

# Prediction of Possible Effects of Arsenic and Cadmium in Human Health Using Chemical-Protein and Protein-Protein Interaction Network

**Md. Taif Ali<sup>1</sup>, Md. Ashraful Alam<sup>2,\*</sup>, Md. Emdad Ullah<sup>1</sup>, Mohammad Arif Ashraf<sup>3</sup>,  
Md. Abu Sayed<sup>4</sup>, Aklima Jahan<sup>5</sup>**

<sup>1</sup>Department of Biochemistry and Molecular Biology, University of Dhaka, Dhaka, Bangladesh

<sup>2</sup>Department of Chemistry and Bioengineering, Iwate University, Morioka, Japan

<sup>3</sup>The United Graduate School of Agricultural Sciences, Iwate University, Morioka, Japan

<sup>4</sup>Department of Biochemistry and Molecular Biology, Hajee Mohammad Danesh Science and Technology University, Dinajpur, Bangladesh

<sup>5</sup>Department of Chemistry, University of Chittagong, Chittagong, Bangladesh

## Email address:

sdashraf84@yahoo.com (Md. A. Alam)

\*Corresponding author

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**Abstract:** Arsenic and cadmium toxicity has demonstrated to be a crucial problem and there are many health issues interconnected with each other. The toxicity of these metals has no biological role even though remain present in some or the other form, hazardous for the human health and its proper functioning. As a result, from the very beginning, the researchers are trying to overcome the serious effects occurred by the heavy metals. The different procedures and methods are followed for minimizing the negative effects. The study was conducted to predict the probable effects and their targeted proteins in human body by recently developed advanced bioinformatics tools and subsequently found 10 proteins are interacted with arsenic and cadmium for each. However, these 10 proteins are independently associated with other 97 and 100 proteins. Finally, 25 common proteins have been identified which are affected by these two heavy metals. Our data mining search revealed that all of these 25 proteins are associated with the causing of cancer in human body.

**Keywords:** Arsenic, Cadmium, Cancer, Interaction, Heavy Metals, Human Health

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## 1. Introduction

Heavy metals and their toxic forms are found in our environment due to natural and anthropogenic activities. It has toxic effects on human health exposure through foodstuff, water, air and soil [1, 2]. Heavy metals pollution in water, air, crops, vegetables and other foodstuffs is a global risk for human health [3, 4]. Bangladesh is a developing and overpopulated country, its industrialization is increasing day by day. Most of the industries are located in Dhaka, Gazipur and Narayanganj. All these three cities are surrounded by some rivers and lake. Everyday industrial untreated and waste water is discharged to the river and the lake [5]. Subsequently, river and lake water is becoming

polluted with some heavy metals like arsenic (As), cadmium (Cd) etc. Intriguingly, the recent report shows that some lake water inside and peripheral rivers water of Dhaka, Gazipur and Narayanganj have been contaminated with some heavy metals like As, Cd, Pb, Cr, Hg, Zn [5]. These river water use for irrigation to cultivate some common agricultural crops like cereals, vegetables etc. Intriguingly, cereals and vegetables absorbed these heavy metals and subsequently contaminated. Now-a-days, it is very concerning issues that fishes, cereals and vegetables have been found toxic metals contaminated inside and surround the Dhaka city [6]. These fishes, cereals and vegetables use daily consumption in Dhaka city. Consequently, serious health problem has been occurring like cancer,

cardiovascular disease, and diabetes etc [7, 8]. Considering above mentioned problem, our present study shows that probable proteins are being affected due to Arsenic (As) and Cadmium (Cd). We identified some common proteins by some Bioinformatics tools which are commonly responsible for some health hazards.

## 2. Methods and Materials

### 2.1. Network Retrieval

The interaction of As and Cd with human (*Homo sapiens*) proteins were searched through STITCH 4.0 (<http://stitch.embl.de/>) web server [9]. STITCH helps to predict the interactions of chemicals and proteins of specific species by evidence derived from experiments, databases and literature mining. The list of human (*Homo sapiens*) proteins interacting with As and Cd further considered to identify the protein-protein interaction (PPI). PPI was done through STRING 10.0 (<http://string-db.org/>) web server [10]. STRING is used to get all known and predicted protein interactions based on direct (physical) and indirect (functional) associations.

