Nova Biotechnologica *et* Chimica

In silico toxicological analyzes of selected toxic compounds from dumpsite or contaminated soils on human health

Omodele Ibraheem[1, ✉], Toluwase Hezekiah Fatoki[1], Jesupemi Mercy Enibukun[2], Bolanle Christianah Faleye[3] and Daniel Uwaremhevho Momodu[4]

[1] *Department of Biochemistry, Federal University Oye-Ekiti, PMB 373, Oye-Ekiti, Ekiti State, Nigeria*

[2] *Department of Microbiology, Federal University of Technology, PMB 704 Akure, Nigeria*

[3] *Department of Chemical Science, Joseph Ayo Babalola University, Ikeji-Arakeji, PMB 5006, Ilesa Osun State, Nigeria*

[4] *Department of Industrial Chemistry, Federal University Oye-Ekiti, PMB 373, Oye-Ekiti, Ekiti State, Nigeria*

Article info

Abstract

The soil is a key component of natural ecosystems because environmental sustainability depends largely on a sustainable soil ecosystem. The objective of this study was to predict the impact of selected toxic compounds from dumpsite or contaminated soils on human health at the molecular level of biological processes. The *in silico* methods that were used include toxicokinetics and target gene prediction, molecular docking, and gene expressing network analysis. The result showed bisphenol A (BPA), 2,20-bis(*p*-chlorophenyl)-1,1-dichloroethane (DDD), 2,20-bis(*p*-chlorophenyl)-1,1-trichloroethane (DDT), diethylhexyl phthalate (DEHP), nonylphenol (NP) and tetrachlorodibenzodioxin (TCDD) as the active toxic compounds that can modulate biological system and are considered as potential cause of several diseases including cancer. The principal target genes include substance-P receptor (also known as Neurokinin 1 receptor), 5-hydroxytryptamine receptor, human serotonin transporter; estrogen receptor alpha; and aryl hydrocarbon receptor. These genes implicated SUZ12, STAT3, and TRIM28 as the major transcription factors while mitogen-activated protein kinases and cyclin-dependent kinases were the major kinases from the protein-protein interaction. All the six toxicants investigated showed good free binding energies (ΔG) which were below - 5.0 kcal.mol^{-1}. These toxic compounds showed ligand efficiency greater than 0.25 kcal.mol^{-1}. HA and would possibly cause fatal damage on human health. The order of *in silico* predicted toxicity of these compounds were BPA > DDD = DDT > TCDD > NP > DEHP. Our results identified potential threats, which the selected toxicants can pose to public health. More importantly, it provides basis for investigation of super bugs (microorganisms) that can remediate these toxicants in our environment. Environmental monitoring and modern wastes management system should be implemented and enforced in the affected countries in order to safeguard the health of the citizenry.

Introduction

The soil is a key component of natural ecosystems because environmental sustainability depends largely on a sustainable soil ecosystem (Lombi *et al.* 1998). The biogeochemical cycles of contaminants have been greatly accelerated by human activities. Typical contaminated sites

✉ *Corresponding author:* deleibraheem2007@yahoo.com

may be classified as either potential or practical, which could be quantitatively described as suspected to cause or constitute harm to human health and the environment – biotic and abiotic processes respectively. The qualitative and quantitative description of potentially contaminated and contaminated sites have been reported (WHO 2013).

The study on soil samples of an animal burial site showed to be characterized by acute toxicity of decayed matter while the area of open waste dumping was found the most dangerous based on the amount of the contaminants (Pasko and Mochalova 2014). Typical study has shown that more industrialized countries had higher bisphenol A (BPA) concentrations in landfill leachate than less industrialized countries (Teuten et al. 2009). Cases of environmental pollution and contamination in developing and developed countries have been reported (Egboka et al. 1989; SCU 2013). Dumpsite has been huge challenge to the global health, because it serves as habitat for carcinogenic chemicals and pathogenic microbes (Odeyemi et al. 2011; Eze and Amaeze 2016). Dumpsites serve as lead for marine and coastal pollution and will account for 8 – 10 % of anthropogenic greenhouse gas emission in 2025 (ISWA 2016).

Soil microorganisms often serve as the catalysts or promoters of reactions in the subsurface. However, the degradation of any contaminant depends on geochemical conditions and on the presence of microorganisms that are capable of adaptation (Boulding and Barcelona 1991). Uptake of contaminants by organisms occurs by a variety of pathways, most commonly inhalation, dermal sorption and ingestion. Contaminant transfer to organisms may occur by any of these routes, and the major transport route will vary according to the organism and the physicochemical properties of the contaminant (Teuten et al. 2009). Likelihood that health effects will occur from any exposure to a contaminant depends on the toxicity of the contaminant, which can be determined through understanding of: how harmful, how much, how long and how often the exposure occurs. However, differences in the health status, age, diet, gender, family traits and lifestyle will also affect the outcome of the level of exposure to a particular

contaminant (Shayler et al. 2009).

The protection of human health has utilized biomonitoring as a vital tool to track and assess the level of exposure of the community to environmental pollutants as well provides measures for local and global health policies (SCU 2013). Characterization of a hazardous waste site provides the understanding to predict future site behavior based on past site behavior (Mercer and Spalding 1991). A basic assumption in performing remediation is that one cannot remediate what is not observed. Consequently, an understanding of what to observe and how to go about making the observations is of utmost importance (Boulding and Barcelona 1991).

