrene, and pyrene. Through the database, genes that related to each exposure markers were obtained (Figure 1). In order to clarify the coal dust exposure-affected biological processes, common affected genes (based on interaction count from CTD) were chosen for further analysis. Genes with more than 100 interaction counts were considered as coal dust exposure-highly related genes. The total number of 62 coal dust-related genes were retrieved. Among those genes, the total number of 20 genes showed more than 100 interactions. Among those selected genes, aryl hydrocarbon receptor, AHR (with 1987 interaction counts); cytochrome P450 family 1 subfamily A member 1, CYP1A1 (with 713 interaction counts); interleukin 6, IL6 (with interaction 588 counts); tumor necrosis factor, TNF (with 464 interaction counts); C-X-C motif chemokine ligand 8, CXCL8 (with 365 interaction counts); interleukin 1 beta, IL1B (with 355 interaction counts); cytochrome P450 family 1 subfamily B member 1, CYP1B1 (with interaction 290 counts); NFE2 like bZIP transcription factor 2, NFE2L2 (with 254 interaction counts); and heme oxygenase 1, HMOX1 (with 220 interaction counts) showed

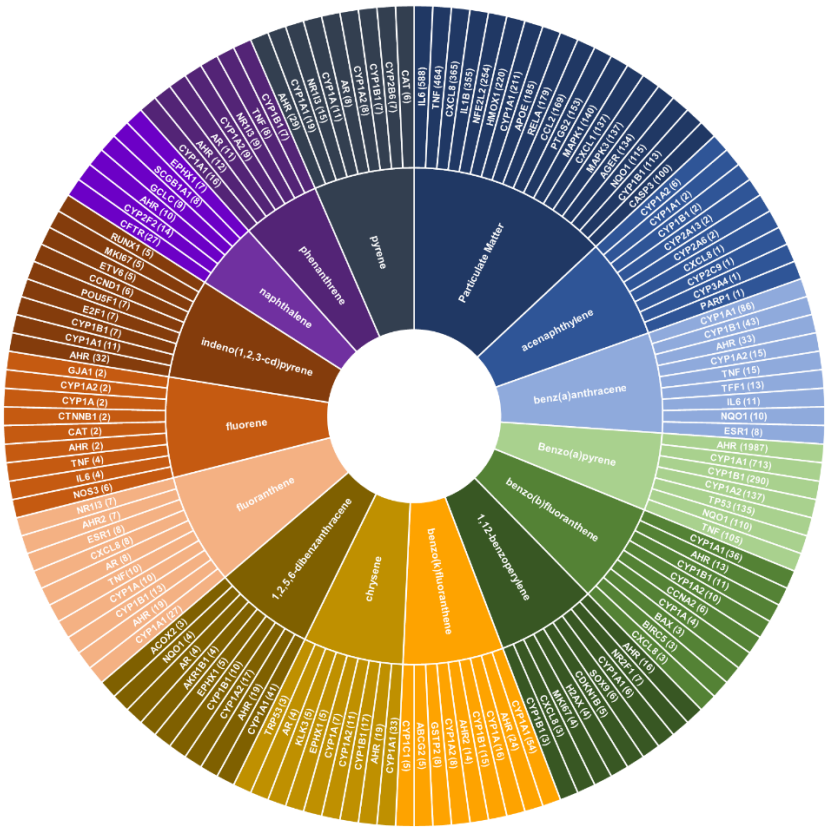

Fig. 1. Exposure markers and related genes with interaction counts

highest interaction levels. In addition, there were downregulated genes found in these findings such as 4-aminobutyrate aminotransferase (ABAT) gene that has significant roles in gamma-aminobutyric acid (GABA) catabolism which is a substantial inhibitory neurotransmitter, and adipogenesis associated Mth938 domain containing (AAMDC) which related to various metabolic enzymes (Golden *et al*., 2021; Parviz *et al*., 2014). However, those genes were not considered as coal dust exposure-highly related genes due to their low amount of interaction counts.