### 2.2. Sequence Collection

The sequences of proteins which were listed through PPI were downloaded in FASTA format for NCBI protein (<http://www.ncbi.nlm.nih.gov/protein>) database. The

repetition was avoided during sequence collection. All the downloaded protein sequences were kept in one FASTA file for further analysis.

### 2.3. Blast 2 GO

Gene ontology of these sequences was done through Blast 2 GO software [11]. This tool was used for functional annotation and analysis of protein sequences. The correlation of sequences in biological process, molecular function and presence in cellular component were analyzed.

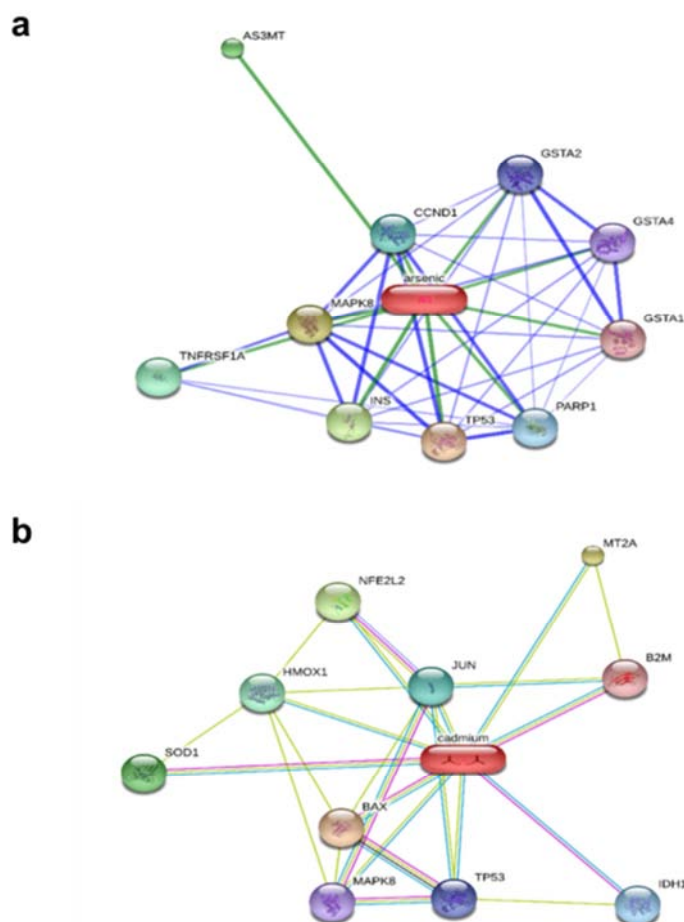
### 2.4. Venny

We used Venny (<http://bioinfogp.cnb.csic.es/tools/venny/>) web server to detect the common proteins in four targeted list. And the list of common protein was also collected from here.

## 3. Results

### 3.1. Interaction Prediction

In our study, we found 10 potential proteins of *Homo sapiens* have been predicted by STITCH 4.0 for As and Cd (Figure 1), respectively. During protein-protein interaction (PPI) prediction by STRING 10.0 bioinformatics tools 97, 100 proteins have been identified for As and Cd (Table 1 and 2), respectively.



**Figure 1.** Interaction of (a) arsenic and (b) cadmium with targeted proteins of *Homo sapiens* predicted through STITCH 4.0.