Almost all typical research of soil quality often carried out solely on the basis of chemical analyses at the oversight of the resulting effect of the level of toxicity on the organism within the ecosystem. Toxicokinetics is the kinetics of toxicant absorption, distribution, metabolism and excretion (ADME). The investigation of ADME profiling and toxicological (ADME/Tox) screenings during biomonitoring and remediation processes are therefore very important. *In silico* prediction of toxicokinetics and impact on biomolecules will serve as an additional assessment tool for screening toxic level of soil and foster understanding of impact of pollutants in the environment considering the huge cost and time involve in bioanalytical testing as well as increasing number of toxicants nowadays. *In silico* prediction of key biomolecular targets of the potential toxic compound will help to ascertain the limit and possible outcome of high exposure. The understanding will help in creating public awareness that is grounded of scientific propositions. The objective of this study was to predict the potential impact of selected toxic compounds from dumpsite or contaminated soils on human health at the molecular level of biological processes.

Experimental

In silico *preparation of toxic ligands*

Among the several known toxicants found in typical dumpsites or contaminated soils from

Table 1. List of 13 selected toxicants among severally found in dumpsites or contaminated soils, which have been implicated in human chronic ailments, among which 6 toxicants (in bold) showed significant predicted targets.

Serial No.	Type of contaminants	SMILES format
1	**Bisphenol A (BPA)**	CC(C)(C1=CC=C(C=C1)O)C2=CC=C(C=C2)O
2	**2,20-bis(*p*-chlorophenyl)-1,1-dichloroethane (DDD)**	C1=CC(=CC=C1C(C2=CC=C(C=C2)Cl)C(Cl)Cl)Cl
3	2,20-bis(*p*-chlorophenyl)-1,1-dichloroethylene (DDE)	C1=CC(=CC=C1C(=C(Cl)Cl)C2=CC=C(C=C2)Cl)Cl
4	**2,20-bis(*p*-chlorophenyl)-1,1-trichloroethane (DDT)**	C1=CC(=CC=C1C(C2=CC=C(C=C2)Cl)C(Cl)(Cl)Cl)Cl
5	**diethylhexyl phthalate (DEHP)**	CCCCC(CC)COC(=O)C1=CC=CC=C1C(=O)OCC(CC)CCCC
6	Hexachlorocyclohexane (HCH)	C1(C(C(C(C(C1Cl)Cl)Cl)Cl)Cl)Cl
7	Octylphenol (OP)	CCCCCCCCC1=CC=C(C=C1)O
8	Perfluorooctanesulfonic acid (PFOS)	C(C(C(C(C(F)(F)S(=O)(=O)O)(F)F)(F)F)(F)F)(C(C(C(F)(F)F)(F)F)(F)F)(F)F
9	**Nonylphenol (NP)**	CCCCCCCCCC1=CC=C(C=C1)O
10	Perfluorooctanoic acid (PFOA)	C(=O)(C(C(C(C(C(C(C(F)(F)F)(F)F)(F)F)(F)F)(F)F)(F)F)(F)F)O
11	Trinonylphenylphosphine (TNPP)	CCCCCCCCC[P+](CCCCCCCCC)(CCCCCCCCC)C1=CC=CC=C1
12	**Tetrachlorodibenzodioxin (TCDD)**	C1=C2C(=CC(=C1Cl)Cl)OC3=CC(=C(C=C3O2)Cl)Cl
13	Toxaphene (SONATOX)	C1C2C(C(C(C1(Cl)Cl)(C2(CCl)CCl)CCl)Cl)Cl

literatures (Teuten *et al*. 2009; Valentin *et al*. 2013; Yao *et al*. 2015), 13 toxicants (Table 1), which were known to be critically implicated in implicated in human chronic ailments such as cancer, chronic cough, and neurological disorder, were selected and used for this study. Available structures of these compounds were obtained from the PubChem Compound Database in structure data file (sdf) and canonical Simplified Molecular Input Line Entry Specification format (SMILES). All file conversion to protein data bank (pdb) format were performed using PyMol v2.0.7.

In silico *targets prediction and toxicokinetics*

In silico targets prediction for the toxicants were done on SwissTargetPrediction server, where *Homo sapiens* was selected as target organism (Diana *et al*. 2019). Among the 13 toxicants, 6 toxicants showed significant predicted targets (i.e. active ligands; Table 1), and these were then subjected to *in silico* Absorption-Distribution-Metabolism-Excretion *(*ADME) screening on SwissADME server (Diana *et al*. 2017). ADME screening was performed at default parameters.

Molecular docking

The molecular docking studies for the 6 toxicants

against the 6 targets were carried out according to the method described by Fatoki *et al*. (2018a). The three-dimension (3D) structures of selected 6 targets were then obtained from RCSB Protein Data Bank (PDB). Briefly, all water molecules, hetero atoms, and multichains were removed from the crystal structure of the prepared targets using PyMol v2.0.7. The Gasteiger partial charges were added to the ligand atoms prior to docking. The docking parameter of each prepared ligand and each prepared target, were setup using AutoDock Tools (ADT) v1.5.6 (Morris *et al*. 2009) and saves the output file in pdbqt format. Molecular docking program AutoDock Vina v1.1.2 (Trott and Olson 2010) was employed to perform the docking experiment from the command line. After docking, the ligands were analyzed and visualized using ADT and PyMol v2.0.7. The ligand efficiency (LE) was evaluated from the equation, LE = -ΔG/HA, where ΔG is the free energy of binding and HA is the number heavy atoms (non-hydrogen atoms) of the ligand (Padmanabhan *et al*. 2016).