GO and KEGG Pathway Enrichment Analysis

GO and KEGG functional annotation pathway enrichment analysis were performed in DAVID Bioinformatics (https://david.ncifcrf.gov/tools.jsp) with the selection of *Homo sapiens* annotation. The result of KEGG pathway enrichment analysis showed that the most common terms were related to lipid and atherosclerosis, IL-17 signaling pathway, AGE-RAGE signaling pathway in diabetic complications, TNF signaling pathway, chemical carcinogenesis - reactive oxygen species, human cytomegalovirus infection, Chagas disease, NOD-like receptor signaling pathway, Yersinia infection, and Pertussis.

Result of the analysis showed involvement of 184 biological process terms, including inflammatory response, cellular response to tumor necrosis factor, positive regulation of gene expression, positive regulation of VEGF production, cellular response to lipopolysaccharide, lipopolysaccharide-mediated signaling pathway, response to oxidative stress, cellular response to organic cyclic compound, cellular response to hydrogen peroxide, and positive regulation of interleukin-6 production. There were 10 cellular component terms, including caveola, endoplasmic reticulum lumen, extracellular region, extracellular space, endoplasmic reticulum

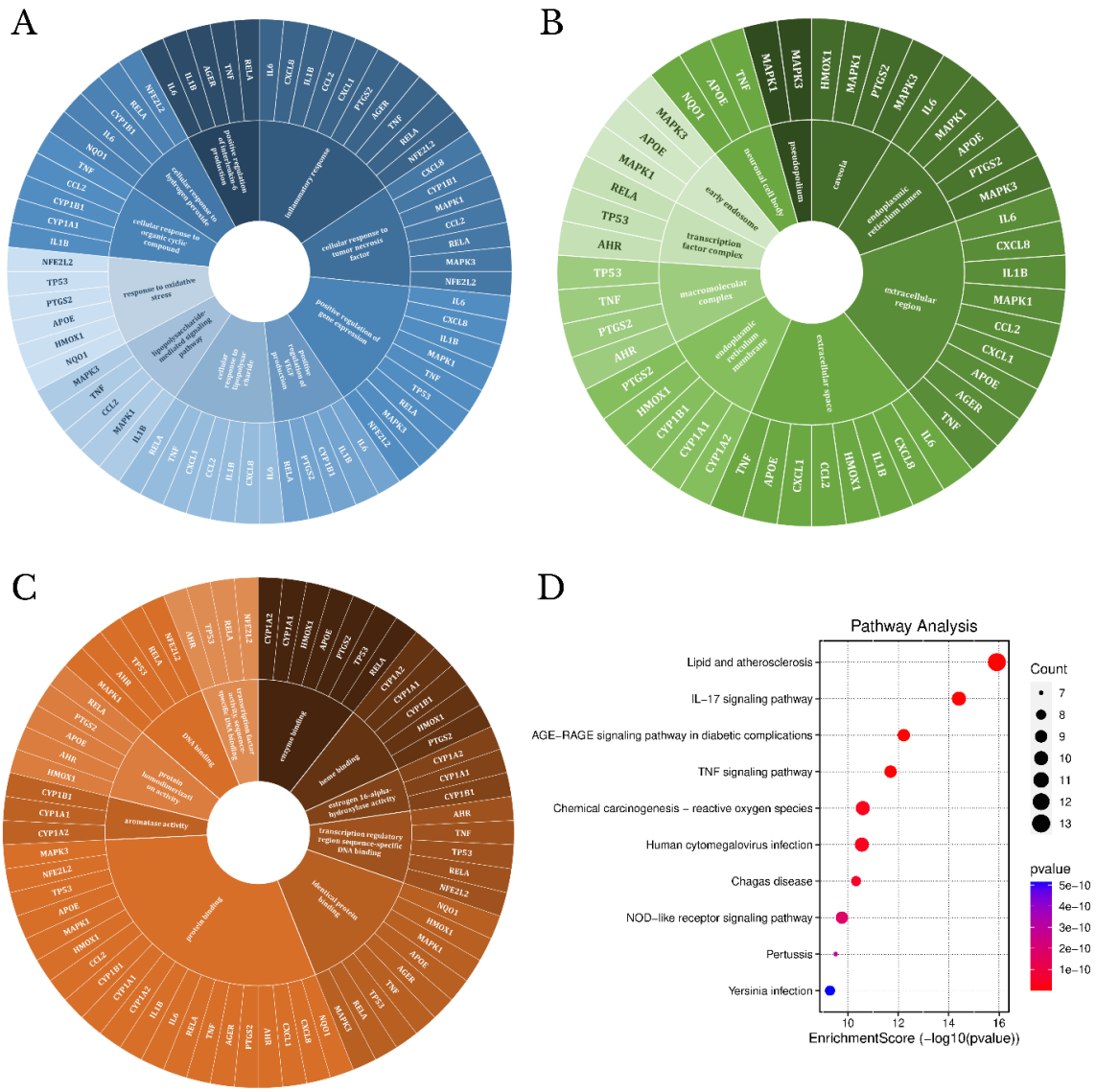

Fig. 2. GO and KEGG pathway analysis. (A) Biological processes. (B) Cellular components. (C) Molecular functions. (D) KEGG

membrane, macromolecular complex transcription factor complex, early endosome, neuronal cell body and pseudopodium. There were 27 molecular function terms including enzyme binding, heme binding, estrogen 16-alpha-hydroxylase activity, transcription regulatory region sequence-specific DNA binding, identical protein binding, protein binding, aromatase activity, protein homodimerization activity, DNA binding transcription factor activity, and sequence-specific DNA binding. Further discussion would focus on three main pathways which are IL-17 and TNF signaling pathway that related to inflammation response and pathway of chemical carcinogenesis - reactive oxygen species.

PPI Network Construction and Hub Genes Identification

PPI Network was constructed using STRING (Figure 3). The PPI Network included 25 nodes and 184 edges. The degree value correlated with node size, and the co-expression value related to small node. Data from STRING was downloaded and analyzed using Cytoscape 3.10.1 to