**Table 1.** Interaction of Arsenic and Proteins found by using STITCH and STRING tools.

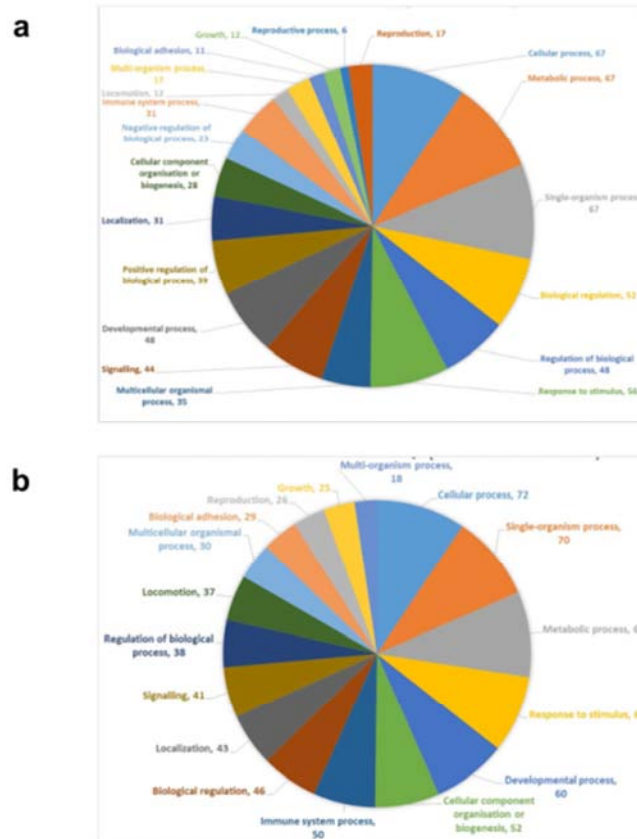
STITCH	TP 53	MAPK 8	INS	AS 3 MT	TNFRSF 1 A	CCND 1	PARP 1	GSTA 2	GSTA 4	GSTA 1
STRING		JUN	INSR	GSTO 1	TRADD	CDK 4	XRCC 1	GSTM 5	GSTM 2	GSTA 2
	CDKN 1 A	ATF 2	IRS 1	MMD	TRAF 2	CDK 6	TP 53	GSTA 1	GSTM 3	CYP 1 A 1
	ATM	TP 53	IRS 2	GSTO 2	RIPK 1	CDKN 1 A	PCNA	NFE 2 L 2	GSTM 1	GSTM 5
	SIRT 1	MAP 2 K 4	PDX 1	C 10 orf 32	BIRC 1	RB 1	CASP 3	GSTA 4	GSTM 4	CYP 1 A 2
	BRCA 1	MAPK 8 IP 1	AKT 1	CNNM 2	FADD	CDKN 1 B	XRCC 5	GSTT 1	GSTM 5	GSTT 2 B
	KAT 2 B	JUND	IGF 1	WBP 1 L	TNFRSF 1 B	UBC	XRCC 6	GSTO 1	GSTT 1	MGST 3
	MAPK 8	IRS 1	IGFBP 1	C 2 orf 82	IKBKB	CDK 2	PARG	GSTM 1	GSTO 1	GSTO 1
	CDKN 2 A	BCL 2	RPS 6 KB 1		MAP 3 K 7	ESR 1	WRN	MGST 3	MGST 3	GSTO 2
	EP 300	MAP 2 K 7	IGF 1 R		BIRC 2	STAT 3	UBC	GSTT 2 B	GSTT 2 B	CYP 1 B 1
	CREBBP	FOS	FOXO 1		TRAF 1	PCNA	CASP 7	CYP 1 A 1	GSTA 2	GSTT 1