Target gene expression analyses

The upstream regulatory networks from signatures of differentially expressed genes obtained from toxicants target prediction, were determined by

Table 2. Predicted targets of the dumpsites/contaminated soils active toxicants.

Serial No.	Targets	Gene name	UniProt ID	Dumpsite toxicants					
				A	B	C	D	E	F
1	Estrogen receptor	ESR1	P03372	****				****	
2	Estrogen receptor beta (by homology)	ESR2	Q92731	****					
3	5-hydroxytryptamine receptor 6	HTR6	P50406	****	***	***			
4	FAD-linked sulfhydryl oxidase ALR	GFER	P55789	***					
5	Carbonic anhydrase 1, 2, 3, 5A, 5B, 7, 13	CA1, CA2, CA3, CA5A, CA5B, CA7, CA13	P00915, P00918, P07451, P35218, Q9Y2D0, P43166, Q8N1Q1	***					
6	Androgen receptor (by homology)	AR	P10275	***			**		
7	Arachidonate lipoxygenase	ALOX5, ALOX12, ALOX15	P09917, P18054, P16050	***					
8	Alpha-2A adrenergic receptor	ADRA2A	P08913		***				
9	Microtubule-associated protein tau	MAPT	P10636		***	**	**		
10	Sodium-dependent noradrenaline transporter	SLC6A2	P23975		***	***		****	
11	Sodium-dependent dopamine transporter	SLC6A3	Q01959		***	***			
12	Sodium-dependent serotonin transporter	SLC6A4	P31645		***	***		****	
13	Sodium-dependent proline transporter (by homology)	SLC6A7	Q99884		***	***			
14	Sodium- and chloride-dependent glycine transporter 1 (by homology)	SLC6A9	P48067		***	***			
15	Sodium- and chloride-dependent neutral and basic amino acid transporter B(0+) (by homology)	SLC6A14	Q9UN76		***	***			
16	5-hydroxytryptamine receptor 2A, 2B, 2C (by homology)	HTR2A, HTR2B HTR2C, HTR6	P28223, P41595, P28335, P50406		***	***		****	
17	Adrenergic receptor Alpha-2B, 2C (by homology)	ADRA2B, ADRA2C	P18089, P18825		***	***		****	
18	Adrenergic receptor Beta-1, Beta-2, Beta-3	ADRB1, ADRB2, ADRB3	P08588, P07550, P13945					****	
19	Protein kinase C alpha type, beta type, gamma type, theta type, delta type regulatory subunit	PRKCA, PRKCB, PRKCG, PRKCQ, PRKCD	P17252, P05771, P05129, Q04759, Q05655				**		
20	Tyrosine-protein phosphatase non-receptor type 1, type 2	PTPN1, PTPN2	P18031, P17706				**		
21	Opioid receptor Mu-type, Delta-type, Kappa-type	OPRM1, OPRD1, OPRK1	P35372, P41143, P41145				**		
22	Adenosine receptor A3	ADORA3	P33765					****	
23	Substance-P receptor, K receptor	TACR1, TACR2	P25103, P21452					****	
24	Testis-specific androgen-binding protein	SHBG	P04278					****	
25	Vascular endothelial growth factor receptor 1, 2, 3	FLT1, KDR, FLT4	P17948, P35968, P35916						****
26	Aryl hydrocarbon receptor	AHR	P35869						****

* (20 – 40%), ** (40 – 60%), *** (60 – 80%), **** (80 – 100%) probability of binding on target. Probabilities have been computed based on a cross-validation. They may therefore not represent the actual probability of success for any new molecule.
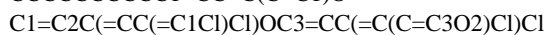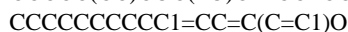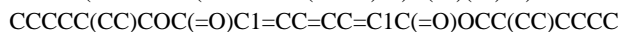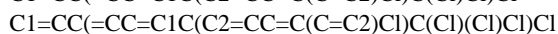
(A) = Bisphenol A (BPA)   CC(C)(C1=CC=C(C=C1)O)C2=CC=C(C=C2)O
(B) = 2,20-bis(*p*-chlorophenyl)-1,1-dichloroethane (DDD)   C1=CC(=CC=C1C(C2=CC=C(C=C2)Cl)C(Cl)Cl)Cl
(C) = 2,20-bis(*p*-chlorophenyl)-1,1-trichloroethane (DDT)   C1=CC(=CC=C1C(C2=CC=C(C=C2)Cl)C(Cl)(Cl)Cl)Cl
(D) = Diethylhexyl phthalate (DEHP)   CCCCC(CC)COC(=O)C1=CC=CC=C1C(=O)OCC(CC)CCCC
(E) = Nonylphenol (NP)   CCCCCCCCC1=CC=C(C=C1)O
(F) = Tetrachlorodibenzodioxin (TCDD)   C1=C2C(=CC(=C1Cl)Cl)OC3=CC(=C(C=C3O2)Cl)Cl

147
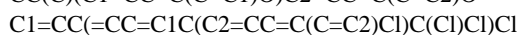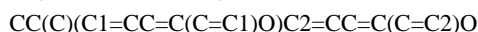
transcription factor enrichment analysis, protein-protein interaction network expansion and kinase enrichment analysis, using the 50 predicted target genes on eXpression2Kinases (X2K) webserver (Clarke et al. 2018).