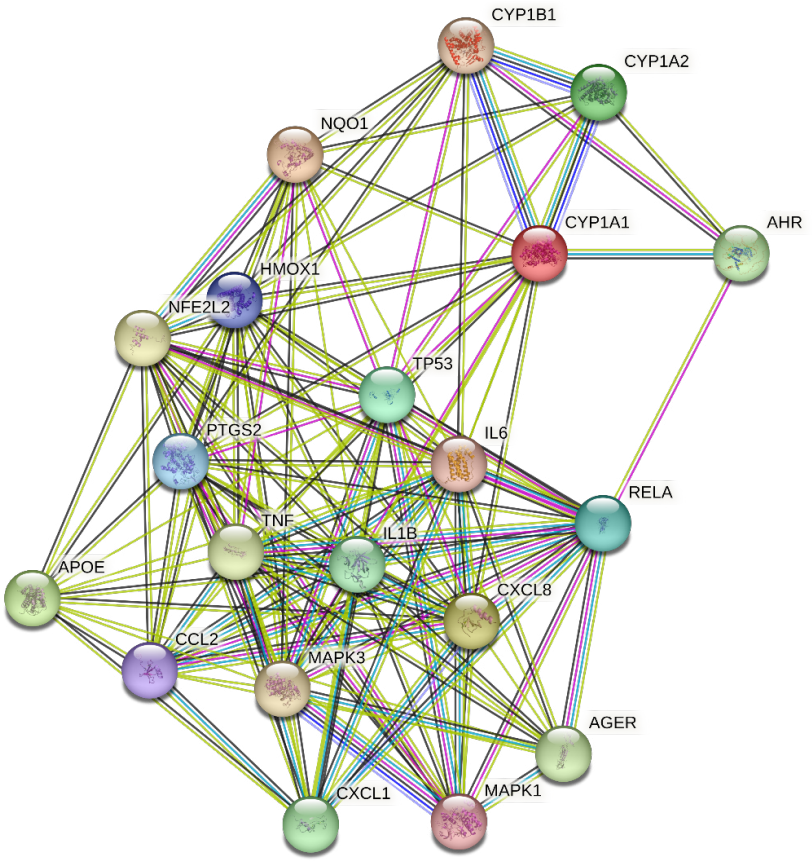

Fig. 3. PPI network construction

find the hub genes for further exploration to identify the role of interactive genes in coal dust exposure. Ten highest degree value genes were obtained (Figure 4). It showed that IL6, PTGS2, TNF, IL1B, CXCL8, MAPK3, TP53, RELA, CCL2, and HMOX1 may have important roles in coal dust exposure-induced disease pathogenesis.

Oral Health Conditions-Related Genes Linked to Coal Dust Exposure Analysis

Further analysis of top 10 highest degree value genes were performed based on the result of PPI network construction. Degree value analysis result showed that IL6, PTGS2, TNF, IL1B, CXCL8, MAPK3, TP53, RELA, CCL2, and HMOX1 had the highest degree value. As a follow-up to determine the gene-mouth disease correlation, gene interaction data were downloaded from CTD database. Manual identification was performed on 150 disease list in each gene based on the inference score. Correspondences between interaction genes and oral health conditions are showed in Figure 5 and Table 1. Main conditions related to coal dust exposure were inflammation, necrosis, edema, pain, hyperplasia and neoplasms. Mouth diseases with lower inference scores were Kaposi sarcoma, Coxsackievirus infection, Behcet syndrome, trigeminal neuralgia, oral leukoplakia, and oral submucous fibrosis. The potential tissue-specific effects for the proximal digestive tract group through hub genes RNA expression (nTPM) analysis are presented in Table 2.

Analysis of Target Gene, Pathways and Oral Health Conditions

This study was based on a specific and integrated coal dust exposure analysis. The results of 15 exposure markers analysis showed 20 genes (AHR, CYP1A1, IL6, TNF, CXCL8, IL1B,

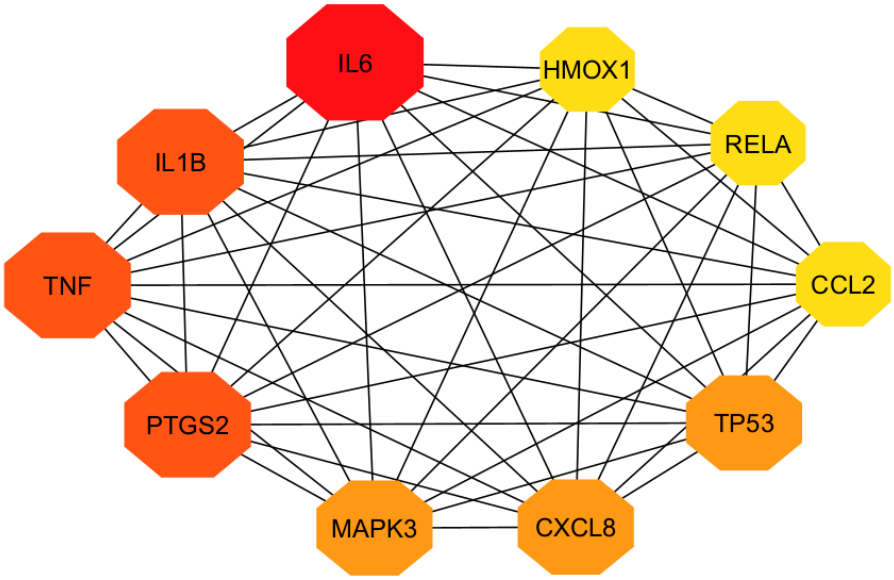

Fig. 4. Hub Genes PPI Network, from yellow to red, the degree value increases gradually