**Table 2.** Interaction of Cadmium and Proteins found by using STITCH and STRING tools.

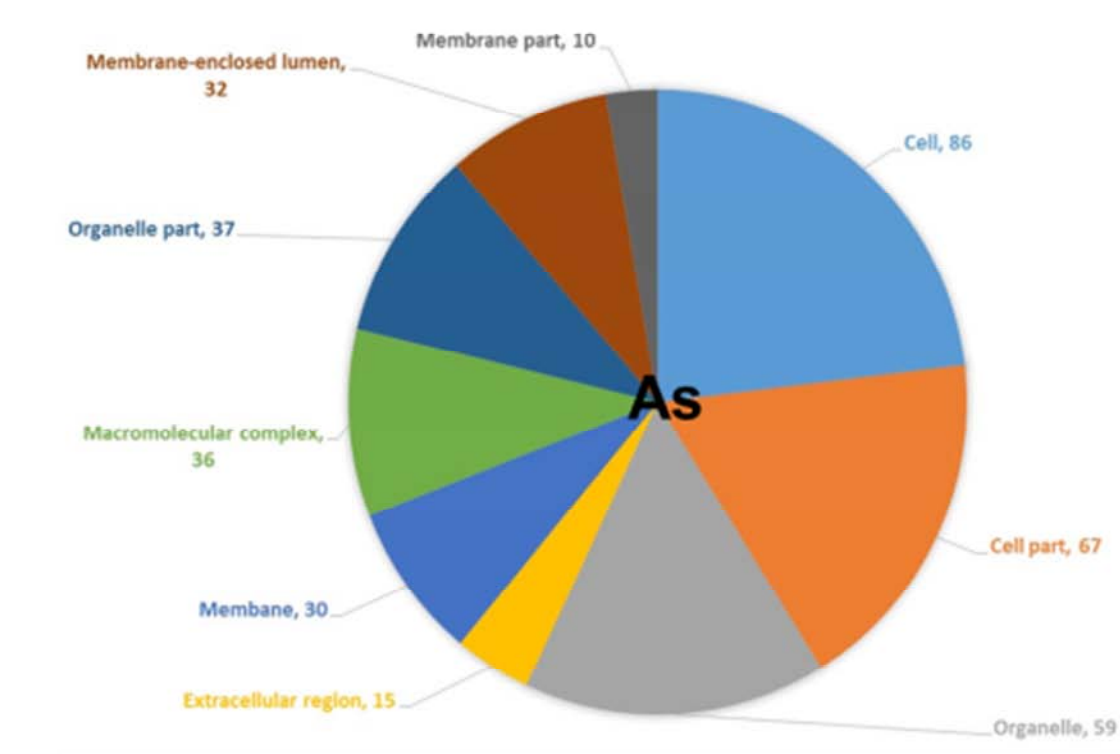
STITCH	BAX	MT 2 A	NFE 2 L 2	SOD 1	HMOX 1	JUN	IDH 1	TP 53	MAPK 8	B 2 M
STRING	BCL 2 L 1	FOS	KEAP 1	UBC	JUN	FOS	IDH 3 A	MDM 2	JUN	HLA-A
	BCL 2	JUN	UBC	SOD 2	HIF 1 A	MAPK 8	IDH 3 B	CDKN 1 A	ATF 2	HFE
	MCL 1	B 2 M	EIF 2 AK 3	GPX 1	BLVRA	ATF 3	ACLY	ATM	TP 53	HLA-C
	BCL 2 L 11	IRF 1	CUL 3	PRDX 1	USF 2	MAPK 9	ACO 2	SIRT 1	MAP 2 K 4	CD 8 A
	TP 53	HLA-DRB 5	GSTA 2	CCS	BLVRB	MAPK 10	ACO 1	BRCA 1	MAPK 8 IP 1	CD 1 D
	XRCC 6	ICAM 1	MAFG	CAT	AKT 1	FOSL 1	OGDHL	KAT 2 B	JUND	MR 1
	BID	GBP 1	MAFK	PRDX 2	NFE 2 L 2	ATF 2	GOT 2	CREBBP	IRS 1	FCGRT
	CLU	OAS 1	HMOX 1	PRDX 6	DECR 1	EP 300	GOT 1	CDKN 2 A	BCL 2	JUN
	VDAC 1	HLA-B	JUN	TXN	MAPK 14	SMAD 3	MDH 1	MAPK 8	MAP 2 K 7	HLA-B
	BAK 1	CD 44	MAFF	GPX 2	FOS	FOSL 2	GLUD 1	EP 300	FOS	CALR

### 3.2. Pathway Detection

Through Blast 2 GO software, we did following steps for a list of target protein sequences: protein Blast, mapping, retrieving Enzyme Codes (EC), tracking KEGG pathways and scanning motifs by Inter Pro Scan. These accomplished jobs helped to generate an overview of biological process, molecular function and cellular component of these listed proteins for As and Cd (Figure 2-4) and Cd (Figure 5).