Results and Discussion

Dumpsite/contaminated soil active toxicants and their predicted targets

In this study, six toxicants from typical dumpsite or contaminated soil were found active in biological system at percentage probability greater than 20 % (Table 2), although octylphenol (data not shown) was also found to be about 20 % less active than nonylphenol. Fifty predicted targets (using gene name or UniProt ID) were obtained (Table 2) of which six were selected for further investigation based on their crucial implication on human health (Table 3). These were classified mainly into: (1) membrane proteins, such as substance-P receptor (also known as Neurokinin 1 receptor), 5-hydroxytryptamine receptor and human serotonin transporter; (2) nuclear proteins which include estrogen receptor alpha; and (3) transcription proteins which include aryl hydrocarbon receptor. The serotonin 2A receptor (5-HT2AR) is associated with diseases, such as bipolar disorder, depression, schizophrenia,

Alzheimer's disease and Parkinson's disease (Aznar and Hervig 2016). Structural elucidation has shown that 5-HT2AR possesses a unique side-extended cavity near the orthosteric binding site and possibly contributes to the high selectivity of ligands such pimavanserin (Kimura et al. 2019). Estrogen receptor (ER), an allosteric signaling protein and example of nuclear receptors, is a well validated therapeutic target for the treatment of estrogen receptor positive breast cancer (Burks et al. 2017; Fatoki et al. 2018a). Study on model compounds that targets ER has provided insight on the close structural similarity with tamoxifen, the FDA-approved drug which is a potent selective estrogen receptor modulator (Fatoki et al. 2018a). TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) is the best known high-affinity ligand for aryl hydrocarbon receptor (AHR), and mediates its toxicity via activation of AHR. Increased levels of AHR and its target genes have been implicated in several belligerent tumors such as skin tumors, glioblastoma, or non-small cell lung cancer (Schulte et al. 2017).

Predicted toxicokinetic properties of the toxicants

The ADME parameter of the selected six toxicants (Table 3) showed that bisphenol A (BPA) and nonylphenol (NP) were soluble and moderately soluble (respectively), and both likely have high

Table 3. Predicted toxicokinetic parameters of the dumpsites/contaminated soils active toxicants.

Serial No.	Parameters	Selected dumpsite toxicants					
		BPA	DDD	DDT	DEHP	NP	TCDD
1	Molecular Weight	228.29	320.04	354.49	390.56	220.35	321.97
2	Heavy Atoms (HA)	17	18	19	28	16	18
3	Molar Refractivity	69.44	80.31	85.15	116.3	71.89	73.07
4	Total Polar Surface Area ($Å^2$)	40.46	0	0	52.60	20.23	18.46
5	Consensus LogP	3.6	5.44	5.89	6.17	4.51	5.29
6	ESOL Class	Soluble	Moderately soluble	Poorly soluble	Poorly soluble	Moderately soluble	Poorly soluble
7	Gastrointestinal Absorption	High	Low	Low	High	High	Low
8	Blood Brain Barrier (BBB) Permeant	Yes	No	No	No	Yes	No
9	P-glycoprotein Substrate	No	No	No	Yes	No	Yes
10	Cytochrome P450 Inhibitor	CYP1A2, CYP2D6	CYP1A2, CTP2C9, CYP2C19, CYP2D6	CTP2C9, CYP2C19	CTP2C9, CYP3A4	CYP1A2, CYP2C19, CYP2D6	CYP2C9
11	Skin permeation log K_p (cm.s^{-1})	-5.34	-3.98	-3.56	-3.39	-3.55	-3.44
12	Lipinski Violation	0	1	1	1	0	1
13	Bioavailability Score	0.55	0.55	0.55	0.55	0.55	0.55
14	Synthetic Accessibility	1.43	2.37	2.37	4.12	1.63	2.71

Table 4. Docking parameters implemented in AutoDockTool for selected 6 targets.

Serial No.	Selected Target	Center grid box [points]	Size [points]	Spacing [Å]
1	Adrenergic receptor alpha-2A (PDB ID: 5UIG, Chain A)	171.339 x 21.415 x 21.578	126 x 108 x 112	0.675
2	Aryl hydrocarbon receptor (PDB ID: 5NJ8, Chain A)	-8.185 x 37.203 x 215.837	126 x 126 x 126	0.375
3	Estrogen receptor (PDB ID: 5T97, Chain A)	-33.601 x 18.875 x -21.737	120 x 126 x 122	0.375
4	Sodium-dependent serotonin transporter (PDB ID: 5I6Z, Chain A)	36.842 x 183.210 x 142.913	126 x 100 x 126	0.475
5	Substance-P receptor (PDB ID: 6HLL, Chain A)	2.367 x 28.422 x -26.136	70 x 80 x 126	0.875
6	5-hydroxytryptamine receptor 2A (PDB ID: 6A93, Chain A)	43.501 x -0.464 x 60.742	126 x 66 x 76	0.775

gastrointestinal absorption (GA), may permeate blood-brain barrier (BBB) and could inhibit cytochrome P450 (CYP1A2 and CYP2D6). On the other hand, diethylhexyl phthalate (DEHP) and tetrachlorodibenzodioxin (TCDD) were identified to possibly have high and low GA respectively, and both are poorly soluble, may not permeate blood-brain barrier (BBB), and serve as P-glycoprotein substrates as well as inhibitors of cytochrome P450 (CYP2C9).