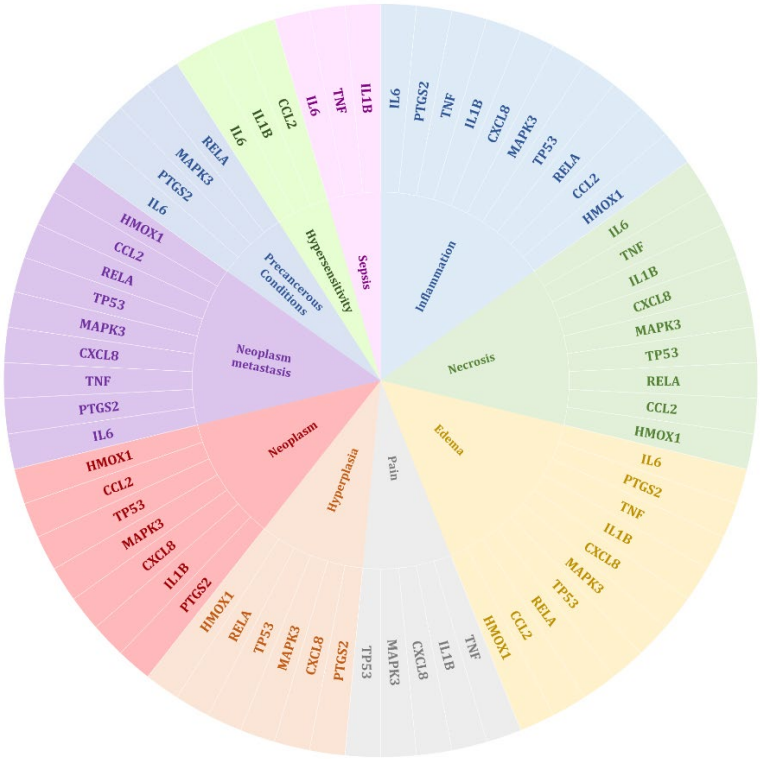

Fig. 5. Coal dust exposure-related oral health condition

CYP1B1, NFE2L2, HMOX1, APOE, RELA, CCL2, PTGS2, MAPK1, CXCL1, MAPK3, CYP1A2, TP53, AGER, and NQO1) with high interaction due to coal dust exposure. Among those genes, AHR showed highest interaction count. AHR gene encodes cytoplasmic receptor protein that plays important role in xenobiotic metabolism through the regulation of xenobiotic

enzyme expression such as CYP1A. AHR protein is known for its important role in various physiological pathways including cell growth, differentiation, barrier function and immune response (Fang *et al*., 2023; Kwong *et al*., 2024). IL6 was identified as the key gene with the third highest interaction count following AHR and CYP1A1. IL6 gene encodes cytokine that