**Figure 2.** Interaction of (a) arsenic and (b) cadmium with targeted proteins of Homo sapiens involved in function with biological process.

a



b

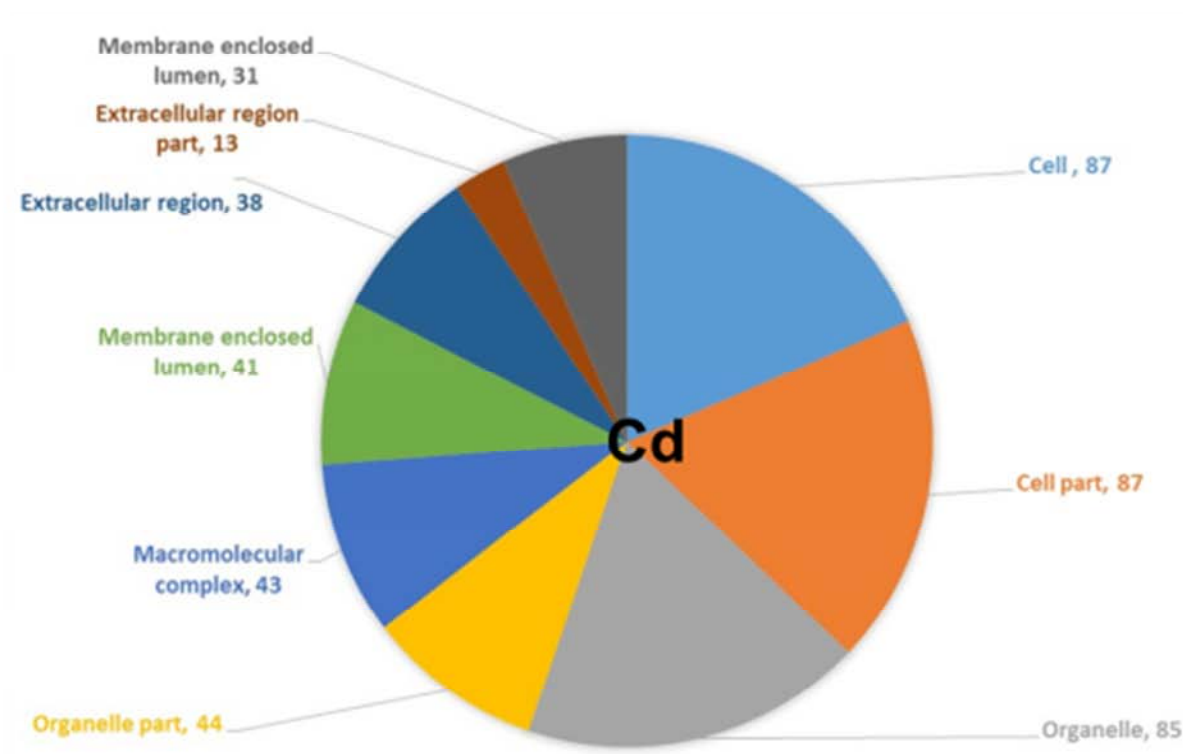
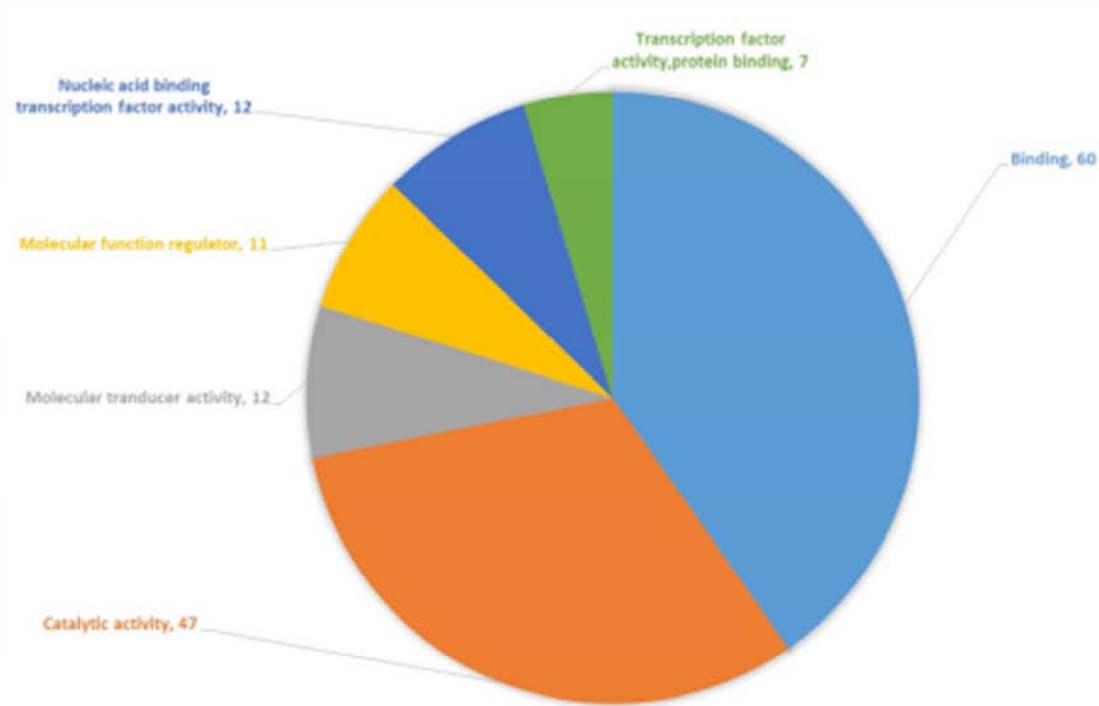