The best bioavailability score and synthetic accessibility (SA) score is 1.0 which is an indication of the amount of the compound that could reach the active site and extent of ease of synthesis of the compound, respectively (Diana *et al*. 2017; Fatoki *et al*. 2018b). The SA of the toxicants in this study ranged between 1.43 and 4.12, and showed that they were from or could make up synthetic materials. Usually, not all contaminant found in soil are biologically available. Bioavailability has been described as the physicochemical access that a toxicant has to the biological processes of an organism (Allen 2002). The bioavailability of a contaminant

depends on the characteristics of the soil and of the site (Shayler *et al.* 2009).

Binding energy and efficiency of the toxicants

The parameter for docking analysis and predicted binding site amino acid residues are shown in Table 4. All the six toxicants investigated in this study show good free binding energies below –5.0 kcal.mol^{-1} as shown in Table 5. DDT and BPA were found to have highest predicted free binding energy in four and two of the targets respectively. The interaction of some of the ligands with the protein targets are shown in Fig. 1.

The ligand efficiency (LE) is a useful metric to assess binding affinity of compounds with respect to the number of non-hydrogen atoms (Schultes *et al*. 2010). The toxic compounds showing LE greater than 0.25 kcal.mol^{-1}. HA will possibly cause fatal damage on human health. Based on the ligand efficiency result (Table 6), the order of toxicity of the compounds investigated in this study is BPA > DDD = DDT > TCDD > NP > DEHP.

Table 5. Docking score for the binding free energy between the selected 6 targets and 6 active toxicants.

| Serial No.	Selected Target	Binding energy [kcal.mol^{-1}] of the selected toxicants					
		BPA	DDD	DDT	DEHP	NP	TCDD
1	Estrogen receptor (PDB ID: 5T97)	- 9.1	- 8.5	- 7.3	- 7.5	- 6.7	- 7.4
2	Sodium-dependent serotonin transporter (PDB ID: 5I6Z)	-9.5	- 8.2	- 9.8	- 8.2	- 7.5	- 8.2
3	Adrenergic receptor alpha-2A (PDB ID: 5UIG)	- 11.9	- 11.1	- 9.2	- 7.6	- 6.8	- 10.3
4	Aryl hydrocarbon receptor (PDB ID: 5NJ8)	- 8.7	- 8.3	- 9.5	- 7.2	- 7.0	- 6.2
5	Substance-P receptor (PDB ID: 6HLL)	- 9.0	- 8.2	- 9.9	- 7.5	- 7.1	- 9.2
6	5-hydroxytryptamine receptor 2A (PDB ID: 6A93)	- 9.2	- 8.6	- 10.5	- 8.3	- 7.8	- 8.8