Table 1. Coal dust exposure-related mouth diseases

Disease	Gene	Pathway	Pathway ID
Mucositis	IL1B	Cytokine Signaling in Immune system	REACT:R-HSA-1280215
		Immune System	REACT:R-HSA-168256
		Interleukin-10 signaling	REACT:R-HSA-6783783
		Signaling by Interleukins	REACT:R-HSA-449147
		Cytokine-cytokine receptor interaction	KEGG:hsa04060
		Amoebiasis	KEGG:hsa05146
		Hematopoietic cell lineage	KEGG:hsa04640
		IL-17 signaling pathway	KEGG:hsa04657
		Malaria	KEGG:hsa05144
		African trypanosomiasis	KEGG:hsa05143
Osteoporosis	IL6	Immune System	REACT:R-HSA-168256
		Signal Transduction	REACT:R-HSA-162582
		Cytokine Signaling in Immune system	REACT:R-HSA-1280215
		Signaling by Interleukins	REACT:R-HSA-449147
		MAPK1/MAPK3 signaling	REACT:R-HSA-5684996
		MAPK family signaling cascades	REACT:R-HSA-5683057
		Cellular responses to stress	REACT:R-HSA-2262752
		Amoebiasis	KEGG:hsa05146
		Cytokine-cytokine receptor interaction	KEGG:hsa04060
		HTLV-I infection	KEGG:hsa05166
Postmenopausal Osteoporosis	TNF|IL1B	Immune System	REACT:R-HSA-168256
		AGE-RAGE signaling pathway in diabetic complications	KEGG:hsa04933
		Amoebiasis	KEGG:hsa05146
		Chagas disease (American trypanosomiasis)	KEGG:hsa05142
		Cytokine-cytokine receptor interaction	KEGG:hsa04060
		Cytokine Signaling in Immune system	REACT:R-HSA-1280215
		HTLV-I infection	KEGG:hsa05166
		Inflammatory bowel disease (IBD)	KEGG:hsa05321
		Influenza A	KEGG:hsa05164
		Interleukin-4 and 13 signaling	REACT:R-HSA-6785807
		African trypanosomiasis	KEGG:hsa05143
Sarcoma, Kaposi	IL6	AGE-RAGE signaling pathway in diabetic complications	KEGG:hsa04933
		Amoebiasis	KEGG:hsa05146
		Antifolate resistance	KEGG:hsa01523
		Cellular responses to stress	REACT:R-HSA-2262752
		Cellular Senescence	REACT:R-HSA-2559583
		Chagas disease (American trypanosomiasis)	KEGG:hsa05142
		Cytokine-cytokine receptor interaction	KEGG:hsa04060
		Cytokine Signaling in Immune system	REACT:R-HSA-1280215
		Cytosolic DNA-sensing pathway	KEGG:hsa04623
Coxsackievirus infections	IL6|TNF	Cytokine-cytokine receptor interaction	KEGG:hsa04060
		Cytokine Signaling in Immune system	REACT:R-HSA-1280215
		Immune System	REACT:R-HSA-168256
		TNFR2 non-canonical NF-kB pathway	REACT:R-HSA-5668541
		TNF signaling pathway	KEGG:hsa04668
		African trypanosomiasis	KEGG:hsa05143
		AGE-RAGE signaling pathway in diabetic complications	KEGG:hsa04933
Trigeminal Neuralgia	TNF|IL1B	Amoebiasis	KEGG:hsa05146
		Antifolate resistance	KEGG:hsa01523
		Chagas disease (American trypanosomiasis)	KEGG:hsa05142
		Immune System	REACT:R-HSA-168256
		Innate Immune System	REACT:R-HSA-168249
		MAPK signaling pathway	KEGG:hsa04010
		Signal Transduction	REACT:R-HSA-162582
		Chagas disease (American trypanosomiasis)	KEGG:hsa05142
		Hepatitis B	KEGG:hsa05161
		IL-17 signaling pathway	KEGG:hsa04657
		Osteoclast differentiation	KEGG:hsa04380
		Pertussis	KEGG:hsa05133
		TNF signaling pathway	KEGG:hsa04668