Figure 3. Interaction of (a) arsenic and (b) cadmium with targeted proteins of Homo sapiens involved in function with cell component.

a



b

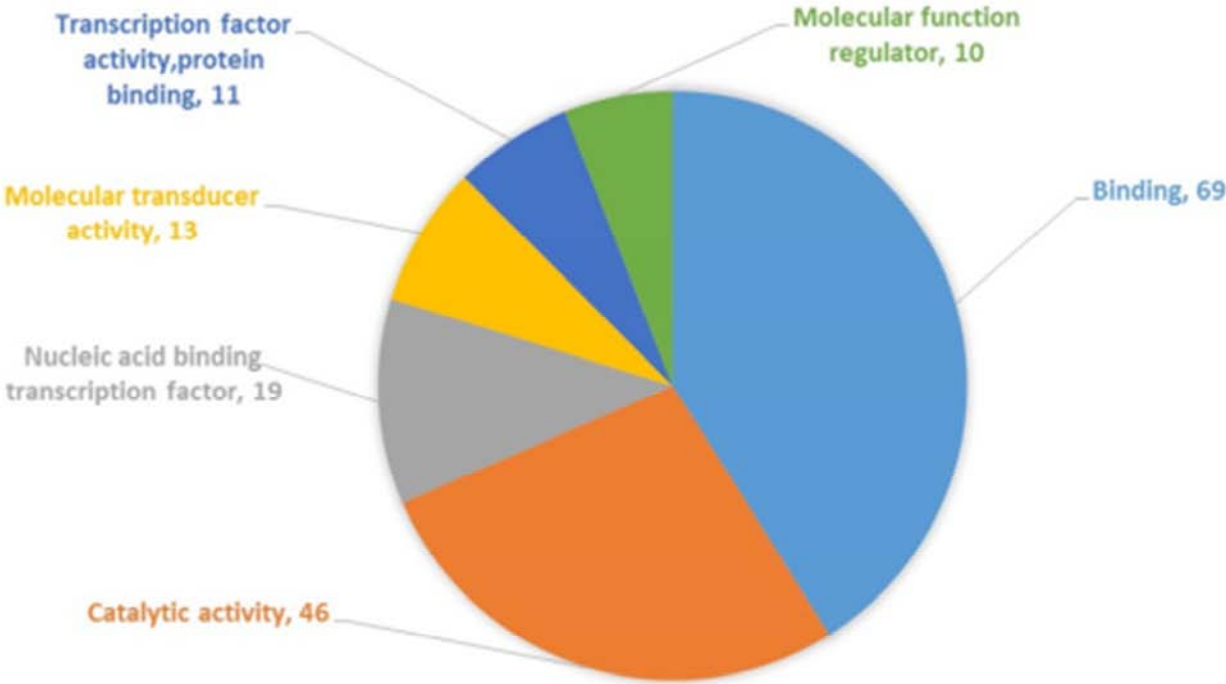


Figure 4. Interaction of (a) arsenic and (b) cadmium with targeted proteins of Homo sapiens involved in with cell function.

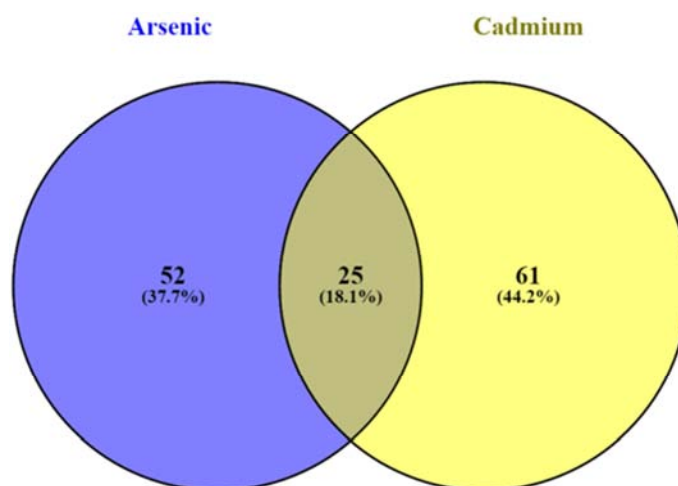


Figure 5. Identification of common targeted proteins of Homo sapiens through Venn web server.

### 3.3. Common Targets Determination

These two heavy metals As and Cd have multiple targets and our study showed that 25 proteins (Table 3) are common targets with As and Cd which were screened by Venn web server (Figure 5).

Table 3. Enlisted of the common proteins with their effects on human health due to toxic effects of Arsenic and Cadmium.