149
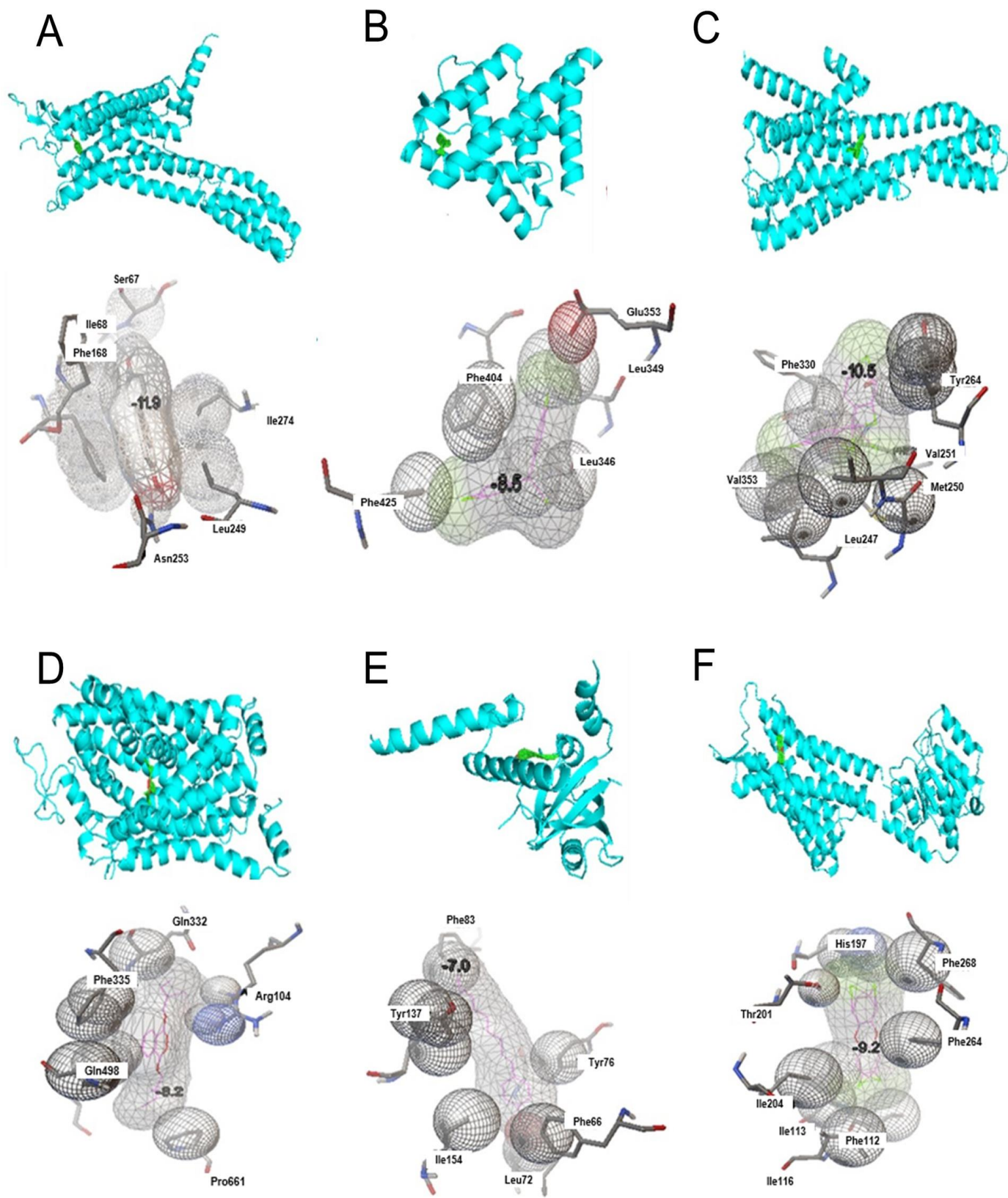
Fig. 1. Binding Pose and Score of the 6 active toxicants, where (**A**) – BPA interaction with 5UIG (- 11.9 kcal.mol^{-1}); (**B**) – DDD interaction with 5T97 (- 8.5 kcal.mol^{-1}); (**C**) – DDT interaction with 6A93 (- 10.5 kcal.mol^{-1}); (**D**) – DEHP interaction with 5I6Z (-8.2 kcal.mol^{-1}); (**E**) – NP interaction with 5NJ8 (-7.0 kcal.mol^{-1}); (**F**) – TCDD interaction with 6HLL (- 9.2 kcal.mol^{-1}) visualized on PyMol and ADT, respectively.

150

Table 6. Ligand Efficiencies (LE) of docked scores of selected 6 targets and 6 active toxicants.

Serial No.	Selected Target	Ligand efficiency of the selected toxicants [kcal.mol⁻¹ HA]					
		BPA	DDD	DDT	DEHP	NP	TCDD
1	Estrogen receptor (PDB ID: 5T97)	0.54	0.47	0.38	0.27	0.42	0.41
2	Sodium-dependent serotonin transporter (PDB ID: 5I6Z)	0.56	0.46	0.52	0.29	0.47	0.46
3	Adrenergic receptor alpha-2A (PDB ID: 5UIG)	0.70	0.62	0.48	0.27	0.43	0.57
4	Aryl hydrocarbon receptor (PDB ID: 5NJ8)	0.51	0.46	0.50	0.26	0.44	0.34
5	Substance-P receptor (PDB ID: 6HLL)	0.53	0.46	0.52	0.27	0.44	0.51
6	5-hydroxytryptamine receptor 2A (PDB ID: 6A93)	0.54	0.48	0.55	0.30	0.49	0.49