Table 1. Coal dust exposure-related mouth diseases

Disease	Gene	Pathway	Pathway ID
Lichenoid Eruptions	IL6|CXCL8	AGE-RAGE signaling pathway in diabetic complications	KEGG:hsa04933
		Amoebiasis	KEGG:hsa05146
		Cellular responses to stress	REACT:R-HSA-2262752
		Cellular Senescence	REACT:R-HSA-2559583
		Chagas disease (American trypanosomiasis)	KEGG:hsa05142
		Cytokine-cytokine receptor interaction	KEGG:hsa04060
		Cytokine Signaling in Immune system	REACT:R-HSA-1280215
		Hepatitis B	KEGG:hsa05161
		IL-17 signaling pathway	KEGG:hsa04657
		Immune System	REACT:R-HSA-168256
Oral Submucous Fibrosis	IL6|PTGS2|CXCL8	Immune System	REACT:R-HSA-168256
		Cytokine Signaling in Immune system	REACT:R-HSA-1280215
		Interleukin-4 and 13 signaling	REACT:R-HSA-6785807
		Signaling by Interleukins	REACT:R-HSA-449147
		Pathways in cancer	KEGG:hsa05200
		AGE-RAGE signaling pathway in diabetic complications	KEGG:hsa04933
		Amoebiasis	KEGG:hsa05146
		IL-17 signaling pathway	KEGG:hsa04657
		Rheumatoid arthritis	KEGG:hsa05323
Behcet Syndrome	CXCL8	Signal Transduction	REACT:R-HSA-162582
		Immune System	REACT:R-HSA-168256
		Cytokine Signaling in Immune system	REACT:R-HSA-1280215
		Malaria	KEGG:hsa05144
		Signaling by Interleukins	REACT:R-HSA-449147
		Signal Transduction	REACT:R-HSA-162582
		Interleukin-10 signaling	REACT:R-HSA-6783783
		Interleukin-4 and 13 signaling	REACT:R-HSA-6785807
		Rheumatoid arthritis	KEGG:hsa05323
Leukoplakia, Oral	PTGS2	AGE-RAGE signaling pathway in diabetic complications	KEGG:hsa04933
		Amoebiasis	KEGG:hsa05146
		Arachidonic acid metabolism	KEGG:hsa00590
		Chemical carcinogenesis	KEGG:hsa05204
		Cytokine Signaling in Immune system	REACT:R-HSA-1280215
		IL-17 signaling pathway	KEGG:hsa04657
		Immune System	REACT:R-HSA-168256
		Interleukin-10 signaling	REACT:R-HSA-6783783
		Interleukin-4 and 13 signaling	REACT:R-HSA-6785807
		Leishmaniasis	KEGG:hsa05140
		Metabolic pathways	KEGG:hsa01100
		Metabolism	REACT:R-HSA-1430728
Carcinoma Squamous Cell	IL6|PTGS2|CXCL8|TP53|CCL2	Signal Transduction	REACT:R-HSA-162582
		Immune System	REACT:R-HSA-168256
		Cytokine Signaling in Immune system	REACT:R-HSA-1280215
		Pathways in cancer	KEGG:hsa05200
		Innate Immune System	REACT:R-HSA-168249
		Signaling by Interleukins	REACT:R-HSA-449147
		Generic Transcription Pathway	REACT:R-HSA-212436
		MicroRNAs in cancer	KEGG:hsa05206
		Metabolism	REACT:R-HSA-1430728
		Proteoglycans in cancer	KEGG:hsa05205
		Gene Expression	REACT:R-HSA-74160
		Signal Transduction	REACT:R-HSA-162582
Osteosarcoma	TP53	Cellular responses to stress	REACT:R-HSA-2262752
		Generic Transcription Pathway	REACT:R-HSA-212436
		Immune System	REACT:R-HSA-168256
		MicroRNAs in cancer	KEGG:hsa05206
		Pathways in cancer	KEGG:hsa05200
		Cell Cycle	REACT:R-HSA-1640170
		Cytokine Signaling in Immune system	REACT:R-HSA-1280215
		Signaling by Interleukins	REACT:R-HSA-449147

Table 2. Tissue-specific hub genes RNA expression

Gene	RNA expression (nTPM)			
	Oral mucosa	Salivary gland	Esophagus	Tongue
IL6	N/A*	11.6	31.9	3.5
PTGS2	N/A*	1.1	6.7	6.2
TNF	N/A*	1.7	0.7	0.1
IL1B	N/A*	3.7	3.3	6.8
CXCL8	N/A*	34.6	3.6	6.5
MAPK3	N/A*	59.2	125.9	54.6
TP53	N/A*	18.4	27.9	5.9
RELA	N/A*	52.6	57.7	25.8
CCL2	N/A*	45.6	44.2	47.8
HMOX1	N/A*	14.6	46.8	20.5

*Note: There were no specific mRNA expression data available in this database.

are involved in inflammation process and B-cells maturation. This gene also involved in various processes such as the positive regulation of cell population and macromolecule biosynthesis (National Center for Biotechnology Information, 2024).