Name	Short Descriptions	Functions	References
BCL 2	Apoptosis regulator Bcl-2	Its role in regulation of apoptotic signaling pathways, is possibly related to carcinogenesis	[15]
TP 53	Cellular tumor antigen p53	Cell cycle regulation	[16]
XRCC 6	X-ray repair cross-complementing protein 6	Function as scaffolding protein in base excision repair and single strand break repair pathways.	[17]
FOS	Proto-oncogene c-Fos	A variety of biological processes, including proliferation, differentiation, tumorigenesis, and apoptosis.	[18]
JUN	Transcription factor AP-1	An important role in melanoma progression and development.	[19]
GSTA 2	Glutathione S-transferase A2	Upregulated during oxidative stress, overexpressed in many tumors and leading to causes during cancer chemotherapy	[20]
AKT 1	RAC-alpha serine/threonine-protein kinase	Inhibits the apoptosis	[21]
NFE2 L 2	Nuclear factor erythroid 2-related factor 2 (No cancer related, blood haemorrhage)	Inflammatory disorder	[22]
ATF 2	Cyclic AMP-dependent transcription factor ATF-2 (Pregnancy related)	Function in the control of uterine activity throughout pregnancy.	[23]
MAPK 8 IP 1	C-Jun-amino-terminal kinase-interacting protein 1	Causing of Alzheimer's disease.	[24]
JUND	Transcription factor jun-D	Interact with tumor suppressor gene <i>MEN 1</i> encoded by nuclear protein menin	[25]
IRS 1	Insulin receptor substrate 1	Cell proliferation and differentiation.	[26]
MAP 2 K 7	Dual specificity mitogen-activated protein kinase kinase 7	Decreased expression of MAP 2 K 7 and causes schizophrenia is a mental illness	[27]
MAP 2 K 4	Protein Map 2 k 4	Human prostate cancer metastasis	[28]
MDM 2	E3 ubiquitin-protein ligase Mdm 2	MDM 2 impairs all-trans retinoic acid induced osteoblastic differentiation in osteosarcoma cells and primary osteosarcoma blasts	[29]
CDKN 1 A	Cyclin-dependent kinase inhibitor 1 A	Modulates cell cycle, apoptosis, senescence and cell differentiation	[30]
ATM	Serine-protein kinase ATM	Regulating the cellular response to genotoxic stress	[31]
SIRT 1	NAD-dependent protein deacetylase sirtuin-1	An important regulator in cellular stress response and energy metabolism.	[32]
BRCA 1	Breast cancer type 1 susceptibility protein	Causes breast cancer	[33]
KAT 2 B	Histone acetyltransferase KAT 2 B	Alterations in human abdominal aortic aneurysm	[34]
MAPK 8	Mitogen-activated protein kinase 8	Participate in a diverse array of cellular programs, including cell differentiation, cell movement, cell division, and cell death	[35]
CDKN 2 A	Cyclin-dependent kinase inhibitor 2 A	Causes salivary gland carcinomas	[36]
EP 300	Histone acetyltransferase p 300	Alzheimer's Disease	[37]
CREBBP	CREB-binding protein	Participate in the activities of hundreds of different transcription factors	[38]
UBC	Polyubiquitin-C	Responsive gene to cellular treatments such as UV irradiation, heat shock, oxidative stress and translational impairment	[39]

## 4. Discussion

Heavy metals are always toxic to animal health in higher doses. Among the heavy metals As is one of most dangerous health hazard to human as because every fourth of the tube well is polluted with As in Bangladesh [12]. In addition that both of As and Cd polluted river and lake water is barning issues in Dhaka, Gazipur and Naraynagnj cities [13]. As a result, some life threatening diseases like cancer, metabolic disorders are common in Bangladesh. We found that some proteins are directly and indirectly affected by As and Cd and subsequently, life threatening diseases have been occurred. However, molecular mechanism of heavy metals has been extensively reported that oxidative DNA damage, inhibition of major DNA repair systems and inactivation of tumor suppressor genes are the main causes for increasing the health problem in human due to exposure of heavy metals [14]. Considering all of these preliminary published data, we investigated the target proteins for As and Cd which have been affected in human body by recent Bioinformatics tools. In our present study, we found total 25 common proteins for As and Cd enlisted in tabular form with their short description and probable functions which have the possibility to affect in the human body (Table 3). Interestingly, most of the identified proteins are responsible for occurring the cancer in the human body. For example, Apoptosis regulator Bcl-2 protein family was expressed in many types of cancer cell and related to cancer pathophysiology [15].

## 5. Conclusions

Effects of heavy metals such as As and Cd on living organism specially human beings is not constant in any locations, hence it is varies due to exposure in environment. Proper guidelines, government policy, rules can be reduced the level of contamination of heavy metals to be made safe and healthy living area for living organisms. Professional discharge to heavy metals can be declined by engineering solutions. Surveilling the exposure and possible intercession for decreasing additional exposure to heavy metals in the environment and in humans can become a momentous step towards prevention. National as well as international co-operation can play a vital role for framing appropriate tactics to prevent heavy metal toxicity.

## Conflict of Interest

The authors have declared no conflict of interest with any parties which may arise from this publication.

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