Gene expression network modulated by the toxicants

The overall expression network of the fifty predicted target genes obtained in this study as shown in Fig. 2, highly implicated SUZ12 (polycomb protein) with hypergeometric *p*-value of 5.44×10^{-10}, as the most enriched transcription factors among others, which are associated with the active toxicants from the typical dumpsite while the mitogen-activated protein kinases (MAPKs) and cyclin-dependent kinases (CDKs) with maximum hypergeometric *p*-value of 2.70×10^{-15} were the major kinases from the protein-protein interaction (PPI) as shown in Fig. 2. Differential gene expression study has become one of the imperative methods to discover genes which are essential in diagnosis and prediction of diseases such cancer (Fatoki *et al.* 2018b). The transcription factors such as TRIM28, SUZ12 and STAT3 are associated with the proliferation of cancer cells. The result of this study was found similar with that of enrichment analysis of urethane-targeted genes which showed TRIM28 and SUZ12 as most
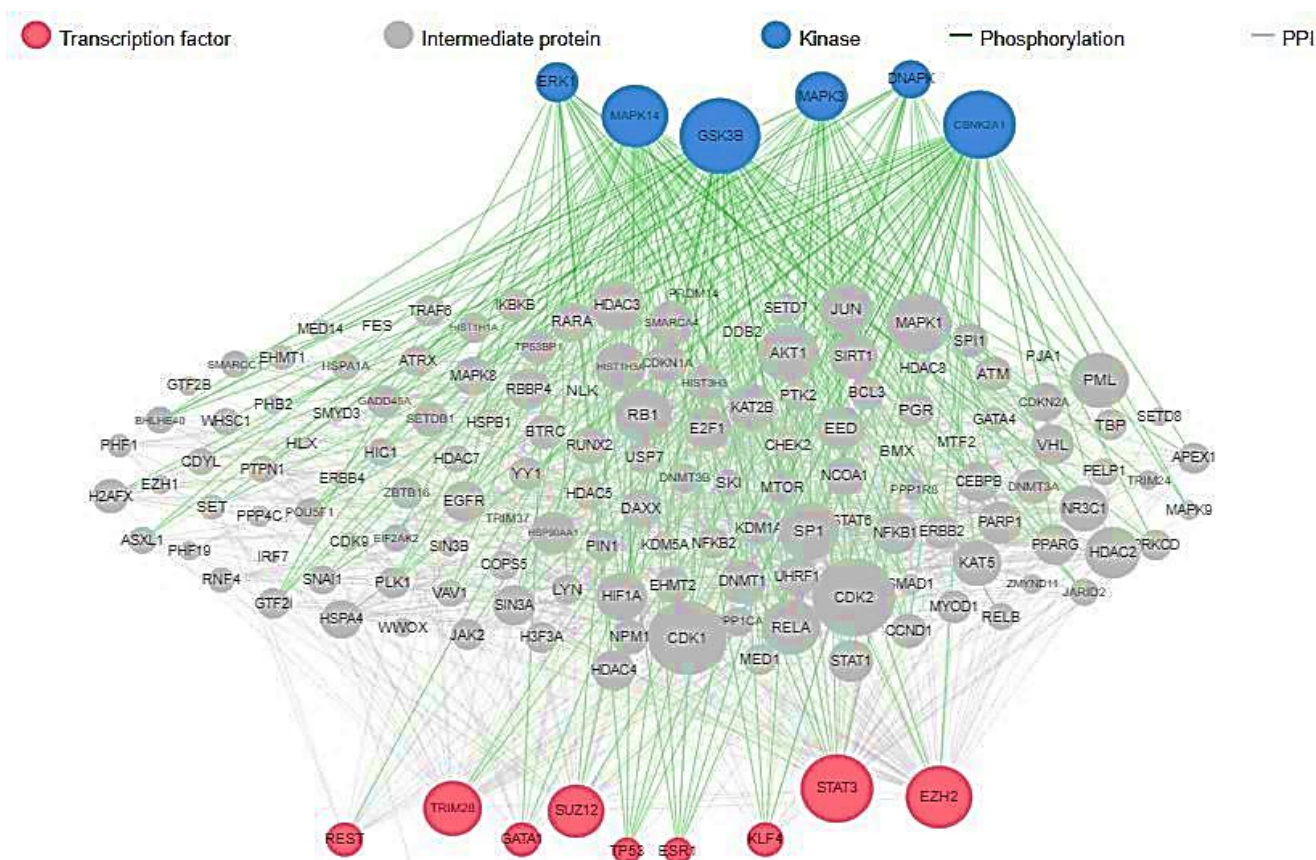

Fig. 2. Overall network of target genes of active toxicants from typical dumpsite or contaminated soil generated by eXpression2Kinases server.

expressed transcription factors (Fatoki *et al.* 2018b). However, endometrial stromal tumors may be a result of a chromosomal aberration involving SUZ12.

Conclusions

This study has unravelled some of the chemical compounds from typical dumpsite or grossly contaminated soil that might actively modulate biological system and are potential cause of several ailments which include cancer, bipolar disorder, schizophrenia, neurodegenerative disease and others. This study has showed the threat which toxicants pose to public health. More importantly, it provides avenue for further investigation of super bugs (microorganisms) that can remediate these toxicants in our environment through bioaugmentation, which improves the biodegradative capacities of contaminated sites. Environmental monitoring and modern wastes management system should be implemented and enforced in order to safeguard the public health and prevent indiscriminate dumping of wastes in the communities and regularize human habitation far away from existing dumpsites.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

Allen HE (2002) Bioavailability of metals in terrestrial ecosystems: importance of partitioning for bioavailability to invertebrates, microbes, and plants. SETAC Press. Pensacola, Florida, USA, 158 p.

Aznar S, Hervig ME (2016) The 5-HT2A serotonin receptor in executive function: implications for neuropsychiatric and neurodegenerative diseases. Neurosci. Biobehav. Rev. 64: 63-82.

Boulding JR, Barcelona MJ (1991) Geochemical variability of the natural and contaminated subsurface environment. *In* Site characterization for subsurface remediation. Center for Environmental Research Information Office of Research and Development U.S. Environmental Protection Agency, Cincinnati, USA, p. 103-122.

Burks HE, Abrams T, Kirby CA, Baird J, Fekete A, Hamann LG, Kim S, Lombardo F, Loo A, Lubicka D, Macchi K, McDonnell DP, Mishina Y, Norris JD, Nunez J, Saran C, Sun Y, Thomsen NM, Wang C, Wang J, Peukert S (2017) Discovery of an acrylic acid based tetrahydroisoquinoline as an orally bioavailable selective estrogen receptor degrader for ER alpha + breast cancer. J. Med. Chem. 60: 2790-2818.

Clarke DJB, Kuleshov MV, Schilder BM, Torre D, Duffy ME, Keenan AB, Lachmann A, Feldmann AS, Gundersen GW, Silverstein MC, Wang Z, Ma'ayan A (2018) eXpression2Kinases (X2K) Web: linking expression signatures to upstream cell signaling networks. Nucleic Acids Res. 46, W1: 171-179.

Diana A, Michielin O, Zoete V (2017) SwissADME: a free web tool to evaluate pharmacokinetics, druglikeness and medicinal chemistry friendliness of small molecules. Sci. Rep. 7: 42717.