Enrichment analysis of 20 high interaction genes showed various pathways related to vital biological process, cellular component, molecular function and diseases. KEGG pathway analysis showed that coal dust exposure was highly correlated with inflammation process including TNF and IL-17 signaling pathway. Both signaling pathways have important roles in tissue inflammation and mucosal injury. As a gene, TNF encodes cytokine that has a significant role in systemic inflammation response through neutrophil activation and leukocyte adhesion induction. This cytokine activates various downstream pathways including mitogen-activated protein kinase (MAPK) and nuclear factor kappa-B (NF-κB) through tumor necrosis factor receptor 1 (TNFR1) leading to increased expression of pro-inflammation factors (Yu *et al*., 2024; Zhu *et al*., 2024). A bioinformatic analysis describes IL-17 signaling pathway as one of Oral Squamous Cell Carcinoma (OSCC) key pathway where the expression of IL-17A increased significantly in early stage of oral cavity carcinogenesis and exacerbated by inflammation, Reactive Oxygen Species (ROS) and antioxidant enzymes depletion (Li *et al*., 2023).

Protein-protein Interaction (PPI) was constructed to determine high interconnection genes. The result showed a total of 10 hub genes that potentially play important roles in disease development due to coal dust exposure namely IL6, PTGS2, TNF, IL1B, CXCL8, MAPK3, TP53, RELA, CCL2, and HMOX1. IL6 is known to have the highest degree value so it is considered as the main biological hub gene. By searching the diseases based on key genes in CTD database, the related oral health conditions were obtained, where inflammation had the highest inference score. It was in accordance with GO and KEGG pathway enrichment analysis, where inflammation was the main pathway that occurred from increased hub genes regulation due to coal dust exposure, especially IL6.

The analysis showed interconnection of the hub genes in various signaling pathways. In TNF signaling pathways, the activation of hub genes occurred, namely RELA, inflammation cytokines (IL6 and IL1B), leukocyte recruitment (CCL2), and inflammation mediator synthesis (PTGS2) through MAPK and NF-kappa B signaling pathway (Wang *et al*., 2024). In IL-17 signaling pathway, MAPK3 was activated in MAPK signaling pathway and RELA was activated in NF-kappa B signaling pathway. This signaling pathway also involved CXCL chemokine as well as IL6 cytokine, TNF and PTGS2 that related to neutrophil recruitment, autoimmune pathology, and extracellular pathogen immunity (Kong *et al*., 2024). In *chemical carcinogenesis* ROS term, MAPK and NF-kappa B signaling pathway were involved in inflammation response activation that indirectly impacted cancer proliferation, angiogenesis and metastasis (Khan *et al*., 2021). It was known that HMOX1 indirectly affected in this signaling pathway.

CONCLUSION

Through bioinformatic approach with *in silico* toxicogenomic analysis, it is predicted that coal dust exposures were involved in various life aspects in human body. Particulate matter and benzo(a)pyrene as the two main exposure markers were identified from CTD. Through GO and KEGG pathway enrichment analysis as well as protein-protein interaction construction, the information of biological processes, cellular components and molecular functions that highly related to inflammation process were obtained. Interleukin-6 was considered as the major indicator of inflammation pathway that influenced oral health conditions due to coal dust exposure based on the bioinformatic software analysis. This computational search showed that coal dust exposure may have a potential to induce pathological conditions in human body, especially in oral cavity. The results of target gene identification, signaling pathway and oral health conditions can be used as considerations in specific biomarker determination and therapy design due to coal dust exposure as well as the arrangement of government regulation for coal mine location and community settlement.

In the present study, exposure markers and biological processes were assessed. However, this study relies entirely on bioinformatic analysis which limits the methods only by performing the computational-based evaluations. We suggest further validation through *in vitro* or *in vivo* approaches in order to collect experimental data including the time-dependent effects of coal dust exposure to oral health conditions. In addition, the epidemiological study of oral diseases in vast population with the various duration of coal dust exposure based on the duration of stay in the local community residences near coal mining areas should be undertaken.

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CONFLICT OF INTEREST

The authors declare that there is no any conflict of interests regarding the publication of this manuscript.

LIFE SCIENCE REPORTING

No life science threat was practiced in this research.

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