Diana A, Michielin O, Zoete V (2019) SwissTargetPrediction: updated data and new features for efficient prediction of protein targets of small molecules. Nucleic Acids Res. 47: W357-W364.

Egboka BC, Enwankwor GI, Orajaka IP, Ejiofor AO (1989) Principles and problems of environmental pollution of groundwater resources with case examples from developing countries. Environ. Health Perspect. 83: 39-68.

Eze CT, Amaeze NH (2016) Microbiological and heavy metal characterization of soil from an open hospital waste dumpsite in Enugu, Nigeria. Asian J. Microbiol. Biotechnol. Environ. Sci. 18: 587-595.

Fatoki TH, Awofisayo OA, Ogunyewo OA, Ugboko HU, Sanni DM (2018a) Impacts of analogy and dimerization of bioactive compounds on molecular biological functions. J. Adv. Med. Pharma. Sci. 19: 1-14.

Fatoki TH, Dutta S, Oyedele AS (2018b) Uncovering the selective drug targets for urethane mediated cancer by network approach. .J Appl. Life Sci. Int. 19: 1-12.

ISWA – International Solid Waste Association (2016) A roadmap for closing waste dumpsites The world's most polluted places. ISWA's Scientific and Technical Committee Work-Program 2015-2016, 124 p.

Kimura TK, Asada H, Inoue A, Kadji FMN, Im, D, Mori C, Arakawa T, Hirata K, Nomura Y, Nomura N, Aoki J, Iwata S, Shimamura T (2019) Structures of the 5-HT2A receptor in complex with the antipsychotics risperidone and zotepine. Nat. Struct. Mol. Biol. 26: 121-128.

Lombi E, Wenzel WW, Adriano DC (1998) Soil contamination, risk reduction and remediation. Land Contamin. Reclamat. 6: 183-187.

Mercer JW, Spalding CP (1991) Site characterization overview. *In* Site Characterization for Subsurface Remediation. Center for Environmental Research Information Office of Research and Development U.S. Environmental Protection Agency, Cincinnati, USA, p. 12-21

Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, Olson AJ (2009) AutoDock4 and AutoDockTools4: automated docking with selective receptor flexibility. J. Comput. Chem. 30(16): 2785-2791.

Odeyemi, AT, Faweya EB, Agunbiade OR, Ayeni SK (2011) Bacteriological, mineral and radioactive contents of leachate samples from dumpsite of Ekiti State Government Destitute Centre in Ado-Ekiti. Arch. Appl.

Sci. Res. 3(4): 92-108.

Padmanabhan B, Ramu M, Mathur S, Unni S, Thiyagarajan S (2016) Identification of new inhibitors for human SIRT1: an *in-silico* approach. Med. Chem. 12(4): 347-361.

Pasko OA, Mochalova TN (2014) Toxicity assessment of contaminated soils of solid domestic waste landfill. IOP Conf. Ser. Earth Environ. Sci, 21: 012044

Schulte KW, Green E, Wilz A, Platten M, Daumke O (2017) Structural basis for aryl hydrocarbon receptor-mediated gene activation. Structure 25(1–9): e1–e3.

Schultes S, de Graaf C, Haaksma EEJ, de Esch IJP, Leurs R, Krämer O (2010) Ligand efficiency as a guide in fragment hit selection and optimization. Drug Discov. Today Technol. 7: e157-e162.

SCU – Science Communication Unit, University of the West of England, Bristol (2013) Science for environment policy in-depth report: Soil contamination: Impacts on human health. Report produced for the European Commission DG Environment, September 2013. Available at: http://ec.europa.eu/science-environment-policy.

Shayler H, McBride M, Harrison E (2009) Sources and impacts of contaminants in soils. Cornell Waste Management Institution, NY, USA, 6 p.

Teuten EL, Saquing JM, Knappe DRU, Barlaz MA, Jonsson S, Björn A, Rowland SJ, Thompson RC, Galloway TS, Yamashita R, Ochi D, Watanuki Y, Moore C, Viet PH, Tana TS, Prudente M, Boonyatumanond R, Zakaria MP, Akkhavong K, Ogata Y, Hirai H, Iwasa S, Mizukawa K, Hagino Y, Imamura A, Saha M, Takada H (2009) Transport and release of chemicals from plastics to the environment and to wildlife. Philos. Trans. R. Soc. Lond. B Biol. Sci. 364: 2027-2045.

Trott O, Olson AJ (2010) AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. J. Comput. Chem. 31(2): 455-461.

Valentın L, Nousiainen A, Mikkonen A (2013) Introduction to organic contaminants in soil: Concepts and risks. *In* Emerging organic contaminants in sludges: Analysis, fate and biological treatment, Vicent T, Caminal G, Eljarrat E, Barceló D (eds.), Springer-Verlag Berlin Heidelberg, p. 1-29.

WHO – World Health Organization (2013) Contaminated sites and health. Report of two WHO workshops; Syracuse, Italy, 18 November 2011 and Catania, Italy, 21-11 June 2012, 106 p.

Yao Y, Sack TU, Volchek K, Brown CE (2015) PFC-contaminated soil and its remediation strategies: A review. Proceedings of the Thirty-Eight AMOP Technical Seminar, Environment Canada, Ottawa, ON, p. 314-339.